Manual of Cardiovascular Medicine

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SIXTH EDITION

Wolters Kluwer

Manual of Cardiovascular Medicine

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For Mary and in memory of my parents—BG
To my parents (Anie and Johny), my sisters (Sonia and Lucia), and my family (Erin, Jack, and Evelyn) for their unwavering support—BA
To our families and to the fellows and staff of the Department of Cardiovascular Medicine, Cleveland Clinic—BG, VM, BA, BL

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PREFACE

The sixth edition of the *Manual of Cardiovascular Medicine* has been updated and revised. Our goal has been to ensure that the *Manual* is a convenient resource for all those involved in the management of cardiovascular disease and especially for those in training. The *Manual* incorporates the newest guidelines from professional and scientific societies where appropriate. It has been compiled by fellows and advanced subspecialty trainees in Cardiovascular Medicine at Cleveland Clinic under the direction of the attending staff. The section editors (Jay Bishop, Tom Callahan, Wilson Tang, Leslie Cho, Margaret Fuchs, Joanna Ghobrial, Neha Quatromoni, and Tom Wang) did a fine job in ensuring the content is succinct and timely. Ben Alencherry and Balint Laczay are the associate editors and as in the past have been chief fellows of the general Cardiovascular Disease Training Program and helped commission the chapters and ensure their completion. We wish to thank all of our colleagues at Cleveland Clinic for their support in continuing the *Manual* into its sixth edition and to the many fellows and staff who helped develop the *Manual* over previous editions.

We are deeply grateful for the philanthropic support we have received for the educational and academic activities of our fellows and faculty, which has allowed us to continue this *Manual*. We thank John and Rosemary Brown, the Robert Tomsich family, the Karos family, the Gene Braun family, and the Lawrence family who have supported fellowship, and educational and academic activities within the Department of Cardiovascular Medicine, Cleveland Clinic. We also thank Dr Lars Svensson, Chair, Heart and Vascular Institute, and Dr Samir Kapadia, Chair, Cardiovascular Medicine at Cleveland Clinic, for their support.

Finally, we wish to express our gratitude to our families for their support, patience, and encouragement.

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Ischemic Heart Disease

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CHAPTER 1

Acute Myocardial Infarction

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I. EPIDEMIOLOGY. Acute myocardial infarction (MI) is the leading cause of death in North America and Europe. Each year, an estimated 605,000 Americans will sustain a new MI, and another 200,000 will have a recurrent MI. Coronary artery disease (CAD) remains the leading cause of death in the United States and has been for the past 90 years. However, the incidence of and mortality associated with acute MI have declined dramatically over the past 50 years with the advent of the coronary care unit, fibrinolytic therapy, catheter-based reperfusion, and lipid-modifying therapy. The aging of the population in advanced economies and the global increased incidence of diabetes and obesity will, however, continue to increase the burden of atherosclerotic CAD in the future.

II. PATHOPHYSIOLOGY. In most patients, coronary plaque rupture is the initiating event of acute MI. **Rupture of the thin fibrous cap of a coronary atheroma exposes the underlying subendothelial matrix to formed elements of circulating blood, leading to activation of platelets, thrombin generation, and thrombus formation.** Erosion of a coronary plaque without rupture can also lead to thrombus formation and is estimated to cause up to 25% of MIs. Rarely in approximately 5% of acute coronary syndrome (ACS), the underlying pathogenesis is due to an underlying calcific nodule. ACS is a dynamic process that involves cyclical transitioning among complete vessel occlusion, partial vessel occlusion, and reperfusion. Occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI). The pathophysiology of STEMI and non-STEMI (NSTEMI) is similar, and this explains the substantial overlap in ACSs with regard to ultimate outcome, extent of

necrosis, and mortality rates. The recognition of ST-segment elevation is particularly important because it generally mandates the need for emergent reperfusion therapy.

III. DEFINITION. A 2018 expert consensus document defined acute MI as evidence of myocardial injury in a clinical setting consistent with acute myocardial ischemia. This concept was further described as the detection of **a rise and/or fall in cardiac troponin (cTn) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of ischemia**. Ischemia was defined as any symptom supportive of ischemia, electrocardiographic changes suggestive of new ischemia, development of pathologic Q waves on electrocardiogram (ECG), imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology, or identification of an intracoronary thrombus on angiography or autopsy. Included in the definition were sudden cardiac death (SCD) with evidence of myocardial ischemia (new ST elevation, left bundle branch block [LBBB], ventricular fibrillation, or coronary thrombus), documented stent thrombosis by angiography or autopsy, and biomarker elevation >5× URL for post–percutaneous coronary intervention (PCI) patients with normal baseline values or a rise of >20% if baseline values are stable or falling and biomarker elevation >10× URL for post–coronary artery bypass grafting (post-CABG) patients (**Table 1.1**). Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q waves on ECG with or without symptoms in the absence of nonischemic causes, imaging evidence of MI, or pathologic findings of healed or healing MI.

TABLE 1.1 Clinical Classification of Different Types of MI

Type 1	Spontaneous MI related to ischemia from a coronary plaque rupture, erosion, or dissection
Type 2	MI because of ischemia resulting from increased oxygen demand or decreased supply (“demand ischemia”)
Type 3	SCD with symptoms of ischemia, new ST elevation, or LBBB, but biomarkers

	are unavailable
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 4c	MI associated with restenosis after PCI
Type 5	MI associated with CABG

CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCD, sudden cardiac death.
Data from Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction. *Circulation*. 2018;138(20):e618-e651; American Heart Association.

IV. CLINICAL DIAGNOSIS. In any patient with a clinical history of chest pain suspected to be of cardiac origin, an ECG should be promptly obtained. Ideally, this should be within 10 minutes of presentation to an emergency department or outpatient center or first medical contact and interpreted promptly to determine eligibility for reperfusion therapy. If the **ECG demonstrates acute ST-segment elevation, emergent reperfusion treatment with primary PCI or fibrinolysis is indicated**. During this evaluation period, a targeted medical history and physical examination should be performed. If the patient's history is compatible with cardiac ischemia and the ECG does not meet the criteria for emergent reperfusion therapy, the patient may have unstable angina or NSTEMI. These syndromes are discussed in Chapter 2.

A. Signs and symptoms

1. The classic symptomatology of an acute MI is characterized by severe, **crushing substernal chest pain** described as a squeezing or constricting sensation with frequent radiation to the left arm, often associated with an impending sense of doom. The discomfort is similar to that of angina pectoris, but it is typically more severe, of longer duration (usually >20 minutes), and is not relieved with rest or nitroglycerin. Peak intensity is usually gradual and not instantaneous, as it would be with other cardiac

emergencies like a pulmonary embolism (PE) or acute aortic syndrome.

a. The chest discomfort may radiate to the neck, jaw, back, shoulder, right arm, and epigastrium. Pain in any of these locations without chest pain is possible. Myocardial ischemic pain localized to the epigastrium is often misdiagnosed as indigestion. **Symptoms may be atypical in older patients, in women, and in patients with diabetes mellitus and prior history of CABG**.

b. If the pain is sudden, radiates to the back, and is described as tearing or knifelike, aortic dissection should be considered.

2. Associated symptoms may include diaphoresis, dyspnea, fatigue, lightheadedness, palpitations, acute confusion, indigestion, nausea, or vomiting. Gastrointestinal symptoms are especially common with inferior infarction. Ischemic chest pain rarely radiates below the umbilicus.

B. Physical examination. Although the physical examination does not add much to the diagnosis of acute MI, the presence of heart failure on examination identifies patients at heightened clinical risk. The examination is also extremely important in excluding other diagnoses that may mimic acute MI, in risk stratification, and in serving as a baseline examination to monitor for mechanical complications of acute MI that may develop. The **mechanical complications** of papillary muscle rupture with acute mitral regurgitation and ventricular septal rupture are often heralded by a new systolic murmur (see Chapter 3). Early diagnosis of these complications relies on well-documented examination findings at baseline and during the subsequent hospital course.

V. DIFFERENTIAL DIAGNOSIS. The differential diagnosis of ST elevation on a surface ECG includes conditions with comorbid ischemia such as acute aortic dissection involving the root, conditions with ST elevation but no ischemia such as left ventricular (LV) hypertrophy or early repolarization abnormality, and conditions with chest pain but no

ischemia such as myopericarditis (**Table 1.2**). The most common differential diagnostic considerations are discussed below.

TABLE 1.2 Differential Diagnostic Considerations for STEMI

Comorbid Ischemia
Aortic dissection
Stress cardiomyopathy
Systemic arterial embolism
Hypertensive crisis
Aortic stenosis
Cocaine use
Arteritis
ST Elevation but No Ischemia
Early repolarization
Left ventricular hypertrophy
Left bundle branch block
Hyperkalemia
Brugada syndrome
Chest Pain but No Ischemia
Aortic dissection
Stress cardiomyopathy
Myopericarditis
Pleuritis
Pulmonary embolism
Gastrointestinal disorders
Costochondritis

STEMI, ST-segment elevation myocardial infarction.
Adapted with permission from Christofferson RD. Acute ST-elevation myocardial infarction. In: Shishehbor MH, Wang TH, Askari AT, et al, eds. *Management of the Patient in the Coronary Care Unit*. Lippincott Williams & Wilkins; 2008:18-19.

A. **Pericarditis.** Chest pain due to pericarditis is typically worse when the person is supine and improves when the person is sitting upright or bends forward. Care must be taken in excluding acute MI, however, because pericarditis can complicate acute MI. The electrocardiographic abnormalities of acute pericarditis may also be confused with acute MI. Diffuse ST-segment elevation is the hallmark of acute pericarditis, but this finding may be seen in acute MI that involves the left main coronary artery or a large "wraparound" left anterior descending artery. PR-segment depression, peaked T waves, or electrocardiographic abnormalities out of proportion to the clinical scenario may favor the diagnosis of pericarditis. The ST-segment elevations in pericarditis are often concave, whereas the ST-segment elevations in acute MI are usually convex. Reciprocal ST-depression does not occur in pericarditis, except in leads aVR and V_1. Early T-wave inversion is not a feature of acute pericarditis. Echocardiography may be useful, not only in evaluating for pericardial effusion, which may occur in either condition, but also in documenting the lack of regional wall motion abnormalities in a coronary distribution in the setting of ongoing pain and ST elevation.

B. **Myocarditis.** As with pericarditis, the symptoms and electrocardiographic findings of myocarditis may be similar to those of acute MI. Echocardiography is less useful in differentiating this syndrome from acute MI, because segmental LV dysfunction may be encountered in either condition. With myocarditis, a complete history may reveal a more insidious onset and an associated preceding viral syndrome. The diagnosis of myocarditis can be confirmed with cardiac magnetic resonance imaging (MRI) with gadolinium. A patchy distribution of delayed hyperenhancement in the epicardium and mid-myocardium with sparing of the endocardium is the characteristic MRI finding with myocarditis. Findings are noted in a noncoronary distribution.

C. **Stress cardiomyopathy (takotsubo).** Following an acute emotional or physical stress, patients may present with typical chest pain, ischemic ECG changes, a mild troponin elevation, and new-onset,

transient regional LV wall motion abnormalities. In **the absence of obstructive epicardial CAD, this clinical presentation may be explained by a stress-induced cardiomyopathy**. The presenting signs and symptoms of this syndrome can be identical to an acute MI, making stress cardiomyopathy a diagnosis of exclusion. Stress cardiomyopathy is also called apical ballooning syndrome as the regional wall motion abnormalities tend to preferentially affect the apex while sparing the basal and mid-ventricular segments, although many other variants have been described. The term "takotsubo" comes from the Japanese word for "octopus pot" as the apical ballooning as seen on imaging represents the shape of this octopus trap. Stress cardiomyopathy occurs most commonly in women and in older adults. In addition to an ECG and an echo, the evaluation of stress-induced cardiomyopathy generally requires coronary angiography to document the absence of acutely obstructive epicardial CAD. The LV wall motion usually returns to normal over time, and recurrence may occur following another precipitating stressful event.

D. **Acute aortic dissection.** Sharp, tearing chest pain that radiates through the chest to the back is typical of aortic dissection. Chest pain with new neurologic deficits or symptoms may also be a presenting sign of an aortic dissection with both coronary and arch vessel involvement. This type of chest pain pattern should be investigated thoroughly before administration of antithrombotic, antiplatelet, or fibrinolytic therapy. Proximal extension of the dissection into either coronary ostium can account for acute MI. A chest radiograph may reveal a widened mediastinum. Transthoracic echocardiography (TTE) may reveal a dissection flap in the proximal ascending aorta. If aortic dissection is strongly considered, a computed tomography (CT) scan of the chest with contrast should promptly be obtained. In the presence of acute renal failure or if CT is unavailable, transesophageal echocardiography is an alternative imaging modality to evaluate for aortic dissection.

E. **PE.** Shortness of breath associated with pleuritic chest pain but without evidence of pulmonary edema is suggestive of PE.

Echocardiography helps to rule out wall motion abnormalities and may identify right ventricular (RV) dilatation and dysfunction in the setting of a hemodynamically significant PE. A clot in transit may rarely be seen on TTE. In the absence of renal dysfunction, a CT PE protocol helps confirm the diagnosis.

F. Esophageal disorders. Gastroesophageal reflux disease, esophageal motility disorders, and esophageal hyperalgesia can cause chest pain, the characteristic of which can mimic cardiac ischemic pain. These disorders can often coexist in patients with coronary disease, thereby complicating the diagnosis. A workup for coronary disease should precede the evaluation of esophageal disorders. Symptoms that may be suggestive but not diagnostic of chest pain of an esophageal origin include postprandial symptoms, relief with antacids, and a lack of radiation of the pain.

G. Acute cholecystitis can occasionally mimic the symptoms and ECG findings of inferior acute MI, but rarely can the two coexist. Tenderness in the right upper quadrant, fever, and an elevated leukocyte count favor cholecystitis. Confirmatory imaging should be obtained if acute cholecystitis is suspected.

H. Brugada syndrome. In this setting, a genetic defect in myocardial sodium channels predisposes patients to ventricular fibrillation and SCD. Patients with Brugada do not typically present with acute chest pain but may present with SCD. Twelve-lead ECG may show a pseudo-right bundle branch block (RBBB) pattern and ST elevation in V_1-V_2, typical findings for type 1 Brugada pattern. The mechanism of SCD in Brugada is secondary to the altered sodium channels and variability in refractory periods in adjacent myocardium that precipitate ventricular fibrillation.

VI. LABORATORY EXAMINATION (FIGURE 1.1)

A. cTn. In patients with suspected ACS cTn testing should be performed as part of the initial evaluation. In the setting of ST elevation on ECG, waiting for confirmatory testing with cTn is not indicated. Troponin elevation (above the 99th percentile) in the absence of acute ischemic-mediated myocardial injury can be found in a number of

clinical settings, including congestive heart failure (CHF), renal failure, myocarditis, PE, acute neurologic disease, cardiac contusion, or drug toxicity.

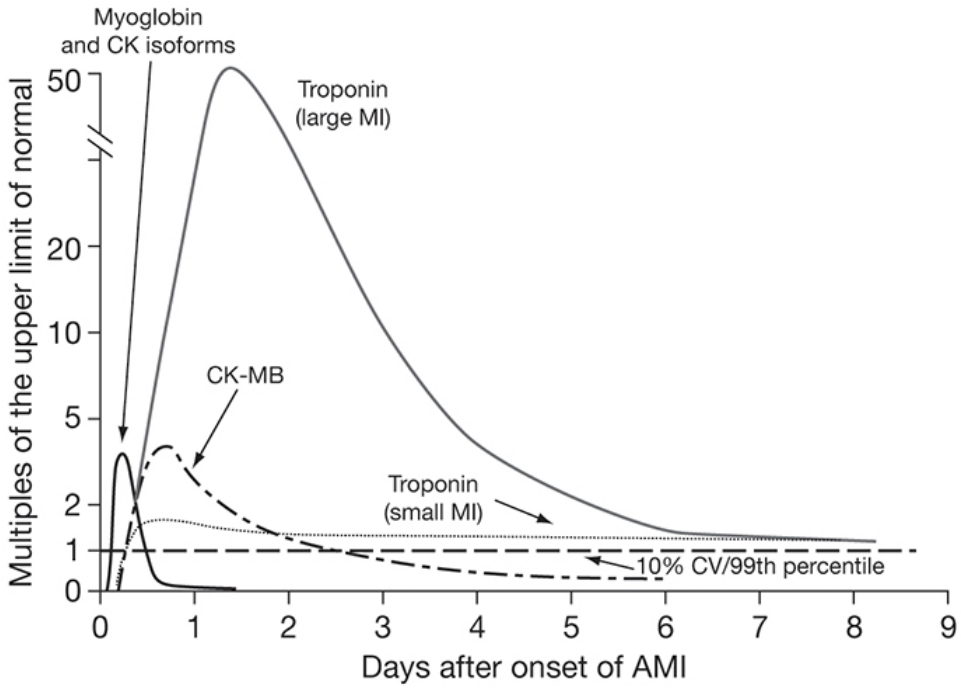


FIGURE 1.1 Timing of biomarker release after acute myocardial infarction (AMI). CK, creatine kinase; CK-MB, creatine kinase myocardial band; CV, coefficient of variation. (Reprinted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol*. 2007;50(7):652-726. Copyright © 2007 American College of Cardiology Foundation and the American Heart Association, Inc, with permission.)

B. High-sensitivity cardiac troponin (hs-cTn). A hs troponin assay is preferred for evaluating the presence of acute myocardial injury, given its increased ability to detect myocardial injury early and accurately. By definition, hs-cTn detects concentrations above the assay's lower limit of detection (LOD) in more than 50% of healthy population and should have a coefficient of variance of <10% at the 99th percentile value. Hs-cTn assays are best utilized to rapidly and reliably rule out myocardial ischemia, especially in patients presenting acutely with chest pain because of the test's high negative

predictive value. A hs-cTn value below the LOD in patients with suspected ischemic symptoms of >3 hours has a high negative predictive value to rule out MI. If the initial hs-cTn value is negative or indeterminate, a second value can be measured as early as 1 to 2 hours following. In the absence of a significant delta increase in hs-cTn levels, MI can be safely ruled out. The shortened time interval to a second biomarker measurement can translate into a more rapid rule out for acute MI and shorten emergency department stays for patients presenting with suspected acute chest pain. As a result of the above, the 2021 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the evaluation and diagnosis of chest pain offer a class I recommendation for hs-cTn as the preferred biomarker for the evaluation of acute chest pain.

C. Creatine kinase and creatine kinase myocardial band (CK and CK-MB). There is no role in the utilization of CK and CK-MB for the evaluation of patients with suspected ACS in the troponin era. **CK levels remain helpful in gauging the size and timing of acute MI.** CK levels peak at 24 hours, but early peaking is noted among patients who undergo successful reperfusion of the infarct-related artery. In the acute setting, the presence of a positive CK, CK-MB assay in the setting of negative troponin indicates a noncardiac source, including skeletal muscle disease or trauma (eg, rhabdomyolysis).

III. DIAGNOSTIC TESTING

A. Electrocardiography

1. **Definitive electrocardiographic diagnosis** of acute MI requires ST elevation of 1 mm or more in two or more contiguous leads, often with reciprocal ST depression in the contralateral leads. In leads V_2-V_3, ST elevation of at least 2 mm in men ≥40 years, 2.5 mm in men <40 years, and 1.5 mm in women are required for accurate diagnosis.
2. **ECG subsets.** ST-segment elevations can be divided into subgroups that may be correlated with the infarction-related artery and risk of death. These five subgroups are listed in **Table 1.3** and illustrated in **Figure 1.2**.

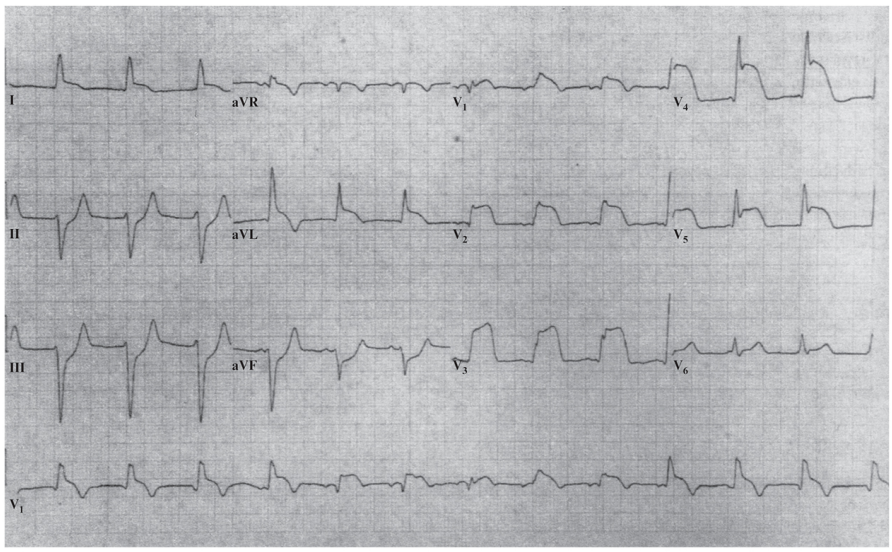
TABLE 1.3 Acute MI: ECG Subsets and Correlated Infarct-Related Artery and Mortality

Category	Anatomy of Occlusion	ECG Findings	30-Day Mortality Rate (%)[a]	1-Year Mortality Rate (%)
Proximal LAD	Proximal to first septal perforator	ST ↑ V_1-V_6, I, aVL, and fascicular or bundle branch block	19.6	25.6
Mid-LAD	Proximal to large diagonal but distal to first septal perforator	ST ↑ V_1-V_6, I, aVL	9.2	12.4
Distal LAD or diagonal	Distal to large diagonal or diagonal itself	ST ↑ V_1-V_4, or I, aVL, V_5, V_6	6.8	10.2
Moderate to large inferior (posterior, lateral, RV)	Proximal RCA or left circumflex	ST ↑ II, III, aVF, and any of the following: (a) V_1, V_3R, V_4R; (b) V_5, V_6; (c) R >S in V_1, V_2	6.4	8.4
Small inferior	Distal RCA or left circumflex branch	ST ↑ II, III, aVF only	4.5	6.7

↑, increased; ECG, electrocardiogram; LAD, left anterior descending (coronary artery); MI, myocardial infarction; RCA, right coronary artery; RV, right ventricular.

[a]Mortality rate based on GUSTO I cohort population in each of the 5-year categories, all receiving reperfusion therapy.

Reprinted with permission from Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Lippincott-Raven; 1998:403.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II
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III
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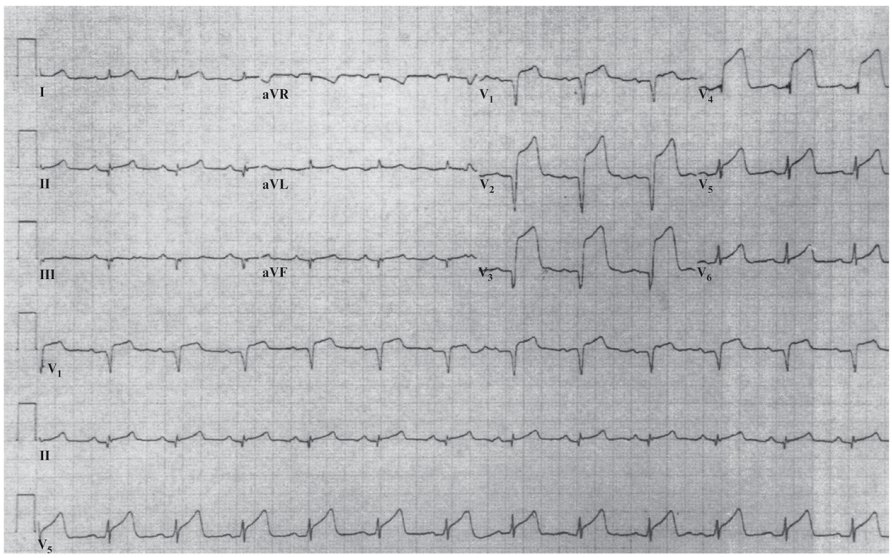
V1

A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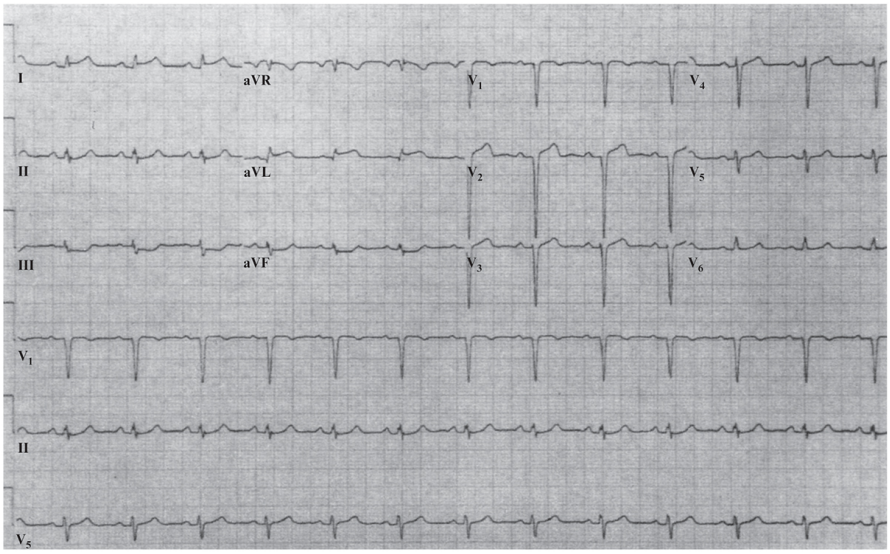
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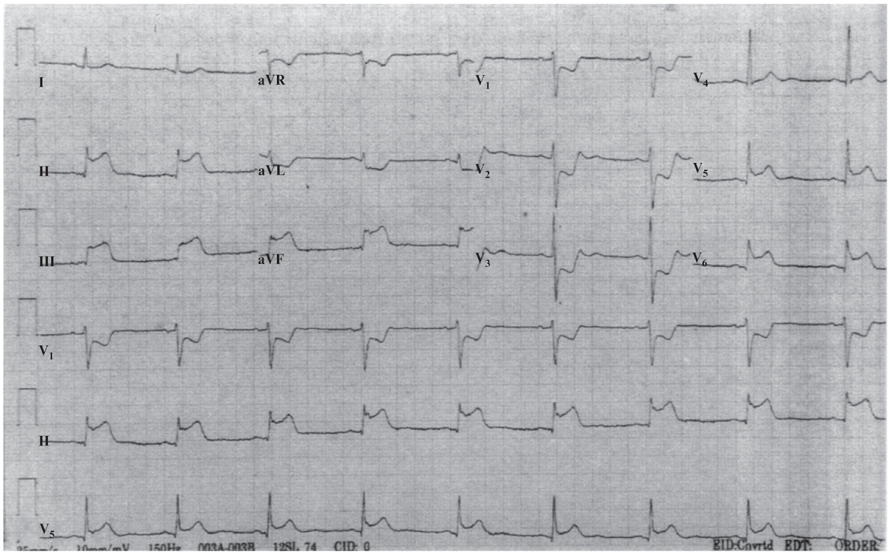
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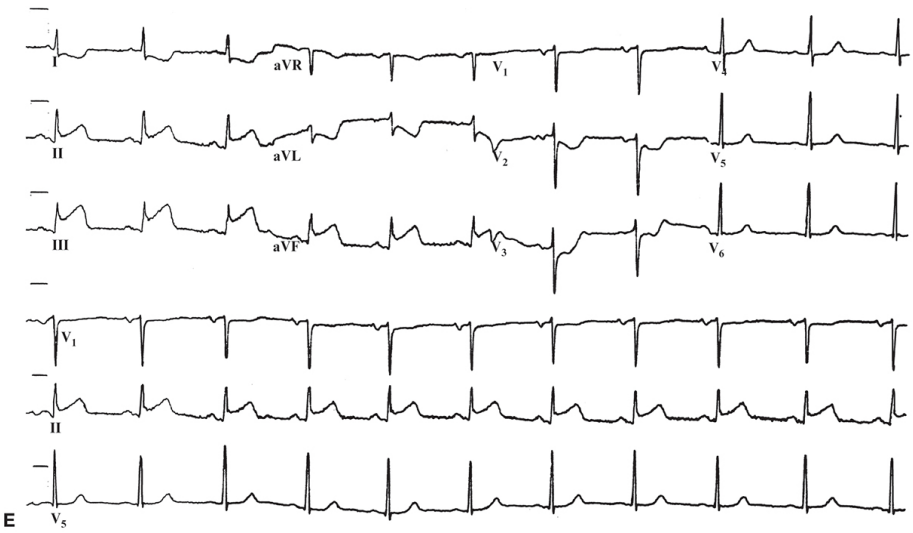

FIGURE 1.2 Electrocardiographic subsets of acute myocardial infarction (MI). **A.** Large anterior MI with conduction disturbance (proximal left anterior descending [LAD] coronary artery). **B.** Anterior MI without conduction disturbance (mid-LAD). **C.** Lateral MI (distal LAD, diagonal branch, or left circumflex branch). **D.** Large inferior MI with reciprocal changes (proximal right coronary artery [RCA]). **E.** Small inferior MI (distal RCA). (Reprinted with permission from Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. 2nd ed. Lippincott-Raven; 2002.)

3. Left bundle branch block

a. New LBBB in the setting of symptoms consistent with acute MI may indicate a large, anterior wall, acute MI involving the proximal left anterior descending coronary artery and should be managed as acute STEMI.

b. In the absence of an old ECG or in the presence of LBBB at baseline, the diagnosis of acute STEMI can be made with >90% specificity on the basis of the criteria listed in **Table 1.4** and illustrated in **Figure 1.3**.

TABLE 1.4 Electrocardiographic Criteria for the Diagnosis of Acute MI in the Presence of LBBB

Criterion	Score[a]
ST-segment elevation ≥1 mm concordant with QRS	5

Criterion	Score[a]
ST-segment depression ≥1 mm in lead V_1, V_2, or V_3	3
ST-segment elevation ≥5 mm discordant with QRS	2

LBBB, left bundle branch block; MI, myocardial infarction.

[a]Point scores for each criterion met are added. Total point score of 3 yields ≥90% specificity and an 88% positive predictive value.
From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med*. 1996;334:481-487. Copyright © 1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

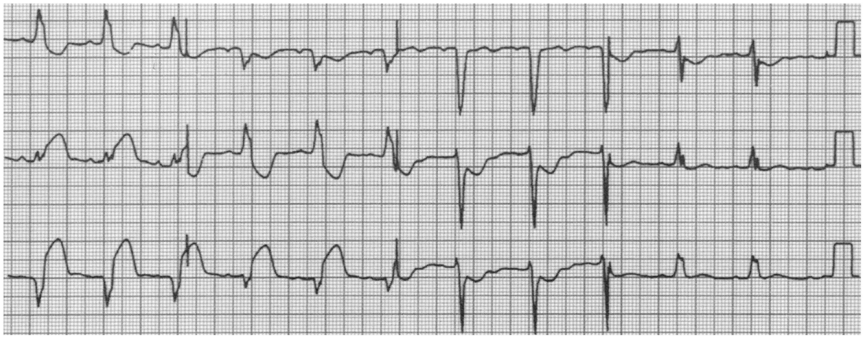

FIGURE 1.3 Electrocardiogram displays all of the criteria for the diagnosis of acute myocardial infarction (MI) in the setting of left bundle branch block: ST-segment elevation >1 mm, concordant with QRS in lead II (5 points); ST-segment depression >1 mm in leads V_2 and V_3 (3 points); and ST-segment elevation >5 mm, discordant with QRS in leads III and VF (2 points). A score of 10 points indicates an extremely high likelihood of inferior MI. (From Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle-branch block. *N Engl J Med*. 1996;334:481-487. Copyright © 1996 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

c. RBBB may challenge interpretation of ST elevation in leads V_1 through V_3. RBBB does not, however, obscure ST-segment elevation, and criteria for ST-elevation apply.

B. Echocardiography may be helpful in the evaluation of LBBB of undetermined duration in that the lack of regional wall motion abnormality in the presence of continuing symptoms makes the diagnosis of acute MI unlikely. It is worth noting that abnormal septal motion is often observed in the setting of LBBB, even in the absence of ischemia. Echo may also be useful in detecting extensive wall motion abnormalities in the posterior circulation when the presenting ECG is normal or reveals ST depression consistent with the presence of a true posterior infarction.

III. RISK STRATIFICATION. Early risk stratification in patients with acute MI is crucial, especially in those being considered for fibrinolysis, because the risks of therapy must be weighed against the potential benefits. Five simple baseline parameters have been reported to account for >90% of the prognostic information for 30-day mortality in this population. These characteristics are given in descending order of importance: age, systolic blood pressure, Killip classification (**Table 1.5**), heart rate, and location of MI (see **Table 1.3** and **Figure 1.2**). **Timely, optimally performed primary PCI is the preferred reperfusion strategy for all patients with STEMI**, but patients with evidence of acute heart failure or cardiogenic shock are especially well suited for treatment with primary PCI. In addition, various risk models have been created to improve risk prediction.

TABLE 1.5 30-Day Mortality Based on Hemodynamic (Killip) Class

Killip Class	Characteristics	Patients (%)	Mortality Rate (%)
I	No evidence of CHF	85	5.1
II	Rales, ↑JVD, or S_3	13	13.6
III	Pulmonary edema	1	32.2
IV	Cardiogenic shock	1	57.8

↑, increased; CHF, congestive heart failure; JVD, jugular venous distention; S_3, third heart sound.
Data from Lee KL, Woodlief LH, Topol EJ, et al; GUSTO-I Investigators. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction: results from an

international trial of 41,021 patients. *Circulation*. 1995;91(6):1659-1668.

A. The Global Registry of Acute Coronary Events score may be utilized to predict in-hospital mortality and postdischarge to 6-month mortality in all patients with ACS. Risk is calculated based on Killip class, heart rate, systolic blood pressure, serum creatinine, age, presence of cardiac arrest at admission, presence of cardiac biomarkers, and ST-segment deviation. Patients with a score of ≤60 have a ≤0.2% probability of in-hospital mortality, whereas patients with a score of ≥250 have a ≥52% probability of in-hospital mortality.

B. The thrombolysis in myocardial infarction (TIMI) risk score was developed in **patients with ST elevation who received thrombolysis** and incorporates eight variables obtained from the history, physical examination, and ECG (**Table 1.6**). In patients treated with fibrinolysis, a TIMI score of 9 or greater predicts a 30-day mortality of approximately 35%. In patients with a TIMI score of 0 or 1, the 30-day mortality rate is <2%. The strongest predictor of poor prognosis is advanced age (where age ≥75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables that predict a poor prognosis include hypotension, Killip class II-IV at presentation, tachycardia, history of diabetes or hypertension, anterior ST elevation (also complete LBBB), low body weight, and a time to treatment of >4 hours.

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in Patients With STEMI

History	
Age 65-74 y	2 points
Age ≥75 y	3 points
Angina or DM/HTN	1 point
Physical Examination	
HR >100 beats/min	2 points
SBP <100 mm Hg	3 points
Killip class II-IV	2 points

History	
Weight <67 kg	1 point
Presentation	
Anterior ST elevation or LBBB	1 point
Time to treatment >4 h	1 point
TIMI risk score = Total points (0-14)	

DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LBBB, left bundle branch block; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Adapted with permission from Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102(17):2031-2037.

IX. THERAPY

A. Prior to reperfusion

1. **Aspirin.** Immediate administration of aspirin (162-325 mg) is indicated for all patients with suspected acute MI, unless there is a clear history of true aspirin allergy (not intolerance). As shown in the ISIS-2 trial, aspirin therapy conveys as much mortality benefit as streptokinase (SK) alone. If oral administration is not possible, a rectal suppository can be given. If true aspirin allergy is present, a loading dosage of a $P2Y_{12}$ agent should be administered as soon as possible, aspirin desensitization therapy should be considered to facilitate treatment with dual-antiplatelet therapy (DAPT).
2. **Oxygen.** The routine administration of supplemental oxygen via nasal cannula to all patients with suspected MI is no longer warranted. The use of supplemental oxygen in patients with STEMI and an O_2 saturation ≥94% was not associated with any benefit in the Air Versus Oxygen in ST-Segment-Elevation Myocardial Infarction (AVOID) trial. In the Efficacy and Outcome Study of Supplemental Oxygen Treatment in Patients With Suspected Myocardial Infarction trial (DETO2X-AMI) trial, routine oxygen administration in patients with suspected MI and

O_2 saturation >90% did not reduce rates of hospitalization or death at 1 year. Supplemental oxygen should be routinely initiated in subjects with an O_2 saturation <90% and in patients who are visibly cyanotic or are in respiratory distress. Administration through a face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.

3. **Nitroglycerin.** Nitroglycerin can be useful in the management of acute MI complicated by heart failure, persistent chest pain, or hypertension. Nitroglycerin should not be administered to patients who are hypotensive, to patients in whom RV infarction is suspected, or to those with recent use of phosphodiesterase inhibitors (24-48 hours). Administration of sublingual nitroglycerin may also identify whether the ST-segment elevation represents a component of coronary artery spasm while arrangements for reperfusion therapy are being initiated. Routine use of oral nitrates after MI had no benefit in two large, randomized trials in the reperfusion era. A 30% reduction in systolic blood pressure can be expected with appropriately aggressive dosing (10-20 mcg/min with 5-10 mcg/min increases every 5-10 minutes).
4. **Pain management.** Nitrates and analgesic agents may be used to reduce the chest pain that accompanies an acute MI. Relieving chest pain provides clinical relief, reduces anxiety, and can decrease the sympathetic drive. Initial treatment with sublingual nitroglycerin tablet (see caution above) and utilization of opioid agents like intravenous (IV) fentanyl or morphine should be considered. The latter may delay absorption of orally administered $P2Y_{12}$ agents in this setting.
5. **Oral platelet P2Y12 receptor antagonists** should be used routinely in all patients with STEMI in the absence of contraindications, regardless of whether primary PCI is performed. Currently, the three agents available for the treatment of STEMI are clopidogrel, prasugrel, and ticagrelor. Clopidogrel and prasugrel are thienopyridines that irreversibly inhibit the

platelet adenosine diphosphate $P2Y_{12}$ receptor, and ticagrelor is a reversible direct inhibitor of this same receptor. In patients in whom PCI is planned, a loading dose should be given as early as possible or at the time of PCI. The Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction (ATLANTIC) trial demonstrated that the administration of ticagrelor in the prehospital setting is safe, may prevent postprocedural acute stent thrombosis, but does not improve preprocedural coronary reperfusion. In contrast, the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial studied the administration of prasugrel before or after diagnostic angiography in patients with NSTEMI. Pretreatment with prasugrel in these patients did not reduce major ischemic events within the first 30 days but did increase the risk of bleeding. The recommended loading dose of clopidogrel is 600 mg. The recommended loading dose of prasugrel is 60 mg, and ticagrelor is given as a 180 mg loading dose. The absorption of prasugrel and ticagrelor may be significantly impaired in patients with STEMI. This may be overcome by crushing these tablets prior to administration for more rapid absorption. In patients receiving fibrinolysis, clopidogrel is the thienopyridine of choice, at a loading dose of 300 mg if the patient is ≤75 years and a loading dose of 75 mg if age >75 years. In patients with fibrinolysis undergoing PCI within 24 hours, clopidogrel is the thienopyridine of choice with a loading dose of 300 mg recommended. The duration of clopidogrel following fibrinolysis should be at least 14 days and ideally up to 12 months. The maintenance dose of clopidogrel and prasugrel is 75 and 10 mg daily, respectively. The maintenance dose for ticagrelor is 90 mg twice a day. It is currently recommended that clopidogrel be held for 5 days, ticagrelor be held for 3 days, and prasugrel be held for 7 days prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding. Following CABG, DAPT should be

reintroduced and continued for at least a year in this setting (class I).

In patients with STEMI receiving DAPT following stent implantation, ticagrelor and prasugrel are preferred to clopidogrel to reduce stent thrombosis and major adverse cardiac events. Prasugrel should, however, not be utilized in patients with a prior history of stroke or transient ischemic attack. Prasugrel was noted to be superior to ticagrelor in reducing the incidence of death, MI, or stroke in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial; however, the reliability of these findings is uncertain. Clopidogrel may be used as an alternative agent in the presence of contraindication or when more potent $P2Y_{12}$ agents are unavailable. The default duration for DAPT following STEMI should be 12 months (class I). For patients at recognized high risk for bleeding, discontinuation of DAPT at 6 months may be considered (class IIb). In selected patients undergoing PCI, a shorter duration of DAPT (1-3 months) with subsequent transition to ticagrelor monotherapy may be considered (class IIa). In patients who are managed medically following an STEMI, the combination of aspirin and ticagrelor constitutes the preferred DAPT strategy.

6. **IV platelet P2Y12 receptor antagonists.** Cangrelor is the only available IV $P2Y_{12}$ inhibitor and binds reversibly to the receptor. Cangrelor is given as a 30 mcg/kg IV bolus followed by an infusion of 4 mcg/kg/min and provides potent platelet inhibition almost immediately (<2 minutes). The short plasma half-life of <5 minutes allows for near-complete restoration of platelet function within 1 to 2 hours after stopping the infusion. The Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events (CHAMPION PHOENIX) trial showed that preprocedural cangrelor reduced ischemic events including stent thrombosis at 48 hours compared with a loading dose of clopidogrel in patients undergoing urgent or elective PCI. Cangrelor currently has a Food and Drug Administration indication for patients undergoing PCI

who have not yet been treated with an oral $P2Y_{12}$ inhibitor and are not receiving glycoprotein (GP) IIb/IIIa inhibitors. This may be most effective in patients with extremely short door-to-balloon times or unreliable oral $P2Y_{12}$ inhibitor absorption because administration in this setting will ensure reliable platelet inhibition with the goal of reducing periprocedure ischemic events.

7. **Parenteral anticoagulants.** Unless there is a contraindication, all patients with STEMI should receive IV antithrombotic therapy. Traditionally, in patients who are undergoing primary PCI, this has been accomplished with unfractionated heparin (UFH). The dose of UFH is 70 to 100 U/kg as a bolus (maximum 4,000 U), followed by 12 U/kg/h infusion (maximum 1,000 U/h) to achieve a therapeutic activated clotting time (ACT). Routine administration of GP IIb/IIIa inhibitors is no longer warranted but can be used as a bailout strategy in patients with a large thrombus burden, inadequate DAPT, loading, or poor reflow. If GP IIb/IIIa inhibitors are used, the dose of UFH is reduced to 50 to 70 U/kg (maximum 4,000 units). Bivalirudin, a direct thrombin inhibitor, may be utilized as an alternative to IV heparin in patients with or without prior administration of UFH. Bivalirudin is given as a 0.75 mg/kg IV bolus, followed by a 1.75 mg/kg/h infusion. Additional boluses of 0.3 mg/kg can be given to maintain therapeutic ACT. However, the How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention trial randomized patients scheduled for emergent angiography to receive upstream UFH or bivalirudin. The results of the trial demonstrated that the rate of major adverse cardiovascular events (all-cause mortality, stroke, reinfarction, or unplanned target lesion revascularization) was significantly lower in the UFH group (5.7%) versus the bivalirudin group (8.7%) with no difference in major bleeding at 28 days. Overall data suggest that the use of bivalirudin was associated with lower bleeding risk in PCI in STEMI while being associated with increased risk of ischemic complications, especially acute stent thrombosis. In contrast, in a recent trial using radial PCI, the use of bivalirudin pre- and for 2

to 4 hours post-PCI using a full dose (0.75 mg/kg bolus +1.75 mg/kg/h infusion) in primary PCI patients in the Bivalirudin with Prolonged Full-Dose Infusion during PPCI versus Heparin (BRIGHT 4) trial was found superior to heparin in reducing mortality. Enoxaparin and fondaparinux are alternative options in patients undergoing fibrinolysis, but fondaparinux is contraindicated in patients undergoing primary PCI because it has been associated with catheter thrombosis.

B. Reperfusion therapy. The primary goal in the management of acute MI is to institute reperfusion therapy as quickly as possible. All patients with STEMI who seek treatment within 12 to 24 hours from the onset of continuous symptoms should be considered for immediate reperfusion therapy. Persistent ischemic symptoms after 12 hours may indicate a stuttering course of occlusion, spontaneous reperfusion, and reocclusion and should be considered for primary PCI.

1. **Benefit.** The benefit of reperfusion therapy has been well documented in the management of acute MI, regardless of age, gender, and most baseline characteristics. However, the patients who derive the most benefit are those treated earliest and those at highest risk, such as those with anterior MI.
2. **Time to treatment is paramount.** Although the guidelines focus on door-to-balloon times and time from first medical contact, total ischemic time is the most important parameter. Patients treated in the first hour have the highest mortality benefit. **There is an inverse relationship between time to treatment and survival benefit.** This relationship appears more consistent with fibrinolytic therapy than with primary PCI. After 12 hours of continuous symptoms, there is little net benefit to pharmacologic reperfusion with fibrinolytics. The therapeutic window for PCI extends beyond that of fibrinolysis, but is not infinite. The Occluded Artery Trial (OAT) suggests that stenting of an occluded infarct-related artery >72 hours after the initial event is not associated with benefit and may be harmful in a hemodynamically stable asymptomatic patient. Currently, the AHA recommends

against PCI of an occluded (TIMI 0/1) infarct-related artery >24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia.

3. **Fibrinolysis versus direct PCI.** After it has been determined that a patient is a candidate for reperfusion therapy, the decision to use fibrinolytic or direct PCI therapy must be made quickly. **Optimally performed primary PCI is the preferred strategy in all patients who present with STEMI, and systems of care should be designed to accomplish the same.** Patients presenting with cardiogenic shock or those presenting late (>2 hours after symptom onset) are especially well suited for primary PCI, given the relative lack of efficacy of fibrinolysis in these settings. Pooled data from several large trials show a significant (22%) reduction in short-term mortality for patients treated with primary angioplasty. This benefit was durable because there were significant reductions in the incidence of death, nonfatal MI, and recurrent ischemia at long-term follow-up. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage (ICH) compared with fibrinolytic therapy.

   a. If a patient presents to a PCI-capable facility, **a door-to-device time of 90 minutes or less is recommended**. If a patient presents to a non–PCI-capable hospital, immediate transfer to a PCI-capable one is recommended if the door-to-device time can be achieved within 120 minutes. If primary PCI or transfer for PCI cannot be performed within 120 minutes of presentation, fibrinolysis should be administered within 30 minutes, assuming no contraindications to fibrinolysis (**Table 1.7**).

TABLE 1.7 Contraindications and Cautions for Use of Thrombolytic Agents to Manage MI

Absolute Contraindications
Previous hemorrhagic stroke at any time or ischemic stroke within 3 mo
Known intracranial neoplasm, structural cerebral vascular lesion, or closed head injury within 3 mo

Absolute Contraindications
Active bleeding or bleeding diathesis (excluding menses)
Suspected aortic dissection
Intracranial or intraspinal surgery within 2 mo
Severe uncontrolled hypertension, unresponsive to medical therapy
For SK, prior exposure within 6 mo
Relative Contraindications
Severe, uncontrolled hypertension at presentation (blood pressure >180/110 mm Hg), or history of chronic severe hypertension
History of ischemic stroke >3 mo, dementia, or known intracerebral pathologic condition not covered in contraindications
Oral anticoagulant therapy
Traumatic or prolonged (>10 min) CPR or major surgery (<3 wk)
Noncompressible vascular punctures
Recent internal bleeding (2-4 wk)
Pregnancy
Active peptic ulcer

CPR, cardiopulmonary resuscitation; MI, myocardial infarction; SK, streptokinase.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1999 guidelines for the management of patients with acute myocardial infarction). *J Am Coll Cardiol*. 2004;44(3):E1-E211. Copyright © 2004 American College of Cardiology Foundation. With permission.

b. Several trials, including the Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI)-2, the Air-Primary Angioplasty in Myocardial Infarction, and the Primary Angioplasty in Patients Transferred from a General Community Hospital to Specialized PTCA Units, have investigated the benefit of on-site fibrinolysis compared with transfer to tertiary centers for direct PCI. These studies have

found improved outcomes in patients randomized to a transfer strategy and direct PCI, even after taking into account the increased time for patient transfer. For example, patients in DANAMI-2 randomized to transfer for PCI had a significantly lower 30-day incidence of death, MI, or stroke (8.5% vs 14.3%; $P = .002$) despite a median time from randomization to balloon inflation of 112 minutes.

4. **Primary PCI.** Once the decision has been made to perform reperfusion with primary PCI, the patient should be moved to the cardiac catheterization laboratory and undergo angiography as rapidly as possible. After the culprit lesion has been identified, reperfusion should be achieved with standard PCI techniques.
   a. **Radial approach.** The reduction in bleeding seen with a radial over a femoral approach is also associated with significant clinical benefit. Based on the results of the RadIal Vs femorAL access for coronary intervention (RIVAL), the Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX (MATRIX), and multiple other clinical trials, a radial approach is the preferred approach for primary PCI in the STEMI setting.
   b. **Culprit versus multivessel PCI.** Performing PCI on a flow-limiting lesion in a noninfarct artery in the setting of a hemodynamically stable STEMI was considered a contraindication in the recent past. Advances in pharmacology, stent technology, and safety of interventional procedures have led to a series of randomized controlled trials (RCTs) that have shown both safety and superior clinical outcomes with a multivessel over culprit-alone strategy. Consequently, PCI of a noninfarct artery may now be considered in patients with STEMI either immediately following revascularization of the culprit lesion or in a staged manner (class I) to reduce the risk of death or MI. In patients with STEMI complicated by cardiogenic shock, routine PCI of a non–infarct-related artery should not be performed at the time of primary PCI due to higher risk of death or renal failure as observed in the Culprit

Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial.

c. **Platelet GP IIb/IIIa inhibitors.** There is no current role for routine GP IIb/IIIa inhibitors in this setting. The historical efficacy of GP IIb/IIIa inhibitors was largely demonstrated in the era prior to potent DAPT. These studies did not demonstrate benefit of the routine administration of GP IIb/IIIa inhibitors in addition to DAPT in patients with STEMI undergoing primary PCI. It remains reasonable to consider the utilization of GP IIb/IIIa therapy as a bailout strategy in the presence of large thrombus burden, slow or no reflow, or inadequate oral $P2Y_{12}$ loading. The risk of bleeding is significantly increased with the use of these agents, but this can be significantly reduced by adopting radial access for the procedure.

d. **Thrombus aspiration.** Although thought to be useful mechanistically in small trials, two large, randomized trials (Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction [TASTE] and the trial of routine aspiration thrombectomy with PCI versus PCI alone in patients with STEMI [TOTAL]) have failed to show any benefit with routine use of thrombus aspiration in patients with STEMI. Consequently, societal guidelines provide a class III recommendation against the routine use of aspiration thrombectomy but do allow for its use as a bailout strategy if reperfusion cannot be successfully established with initial attempts.

e. **Distal embolic protection devices (EPDs)** have failed to show any benefit in multiple trials. These devices are not routinely recommended for acute PCI of native coronary arteries. If the culprit vessel is a saphenous vein bypass graft, an EPD should be used because it has been shown to reduce a 30-day composite outcome of death, MI, emergency CABG, and target lesion revascularization.

f. **Coronary stenting.** Primary PCI is the preferred modality for all patients presenting with STEMI. Historically, primary PCI was initially achieved with balloon angioplasty, but with the development of intracoronary stents, the use of balloon angioplasty is extremely limited in STEMI. Bare-metal stents (BMSs) were the first stents developed and reduced the high rates of acute closure and long-term restenosis associated with balloon angioplasty. The STENT-Primary Angioplasty in Myocardial Infarction study found that coronary stenting significantly reduced the need for target vessel revascularization at 6 months (7.7% vs 17.0%; $P < .001$). These findings were confirmed in the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications trial, which found that coronary stenting significantly reduced the incidence of restenosis at 6 months (40.8% vs 22.2%; $P < .0001$), independent of abciximab use. BMSs are also prone to in-stent restenosis (ISR), which led to the development of drug-eluting stents (DESs). DESs have antiproliferative agents attached to the struts that reduce neointimal hyperplasia and thus ISR. DESs have reduced the rates of long-term restenosis. The placement of DES should be considered first-line therapy for all patients with STEMI who are candidates for primary PCI. New-generation DESs have proven superior to use of BMS in patients with STEMI in the Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) as well as Everolimus-Eluting Stents versus Bare Metal Stents in ST Segment Myocardial Infarction (EXAMINATION) trials, mainly because of reduced reintervention rates.

5. Fibrinolysis

a. **Fibrinolytic therapy.** Fibrinolysis is considered a second-line option for patients presenting with STEMI when timely, optimally performed primary PCI is not available. It remains the reperfusion agent of choice in many areas of the world that

cannot support primary PCI networks. In this context, it is worthwhile to review the data and clinical considerations associated with fibrinolysis. The lifesaving capability of early fibrinolytic therapy has been well established, beginning with the Gruppo Italiano per lo Studio della Sopravivenza nell'Infarto Miocardico (GISSI) 1 trial in 1986. Pooled data show a relative reduction in mortality of 18% and an absolute reduction of nearly 2%.

b. Contraindications. As discussed previously (**Table 1.7**), the only **absolute contraindications to fibrinolytic therapies are recent cerebrovascular accident (CVA), hemorrhagic CVA, intracranial neoplasm, active internal bleeding, and suspected aortic dissection.** The presence of one of these or one or more of the relative contraindications would favor PCI, even if it meant delaying reperfusion.

c. Choice of agent

(1) Alteplase (tissue plasminogen activator or tPA). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial I showed that the use of accelerated tPA significantly reduced the 30-day mortality rate by 15% relative to SK plus subcutaneous or IV heparin. This mortality reduction correlated with significantly higher rates of TIMI 3 flow at 90 minutes compared with SK (54% vs 31%; $P < .001$). The benefit was seen across all subgroups, although the patients at highest risk derived the most benefit. The accelerated protocol consisted of an IV bolus dose of 15 mg followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg over 60 minutes. tPA is considered a fibrin-specific agent because of its relative selectivity for clot-bound fibrin. The use of continuous infusion fibrinolytics has been replaced by bolus-dosed fibrinolytics, such as reteplase and tenecteplase (TNK), because of the ease of administration of bolus-dosed agents and a lower risk of medication error.

(2) **Reteplase.** The first of the third-generation fibrinolytic agents approved for use in the United States, reteplase is a less fibrin-specific mutation of tPA. Reteplase has a longer half-life than tPA and can be administered in a double bolus (10 mg each, 30 minutes apart). The GUSTO III trial showed no mortality benefit of reteplase over tPA, but its ease of use may help reduce time to administration.

(3) **TNK,** another third-generation fibrinolytic, is characterized by its improved fibrin specificity, enhanced resistance to plasminogen activator inhibitor 1, and decreased plasma clearance. These properties allow it to be administered as a single bolus, and it is **the currently preferred agent**. The Assessment of the Safety and Efficacy of a New Treatment Strategy for Acute Myocardial Infarction 2 (ASSENT 2) trial found no mortality difference between TNK and tPA at 30 days. However, TNK was associated with significantly less noncerebral bleeding and improved mortality in patients treated for >4 hours after symptom onset. The weight-adjusted dose of TNK is 30 to 40 mg (ASSENT 1). The Strategic Reperfusion Early after Myocardial Infarction (STREAM) trial compared primary PCI to prehospital fibrinolysis with TNK in early presenting (within 3 hours) patients with STEMI who were unable to undergo primary PCI within 1 hour of first medical contact. Prehospital fibrinolysis coupled with timely angiography was found to be an effective reperfusion strategy in this select group of patients with similar rates of the primary end point (composite of death, shock, CHF, and reinfarction up to 30 days) in both groups, but there was a slightly higher risk of intracranial bleeding associated with fibrinolysis. In Strategic Reperfusion in Elderly Patients Early After Myocardial Infarction (STREAM-2), the dose of TNK in the pharmacoinvasive arm was halved. Similar clinical outcomes in patients with STEMI aged over 60 years presenting within 3 hours of

STEMI were noted. However, even with halving the dose of TNK, six ICH events occurred in the pharmacoinvasive arm compared to none with primary PCI.

(4) SK is no longer commercially available in the United States and is of historical significance. Because of the possible development of antibodies, SK should not be administered to a patient who has received it in the past. The overall rate of ICH is lower with SK (0.5%) than with tPA (0.7%). SK is a nonfabric-specific agent capable of lysing circulating and clot-bound plasminogen to plasmin. This process results in substantial systemic fibrinogenolysis, fibrinogenemia, and elevation in fibrin degradation products.

d. Bleeding complications after fibrinolysis. The most serious **complication** of fibrinolytic therapy is **ICH, which occurs in approximately 0.5% to 0.7% of patients receiving such therapy. The major risk factors for intracranial hemorrhage include age >75 years, hypertension, low body weight, female gender, and coagulopathy** (eg, prior coumadin use). The diagnosis must be considered if a patient has severe headache, visual disturbances, new neurologic deficit, acute confusional state, or seizure. If the clinical suspicion is high, fibrinolytic, antithrombin, and antiplatelet therapy should be interrupted while emergency CT or MRI is performed, and neurosurgical consultation is obtained. Surgical evacuation may be lifesaving. Even with prompt recognition and treatment, the mortality rate is higher than 60%, and older patients (>75 years) have a mortality rate greater than 90%. There is controversy regarding the risk of fibrinolytic therapy in older patients. An observational study from the Medicare database found that patients older than 75 years had an increased risk of death at 30 days with fibrinolytic therapy (relative risk [RR] = 1.38; 95% confidence interval [CI] 1.12-1.71; P = .003). However, an updated meta-analysis of nine randomized trials found that the risk reduction with fibrinolysis

in patients older than 75 years was 16% (odds ratio = 0.84; 95% CI 0.72-0.98; $P < .05$). There appears to be a decreasing relative benefit with fibrinolysis in the older patients, but an absolute gain in lives saved. Gastrointestinal, retroperitoneal, and access site bleeding may also complicate fibrinolytic therapy but are usually not life-threatening if promptly recognized and managed. In any case, the best treatment of acute STEMI in older patients appears to be primary PCI.

6. **Rescue percutaneous revascularization** is defined as the use of PCI when fibrinolytic therapy has proved unsuccessful. Despite the proven mortality benefit, >30% of patients who received lytic therapy have TIMI 0 to 1 flow at 90 minutes, whereas patency at 90 minutes has been shown to correlate with long-term survival. If reperfusion is not clearly evident 90 minutes after initiation of lytic therapy, particularly among patients with a large acute MI, the decision to perform emergency angiography and mechanical reperfusion should be made. Patients in cardiogenic shock, with severe heart failure, or with compromising arrhythmias after lytic therapy should undergo immediate coronary angiography and should not await clinical assessment of reperfusion.
   a. **Clinical determination of successful reperfusion.** It can be difficult to determine clinically whether a patient has successful reperfusion with fibrinolytic therapy. Resolution of chest pain is an inaccurate measure of reperfusion, because the pain may be blunted by narcotic analgesia or the partial denervation that is known to occur among some patients with MI. Serial assessment of 12-lead ECGs is a more reliable indicator of reperfusion, although it is also suboptimal. An accelerated idioventricular rhythm (AIVR) is fairly specific for reperfusion, but arrhythmias other than AIVR are not reliable indicators because a variety of ventricular and supraventricular arrhythmias may be observed in patients with nonreperfused infarction-related artery. The complete resolution of chest pain and electrocardiographic changes (defined as >70% resolution of ST-segment elevation), accompanied by a run of AIVR, is

highly specific for successful reperfusion, but it occurs in <10% of patients receiving lytic therapy. Resolution of ST-segment elevation by >70% is correlated with effective tissue-level reperfusion, and this finding has been correlated with better clinical outcomes and angiographic reperfusion.

b. **Benefit.** It has been shown in the Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints trial that patients with anterior MI who have unsuccessful thrombolysis (TIMI 0 or 1 flow) have a significant benefit from rescue angioplasty. In addition, the Rapid Early Action for Coronary Treatment trial demonstrated that among patients with failed reperfusion with lytics, treatment with rescue angioplasty with or without PCI is associated with a ~50% reduction in death, reinfarction, stroke, and severe heart failure. The Grupo de Análisis de la Cardiopatía Isquémica Aguda I trial evaluated an early invasive strategy (within 24 hours) versus an ischemia-guided approach among patients with STEMI treated with fibrinolytic therapy. This trial primarily demonstrated a reduction in revascularization events with the early invasive approach, although a trend was seen toward fewer deaths and reinfarctions. Based on the above data, an early angiography strategy (within 24 hours) is a reasonable approach in all patients who receive lytic therapy.

7. **Pharmacoinvasive strategy.** Although it is clear that routine fibrinolysis prior to transfer for PCI in all patients who present with STEMI (facilitated PCI) results in worse outcomes, fibrinolysis is still necessary to achieve early reperfusion in some patients who present to non–PCI-capable facilities. More recent data suggest that high-risk patients who receive fibrinolytic therapy benefit from immediate transfer for PCI. The Combined Abciximab Reteplase Stent Study in Acute Myocardial Infarction trial randomized patients presenting to a non–PCI-capable facility, who received half-dose fibrinolytics and abciximab, to either immediate transfer for PCI or rescue PCI. Patients who were transferred immediately for PCI had a significant reduction in the

primary end point of death, reinfarction, or refractory ischemia at 30 days. In addition, the Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction study showed that high-risk patients benefit from this pharmacoinvasive strategy. This trial looked at 1,059 high-risk patients with STEMI who presented to a non–PCI-capable facility within 12 hours of symptom onset. All patients received fibrinolysis with TNK and were then randomized to immediate transfer for PCI or rescue PCI dictated by continued chest pain, <50% resolution of ST elevation, or hemodynamic instability. The primary end point was 30-day composite of the first occurrence of death, MI, recurrent ischemia, new or worsening heart failure, and cardiogenic shock. The primary end point was significantly less common in the pharmacoinvasive group compared with the group who received rescue PCI (11% vs 17.2%; RR = 0.64; 95% CI 0.47-0.87; *P* = .004). Immediate transfer to a PCI-capable hospital should occur for all patients with cardiogenic shock or acute severe heart failure. Urgent transfer to a PCI-capable hospital should occur for patients with evidence of failed reperfusion or acute reocclusion. Hemodynamically stable patients with evidence of successful reperfusion should be transferred to a PCI-capable hospital for coronary angiography to be performed within 24 hours.

8. **The late open artery hypothesis** postulates that benefit in terms of improved ventricular function, increased electrical stability, and provision of collaterals can be gained by late patency of occluded infarct arteries. However, the OAT failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI. It should be noted that the OAT excluded high-risk patients with New York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three-vessel disease), or severe inducible ischemia on stress testing. Patients in OAT were hemodynamically stable, were asymptomatic, and had TIMI 0 flow in the infarct-related artery. This study has led to a **class III recommendation against PCI of**

a totally occluded artery >24 hours after STEMI in OAT-eligible patients.

9. **Emergency coronary bypass surgery** may be the treatment of choice for patients in whom the intent is to perform direct or rescue percutaneous mechanical reperfusion but who are found to have a critical left main or severe three-vessel disease unapproachable with percutaneous revascularization. Studies of this strategy are fairly encouraging, especially when patients can be taken to the operating room early in the course of infarction, before severe myocardial necrosis has occurred. RV infarction is a relative contraindication to bypass surgery because it complicates the discontinuation of cardiopulmonary support.
10. **PCI in hospitals without surgical backup.** Several trials and two meta-analyses have shown no difference in in-hospital or 30-day mortality in patients undergoing primary PCI at sites with or without surgical backup. Consensus guidelines recommend that primary PCI without on-site surgical backup is reasonable with the intent of providing timely, high-quality STEMI care.

C. Adjuvant therapy

1. **Beta-blockers.** Extensive data from the era before reperfusion established the usefulness of beta-blockers in reducing recurrent ischemia, arrhythmias, and mortality. Several small, randomized trials performed in the fibrinolytic reperfusion era confirmed the anti-ischemic and antiarrhythmic benefits, although short-term mortality was not affected. As a result, prior recommendations have stated that beta-blockers should be administered to all patients within the first 24 hours of acute MI, unless contraindicated by severe reactive airway disease, hypotension, bradycardia, or cardiogenic shock. However, more recent data from the PCI era have shown no difference in mortality and no difference in the composite end point of death, reinfarction, or ventricular fibrillation arrest. The Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study trial, a large (n = 22,929) RCT, found that the metoprolol group had more ventricular fibrillation arrest (2.5% vs 3.0%; P = .001) and shock

(5.0% vs 3.9%; $P < .001$). The incidence of shock was most notable in patients with Killip class II and III heart failure. This has led to a change in guidelines recommending more judicious use of early (<24 hours) beta-blockers, avoiding use in patients with significant signs of heart failure, low cardiac output, risk of cardiogenic shock, or other relative contraindications to their use. The role and duration of routine beta-blockade in patients receiving primary PCI with preserved LV function in the current era is debatable and is being evaluated in a number of ongoing clinical trials.

2. **Angiotensin-converting enzyme (ACE) inhibitors** can be started orally in the first 24 hours for all patients without hypotension, acute renal failure, or other contraindications. These medications were shown to reduce mortality in the GISSI 3 and International Study of Infarct Survival-4 trials. ACE inhibitors should be continued indefinitely in patients with LV dysfunction or clinical CHF, because these patients have been shown to derive a mortality benefit. In addition, the Heart Outcomes Prevention Evaluation study found that high-risk patients, including those with prior MI but normal LV function, still had long-term benefit from ramipril. IV formulations of these agents should not be used because they have not demonstrated benefit and may increase mortality. Rather, a graded oral regimen is advised. Angiotensin receptor blockers remain a viable option for ACE inhibitor–intolerant patients. The Prospective ARNI versus Ace Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction (PARADISE-MI) trail evaluated the use of the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan in patients with acute MI complicated by reduced LV ejection fraction (LVEF), pulmonary congestion, or both. This study did not show significant improvement in death from cardiovascular causes or incident heart failure with the use of sacubitril-valsartan as compared to ramipril (11.9% vs 13.2%, $P = .17$).
3. **Calcium channel blockers.** Evidence for a potential increase in mortality has limited the use of calcium channel blockers in the

care of patients with acute MI. They are indicated for the management of supraventricular tachyarrhythmia, cocaine-induced MI, or relief of postinfarction angina unresponsive to beta-blockade. Otherwise, these agents should be avoided. Short-acting agents, such as nifedipine, are contraindicated because of their reflex sympathetic activation. Verapamil and diltiazem should be avoided in patients with LV dysfunction or heart failure. Amlodipine is an effective antianginal agent and appears safe to use for this indication in patients with CHF.

4. **Aldosterone antagonists.** The use of aldosterone-blocking agents has been shown to be beneficial in post-MI patients. The Randomized Aldactone Evaluation Study found a reduction in all-cause mortality with the use of aldactone in patients with ischemic cardiomyopathy and NYHA class III or IV heart failure. However, the only randomized trial to address the use of such agents among patients with ventricular dysfunction after STEMI is the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, where eplerenone was found to reduce death, cardiovascular death, and hospitalization for heart failure. The routine use of early spironolactone in patients with ACS was not associated with a clinically meaningful benefit in the Aldosterone Lethal effects Blocked in Acute MI Treated with or without Reperfusion to improve Outcome and Survival at Six months follow-up (ALBATROSS) trial, and similar results were noted with eplerenone in the REMINDER trial.
5. **Diabetes control.** The Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction study found a significantly lower mortality rate at 1 year compared with standard therapy (8.6% vs 18.0%; $P = .020$) in patients with diabetes treated with aggressive blood glucose reduction with an insulin infusion during hospitalization, followed by multidose subcutaneous insulin injections. However, a small trial Organization to Assess Strategies in Ischemic Syndromes-6 Glucose-insulin-potassium (OASIS-6 GIK) and a large (>20,000 patients) randomized trial (CREATE-ELCA) failed to show any benefit to glucose-insulin-

potassium (GIK) infusions. As a result, it appears prudent to institute sound glucose control, but it is not necessary to aggressively pursue glucose control with GIK infusions. Current guidelines suggest insulin therapy to achieve and maintain blood glucose levels <180 mg/dL while avoiding hypoglycemia. Although trials with sodium-glucose linked transporter-2 (SGLT-2) inhibitors initiated during index MI have not been associated with reduction in major adverse clinical events, the safety of these agents if initiated in patients with diabetes appears established.

6. **Lipid-lowering therapy.** A fasting lipid profile should be obtained in patients with STEMI, preferably on presentation. Treatment with statins in patients with ACS has shown to decrease the risk of recurrent MI, stroke, need for revascularization, and death due to CAD. In addition, initiation of high-intensive statin therapy to reduce major adverse cardiac events is recommended. As such, the current guidelines recommend initiation or continuation of high-intensity statin therapy in all patients with STEMI and no contraindications to its use. Patients with acute MI who are previously on high-intensity statins should have additional agents like ezetimibe, bempedoic acid, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors added if the measured low-density lipoprotein cholesterol (LDL-C) exceeds 70 mg/dL, and similar consideration should be extended to those with LDL-C levels exceeding 55 mg/dL. Statin-intolerant patients should be treated with proven nonstatin lipid-lowering agents.
7. **Antiarrhythmics.** The use of lidocaine or other antiarrhythmic agents is not warranted for the prophylactic suppression of ventricular tachycardia (VT) and fibrillation. Although lidocaine may decrease tachyarrhythmias, there is no survival benefit. There is also evidence to suggest an increase in mortality related to an increased incidence of bradycardia and asystole. The Resuscitation Outcomes Consortium published “Amiodarone, Lidocaine or Placebo in Out-of-Hospital Cardiac Arrest,” a randomized trial comparing IV amiodarone versus lidocaine versus placebo in adults with nontraumatic out-of-hospital cardiac arrest with VT or

ventricular fibrillation. Neither lidocaine nor amiodarone significantly improved survival or favorable neurologic outcomes compared to placebo.

8. **Implantable cardioverter-defibrillators (ICDs).** Posited to reduce the risk of sudden death following acute MI, the utility of ICDs implanted at an average of 18 days following the index MI was tested in patients with reduced ventricular function and autonomic dysfunction Defibrillator in Acute Myocardial Infarction (DINAMIT) trial. Although there was a decrease in cardiovascular death, this study failed to demonstrate any reduction in all-cause mortality. Similarly, no difference in overall mortality was noted in the Immediate Risk Stratification Improves Survival trial that randomized 898 patients with recent MI (5-31 days) and either LVEF <40% with initial heart rate >90 beats/min, or nonsustained ventricular tachycardia (NSVT) >150 beats/min over a mean follow-up of 37 months. The Multicenter Automatic Defibrillator Implantation trial II evaluated the benefit of delayed ICD insertion in patients with prior MI. The trial enrolled 1,232 patients with a history of MI at least 1 month prior to enrollment (90 days if bypass surgery was performed) and an LVEF ≤30%. Patients were randomized to prophylactic ICD insertion or standard medical therapy. At an average follow-up of 20 months, prophylactic insertion of an ICD significantly reduced all-cause mortality (14.2% vs 19.8% for standard therapy; hazard ratio [HR] = 0.69; 95% CI 0.51-0.93; *P* = .016). According to the current ACC/AHA guidelines, an ICD should be inserted in patients with ventricular fibrillation or hemodynamically significant sustained VT that occurs 48 hours after acute MI, assuming there is no recurrent ischemia or MI. Patients with an EF ≤35% and NYHA class II or III heart failure secondary to an MI that occurred at least 40 days prior should also receive an ICD. In addition, patients who are 40 days post-MI with NYHA class I heart failure and an EF ≤30% are candidates for ICD insertion. Lastly, any patient with a prior MI, nonsustained VT, EF ≤40%, and inducible ventricular fibrillation or sustained VT during an

electrophysiologic study are candidates for an ICD. Patients who have received CABG should have their LVEF and NYHA functional class reassessed 90 days after the procedure to determine ICD candidacy.

9. **Wearable cardioverter-defibrillators.** Patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after percutaneous or surgical revascularization, can be given the option of a wearable cardiac defibrillator as a bridge to ICD implantation or recovery of LVEF. The results of the randomized VEST Prevention of Early Sudden Death trial, however, showed no benefit utilizing this approach in post-MI survivors with LVEF <35% over 90 days of follow-up.
10. **Anticoagulation for large anterior wall MIs.** Historical teaching (not based on randomized data) has advocated anticoagulating patients for 6 weeks after a large anterior wall MI, with the goal of preventing LV thrombus development. However, in the era of primary PCI, the rates of LV thrombus have been reduced. Therapeutic anticoagulation is recommended in the presence of objective imaging evidence of LV thrombus. Prophylactic anticoagulation, however, is not currently recommended, because the routine addition of oral anticoagulation in all patients with STEMI would lead to "triple therapy"—warfarin and DAPT—leaving patients at an increased risk of bleeding without any demonstrable benefit.

X. ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH COCAINE ABUSE.

The pathophysiologic process and management of acute MI associated with cocaine use differ from those of classic MI.

A. Pathophysiology

1. **The underlying pathophysiologic factor** in acute MI associated with cocaine abuse is believed to be coronary spasm or thrombus formation caused by alpha-adrenergic stimulation. This can occur in a normal segment of artery or be superimposed on mild-to-

moderate atherosclerosis. Atherosclerosis is accelerated by chronic cocaine use.

2. **Increased oxygen demand** caused by beta-adrenergic stimulation of heart rate and contractility also contributes to the onset of ischemia.

B. Clinical presentation. Chest pain caused by infarction after cocaine ingestion typically occurs within 3 hours, although it can vary from minutes to days, and depends on the route of administration (median of 30 minutes with IV cocaine, 90 minutes with crack smoking, and 135 minutes with nasal inhalation). More than 80% of persons with infarction are also cigarette smokers. Studies with animals have demonstrated a synergistic effect between cigarette smoking and cocaine use.

C. Therapy

1. The **initial management** of ST-segment elevation associated with cocaine use includes the routine administration of antiplatelets and heparin. Aggressive use of sublingual and IV nitroglycerin or IV calcium channel blockers is advised in an effort to relieve coronary spasm. IV benzodiazepines can also be given because they not only relieve cocaine-induced chest pain but can also improve cardiac hemodynamics.
2. **Beta-Blockers are contraindicated in patients with cocaine-induced acute MI.** Although they block undesirable beta-adrenergic effects, these agents allow unopposed alpha-adrenergic stimulation and have been associated with increased mortality in nonrandomized analyses.
3. **Reperfusion therapy must be considered if vasodilator therapy is unsuccessful** in relieving symptoms and ST-segment changes.
4. **Immediate angiography and mechanical revascularization as appropriate** may be even more beneficial in patients with cocaine-induced MI. Many patients who use cocaine have contraindications to thrombolysis, such as severe hypertension or persistent vasospasm without thrombosis, which is not amenable to thrombolytic therapy.

XI. POSTOPERATIVE ACUTE MYOCARDIAL INFARCTION

A. Etiology and pathophysiology. Acute MI following noncardiac operations most commonly occurs on the third or fourth postoperative day. Conventional theory was that MI was caused by a combination of increased oxygen demand and arterial shear stress associated with the increased adrenergic drive that accompanies pain and ambulation in the postoperative period. Intravascular volume shifts caused by redistribution of fluids, IV administration of fluids, and decreased enteral intake all contribute to the risk of postoperative MI. It is apparent that there is a postoperative inflammatory state associated with hypercoagulability, marked by an increase in fibrinogen and other acute-phase reactants. Significant myocardial injury has been observed in postoperative patients in the absence of traditional signs and symptoms of ACS, often labeled as a "troponin leak" or demand ischemia. These events are termed *myocardial injury after noncardiac surgery* (MINS) and are associated with an increase in long-term mortality when compared with patients without evidence of myocardial injury. There are currently no identifiable therapeutic targets for patients with MINS.

B. Therapy. Management of true postoperative STEMI is complicated by limitations on the use of fibrinolytic agents and anticoagulant therapies. Therapy relies on urgent angiography and mechanical reperfusion when feasible. The optimal antiplatelet or anticoagulation regimen for recent (<1 year) DES patients undergoing noncardiac surgery is not known.

XII. SIMPLIFIED REPERFUSION STRATEGY.

The wealth of data regarding reperfusion strategies and adjunctive therapies in acute MI detailed previously may lead to confusion regarding the optimal approach. Based on guideline recommendations, a simplification of the STEMI management strategy can be achieved.

A. For patients presenting with STEMI where primary PCI is available with 90 minutes, a reasonable strategy would involve administration of aspirin, parenteral anticoagulation, and an oral platelet $P2Y_{12}$ receptor inhibitor, as well as nitrates and beta-blocker

therapy if not contraindicated, and immediate transfer to the catheterization laboratory for primary PCI with DES.

B. For patients presenting to a hospital where primary PCI is not available, but immediate transfer (medical contact to balloon time <120 minutes) to a PCI facility is available, a similar strategy is employed, with initiation of aspirin, platelet $P2Y_{12}$ receptor inhibitors, and anticoagulation prior to transfer to the PCI facility.

C. If anticipated transfer times will exceed the medical contact-to-PCI time of 120 minutes, then fibrinolytic therapy should be instituted in eligible patients within 30 minutes of first medical contact in addition to therapy with aspirin, clopidogrel, and parenteral anticoagulation. The choice of UFH or enoxaparin remains operator dependent, with either option reasonable. Among patients receiving fibrinolytics, immediate transfer to a PCI facility is preferable, and early angiography (<24 hours) is recommended. Following the administration of fibrinolytics, any patient with cardiogenic shock, ventricular arrhythmias causing hemodynamic compromise, or evidence of failed reperfusion should be immediately transferred for urgent coronary angiography.

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CHAPTER 2

Non–ST-Segment Elevation Acute Coronary Syndrome

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I. INTRODUCTION.

Non–ST-elevation acute coronary syndrome (NSTE-ACS) remains a leading cause of morbidity and mortality across the globe. NSTE-ACS may be subclassified into unstable angina (UA) or non–ST-elevation myocardial infarction (NSTEMI). These clinical entities cannot be differentiated on the basis of chest pain characteristics or electrocardiogram (ECG) abnormalities alone. The only way this determination can be made is with evidence of myocardial necrosis by measurement of cardiac biomarkers. With improvements in the diagnosis and risk stratification of patients, therapeutic approaches to NSTE-ACS have continued to evolve.

II. CLINICAL PRESENTATION

A. Signs and symptoms. Chest pain described as heaviness or pressure usually lasting >20 minutes is the typical symptom in NSTE-ACS. Chest pain may be triggered with minimal exertion and can be new onset or increased in severity and frequency or precipitated with less effort than prior angina. Compared with stable angina, **chest pain in NSTE-ACS** is usually more **severe and protracted**, often requiring several doses of sublingual nitroglycerin or extended periods of rest for relief.

B. Demographics. Compared with ST-elevation myocardial infarction (STEMI), patients with **NSTE-ACS** tend to be **older** and have a higher incidence of **cardiac risk factors or comorbid conditions (eg, diabetes, hypertension, and hypercholesterolemia)** and a greater likelihood of **prior myocardial infarction (MI) and**

revascularization procedures (ie, percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]).

C. Differential diagnosis. It is crucial to determine the clinical probability that the chest pain or presenting symptom(s) represent ACS resulting from obstructive coronary artery disease (CAD). The exclusion of other diagnoses that mimic angina such as costochondritis, pneumonia, or pericarditis, as well as other life-threatening conditions such as aortic dissection, pneumothorax, and pulmonary embolus, is essential. Hypertensive urgency or emergency, thyrotoxicosis, systemic infection, anemia because of blood loss, and other precipitating causes of myocardial ischemia should also be sought.

D. Physical findings. Physical examination is often noncontributory in making the clinical diagnosis. **Signs of heart failure** (elevated jugular venous pressure, S_3), impaired myocardial performance (S_4), or peripheral vascular disease (ie, bruits over major vessels) may be present. The presence of hemodynamic instability identifies a patient at extreme risk.

E. Risk factors

1. **Clinical characteristics indicative of high risk.** Symptoms may include an **acceleration of ischemic symptoms within the preceding 48 hours, angina at rest (>20 minutes), congestive heart failure (CHF; S3 gallop, pulmonary edema, and rales), known reduced left ventricular (LV) function, hypotension, new or worsening mitral regurgitation murmur, age >75 years, diffuse ST-segment changes on an ECG (≥0.5-1 mm), and the presence of elevated serum cardiac biomarkers**. Patients at intermediate or low risk have angina of short duration, have no ischemic ST-segment changes on ECG, are negative for cardiac biomarkers, and are hemodynamically stable (**Table 2.1**). **ECG.** The initial ECG can help risk-stratify patients with NSTE-ACS. Ideally, this should be performed within 10 minutes of arrival to the emergency department (ED). Patients with ST-segment deviation (ie, ST depression or transient ST elevation) ≥0.5 mm or with preexisting left bundle branch block (LBBB) are at increased

risk for death or MI at 1 year after presentation. ST-segment elevation ≥0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. **T-wave inversions alone are generally not predictive of adverse ischemic events.** It is important to compare the presenting ECG to a prior one for the presence of new ECG changes. When the diagnosis is suspect, serial ECG tracings should be performed and analyzed for dynamic ECG changes.

TABLE 2.1 Initial Risk Stratification of Patients With Unstable Angina

High Risk[a]	Intermediate Risk	Low Risk
One of the following must be present:	No high-risk feature but must have one of the following:	No high- or intermediate-risk features present
Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease	
Prolonged ongoing rest pain (>20 min): moderate or high likelihood of CAD	Prolonged rest pain (>20 min) that resolves	Increased frequency or duration of angina
Pulmonary edema: most likely caused by ischemia	Rest angina (>20 min or relieved with rest or sublingual NTG)	Angina provoked by less exertion
Rest angina with dynamic ST-changes ≥0.5 mm	Nocturnal angina	New-onset angina (within 2 wk-2 mo)
New or worsening rales, S_3, or MR murmur	New-onset, severe angina within 2 wk with moderate or high likelihood of CAD	
Hypotension, bradycardia, tachycardia		
Bundle branch block, new or presumed new	T-wave changes	Normal or unchanged ECG
Sustained ventricular tachycardia	Pathologic Q waves or resting ST depression (<1	

High Risk[a]	Intermediate Risk	Low Risk
	mm) in multiple lead groups	
Positive serum cardiac biomarkers	Normal cardiac markers	Normal cardiac markers
	Age older than 70 y	

CAD, coronary artery disease; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerin.

[a]Risk stratification involves considering clinical characteristics and ECG findings to make early triage decisions.

2. **NSTEMI.** NSTEMI predicts a poorer prognosis among patients with NSTE-ACS. Multivariate predictors of NSTEMI in patients with ACS include **prolonged chest pain** (>60 minutes), **ST-segment deviations** (depression or transient elevation), and **new or recent onset of angina** (in the past month). Elevations in the levels of troponin I or troponin T, contractile proteins released from necrotic cardiac myocytes, help establish the diagnosis when NSTE-ACS is suspected and remain independently predictive of morbidity and mortality.
3. **Clinical risk classification systems.** Numerous scores have been derived to facilitate risk assessment and guide medical therapy in patients with NSTE-ACS. It is important to note that these scores can also be used to determine which patients may benefit most from early invasive therapy as opposed to a more conservative approach. The thrombolysis in myocardial infarction (TIMI) risk score, based on the TIMI IIB and Efficacy and Safety of Subcutaneous Enoxaparin in Non–Q-Wave Coronary Events (ESSENCE) trials, incorporates **the combination of age, clinical characteristics, ECG changes, and cardiac markers for risk stratification** (**Table 2.2**). A higher risk score correlated with an increase in the incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization. The Global Registry of Acute Coronary Events (GRACE) prediction score, which incorporates nine clinical variables derived from the medical history and clinical findings on initial presentation and

during hospitalization, can be used to estimate the in-hospital and 6-month outcomes for patients hospitalized with any form of ACS. Together, these various clinical risk stratification systems help identify high-risk patients likely to benefit most from more aggressive therapy.

TABLE 2.2 Thrombolysis in Myocardial Infarction Risk Score

Score	Incidence of Death, New or Recurrent Myocardial Infarction, and Recurrent Ischemia Requiring Revascularization (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9
Scoring System	
One point when risk factor is present, zero points if absent (a total of seven points are possible): age >65 y	
Presence of more than three risk factors for coronary artery disease	
Prior coronary stenosis ≥50%	
Presence of ST-segment deviation on admission electrocardiogram	
More than two episodes of angina within the past 24 h	
Prior use of aspirin in past 7 d	
Elevated cardiac markers	

III. PATHOPHYSIOLOGY. The pathophysiology of ACS encompasses a complex interplay of plaque erosion or rupture, platelet activation and aggregation leading to thrombus formation, endothelial dysfunction, vasospasm, and vascular remodeling eventually leading to imbalance between myocardial oxygen consumption and demand.

A. Plaque erosion and rupture. UA, NSTEMI, and STEMI share a common initiating event: atheromatous plaque fissure or rupture.

Plaque rupture or erosion exposes thrombogenic components stimulating platelet deposition, activation, and aggregation at the site of vascular injury, followed by activation of the coagulation cascade and thrombus formation. There is evolving evidence that management of plaque erosion can be conservative and requires no PCI. Differentiation between these two entities can be achieved with intracoronary optical coherence tomography (OCT). In case of plaque rupture due to factors that contribute to plaque instability (eg, lymphocyte and macrophage activation and increased inflammation), disruption of thin cap occurs that leads direct exposure of prothrombotic factors to necrotic core. On OCT imaging, plaque rupture tends to have flaps that remain after a tear of the fibrinous cap that protrudes into the vessel lumen. In contrast, plaque erosion is more likely to occur with thick cap fibroatheromas where there is a lack of disruption of fibrous cap and the thrombus not in contact with underlying lipid pool or necrotic core.

B. **Thrombus formation.** Exposure of circulating platelets to subendothelial contents results in platelet adhesion, aggregation, and, ultimately, thrombus formation. With platelet activation, the glycoprotein (GP) IIb/IIIa receptor on the platelet surface undergoes a conformational change, facilitating further platelet activation and aggregation. This markedly increases thrombin production, further expanding and stabilizing the thrombus.

C. **Vasospasm** can be induced by the local production of vasoactive substances released from the subendothelial matrix or propagating thrombus, or it can occur as a primary phenomenon. Severe localized spasm of a coronary artery segment (ie, Prinzmetal angina) may also result in ACS. This vasospasm frequently occurs at sites of unstable plaque and is thought to contribute to thrombus formation. Even angiographically, normal coronary arteries with underlying endothelial dysfunction may be subject to vasospasm.

D. **Multiple lesions.** Although a single culprit lesion is often found at angiography, multiple culprit lesions are not uncommon in patients presenting with NSTE-ACS, attesting to the systemic nature of the disease. An intravascular ultrasound study of patients with NSTEMI

undergoing angiography and possible PCI revealed an average of 2.1 plaque ruptures per patient, with 79% of patients having a lesion in a location different from that of the culprit lesion.

E. Secondary causes. NSTE-ACS can occasionally result from a supply-demand mismatch of oxygen delivery to the myocardium. With stable obstructive coronary lesions, precipitants of NSTE-ACS include **increased myocardial oxygen demand** (ie, tachycardia, severe hypertension, cocaine use, hyperthyroidism, fever, or sepsis) and **decreased oxygen supply** (ie, anemia, active bleeding, or hypoxemia).

IV. INITIAL EVALUATION AND MANAGEMENT

A. Initial triage and clinical assessment recommendations

1. Patients with symptoms suggestive of ACS should be instructed to call 911 immediately. It is recommended that the patient be transported to the hospital by ambulance rather than by friends or relatives.
2. Prehospital emergency service providers should perform an ECG at first medical contact. Aspirin at a dosage of 162 to 325 mg of aspirin should be administered to patients who have symptoms suggestive of ACS, unless it is contraindicated. The patient should be instructed to chew the aspirin rather than swallow it whole so as to facilitate rapid absorption.
3. Patients who have been prescribed nitroglycerin should be instructed to take only one dose in response to chest pain. If the symptoms have not improved or are worsening within 5 minutes, then the patient should call 911 immediately before taking additional nitroglycerin. If the patient is known to have chronic stable angina and the chest pain is significantly improving after taking a dose of nitroglycerin, it is appropriate to instruct the patient to take additional doses of nitroglycerin every 5 minutes for a total of three doses and then call 911 if symptoms have not completely resolved.
4. Patients with suspected ACS who have had anginal symptoms at rest for greater than 20 minutes, hemodynamic instability, or

recent syncope should be referred immediately to the ED.

B. Early risk stratification recommendations

1. Patients who present with suspected ACS should be quickly assessed and should undergo risk stratification. This should include a history and physical examination focused on high-risk features of ACS (prolonged chest pain at rest, syncope, signs of CHF, etc), an ECG, and laboratory biomarkers of cardiac injury, preferably troponin I or T.
2. **A 12-lead ECG should be performed immediately.** Common ECG findings in NSTE-ACS include ST-segment depression, transient ST-segment elevation, and T-wave inversion. However, approximately 20% of patients with an NSTEMI confirmed by cardiac enzymes have no ischemic ECG changes. Moreover, a "normal" ECG pattern is not sufficient to rule out NSTE-ACS in patients with chest pain (>4% of patients presenting with chest pain and normal ECG patterns are diagnosed with UA). Persistent ST-segment elevation of ≥1 mm in two or more contiguous leads or new LBBB suggests acute STEMI and should be considered for emergency reperfusion therapy (see Chapter 1). As previously mentioned, ST-segment elevation of ≥0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. T-wave inversions are the least specific of ECG changes in ACS. However, new, deep, symmetric T-wave inversions of ≥2 mm across the precordium in patients presenting with suspected NSTE-ACS (Wellens syndrome) often correspond to acute ischemia, usually related to a severe proximal left anterior descending artery stenosis.
3. **In patients in whom the initial ECG is not diagnostic** but the anginal symptoms persist, serial ECGs should be performed in 15- to 30-minute intervals. This is done in order to detect the development of ST-segment depression or elevation. Posterior circulation ischemia/infarction should be suspected, and the use of posterior ECG leads and echo imaging should be considered.
4. **Cardiac biomarkers should be measured in all patients presenting with symptoms suggestive of ACS.** The preferred and

recommended biomarker is a cardiac-specific troponin (troponin I or T).

a. **Troponins.** Cardiac troponins I and T are contractile proteins found only in cardiac myocytes and are the **preferred assays to document the presence of cardiac necrosis**. Patients with clinical suspicion for NSTE-ACS should have serial troponins measured. When utilizing a fourth-generation assay, cardiac troponins I and T typically rise within 3 to 6 hours after myocardial necrosis. Elevated troponin levels are a marker of myocyte necrosis and not specific for ischemic mechanism of injury. As a result, elevated troponin levels can also be seen in a number of other nonischemic cardiac conditions and in the setting of renal insufficiency. A rise and fall in troponin levels above the 99th percentile is highly suggestive of ischemic injury. **In the setting of NSTE-ACS, the presence and magnitude of troponin elevation have important prognostic significance beyond that specified by clinical criteria.** In the **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries IIb (GUSTO IIb)** trial of patients with ACS, the 30-day mortality rate for patients with an elevated troponin T level (>0.1 ng/mL) was 11.8%, compared with 3.9% for patients with normal troponin levels. Elevated troponin levels in the setting of NSTE-ACS have also been associated with increased likelihood of multivessel disease, high-risk culprit lesions, and intracoronary thrombus visible at the time of angiography.

b. **Highly sensitive (Hs) troponin** assays are currently utilized worldwide and are now approved for use in the United States. These assays enable diagnosis of MI within 1 to 3 hours of symptom onset. Because of the high sensitivity and precision of the assay, Hs troponin use results in approximately 4% absolute increase and 20% relative increase in the rates of MI and a resultant decrease in UA. Patients with suspected NSTE-ACS with negative protocol–directed Hs troponin assays can be promptly discharged from the ED as the negative predictive

value is >99%. Clinicians, however, need to closely evaluate patients with suspected NSTE-ACS in the intermediate and high range to distinguish those with a true NSTE-ACS and others with alternate etiologies of troponin elevation. The delta increase in Hs troponin levels along with the clinical history helps facilitate decision-making because it distinguishes between ongoing acute and chronic cardiac myocyte injury. An Hs troponin greater than 5 times the upper reference limit of the assay is 90% predictive of an ACS, but a level up to 3 times above the upper reference limit has a limited 50% to 60% positive predictive value. As a result, additional testing may be indicated to risk-stratify patients in whom the diagnosis remains ambiguous.

c. **Creatine kinase (CK).** Historically, CK and the myocardial band (MB) isoenzyme of CK (CK-MB), measured serially every 6 to 8 hours for the first 24 hours, were utilized to measure cardiac necrosis. Following an MI, CK levels peak at 12 to 24 hours and CK-MB levels peak at 10 to 18 hours after the onset of symptoms. **However, with the development of contemporary troponin assays, these agents are no longer utilized for the diagnosis of ACS.**

5. **Point-of-care echocardiography** has become more available. In patients with NSTEMI or UA, point-of-care echocardiography can be helpful in risk stratification. Evidence so far suggests that early echocardiography in patients with NSTEMI could predict outcomes, such as heart failure, arrhythmias, and recurrent myocardial ischemia. Abovementioned outcomes were mainly predicted based on the assessment of regional wall motion abnormality. Of course, the availability of point-of-care ultrasound devices and the high level of training and expertise to interpret the images remain the major limitations of widespread use. Point-of-care echocardiography is essential in evaluation of patients who deteriorate suddenly following an ACS due to possible mechanical complication of MI.

6. The initial evaluation should include consideration and appropriate evaluation of **noncoronary causes of the unexplained symptoms**.

C. **Recommendations for immediate management and triage.** The initial management of patients with suspected NSTE-ACS is dependent on the predicted risk of adverse ischemic cardiovascular outcomes. Patients can be initially categorized as low, intermediate, or high risk depending on the historical and clinical findings (**Table 2.1**). The use of risk stratification models such as the TIMI (**Table 2.2**) and GRACE risk scores can also assist in determining which patients are at increased risk. In addition, it is very useful to simultaneously assess the patients' risk for bleeding, especially in those being considered for coronary angiography. A number of acute bleeding risk scores are available, but rapid risk stratification of patients with UA suppresses adverse outcomes with early implementation of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines (CRUSADE) and acute catheterization and urgent intervention triage strategy (ACUITY) bleeding scores are commonly utilized. Patients with probable or possible ACS whose initial 12-lead ECG and cardiac biomarker levels are normal should be monitored on telemetry. Repeat ECGs and repeat cardiac biomarker measurements should be performed.

When a fourth-generation troponin is utilized, **low- and intermediate-risk patients** (**Table 2.1**) whose serial ECGs and cardiac biomarkers are normal may be managed conservatively. **Cardiac stress testing** or computed tomography (CT) coronary angiography may be performed in the ED or monitoring facility or as an outpatient. The optimal time for testing may be determined at the discretion of the physician. When performed in the ED, the use of multidetector CT (MDCT) compared to stress testing was associated with a decreased cost and length of stay. However, MDCT was associated with increased rates of referral for angiography without favorable clinical outcomes. MDCT has the advantage of being able to exclude other etiologies of chest discomfort such as pulmonary embolism, pneumothorax, and dissection, but has technical

limitations in patients with rapid and irregular heart rate, underlying stents, and extensive calcification. For such patients who are referred for outpatient stress testing, the initiation of antiplatelet and anti-ischemic pharmacotherapy (nitroglycerin and beta-blockers) should be strongly considered. In the absence of medical contraindications, **high-risk patients** (**Table 2.1**) should have coronary angiography performed with a plan for revascularization with PCI or CABG when indicated.

When an Hs troponin assay is utilized, patients with a negative assay can be safely discharged with an outpatient follow-up as early as 1 to 3 hours depending on the assay and protocol utilized. Rates of UA have decreased significantly with the use of these sensitive assays, but when strongly suspected based on history and ECG findings, these rare patients should be admitted for further evaluation. Patients with typical clinical symptoms, ECG changes, and elevated Hs troponin levels above the 99th percentile for the assay have a confirmed NSTE-ACS and should be considered for coronary angiography and revascularization. The remainder of subjects with intermediate and elevated Hs troponin levels of uncertain etiology in whom the clinical diagnosis remains ambiguous may be considered for further evaluation with stress testing, CT angiography, or coronary angiography.

Noninvasive stress testing. When a conservative strategy is adopted, patients who have **normal myocardial perfusion scan** without fixed or reversible perfusion defects can be safely **discharged** from the hospital and followed up on an outpatient basis. **Cardiac catheterization** should be considered for patients found to have high-risk features on stress testing because they are at increased risk for adverse ischemic events. If patients are unable to exercise, **pharmacologic stress testing** can be performed with a vasodilator, such as adenosine or regadenoson. In appropriate patients without concerns for renal failure, a CT coronary angiogram can accurately identify coronary artery anatomy.

V. EARLY HOSPITAL CARE. The mainstay of treatment for ACS is directed at anti-ischemic therapy and antithrombotic (antiplatelet and

anticoagulation) therapy.

A. Anti-ischemic therapy

1. **Oxygen therapy.** Routine use of supplemental oxygen is not recommended in this setting. It should be administered in patients noted to be in respiratory distress or with resting oxygen saturation <94%.
2. **Nitrates.** Nitrates are endothelium-independent vasodilators that increase myocardial blood flow and reduce myocardial demand (by reducing preload and afterload). Despite a lack of randomized clinical trial data, nitrates remain the mainstay of treatment for patients with suspected spontaneous ischemia.
   a. **Dosing.** Sublingual nitroglycerin or nitroglycerin spray (0.4 mg) should be administered immediately and repeated every 5 minutes (3 times) to relieve anginal discomfort. If angina persists or in the setting of heart failure or significant hypertension, intravenous nitroglycerin may be started (at 10-20 mcg/min). Intravenous nitroglycerin can be quickly titrated (5-10 mcg/min increases every 5-10 minutes) to relieve angina. Caution must be exercised because it may cause profound hypotension. Topical (nitroglycerin transdermal patch, 0.2-0.6 mg/h, or nitropaste, 1-2 inches, replaced every 6 hours) or oral (isosorbide dinitrate, 10-40 mg orally 3 times daily, or isosorbide mononitrate, 30-120 mg orally each day) nitrates can also be used in patients to prevent recurrent anginal symptoms. Tolerance to nitrates is dose and interval dependent and can occur within 24 hours of initiation, requiring higher doses of nitrates. After symptoms are controlled, changing from intravenous to topical or oral formulations with nitrate-free intervals can limit this phenomenon.
   b. **Contraindications.** Contraindications are known **hypersensitivity to nitrates and hypotension. Use of oral phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil (Viagra), vardenafil (Levitra, Staxyn), tadalafil (Cialis), and avanafil (Stendra)** within the prior 24 hours has been associated with hypotension, MI, and death.

3. **Beta-blockers.** These agents relieve myocardial ischemia by lowering myocardial oxygen demand through their effects on blood pressure, heart rate, and contractility. In a meta-analysis from the pre-PCI era, the use of beta-blockade was associated with a substantial 13% relative reduction in death following presentation with NSTE-ACS. Cardioselective beta-blockers (eg, metoprolol and atenolol) are typically used to minimize side effects.
    a. **Dosing.** Oral beta-blockers should be initiated within 24 hours of presentation in the absence of heart failure, low output state, and risk for cardiogenic shock or other contraindications to beta-blockade. Beta-blockers with proven benefits in heart failure such as sustained-release metoprolol succinate, carvedilol, and bisoprolol should be given in patients with NSTE-ACS, heart failure, and reduced systolic function once they are stabilized.
    b. **Contraindications.** Contraindications to beta-blocker therapy include **advanced atrioventricular block, active bronchospasm, cardiogenic shock, hypotension, baseline bradycardia, and CHF**.
4. **Calcium channel blockers.** Calcium channel blockers have diverse physiologic effects, including vasodilation, decreased or slowed atrioventricular conduction, and negative inotropy and chronotropy. Data from several trials indicate no effect on death or nonfatal MI with calcium channel blocker trials in NSTE-ACS. Several agents have shown harm such as short-acting nifedipine that increased the risk of MI or recurrent angina compared with metoprolol. In addition, patients with LV dysfunction or pulmonary congestion on physical examination are reported to have worse outcomes when treated with diltiazem.
    a. **Indications.** Calcium channel blockers are recommended for patients with NSTE-ACS, but **only in patients with contraindications to beta-blockers or when beta-blockers and nitrates fail to fully relieve symptoms of ischemia**.

Calcium channel blockers are preferred in patients with variant angina or cocaine-induced vasospasm.

b. **Contraindications.** Contraindications to calcium channel blockers include LV dysfunction or signs and symptoms of CHF, hypotension, or atrioventricular conduction abnormalities.

5. **Morphine.** Morphine acts as an anxiolytic and analgesic and potentially reduces ventricular preload by venodilation. Morphine can be considered in patients with continued chest pain after maximally tolerated nitrates and beta-blockers. It should be administered at a dosage of 1 to 5 mg intravenously and may be repeated with close monitoring. In a retrospective evaluation of the CRUSADE registry, the use of morphine in NSTE-ACS was associated with an increase in hospital mortality.

B. Antiplatelet and anticoagulant therapies. There are many different antiplatelet and antithrombotic agents currently available for the treatment of ACS. As such, the decision of which combination of medications to use and when to administer them can be challenging. In general, the decision of which agents to use depends on (1) whether an early invasive strategy is used and (2) what post-angiography management strategy is employed. Regardless of which strategy is chosen, all patients presenting with ACS should receive a loading dose of aspirin (162-325 mg) to be chewed and swallowed; if the patient is aspirin intolerant, then a loading dose of clopidogrel (300-600 mg) should be given. The antiplatelet and anticoagulant therapies available for each of the following strategies are listed below. The specific doses, adverse effects, and pharmacokinetics of these agents are then listed separately.

1. **Initial conservative strategy.** After receiving aspirin, patients who undergo an initial conservative strategy should receive an **anticoagulant** and be started on **clopidogrel or ticagrelor** therapy. Enoxaparin and fondaparinux are the anticoagulants of choice; unfractionated heparin (UFH) is an acceptable alternative. Of note, if fondaparinux is used and an invasive strategy is ultimately employed, then another anticoagulant with factor IIa

activity must be initiated to prevent catheterization-associated thrombosis.

2. **Initial invasive strategy.** After receiving aspirin, patients who undergo an initial invasive strategy should receive **anticoagulation with enoxaparin, UFH, or bivalirudin**. All patients should be treated with dual-antiplatelet therapy (DAPT). These agents include clopidogrel or ticagrelor. Prasugrel may also be utilized after angiographic definition. A GP IIb/IIIa inhibitor such as eptifibatide or tirofiban may be considered in selected patients with breakthrough angina despite medical therapy if coronary angiography and revascularization are delayed.
3. **Once angiography is performed, the appropriate subsequent therapy depends on the management plan.**
   a. For patients undergoing **CABG surgery**, it is recommended to **continue aspirin therapy**. Clopidogrel or ticagrelor therapy should be discontinued 5 days and prasugrel 7 days prior to CABG. GP IIb/IIIa inhibitors should be discontinued 4 hours prior to CABG. UFH can be continued until CABG; however, enoxaparin should be discontinued 12 to 24 hours prior to CABG, and bivalirudin should be discontinued 3 hours prior to CABG.
   b. **PCI.** All patients undergoing PCI should be on DAPT. Routine GP IIb/IIIa inhibitor prior to PCI is not warranted and is utilized only as bailout during PCI.
   c. **Medical therapy.** Patients who are medically managed should continue aspirin therapy and either clopidogrel or ticagrelor. UFH should be continued for 48 hours; enoxaparin or fondaparinux should be continued for the duration of the hospitalization. Bivalirudin should be discontinued after angiography if medical therapy is pursued.
4. **Aspirin.** There are several pathways that lead to platelet activation, of which aspirin blocks only the cyclooxygenase-1–derived thromboxane A_2 pathway. Aspirin therapy for NSTE-ACS has been studied in five major clinical trials at doses ranging from

75 to 325 mg/d. Overall, treatment with aspirin reduced the combined end point of death or nonfatal MI by 50%.

a. **Pharmacokinetics.** The onset of aspirin's antiplatelet effect is quite rapid, with substantial inhibition of thromboxane A_2 production within 15 minutes, translating into measurable platelet inhibition within 60 minutes. It should be administered at first medical contact. Aspirin's inhibition of cyclooxygenase is irreversible and its antiplatelet effect is durable, lasting 7 to 10 days.

b. **Dosing.** Unless contraindicated (eg, active bleeding and documented hypersensitivity to aspirin), an initial dose of 162 to 325 mg of nonenteric-coated aspirin (chewed and swallowed) should be given to all patients with suspected NSTE-ACS, followed by a maintenance dose of 75 to 100 mg daily indefinitely. This is based on results from several trials that compared a higher dose of aspirin (300-325 mg) to low dose (75-100 mg) and showed no reduction in death, stroke, or MI but an increased risk of gastrointestinal (GI) bleeding with higher dose of aspirin. Those patients allergic or intolerant to aspirin should receive clopidogrel loading dose as soon as possible followed by a daily maintenance dose.

5. **P2Y12 (adenosine diphosphate) inhibitors.** Current guidelines recommend addition of a second antiplatelet agent in addition to aspirin in all patients with ACSs including those with NSTE-ACS. Several options are currently available and approved for this indication.

a. **Clopidogrel.** Clopidogrel is the most extensively studied member of this group. As evidence, in the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, addition of clopidogrel to aspirin led to a 20% reduction in incidence of cardiovascular death, nonfatal MI, or stroke in both low- and high-risk patients with NSTE-ACS, regardless of revascularization strategy (PCI, CABG, or medical therapy alone). An increased rate of major bleeding (3.7% vs 2.7% for aspirin) was seen in patients receiving clopidogrel,

predominantly in those undergoing CABG. In a substudy of the CURE trial, PCI-CURE, pretreatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization at 30 days (4.5% vs 6.4%) in patients with NSTE-ACS undergoing PCI. Long-term treatment with clopidogrel also resulted in lower rates of cardiovascular death, nonfatal MI, or revascularization, without a significant increase in major bleeding. The benefit of clopidogrel pretreatment in PCI was further confirmed in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial in which patients receiving a 300-mg loading dose plus 1 year of 75 mg daily maintenance therapy of clopidogrel had a 26.9% relative reduction in death, nonfatal MI, or stroke at 1 year compared with those receiving only 1 month of maintenance therapy without any loading dose of clopidogrel.

(1) **Pharmacokinetics.** Clopidogrel is a prodrug that is metabolized to a pharmacologically active metabolite. Clopidogrel has a shorter onset of action than ticlopidine when 300 mg is given, with antiplatelet activity being detected within 2 hours after administration. Loading with 600 mg has been shown to have an even more rapid onset of action.

(2) **Side effects.** Clopidogrel is generally well tolerated. Exposure can rarely produce an allergic reaction, typically resulting in diffuse urticaria. Rare case reports of thrombotic thrombocytopenic purpura with clopidogrel therapy have been reported.

(3) **Dosing.** Clopidogrel loading dose can be 300 to 600 mg, although the latter leads to a faster onset of steady-state plasma concentration. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events—Seventh Organization to Assess Strategies in Ischemic Symptoms-7 (CURRENT OASIS-7) trial compared 600- versus 300-mg loading dose clopidogrel in patients

presenting with ACS. Although the results were neutral, subgroup analysis in patients undergoing PCI noted a lower rate of cardiovascular death, MI, and stroke with the 600-mg dose. Results of large meta-analysis including more than 25,000 patients undergoing PCI confirmed this finding, making 600 mg the preferred loading dose in patients with NSTE-ACS undergoing PCI. Clopidogrel maintenance therapy is 75 mg daily.

b. Prasugrel. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) trial evaluated the efficacy of prasugrel versus clopidogrel in patients presenting with ACS with planned PCI. In this study of 13,608 patients, the use of prasugrel as compared with clopidogrel resulted in a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs 12.1%, $P < .001$). The benefit was even more pronounced (30% relative reduction) in patients with diabetes receiving prasugrel. However, the salutary benefits in reduction of ischemic events with prasugrel came at the expense of an increase in bleeding events, including a significant increase in rates of both major bleeding (2.4% vs 1.1%, $P = .03$) and fatal bleeding (0.4% vs 0.1%, $P = .002$). It is an absolute contraindication to use prasugrel in patients with a history of transient ischemic attack or stroke (because of high risk of intracranial hemorrhage) and a relative contraindication in patients ≥75 years of age or <60 kg because of higher incidence of bleeding in these patient subgroups. Prasugrel was also compared with clopidogrel in patients being managed medically after NSTE-ACS in The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial. There were no differences in incidence of ischemic or bleeding end points between the two groups. The Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention or as Pretreatment

at the Time of Diagnosis in Patients with Non–ST Elevation Myocardial Infarction trial compared pretreatment with prasugrel 30 mg with an additional 30 mg given during PCI to prasugrel 60 mg admitted during angiography but prior to PCI in the setting of NSTE-ACS. Pretreatment with prasugrel in this trial (median 4.3 hours before angiography) was not associated with clinical benefit but resulted in increased TIMI major bleeding (2.6% vs 1.4%, $P = .006$). As a result, pretreatment with prasugrel is not recommended in this setting.

(1) **Pharmacodynamics.** Like clopidogrel, prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. After a 60-mg loading dose of prasugrel is given, 90% of patients achieve ≥50% inhibition of platelet aggregation within 1 hour, with a maximum achieved platelet inhibition being approximately 80%. The mean steady-state inhibition of platelet aggregation with prasugrel is 70% after 3 to 5 days of treatment. Platelet aggregation returns to baseline 5 to 9 days after discontinuation of therapy.

(2) **Side effects.** Prasugrel is generally well tolerated. Allergic reactions to prasugrel are rare; however, bleeding-related complications such as epistaxis or easy bruising are not uncommon.

(3) **Dosing.** The loading dose for prasugrel is 60 mg followed by a maintenance dose of 10 mg/d.

c. **Ticagrelor.** Ticagrelor is a nonthienopyridine, reversible $P2Y_{12}$ receptor antagonist that was approved by the Food and Drug Administration in 2011. In the pivotal PLATelet inhibition and patient Outcomes (PLATO) trial involving 18,624 patients presenting with ACS (59% of whom had NSTE-ACS), there was a significant 16% relative reduction in major adverse cardiac events and a 22% relative reduction in all-cause mortality in patients receiving ticagrelor versus clopidogrel. A significant benefit was noted across several subgroups, including those treated medically and those who had previously

received clopidogrel. On the basis of PLATO, ticagrelor is recommended in all patients with ACS, irrespective of the initial treatment strategy including those pretreated with clopidogrel.

(1) **Pharmacodynamics.** Ticagrelor is not a prodrug and does not require bioactivation. Ticagrelor has a faster onset of action (50% platelet inhibition at 30 minutes) and provides more potent platelet inhibition than clopidogrel. Although more potent, ticagrelor has a shorter half-life of 12 hours.

(2) **Side effects.** Ticagrelor is generally well tolerated. Dyspnea is the most common side effect experienced in as many as 20% of patients. This is often short limited and does not require drug discontinuation in most patients.

(3) **Dosing.** The loading dose of ticagrelor is 180 mg followed by a maintenance dose of 90 mg twice daily. Subgroup analysis of the PLATO trial showed higher rates of bleeding in patients receiving ticagrelor and high aspirin dose (162-325 mg). The current guidelines, therefore, recommend only low-dose aspirin (81 mg) in patients receiving concomitant ticagrelor.

d. **Cangrelor.** This is an intravenous adenosine triphosphate analog that reversibly binds with high affinity to the $P2Y_{12}$ receptor and has an extremely short half-life of less than 10 minutes. It is given at a dose of 30 mcg/kg/bolus followed by 4 mcg/kg/min infusion. In the setting of NSTE-ACS, it is best utilized to ensure adequate platelet inhibition at the initiation of PCI in the setting of inadequate oral DAPT bioavailability. To reduce the risk of GI bleeding, concomitant proton pump inhibitors should be utilized with DAPT, especially in high-risk patient. This includes patients aged >65 years and subjects with a history of prior GI bleeding, dyspepsia, gastroesophageal reflux disease, significant alcohol use, and known *Helicobacter pylori* infection.

e. **Treatment duration.** Precise determination of DAPT duration depends on the art of balancing between benefits (fewer

ischemic events) versus risks (bleeding). For patients with stable CAD, recommended duration of DAPT after PCI is 6 months. Patients who presented with ACSs are recommended to complete 12 months of DAPT duration. Consideration should be given to patients with high bleeding risk (based on PRECISE-DAPT score of ≥25). At least 3 months of DAPT duration is recommended in patients with stable CAD and at least 6 months of DAPT is recommended for patients with ACS who underwent PCI.

TWILIGHT trial suggests a different strategy of aspirin discontinuation after 3 months and continuation with ticagrelor monotherapy to decrease the risk of bleeding without an increase in major adverse outcomes.

DAPT duration of >12 months can be considered, especially in patients who have low/mild risk of bleeding and have elevated risk of recurrent ischemic events. DAPT score is commonly used in clinical practice to evaluate risks of recurrent ischemic events. Links to DAPT and PRECISE-DAPT score online calculators are provided at the end of the chapter.

f. Switching between oral P2Y12 inhibitors. In several clinical scenarios, it is occasionally necessary to switch between oral $P2Y_{12}$ inhibitors. International expert consensus on switching platelets $P2Y_{12}$ receptor inhibiting therapies in most cases recommends administration of loading dose during acute/early phase (<30 days from an index event), with the exception of patients who are de-escalating therapy because of bleeding concerns. Timing of switching should be 24 hours after the last dose of the previous $P2Y_{12}$ drug, with the exception of switching to prasugrel or ticagrelor, when the loading dose can be given regardless of the timing and dosing of the previous clopidogrel regimen.

In patients in whom switching is required during the late phase (>30 days after an index event), switching should occur with administration of a maintenance dose 24 hours after the

last dose of the previous $P2Y_{12}$ agent, with the exception of patients changing from ticagrelor to prasugrel therapy, for whom a loading dose should be considered.

6. **Anticoagulant therapy.** In addition to DAPT, all patients with NSTE-ACS should be started on an anticoagulant. Several agents have been tested for this indication.

   a. **Heparin.** UFH prevents coagulation by blocking thrombin and factor Xa. Because of a short half-life, UFH has to be administered as a continuous infusion in patients with ACS. A meta-analysis of six trials in patients with UA demonstrated that treatment with aspirin plus UFH reduced the incidence of death or nonfatal MI by 33% compared with treatment with aspirin alone.

      (1) **Duration of therapy.** Current guidelines recommend that heparin (adjusted for activated plasma thromboplastin time) be continued for 48 hours or until PCI is performed.

      (2) **Rebound ischemia.** Rebound ischemia is thought to result from the accumulation of thrombin during UFH administration and the ensuing platelet aggregation. Studies have shown that this rebound ischemia can be attenuated with the concomitant use of aspirin.

      (3) **Recommendations.** Intravenous UFH can be used for anticoagulant therapy in patients with NSTE-ACS undergoing either an invasive or conservative treatment strategy unless contraindicated (eg, active bleeding, known hypersensitivity, and history of heparin-associated thrombocytopenia).

      (4) **Dosing.** Initially, heparin should be given as a weight-adjusted bolus (60 U/kg), followed by an infusion (12 U/kg/h). The activated partial thromboplastin time (aPTT) should be monitored every 6 hours until it stabilizes between 50 and 70 seconds and monitored subsequently every 12 to 24 hours thereafter. Standardized heparin nomograms have simplified and streamlined the initial

orders for UFH and the subsequent adjustment of dosing based on the aPTT levels.

b. Low-molecular-weight heparin (LMWH). LMWH is a more selective factor Xa inhibitor than heparin. The advantages of LMWH compared with UFH include increased bioavailability, a fixed dosing regimen, more effective thrombin inhibition, lower rates of heparin-induced thrombocytopenia (HIT), and more predictable and sustained anticoagulation.

(1) Comparison with heparin. Multiple trials have compared LMWH and UFH in patients with NSTE-ACS and shown similar or reduced rates of death or nonfatal MI, primarily a significant reduction in the latter. A meta-analysis of 12 trials involving 17,157 patients with NSTE-ACS that compared the use of different LMWHs with UFH found no significant benefit with LMWHs compared with UFH (odds ratio = 0.88, 95% confidence interval 0.69-1.12, P = .34).

(2) Dosing. Enoxaparin is administered as a 1-mg/kg dose given subcutaneously (SQ) every 12 hours. No routine laboratory values have to be followed. The dosing is reduced to once a day in patients with creatinine clearance (CrCl) <30 mL/min.

(3) Recommendations. In patients with NSTE-ACS who may undergo either a conservative or an early invasive therapy, enoxaparin is an acceptable agent for anticoagulation.

c. Direct thrombin inhibitors (DTIs). DTIs inhibit clot-bound thrombin more effectively than UFH and are not inactivated by plasma proteins or platelet factor 4, making them an ideal agent in patients with HIT. Hirudin is an older-generation DTI that is no longer used clinically and has been supplanted by its synthetic derivative, bivalirudin. **Bivalirudin** reversibly inhibits thrombin and has a short half-life of 25 minutes. In the **ACUITY** trial of 13,819 patients with high-risk NSTE-ACS with planned invasive strategy, bivalirudin was noninferior to heparin plus GP IIb/IIIa inhibition, with 30-day rates of

ischemia of 7.7% versus 7.3%, but there was a significantly lower rate of major bleeding with bivalirudin. Similar results were also noted in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4 (ISAR-REACT 4) trial. In the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox trial, the use of bivalirudin compared with heparin was not associated with any clinical benefit on the composite of death, MI, stroke, or major bleeding in 7,213 patients with ACS (3,203 with NSTE-ACS). Randomization to bivalirudin, however, did result in decreased rates of Bleeding Academic Research Consortium (BARC) bleeding (11% vs 16%, $P = .001$) and major BARC 3-5 bleeding (1.4% vs 2.5%, $P < .001$).

(1) **Recommendation.** Bivalirudin is now rarely utilized in the era of radial artery catheterization, given its increased cost. Bivalirudin should be considered when patients with NSTE-ACS who are at high risk for bleeding undergo PCI.

d. Factor Xa inhibitors. Fondaparinux is a heparin pentasaccharide analog that selectively inhibits factor Xa. In comparison with UFH, fondaparinux has decreased binding to plasma proteins along with dose-independent clearance with a longer half-life. These properties translate into more predictable and sustained anticoagulation, which permits fixed-dose, once-daily administration.

(1) **Comparison with enoxaparin.** The **Organization to Assess Strategies in Acute Ischemic Syndromes 5 (OASIS-5)** trial evaluated the efficacy of fondaparinux versus enoxaparin in 20,078 patients with NSTE-ACS. Patients receiving fondaparinux (2.5 mg SQ once daily) had a similar rate of the combined end point of death, MI, or refractory ischemia at 9 days as those randomized to enoxaparin (1.0 mg/kg SQ twice daily). The use of fondaparinux was associated with a lower rate of major bleeding at 9 days as compared with enoxaparin (2.2% vs

4.1%, $P < .001$). However, in this trial, there was an increased incidence of catheter-associated thrombus noted, and the trial protocol was modified to allow for the use of open-label UFH, which initially was not allowed during PCI.

(2) Dosing. The dosing of fondaparinux for NSTE-ACS is 2.5 mg SQ once daily. Fondaparinux is renally cleared, and its use is contraindicated in those patients with a CrCl <30 mL/min.

(3) Recommendations. Fondaparinux can be used for anticoagulant therapy in those patients selected to undergo a conservative medical approach. It is the preferred therapy in patients with increased risk of bleeding being managed with medical therapy. For patients who undergo angiography and PCI, an additional agent with anti-IIa activity (UFH or bivalirudin) should be administered, given the increased rates of catheter-associated thrombus with fondaparinux alone.

e. Glycoprotein IIb/IIIa inhibitors

(1) Background. Platelet aggregation eventually requires the activation of GP IIb/IIIa receptors on the platelet surface. The GP IIb/IIIa receptors of adjacent platelets bind fibrinogen molecules that allow cross-linking of the platelets, which subsequently initiates thrombus formation. Blocking the GP IIb/IIIa receptor, therefore, inhibits platelet aggregation and reduces thrombus formation. With the availability of potent DAPT, the use of these agents has significantly decreased over time. Currently, these agents are mainly utilized for bailout and thrombotic complications in the cath lab. When PCI is indicated in the absence of effective DAPT, tirofiban/Integrilin may be administered to endure adequate and complete platelet inhibition while allowing the oral DAPT agents to be adequately absorbed and bioavailable. Three agents, namely, **abciximab** (a monoclonal antibody to the human

GP IIb/IIIa receptor), **eptifibatide**, and **tirofiban**, with the latter two being small molecule, reversible inhibitors, were significantly utilized in the past. The trials that evaluated the benefit of GP IIb/IIIa inhibitors in patients with NSTE-ACS are now only of historical significance.

(2) **Recommendations: Based on current evidence**, GP IIb/IIIa inhibitors have a selective role, mainly as a bailout indication during the performance of PCI.

f. **Fibrinolytic agents.** There is no role for fibrinolytic therapy in patients with NSTE-ACS because it is associated with worse outcomes. A meta-analysis of fibrinolytic therapy in the management of UA demonstrated an increase in death or nonfatal MI in patients receiving fibrinolytics (9.8% for fibrinolytics vs 6.9% for placebo).

g. **Protease-activated receptor-1 antagonist.** The novel, oral thrombin receptor (protease-activated receptor-1) antagonist, vorapaxar, has been evaluated in patients with ACS and peripheral arterial disease. The addition of vorapaxar to standard therapy did not significantly reduce major adverse cardiac events and was associated with increased risk of bleeding and intracranial hemorrhage. Although the drug is approved in patients with ACS, it is not given any recommendation by the ACC/AHA guidelines for this indication.

h. **Oral anticoagulation.** Patients presenting with ACS continue to have significant residual risk even with optimal medical therapy, and ~10% of subjects have another cardiovascular event within 1 year of initial ACS presentation. Because of this residual risk, addition of oral anticoagulant to standard DAPT has also been tested in patients with ACS. Addition of low-dose rivaroxaban (2.5 and 5 mg twice daily) to predominantly DAPT with aspirin and clopidogrel was tested in patients with recent ACS. Although there was significant reduction in composite of MI, death, and stroke as well as stent thrombosis, it was at the cost of slightly higher risk of bleeding, including intracranial

hemorrhage. Although not currently approved in the United States, the European Society of Cardiology guidelines have given a class IIb indication for addition of low-dose rivaroxaban (2.5 mg twice daily) in high-risk patients with NSTE-ACS.

C. Ischemia-guided versus early invasive strategy. In the absence of contraindications, high-risk patients with NSTE-ACS should be managed by an early invasive strategy. This includes all patients with a confirmed NSTEMI. This strategy is guided by early angiographic definition of coronary anatomy and subsequent revascularization by PCI or CABG based on the nature and extent of disease. When performed by experienced operators, radial access for the performance of coronary angiography as well as PCI should be utilized. A meta-analysis of multiple randomized clinical trials has confirmed a reduction in death, MI, stroke, and bleeding with a radial compared to a femoral approach. An ischemia-guided strategy may be utilized in intermediate- and low-risk patients. In the absence of spontaneous ischemia during medical therapy, these patients usually undergo evaluation for inducible ischemia with a functional study. Select patients who meet the criteria for high risk on stress testing are then referred for coronary angiography, whereas the remainder are discharged on optimal medical therapy.

The evidence basis to support adoption of an invasive approach in high-risk patients is strong. A contemporary meta-analysis of seven randomized trials evaluated an early invasive versus a conservative approach in the management of patients with NSTE-ACS. In this pooled analysis of 8,375 patients, there was a 25% relative reduction in all-cause mortality at 2 years with the use of early invasive as compared with conservative therapy (4.9% vs 6.5%, $P = .001$). **Table 2.3** summarizes the approach to NSTE-ACS.

TABLE 2.3 Initial Management Strategy in NSTE-ACS: Early Invasive versus Ischemia-Guided Approach

Immediate invasive (within 2 h)	Refractory angina Signs/symptoms of HF with new or worsening mitral regurgitation

	Hemodynamic instability Sustained VT or VF
Early invasive (within 24 h)	GRACE risk score >140 Troponin elevation New or presumable new ST depression
Delayed invasive (within 25-72 h)	Prior PCI within 6 mo or prior CABG LV function <40%
Ischemia-guided therapy	Low-risk score (TIMI 0 or 1 or GRACE <109) Low-risk troponin-negative female patients Physician or patient preference in low- to intermediate-risk patient

CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; HF, heart failure; LV, left ventricular; NSTE-ACS, non–ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VT, ventricular tachycardia.

1. The **2014 ACC/AHA guidelines** provide specific treatment strategies for the following patient populations:
   a. Patients who have **refractory angina despite medical therapy, hemodynamic instability, or electrical instability** are recommended to undergo an **urgent/immediate invasive strategy**.
   b. For patients who are **initially stabilized but are at high risk for adverse events**, it is reasonable to undergo an **early invasive strategy** (within 24 hours). This includes patients who are troponin positive, those with GRACE score >140, and those with new or presumably new ST-segment depressions.
   c. A **delayed invasive strategy** (within 25-72 hours) is reasonable in patients with diabetes, renal insufficiency, reduced systolic function, and early postinfarct angina.
   d. For patients with a low-risk score (TIMI 0 or 1 or GRACE <109) or low-risk, troponin-negative female patients, it is reasonable to proceed with an ischemia-guided approach.
   e. An early invasive strategy is not recommended in patients with extensive comorbidities (eg, hepatic, renal, pulmonary failure; cancer), in whom the risks of revascularization and comorbid

conditions are likely to outweigh the benefits of revascularization and in those with acute chest pain and a low likelihood of ACS who are troponin negative, especially women.

f. Patients being treated with an initial ischemia-guided approach benefit from an early echocardiogram to evaluate LV function and should undergo risk stratification with a stress test before or shortly after discharge to identify patients who would benefit from revascularization.

2. **Randomized trials.** The following is a summary of the randomized trials that have compared an early invasive versus an early conservative approach in different patient populations.

   a. Two earlier trials performed prior to the current era of antiplatelet therapy and coronary stenting were the **TIMI IIIB** and **Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH)** trials. Both of these trials showed similar long-term outcomes (death or MI) between early invasive and conservative treatment strategies; however, there was an increase in early mortality associated with invasive therapy in the VANQWISH study.

   b. In the **Fast Revascularization during InStability in Coronary artery disease II (FRISC II)** trial, patients with NSTE-ACS were randomized in a factorial design to an early invasive or conservative strategy and to dalteparin or placebo. An early invasive strategy was associated with a reduction in the rate of death or MI at 6 months (9.4% vs 12.1%, $P = .031$) and reduced symptoms of angina and rehospitalization, regardless of treatment with dalteparin.

   c. In the **Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 (TACTICS-TIMI 18)** trial, patients with NSTE-ACS treated with aspirin, heparin, and tirofiban were randomized to an early invasive or a conservative strategy. Patients assigned to an **early invasive approach underwent catheterization within 4 to 48 hours**,

with revascularization as appropriate. Patients assigned to the conservative arm underwent cardiac catheterization only if there was objective evidence of recurrent ischemia or abnormal stress test. An early invasive strategy was associated with a reduction in the composite of death, nonfatal MI, or rehospitalization for ACS at 6 months (15.9% vs 19.4%, $P = .025$), as well as a reduction in the incidence of death or nonfatal MI at 6 months (7.3% vs 9.5%, $P < .05$).

d. In the **Randomized Intervention Treatment of Angina 3 (RITA 3)** trial, an early invasive strategy for moderate-risk patients with NSTE-ACS was associated with a decreased rate of all-cause mortality, MI, or refractory angina compared with conservative therapy at 5 years. However, the reduction in mortality dissipated at 10-year follow-up with no statistical differences between groups.

e. In the **Intracoronary Stenting With Antithrombotic Regimen Cooling-Off (ISAR-COOL)** trial, patients with NSTE-ACS treated with intensive medical therapy (aspirin, heparin, clopidogrel [600-mg loading dose], and tirofiban) were randomized to immediate invasive therapy (median time of 2.4 hours) versus delayed invasive therapy after a "cooling-off" period (median time of 86 hours). Those who had early intervention had a significant reduction in death or MI at 30 days compared with those who had a "cooling-off" period (5.9% vs 11.6%, $P = .04$).

f. In the **Invasive versus Conservative Treatment in Unstable Coronary Syndromes (ICTUS)** trial, 1,200 patients with NSTE-ACS with elevated troponins were randomized to either early invasive therapy (angiography within 24-48 hours) or initial conservative strategy with selective invasive therapy. There was no difference in the primary composite end point of death, MI, or rehospitalization for ACS at 1 year between the two groups (22.7% vs 21.2%, $P = .33$). The aggressive medical therapies and high rates of revascularization (47%) in the initial

conservative strategy group are two among many potential explanations for the findings of this trial.

g. In **The Timing of Intervention in Acute Coronary Syndromes (TIMACS)** trial, patients with NSTEMI presenting within 24 hours of onset of symptoms were randomized to undergo angiography as soon as possible (within 24 hours) or after a minimum delay of 36 hours. These patients received contemporary medical therapy, including acetylsalicylic acid, clopidogrel (>80%), heparin or fondaparinux, and GP IIb/IIIa inhibitors (23%). Overall, there was a nonsignificant trend toward a reduction in death, new MI, or stroke at 6 months for patients who received an early invasive strategy (11.3% for delayed angiography vs 9.6% in the early intervention, $P = .15$). However, there was a significant reduction in the secondary end point of death, MI, or refractory ischemia for patients randomized to an early invasive strategy (12.9% vs 9.5%, $P = .003$) that was primarily driven by a decrease in refractory ischemia. Overall, this study supports an early invasive strategy for patients presenting with NSTE-ACS, particularly for those among the highest tertile of risk according to the GRACE scale.

h. The **Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD)** trial assessed whether a very aggressive strategy of emergent intervention (analogous to primary PCI for STEMI) would benefit patients presenting with NSTE-ACS versus delayed angiography and intervention. Immediate angiography and intervention did not decrease the rate of the primary outcome of median troponin I release (2.1 ng/mL for the invasive strategy vs 1.7 ng/mL for the delayed strategy) nor did it show a trend toward improved outcomes in the secondary end point of death, MI, or urgent revascularization at 1 month (13.7% for early invasive management vs 10.2% for the conservative approach, $P = .31$).

VI. HOSPITAL DISCHARGE AND POSTDISCHARGE CARE. The risk of recurrent MI or death is highest during the first 2 months after NSTE-ACS. Although patients with NSTE-ACS usually receive definitive therapy during hospitalization, close follow-up care after hospital discharge is imperative. Follow-up must include lifestyle alteration, risk factor modification, and secondary prevention. Referrals for cardiac rehabilitation in stable patients, smoking cessation efforts, and dietary changes have all been shown to improve outcomes. Hypertension, dyslipidemia, depression, and diabetes mellitus must be diagnosed and aggressively treated. Patients must be reassured and educated about their acceptable level of activity. Compliance with DAPT **beta-blockers, statins/cholesterol-lowering regimens, and/or angiotensin-converting enzyme inhibitors should be emphasized**. Specific recommendations regarding a secondary prevention postdischarge medication regimen are discussed in the chapter on post-MI risk stratification.

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CHAPTER 3

Complications of Acute Myocardial Infarction

Travis M. Howard and Venu Menon

I. INTRODUCTION. In-hospital mortality after acute myocardial infarction (MI) is primarily caused by circulatory failure from severe left ventricular (LV) dysfunction and/or other acute complications of MI. These complications can be broadly classified as **mechanical, arrhythmic, embolic, and inflammatory (eg, pericarditis)**.

II. MECHANICAL COMPLICATIONS. Mechanical complications of acute MI include ventricular septal rupture (VSR), acute mitral regurgitation (MR), ventricular free wall rupture, ventricular pseudoaneurysm, and ventricular aneurysm. With the exception of aneurysm, they are associated with high in-hospital mortality, and transfer to a center with surgical expertise is recommended as soon as the diagnosis is made. Decision-making is complex and is best made by a multidisciplinary team with input from critical care cardiology, interventional cardiology, cardiothoracic surgery, and heart failure and palliative care.

A. Ventricular septal rupture

1. **Clinical presentation.** VSR occurred in 1% to 2% of patients after acute MI in the prethrombolytic era and accounted for 5% of the peri-infarction mortality. The incidence has dramatically decreased in the primary percutaneous coronary intervention (PCI) era. In the substudy of the Assessment of Pexelizumab in Acute Myocardial Infarction of 5,745 patients with ST-elevation MI from 2004 to 2006, VSR occurred 0.17% of the time. VSR is more likely to occur in patients who are **older, are female, had prior stroke, have chronic kidney disease, and have congestive heart**

failure. It commonly occurs in the setting of a **first MI, in the background of delayed or absent reperfusion therapy.** Early revascularization has been associated with lower risk of VSR and may account for the decreasing incidence.

a. Signs and symptoms. Patients with post-MI VSR may appear relatively stable early in the disease course. Recurrence of angina, pulmonary edema, hypotension, and shock may develop abruptly later in the course. Alternatively, precipitous onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new murmur may be the initial manifestation.

b. Physical findings. The diagnosis should be suspected when a new **harsh pansystolic murmur** develops, especially in the setting of worsening hemodynamic profile and biventricular failure. For this reason, it is important that **all patients with MI have a well-documented cardiac examination** at presentation and frequent evaluations thereafter.

(1) The murmur is usually best heard at the **lower left sternal border**; it is accompanied by a **thrill in 50% of the cases**. In patients with a large VSR and severe heart failure or cardiogenic shock, the murmur may be of low intensity or inaudible, but **the absence of a murmur does not rule out VSR**.

(2) Several features differentiate the murmur of VSR from that of acute MR (**Table 3.1**). The murmur may radiate to the base and apex of the heart. A third heart sound (S_3), loud P_2, and signs of tricuspid regurgitation may be present.

TABLE 3.1 Differential Diagnosis of a New Systolic Murmur After Acute Myocardial Infarction

Differentiating Features	Ventricular Septal Rupture	Acute Mitral Regurgitation
Location of MI	Anterior = nonanterior	Inferoposterior > anterior
Location of murmur	Lower left sternal border	Cardiac apex

Differentiating Features	Ventricular Septal Rupture	Acute Mitral Regurgitation
Intensity	Loud	Variable; may be faint
Thrill	50% of patients	Rare
RV failure	More likely	Less likely
Pulmonary edema	Less likely	More likely
V waves in PCWP	Present or absent	Almost always present
V waves in PA tracing	Absent	Present
O_2 step-up in PA	Almost always present	Absent

MI, myocardial infarction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

2. **Histopathology.** The defect usually occurs at the MI border zone, located in the **apical septum with anterior MI** and in the **basal posterior septum with inferior/lateral MI**, and with similar frequency. A VSR almost always occurs in the setting of a transmural MI. The defect can be one single large defect or a meshwork of serpiginous channels. Multiple fenestrations are especially common with inferior MIs.

3. **Diagnostic testing**

   a. **An electrocardiogram** (ECG) may show atrioventricular (AV) node or infranodal conduction abnormalities in approximately 40% of patients.

   b. **Echocardiography**

      (1) **Transthoracic echocardiography is the test of choice** for the diagnosis of VSR. It is important for the clinician to interrogate the area of interest with color Doppler ultrasound. Lowering the Nyquist limit will enable definition and help define the size of the defect. The echocardiogram will also provide insight into the choice of management.

      Basal VSR is best visualized in the parasternal long axis with medial angulation, the apical long axis, and the

subcostal long axis. **Apical VSR** is best visualized in the apical four-chamber view.

(2) In some cases, **transesophageal echocardiography** may help in determining the extent of the defect and assessing suitability for potential percutaneous closure.

(3) Echocardiography may help determine the size of the defect and the magnitude of the left-to-right shunt by comparing flow across the pulmonary valve with flow across the aortic valve.

(4) An assessment of right ventricular (RV) and LV function is key to prognostication and management as they remain important determinants of mortality.

c. Right heart catheterization. Pulmonary artery (PA) catheterization with oximetry measurement can help diagnose the presence and size of a left-to-right shunt. Diagnosis involves fluoroscopically guided measurement of the oxygen saturation in the superior vena cava (SVC) and inferior vena cava (IVC); high, mid, and low right atrium (RA); base, mid, and apical levels of the RV; and the PA.

(1) Normal oxygen saturations for these chambers are 64% to 66% in the SVC, 69% to 71% in the IVC, 64% to 67% in the RA, 64% to 67% in the RV, and 64% to 67% in the PA.

(2) An oxygen step-up at the level of the RV is characteristically seen with VSR. A left-to-right shunt across the ventricular septum typically results in a **5% or greater** increase in oxygen saturation between the RA and the RV or PA.

Shunt fraction is calculated as follows:

$$Q_p/Q_s = (Sa_{O_2} - MV_{O_2})/(PV_{O_2} - Pa_{O_2})$$

In this equation, Q_p is pulmonary flow; Q_s is systemic flow; Sa_{O_2} is peripheral arterial oxygen saturation; MV_{O_2} is mixed venous oxygen saturation; PV_{O_2} is pulmonary venous oxygen saturation; and Pa_{O_2} is pulmonary arterial oxygen saturation. MV_{O_2} is calculated by multiplying the

SVC oxygen saturation by three, adding the IVC oxygen saturation, and then dividing the sum by 4. PVO_2 is generally assumed to be equal to the peripheral oxygen saturation. **$Q_p/Q_s \geq 2$ suggests the presence of a considerable shunt.**

d. For a patient with an intracardiac shunt, **cardiac output measured by means of the thermodilution technique is inaccurate; the Fick method should be used**. The key to measurement of accurate systemic flow in the presence of a shunt is that the oxygen content measured in the PA will be abnormally elevated and must be measured in the chamber immediately **proximal** to the shunt (ie, the RA or the SVC and IVC in the case of VSR).

e. Left heart catheterization. Ventriculography performed after angiography or PCI may reveal VSR if the suspicion is high. Visualization is best in the left anterior oblique projection with cranial angulation.

f. Cardiac magnetic resonance imaging (MRI) and computed tomography (CT) are additional imaging modalities that can be utilized. However, the studies are more difficult to perform in hemodynamically unstable patients and do not play a significant role in this setting.

4. Therapy

a. Priority of therapy. Surgical closure is the treatment of choice (American Heart Association [AHA]/American College of Cardiology [ACC] class I recommendation), although the timing of surgical repair is controversial. Data from the Society of Thoracic Surgeons (STS) database suggest lower mortality in those undergoing delayed repair allowing for evolution of the infarct and stability of the friable myocardium; however, this may simply be a result of survival bias. The mortality rate for patients with VSR treated medically is extremely poor. Ultimately, the timing of closure must take into account the

patient's stability, the risk of clinical deterioration, surgical comorbidities, and the VSR anatomy.

b. Vasodilators can decrease left-to-right shunt and increase systemic flow by means of reducing systemic vascular resistance (SVR); however, a greater decrease in pulmonary vascular resistance may increase shunting. The vasodilator of choice is **intravenous nitroprusside.**

(1) Temporary **mechanical support**: The availability of reliable temporary circulatory support with Impella and Tandem heart now enables the clinician to support the circulation, reverse end-organ injury, and delay definitive surgery by promoting tissue healing and scar formation. An **intra-aortic balloon pump (IABP)** may be inserted as a bridge to a surgical procedure, unless there is marked aortic regurgitation. IABP counterpulsation decreases SVR, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP, vasodilators can be tailored with hemodynamic monitoring.

(2) In the setting of circulatory collapse, other mechanical support devices like Tandem Heart or Impella or venoarterial extracorporeal membrane oxygenation (VA ECMO) may be utilized as a bridge to definitive surgery.

c. Surgical therapy

(1) Cardiogenic shock and multisystem failure are associated with high surgical mortality, further supporting earlier operations on these patients before complications develop. Mortality in patients with cardiogenic shock and VSR was 81% in the SHould we emergently revascularize Occluded coronaries for Cardiogenic shocK? (SHOCK) trial registry. When surgical repair is considered unlikely or futile, appropriate patients may be considered for cardiac transplantation.

(2) Surgical mortality is high among patients with **basal septal rupture associated with inferior MI** (70%

compared with 30% in patients with anterior infarcts) because of the greater technical difficulty and the need for concomitant mitral valve repair/replacement in these patients, who often have coexisting MR. RV dysfunction because of infarction and/or pressure and volume overload further increases the risk profile of these subjects.

d. Percutaneous therapy. Although surgical closure remains the treatment of choice for VSR, emerging data suggest that **percutaneous closure** may be a viable treatment for high-risk surgical patients and patients in whom surgical closure has failed. Although the procedure success rate approaches 80% to 100% in centers of excellence, hospital mortality remains high, and procedural complications are common. In a 2013 series of 30 patients treated with percutaneous VSR closure (12 as primary closure and 18 for residual VSR after surgery), mortality at 30 days was 42% and 11% in the respective groups. In our institution, a percutaneous approach is utilized for temporary palliation and as a bridge to surgical repair only in patients considered too high risk to undergo surgery.

B. Acute severe MR. Like other mechanical complications of acute MI, severe MR caused by papillary muscle rupture is a life-threatening complication with decreased incidence in the reperfusion era, occurring in 0.25% of patients following an MI. Acute severe MR accounted for 7% of the cases of cardiogenic shock and 5% of the mortality observed after cardiogenic shock complicating acute MI in the SHOCK registry.

1. Clinical presentation

a. Signs and symptoms. These are variable and depend on the anatomy of the papillary muscle involved and its impact on the integrity of the mitral valve. Patients with partial or complete rupture of one or more heads of the papillary muscle lose significant leaflet support. The resultant torrential MR can result in pulmonary edema and severe respiratory distress along with cardiogenic shock. In the setting of rupture of a minor

papillary head or a chordae tendinea, MR may occasionally be better tolerated.

b. **Physical findings.** A new **pansystolic murmur that is audible at the cardiac apex with radiation to the axilla or the base of the heart suggests acute MR**. In posterior papillary muscle rupture, the murmur radiates to the left sternal border and may be confused with the murmur of VSR or aortic stenosis. The intensity of the murmur does not predict the severity of the MR. The **murmur may often be quiet, soft, or absent** in patients with poor cardiac output or in persons with elevated left atrial pressure because of the rapid equilibration of pressures. Resting tachycardia and mechanical ventilation can also make murmur recognition challenging.

2. **Pathophysiology.** Papillary muscle rupture is **more common with an inferior MI** because the posteromedial papillary muscle receives blood supply from the posterior descending artery, whereas the anterolateral papillary muscle has dual blood supply from the left anterior descending and circumflex arteries. Papillary muscle rupture is more likely to occur in patients with a **first MI**, and in many patients, the **infarct size may be relatively small. The discordance between the degree of hemodynamic instability and the extent of myocardium in jeopardy is often a clue to this diagnosis.**

3. **Diagnostic testing**

   a. An **ECG** usually shows evidence of recent inferior or posterior MI.

   b. A **chest radiograph** may demonstrate pulmonary edema. In some patients, focal pulmonary edema may be seen in the right upper lobe because of flow directed at the right pulmonary veins.

   c. **Transthoracic echocardiography** with Doppler and color-flow imaging is the diagnostic modality of choice.

      (1) The **mitral valve leaflet is usually flail** with severe MR.

(2) Color Doppler imaging is useful in differentiating papillary muscle rupture with severe MR from VSR after MI.

d. **Transesophageal echocardiography. Transthoracic echo may underestimate the degree of acute MR.** Rapid equalization of pressure, resting tachycardia, and poor acoustic windows may contribute to this finding. An eccentric jet in this setting should lead to the performance of **transesophageal echocardiography** to quantify the severity and elucidate the mechanism of MR.

e. **PA catheterization.** Hemodynamic monitoring with a PA catheter may reveal **large V waves in the pulmonary capillary wedge pressure (PCWP) tracing**. However, patients with VSR may also have large V waves because of increased pulmonary venous return in a normal sized and normally compliant left atrium. Among patients with severe MR and reflected V waves in the PA tracing, oxygen saturation in the PA may be higher than that in the RA, complicating differentiation from VSR. There are two methods for differentiating MR from VSR with a right heart catheter:

(1) Prominent V waves in the PA tracing before the incisura are almost always associated with acute severe MR (**Figure 3.1**).

(2) Blood for oximetry is obtained with fluoroscopy to ensure sampling from the main PA rather than distal branches.

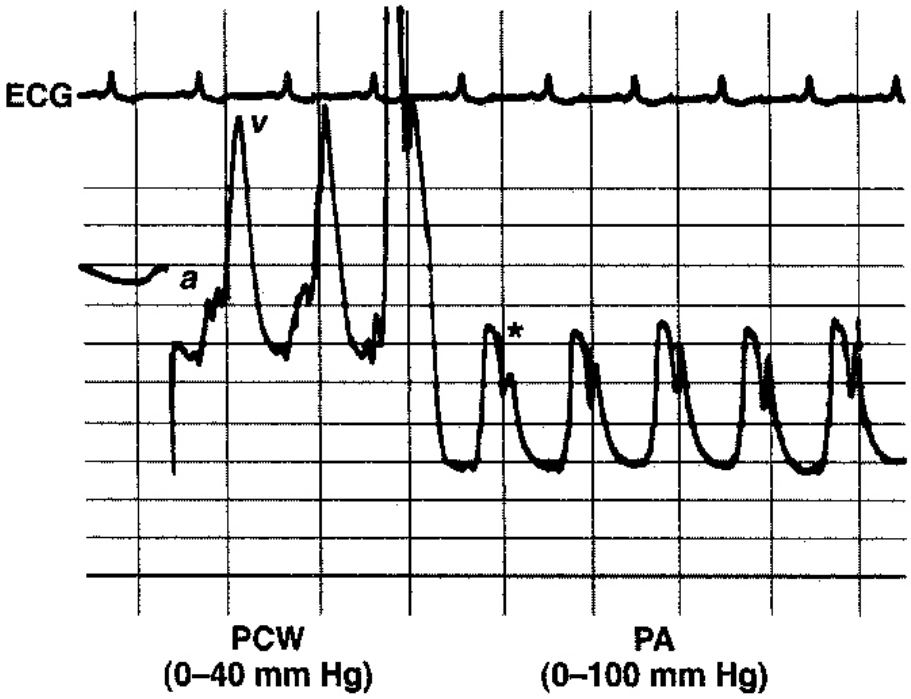

FIGURE 3.1 Giant V waves on the pulmonary capillary wedge (PCW) tracing can be transmitted to the pulmonary artery (PA) pressure, producing a notch (asterisk) on the PA downslope. ECG, electrocardiogram. (Adapted from Kern M. *The Cardiac Catheterization Handbook*. 2nd ed. Mosby-Year Book; 1991. Copyright © 1991 Elsevier. With permission.)

4. Therapy

a. Priority of therapy. Papillary muscle rupture should be identified early. Patients should receive **aggressive medical therapy** and consideration for **emergent surgical valve repair/replacement**. In select patients with adequate mean arterial pressure (MAP), **vasodilator therapy** is beneficial in the treatment of patients with acute MR. **Intravenous nitroprusside** decreases SVR, reduces regurgitant fraction, and increases stroke volume and cardiac output. Nitroprusside can be titrated to a MAP of 70 to 75 mm Hg.

b. Mechanical support

(1) IABP. Vasodilator therapy is contraindicated in patients with significant **hypotension**, and an IABP should be inserted promptly. An IABP decreases LV afterload,

improves coronary perfusion, and increases forward cardiac output. Patients with hypotension can often be given vasodilators after insertion of an IABP to improve hemodynamic values.

(2) **ECMO, left ventricular assist device (VAD), and percutaneous VAD (pVAD)** are also potential mechanical support devices that can be used as a bridge to surgical intervention.

(3) **Revascularization.** Coronary angiography should be performed before surgical correction, because concomitant revascularization is associated with improved short- and long-term mortality. Improvement in hemodynamic values and reduction in MR has been reported after PCI in patients with severe MR caused by papillary muscle dysfunction from ischemia but is unlikely to affect severity when the mechanical integrity of the valve is compromised. **PCI of the infarct-related artery has no role in this setting.**

c. **Surgical therapy with concomitant revascularization should be considered immediately for patients with papillary muscle rupture. When surgical risk is considered prohibitive, bridging with mechanical circulatory support devices to reverse end-organ injury, decongest the lungs, and plan for delayed definitive surgery should be considered.**

(1) The prognosis is very poor among patients treated medically. Even though perioperative mortality (20%-25%) is higher than that for elective surgical treatment, surgical therapy should be considered for every patient. Long-term survival in those with successful surgical correction is similar to those with an uncomplicated MI.

d. **Percutaneous therapy.** There is a growing experience and expanding role for transcatheter edge-to-edge mitral valve repair in select anatomically suitable patients who are at

prohibitive surgical risk. In select patients, optimal results can be achieved by avoiding the need for open heart surgery

C. Ventricular free wall rupture

1. **Clinical presentation.** Ventricular free wall rupture occurs in the setting of a transmural MI, and its incidence in the reperfusion era is <1%. While reperfusion decreases the overall risk of myocardial rupture, it may increase the risk of early free wall rupture due to myocardial hemorrhage into the infarct zones, especially in late presenters. Despite the low incidence of ventricular free wall rupture, it accounts for approximately **10% of observed mortality after MI**. In the SHOCK registry, in-hospital mortality associated with ventricular rupture was >60%. Rupture occurs in the first 5 days in 50% of patients and within 2 weeks in 90% of patients. Risk factors include advanced age, female sex, first MI, and poor coronary collateral vessels. The incidence of ventricular free wall rupture is lower in patients treated with primary PCI compared with thrombolytics.

   a. **Signs and symptoms**

      (1) **Acute course.** With acute rupture, patients develop tamponade, electromechanical dissociation, and sudden death. Sudden onset of chest pain with straining or coughing may suggest the onset of myocardial rupture.

      (2) **Subacute course.** Some patients may have a contained rupture and present subacutely with pain suggestive of pericarditis, nausea, and hypotension. Bedside echocardiography may reveal localized pericardial effusion or a pseudoaneurysm.

   b. **Physical findings.** Jugular venous distention, pulsus paradoxus, diminished heart sounds, and a pericardial rub suggest subacute rupture. New to-and-fro murmurs may be heard in patients with subacute rupture or pseudoaneurysm.

2. **Pathophysiology**

   a. Rupture most commonly occurs at the anterior or lateral wall, although any wall may be involved.

b. There are **three distinct types of ventricular free wall rupture** (**Figure 3.2**):

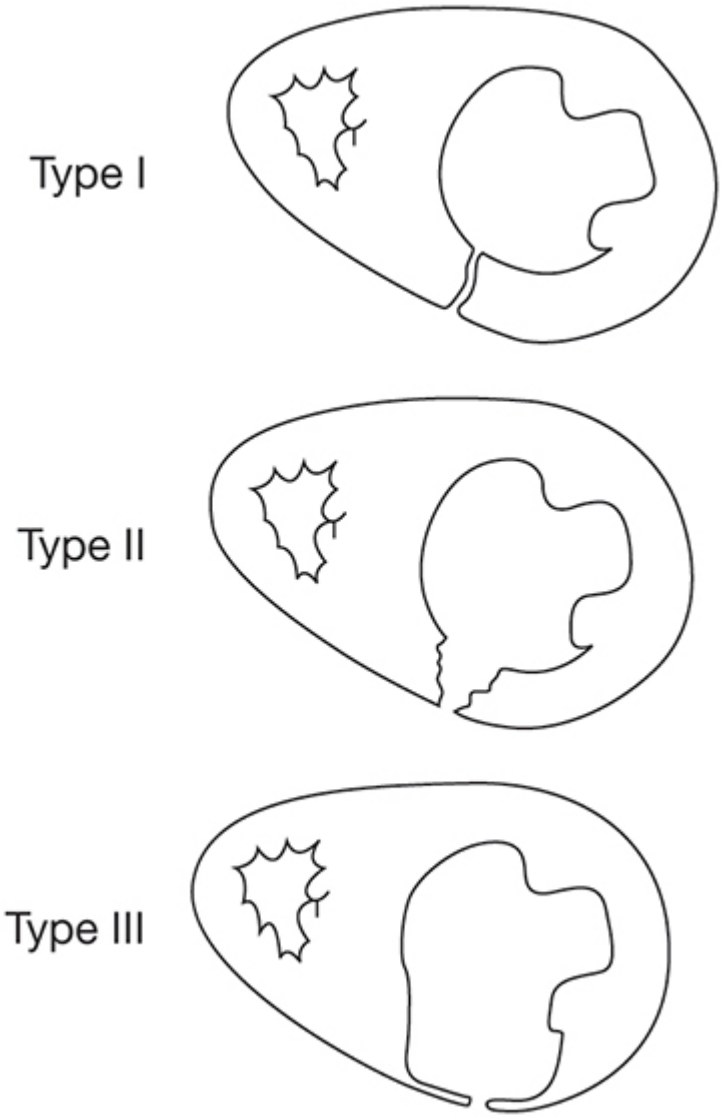

FIGURE 3.2 Morphologic classification of ventricular free wall rupture. (Reprinted from Becker AE, van Mantgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol*. 1975;3:349-358. Copyright © 1975 Elsevier. With permission.)

(1) Type I generally occurs within the first 24 hours and is a slit-like full-thickness rupture characterized by abrupt

onset of symptoms (this rupture type increases with thrombolytics).

(2) **Type II** occurs as a result of erosion of the myocardium at the site of infarction. The rupture progresses more slowly, and symptoms may be subacute.

(3) **Type III** occurs late and is characterized by expansion of the infarct zone with marked wall thinning and then rupture through the subsequent aneurysmal segment.

3. **Diagnostic testing.** There may not be time for diagnostic testing in the treatment of patients with acute ventricular free wall rupture.

   a. In addition to evidence for new MI, an **ECG** may show junctional or idioventricular rhythm, low-voltage complexes, and tall precordial T waves. A large proportion of patients have transient bradycardia immediately preceding rupture.

   b. **Transthoracic echocardiography** reveals findings of **cardiac tamponade** in patients with a subacute course. Visualization of ventricular free wall rupture may be improved with echocardiographic contrast agents.

   c. **Cardiac catheterization.** Hemodynamic evaluation with a PA catheter may reveal **equalization of the RA pressure, RV diastolic pressure, PA diastolic pressure, and PCWP**, consistent with tamponade. During left heart catheterization, analysis of the arterial waveform may reveal significant **respiratory variations in the systolic blood pressure (pulsus paradoxus)**. Ventriculography performed in the right anterior or left anterior oblique orientation may allow visualization of the rupture.

   d. **Cardiac MRI and CT** can be utilized in hemodynamically stable patients with contained rupture but are usually not available for critical decision-making.

4. **Therapy.** Reperfusion therapy has reduced the overall incidence of cardiac rupture.

a. **Priority of therapy**. The goal is to rapidly identify the problem and perform emergency surgical treatment.

b. **Medical therapy** has little role in the treatment of these patients, except for aggressive supportive care in anticipation of surgical correction.

c. **Percutaneous therapy**

(1) **In the setting of hemodynamic extremis, immediate pericardiocentesis** should be performed in patients with tamponade as soon as the diagnosis is made and while arrangements are being made for transport to the operating room.

(2) An indwelling catheter should be clamped and left in the pericardial cavity and connected to a drainage bag during transfer to the operating room so that continued decompression of the pericardial cavity with recurrent hemodynamic compromise can be achieved.

d. **Surgical therapy.** Emergency thoracotomy with surgical repair is the definitive therapy and is the **only chance for survival among patients with acute ventricular free wall rupture**.

D. Ventricular pseudoaneurysm (ie, contained rupture)

1. **Clinical presentation.** Ventricular pseudoaneurysm is **more likely to occur with inferior MI than with anterior MI**.

a. **Signs and symptoms.** Pseudoaneurysms may remain clinically silent and be discovered during routine investigation; however, patients may present with chest pain, dyspnea, recurrent tachyarrhythmia, and sudden cardiac death.

b. **Physical findings.** Systolic, diastolic, or to-and-fro murmurs related to flow of blood across the narrow neck of the pseudoaneurysm during systole and diastole may be appreciated.

2. **Pathophysiology.** Ventricular pseudoaneurysm is caused by contained rupture of the LV free wall.

a. The **outer walls of a true ventricular aneurysm are formed by infarcted myocardium and scar**, whereas the **outer walls**

of a pseudoaneurysm are formed by the pericardium and mural thrombus. A pseudoaneurysm may remain small or undergo progressive enlargement.

b. Ventricular pseudoaneurysms communicate with the body of the ventricle through a **narrow neck, the diameter of which is typically <50% of the diameter of the fundus**.

3. Diagnostic testing

a. A **chest radiograph** may show cardiomegaly with an abnormal bulge on the cardiac border.

b. An **ECG** may demonstrate persistent ST-segment elevation, as with true aneurysms.

c. Ventriculography is a reliable method of diagnosis.

d. Echocardiography, cardiac MRI, and cardiac CT may be utilized in evaluation as well. Echocardiographic contrast agents may increase the diagnostic accuracy.

4. Therapy. Spontaneous rupture may occur without warning in approximately one-third of patients with a pseudoaneurysm. **Surgical resection is recommended for patients with or without symptoms, regardless of the size of the pseudoaneurysm, to minimize the risk of death.** Case reports have demonstrated the potential feasibility of percutaneous repair in high surgical risk patients with appropriate anatomy.

E. Ventricular aneurysm

1. Clinical presentation. The incidence of ventricular aneurysm after MI in the reperfusion era is approximately <5% and occurs **more commonly with anterior MI than with inferior or posterior MI**.

a. Signs and symptoms

(1) Acute aneurysm. Acute development of a large ventricular aneurysm can result in severe LV dysfunction and cardiogenic shock. Patients with an acute MI that involves the apex of the LV, particularly those with transmural anteroapical infarcts, are at greatest risk. Acute aneurysms expand during systole. This expansion wastes contractile

energy generated by normal myocardium and puts the entire ventricle at a mechanical disadvantage.

(2) **Chronic aneurysms** persist >6 weeks after MI, are less compliant than acute aneurysms, and rarely expand during systole. Patients with chronic aneurysms may experience heart failure, ventricular arrhythmias, mural thrombus, and systemic embolism, but frequently are asymptomatic.

b. **Physical findings.** A dyskinetic segment of the ventricle may be apparent during inspection or may be felt during palpation. The apical impulse may be displaced to the left of the mid-clavicular line because of cardiac enlargement. An S_3 or S_4 gallop may be appreciated due to LV dilation and stiffening. A systolic murmur of MR may occur due to changes in LV geometry.

2. **Pathophysiology.** Infarct expansion and progressive LV dilation are consequences of absent or ineffective coronary reperfusion. The aneurysmal segment initially consists of necrotic tissue and is later replaced by fibrous scar tissue.

3. **Diagnostic testing**

a. **Electrocardiogram**

(1) **Acute aneurysm.** The ECG reveals evidence of ST-segment elevation MI, which may persist despite evidence of reperfusion.

(2) **Chronic aneurysm.** ST-segment elevation that persists >6 weeks occurs in patients with chronic ventricular aneurysms.

b. **Chest radiography** may reveal a localized bulge in the cardiac silhouette.

c. **Transthoracic echocardiography** is the diagnostic **test of choice** and accurately depicts the aneurysmal segment. It may also reveal the presence of a mural thrombus. Echocardiography is useful in differentiating a true aneurysm from a pseudoaneurysm. Typically, true aneurysms have a wide

neck, whereas pseudoaneurysms have a narrow neck in relation to the diameter of the aneurysm.

d. Cardiac **MRI and CT** may also be utilized to characterize ventricular aneurysm and better detect the presence of thrombus.

4. Therapy

a. Medical therapy

(1) Acute aneurysm. LV failure caused by acute aneurysm is managed with **intravenous vasodilators** and **IABP** therapy. **Angiotensin-converting enzyme (ACE) inhibitors** have been shown to reduce infarct expansion and progressive LV remodeling. Because infarct expansion starts early, ACE inhibitors should be initiated within the first 24 hours of the onset of acute MI if blood pressure allows.

(2) Chronic aneurysm. Heart failure associated with chronic aneurysm formation is managed with afterload reduction, namely, with ACE inhibitors.

(3) Anticoagulation. Oral anticoagulation should be prescribed to patients found to have an LV mural thrombus. See below for discussion.

b. Surgical therapy. Patients with refractory heart failure and/or refractory ventricular arrhythmias may be considered for aneurysmectomy. Surgical resection may be followed by conventional closure or newer techniques (eg, inverted T closure and endocardial patch) to maintain LV geometry. Because of the high surgical risk of these patients, novel percutaneous devices are currently under investigation.

F. LV failure and cardiogenic shock. Refer to Chapter 4 addressing this condition.

G. RV failure. Mild RV dysfunction is common after **MI of the inferior or inferoposterior wall**; however, hemodynamically significant RV impairment occurs in only 10% of patients. The **proximal right coronary artery** (RCA) is commonly involved. Extensive,

irreversible RV damage is unusual because the RV has lower oxygen requirements because of its smaller muscle mass, is perfused during systole and diastole, and often receives extensive left-to-right collateral blood flow. Restoring patency of the infarct-related artery usually results in restoration of RV function within 48 to 72 hours.

1. Clinical presentation

a. Signs and symptoms. The triad of **hypotension, jugular venous distention, and clear lung fields** is highly specific (but has poor sensitivity) for RV infarction. Patients with severe RV failure have symptoms of a low cardiac output state, including diaphoresis; cool, clammy extremities; and altered mental status. Patients often are hypotensive and oliguric. The use of **nitrates or beta-blockers during routine MI treatment may precipitate profound hypotension** and provides the first clue of RV involvement. **Table 3.2** lists causes of hypotension among patients with inferior wall MI.

TABLE 3.2 Causes of Hypotension in Patients Presenting With Inferior Myocardial Infarction

Right ventricular infarction
Left ventricular failure
Bradyarrhythmia
Acute severe mitral regurgitation
Ventricular septal rupture
Bezold-Jarisch reflex

b. Physical findings. Patients with RV failure without concomitant LV failure may have elevated jugular venous pressure (JVP) and an RV S_3 with clear lungs. The combination of JVP >8 cm H_2O and **Kussmaul sign** (ie, failure of JVP to decrease with inspiration) is sensitive and specific for severe RV failure. Elevated right-sided pressures can occasionally result in **right-to-left shunting** through a patent foramen ovale and manifest as desaturation. This should be considered in

patients with RV infarction and hypoxia. **Table 3.3** lists the clinical findings associated with an RV infarction.

TABLE 3.3 Clinical Findings Associated With Right Ventricular Infarction

Hypotension
Elevated jugular venous pressure
Kussmaul sign
Abnormal jugular venous pressure pattern (y ≥ x descent)
Tricuspid regurgitation
Right-sided S_3 and S_4
Pulsus paradoxus
High-grade atrioventricular block

2. **Pathophysiology.** RV involvement depends on the location of the RCA occlusion. Marked dysfunction occurs only if occlusion is proximal to the acute marginal branch. The degree of RV involvement also depends on the presence of left-to-right collateralization and the extent of diastolic reverse perfusion through the Thebesian veins.
3. **Diagnostic testing**
   a. An **ECG** usually shows **inferior ST-segment elevation**. ST-segment elevation in **V_4R** in the setting of suspected RV infarction has a positive predictive value of 80%. RV infarction is also suggested by ST-segment elevation that is greater in lead III than in lead II. ST-segment elevation exceeding 1 mm may be seen in V_1 and occasionally in V_2 and V_3 (**Figure 3.3**).

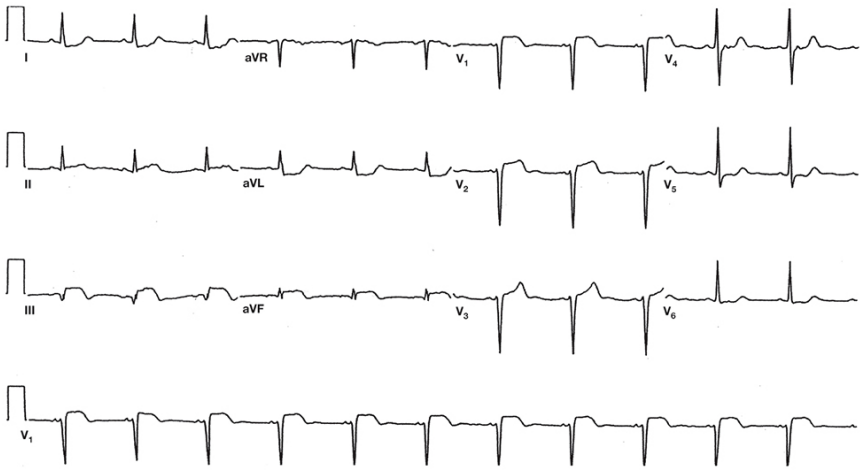

FIGURE 3.3 Electrocardiogram demonstrating acute inferior myocardial infarction with right ventricular involvement.

b. A **chest radiograph** is usually normal, and there is no evidence of pulmonary congestion.

c. Transthoracic echocardiography is the diagnostic **study of choice** for RV infarction. It may demonstrate RV dilation and severe RV dysfunction and usually shows LV inferior wall dysfunction. It is also useful in differentiating RV infarction from other syndromes that can mimic it, such as cardiac tamponade.

d. PA catheterization. Hemodynamic monitoring with a PA catheter usually reveals **high RA pressures with low PCWP**. Acute RV failure results in underfilling of the LV and a low cardiac output state. The PCWP is usually low unless concomitant, severe LV dysfunction is present. In some patients, RV dilation can cause decreased LV performance resulting from ventricular interdependence. As the RV dilates, the septum flattens or bows into the LV and restricts ventricular filling. RA pressure >10 mm Hg with an RA pressure to PCWP ratio ≥0.8 strongly suggests RV infarction.

4. Therapy

a. Medical therapy

(1) Fluid administration. Management of RV infarction involves volume loading to increase preload and cardiac

output. Fluid boluses up to a liter may be considered with monitoring of hemodynamic status. Overzealous fluid administration in a patient may result in marked RV dilation with a shift in the interventricular septum that can impede LV filling and further decrease LV preload. A central venous pressure of approximately 15 mm Hg may serve as a target.

(2) **Inotropes.** When volume loading fails to increase cardiac output, the use of inotropes is indicated. Administration of **dobutamine** will augment RV contractility and increases cardiac output.

b. Percutaneous therapy

(1) Patients who undergo successful **reperfusion** of the infarct-related artery have improved RV function and decreased 30-day mortality rates. This is ideally achieved by performing immediate primary PCI.

(2) **AV sequential pacing** may markedly improve hemodynamics in a patient with RV infarction and bradyarrhythmia or loss of sinus rhythm. **A longer AV delay of approximately 200 ms and a heart rate of 80 to 90 beats/min are usually optimal for these patients.**

(3) In a patient with refractory shock, an IABP may be considered. When available, support with a temporary RV support device like an RP Impella or a Protek Duo should be considered.

H. Dynamic left ventricular outflow tract (LVOT) obstruction.

Dynamic LVOT obstruction is an **uncommon complication** of acute anterior MI. Although this complication has been cited only in case reports, it may be an underappreciated and underreported complication.

1. Clinical presentation

a. Signs and symptoms. Patients may have respiratory distress, diaphoresis, and cool, clammy extremities in addition to the typical signs and symptoms of acute MI. Patients with severe

obstruction may appear to be in cardiogenic shock, with severe orthopnea, dyspnea, and oliguria in addition to altered mental status from cerebral hypoperfusion.

b. **Physical findings** frequently include a new systolic ejection murmur heard best at the left upper sternal border with radiation to the neck. A new systolic murmur can be heard at the apex with radiation to the axilla, as a result of systolic anterior motion (SAM) of the mitral leaflet. An S_3 gallop, pulmonary rales, hypotension, and tachycardia may also occur.

2. **Pathophysiology.** The dynamic LVOT obstruction that may occur as a complication of acute anterior MI is related to compensatory hyperkinesis of the basal and mid-segments of the LV. The increased contractile force of these regions decreases the cross-sectional area of the LVOT. The resultant increase in the velocity of blood through the outflow tract can produce decreased pressure below the mitral valve and cause anterior mitral valve leaflet displacement toward the septum (ie, Venturi effect). This results in further outflow tract obstruction and MR. It has been postulated that this complication can play a role in ventricular free wall rupture. LVOT obstruction leads to increased end-systolic intraventricular pressure, which leads to increased stress of the weakened, necrotic infarcted zone.

3. **Diagnostic testing. Transthoracic echocardiography** is the diagnostic test of choice and helps evaluate the hyperkinetic segments, the LVOT obstruction, and the presence of SAM of the mitral leaflet.

4. **Medical therapy** is focused on decreasing myocardial contractility and heart rate while expanding intravascular volume and increasing afterload modestly.

   a. **Beta-blockers** should be added judiciously and with careful monitoring of the heart rate, blood pressure, and cardiac output.

   b. **Intravenous hydration** should be initiated with several small (250 mL) boluses of normal saline to increase preload and decrease LVOT obstruction and SAM. The patient's

hemodynamic and respiratory status should be monitored closely during this therapeutic intervention.

III. ARRHYTHMIC COMPLICATIONS. Arrhythmias are a common complication after acute MI and are associated with significant mortality. Refer to the dedicated chapters for further discussion.

IV. EMBOLIC COMPLICATIONS. The contemporary incidence of LV mural thrombus after acute MI is approximately 1% to 2%. The incidence of mural thrombus in patients with a **large anterior wall MI** may increase to approximately 10%, especially in the absence of timely reperfusion. Other factors associated with LV mural thrombus include **decreased LV ejection fraction, wall motion abnormalities, and LV aneurysm**.

A. Clinical presentation

1. **Signs and symptoms.** The most common clinical presentation of an embolic complication is stroke, although patients may have limb ischemia, renal infarction, and intestinal ischemia. Most episodes of systemic embolization occur in the first 2 weeks after acute MI.
2. **Physical findings.** The physical findings depend on the site of embolism.
   - **a.** Patients with stroke present with neurologic deficits.
   - **b.** Embolism to the peripheral circulation results in limb ischemia and cold, pulseless, and painful extremities.
   - **c.** Renal infarctions may cause hematuria and flank pain.
   - **d.** Mesenteric ischemia causes abdominal pain and bloody diarrhea.
3. **Diagnostic testing**
   - **a. Transthoracic echocardiography** is the initial diagnostic test of choice to evaluate for LV mural thrombus. Echocardiographic contrast agents may increase the diagnostic accuracy.
   - **b. Cardiac MRI** has similar specificity but is more sensitive than echocardiography in the detection of an LV mural thrombus.

B. Therapy with anticoagulation is recommended in the early setting of a ventricular thrombus associated with an acute MI. **Vitamin K antagonists** reduce the rate of embolization. Intravenous heparin or low-molecular-weight heparin can be used in the acute setting until therapeutic on warfarin. Goal international normalized ratio is 2:3. Anticoagulation does not necessarily resolve the thrombus, and it may become calcified and laminated over time. Controversy exists on the duration of anticoagulation necessary if there is persistence of the thrombus beyond 3 to 6 months.

C. Novel anticoagulants such as dabigatran, rivaroxaban, and apixaban have not been studied in randomized trials in this population and are **not currently approved** for this indication.

D. For those requiring dual antiplatelet, care must be taken when initiating "**triple therapy.**" **Bleeding risks must be considered** in each individual patient. Strategies, such as early discontinuation of aspirin, have been proven beneficial for other indications, but whether that advantage extends to patients with LV thrombus and embolic events following MI is unknown.

V. INFLAMMATORY COMPLICATIONS

A. Early pericarditis. The incidence of pericarditis has decreased in the reperfusion era. Cardiac MRI studies, however, suggest that it is underdiagnosed as it may be asymptomatic, or masked by the ECG changes and symptoms that accompany acute MI.

1. Clinical presentation. Early pericarditis occurs in patients with transmural MI. A transient pericardial friction rub may be audible in some patients before symptoms become prominent.

a. Signs and symptoms

(1) Patients report progressive, severe chest pain that lasts for hours. The **pain is postural**: worse when the patient is supine and alleviated if the patient sits up and leans forward. The pain is usually pleuritic in nature and is worsened with deep inspiration, coughing, and swallowing.

(2) **Radiation of pain to the trapezius ridge** is nearly pathognomonic for acute pericarditis and does not occur in patients with ischemic pain. The pain may also radiate to the neck and less frequently to the arm or back.

b. Physical findings. The presence of a pericardial friction rub is pathognomonic for acute pericarditis; however, it can be evanescent.

(1) The rub is best heard at the left lower sternal edge with the diaphragm of the stethoscope.

(2) The rub has three components: one component each in atrial systole, ventricular systole, and ventricular diastole. In about 30% of patients, the rub is biphasic, and in 10%, it is uniphasic.

(3) The development of pericardial effusion may cause fluctuations in the intensity of the rub, although the rub may still be heard despite substantial pericardial effusion.

2. Etiology and pathophysiology. Pericarditis typically results from an area of localized pericardial inflammation overlying the infarcted myocardium. The inflammation is fibrinous in nature. The development of an evanescent pericardial rub correlates with a larger infarct and hemodynamic derangements.

3. Diagnostic testing

a. An **ECG** is important in the diagnosis of pericarditis; however, evolving electrocardiographic changes may make the diagnosis difficult for patients who have had MI. Unlike ischemia, in which the changes are limited to a particular territory, pericarditis produces generalized electrocardiographic changes.

(1) The ST-segment elevation seen with pericarditis is a concave upward or saddle-shaped curve.

(2) In pericarditis, T waves become inverted after the ST segment becomes isoelectric, whereas in acute MI, T waves may become inverted when the ST segment is still elevated.

(3) Four phases of electrocardiographic abnormality have been described in association with pericarditis (**Table 3.4**).

TABLE 3.4	Electrocardiographic Changes of Pericarditis
Stage I	ST elevation, upright T waves
Stage II	ST elevation resolves, upright to flat T waves
Stage III	ST isoelectric, inverted T waves
Stage IV	ST isoelectric, upright T waves

b. Echocardiography may reveal pericardial effusion, which strongly suggests pericarditis, although the absence of effusion does not rule out the diagnosis. When suspected, an MRI may be confirmatory with enhancement of the involved pericardium noted on gadolinium imaging.

4. Therapy

a. Aspirin is used to manage post-MI pericarditis, and doses as high as 650 mg every 4 to 6 hours may be needed (class I recommendation).

b. Nonsteroidal anti-inflammatory agents and corticosteroids should not be used to treat these patients (class III recommendation). These agents may interfere with myocardial healing and contribute to infarct expansion.

c. Colchicine may be beneficial in those when aspirin is not effective. Colchicine 0.6 mg every 12 hours plus conventional therapy with aspirin decrease symptom recurrence in patients with idiopathic pericarditis.

B. Late pericarditis (ie, Dressler syndrome). This is rarely seen and occurs 1 to 8 weeks after MI. The pathogenesis is unknown, but an autoimmune mechanism has been suggested.

1. Clinical presentation. Patients may present with chest discomfort that suggests pericarditis, pleuritic pain, arthralgia, malaise, fever, pericardial friction rub, elevated leukocyte count, and an elevated sedimentation rate. Echocardiography may reveal a pericardial effusion.

2. **Therapy** is similar to that for early post-MI pericarditis: aspirin, colchicine, and avoidance of nonsteroidal anti-inflammatory drugs and corticosteroids. However, if >4 weeks have elapsed since the MI, nonsteroidal anti-inflammatory agents may be indicated for severe symptoms.

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CHAPTER 4

Cardiogenic Shock Complicating Acute Myocardial Infarction

Weili Zheng and Ran Lee

I. INTRODUCTION. Cardiogenic shock (CS) occurs with **primary failure of the left (LV) and/or right ventricular (RV) function, leading to low cardiac output (CO) and resultant tissue malperfusion**. The causes of CS are heterogeneous, with decompensated heart failure (HF-CS) and acute myocardial infarction (AMI-CS) as the most common. AMI-CS complicates 5% to 8% of ST-elevation myocardial infarction (STEMI) and 2.5% of non–ST-elevation acute coronary syndrome (NSTE-ACS) cases in the modern percutaneous coronary intervention (PCI) era. Classically, CS manifests with hypotension accompanied by signs of hypoperfusion, including, but not limited to, cold and clammy peripheries, oliguria, and altered mentation. Typically, invasive hemodynamics in CS reveal a low cardiac index (CI) (<2.2 L/min/m^2), adequate or elevated LV and/or RV filling pressures, and significant heterogeneity in systemic vascular resistance that depends on the degree of vasodilatory inflammatory response. There have been recent efforts to define, risk-stratify, and hemodynamically profile CS to standardize and improve care. Emphasis is placed on early recognition and staging of CS to expedite treatment in order to improve outcomes.

II. CLINICAL PRESENTATION. Patients may present anywhere along a spectrum of severity, and mortality increases exponentially with worsening clinical presentation, hemodynamic and metabolic derangements (**Figure 4.1**). For AMI-CS, onset is typically within the first 24 hours of the inciting event. Though signs of congestion are common, CS can occur with deficits in perfusion only. As such, attention should be paid to the following signs and symptoms:

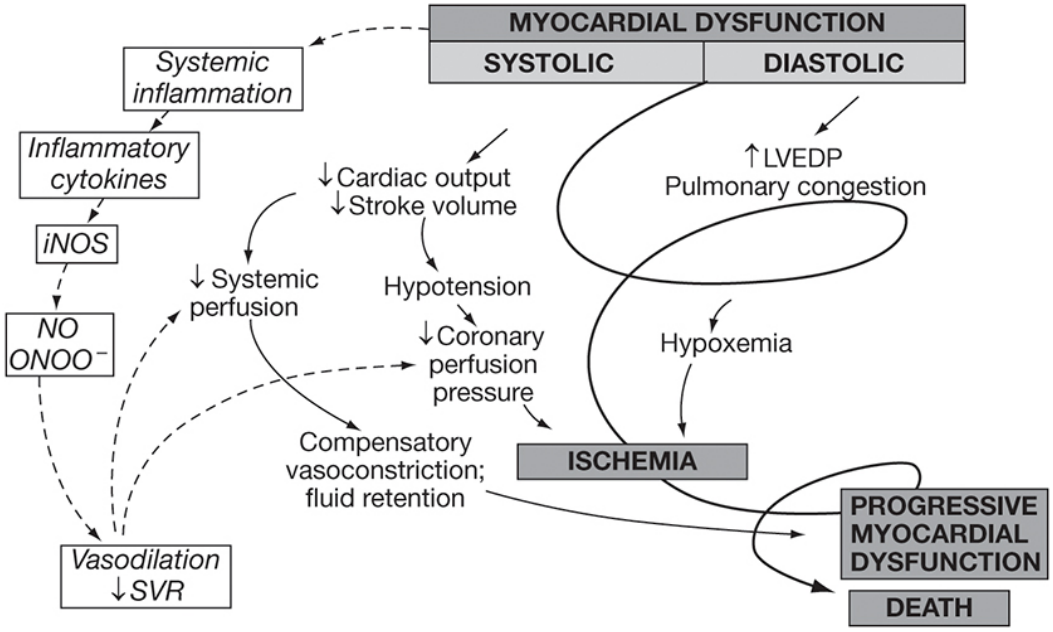

FIGURE 4.1 Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. iNOS, inducible nitric oxide synthase; LVEDP, left ventricular end-diastolic pressure; NO, nitric oxide; $ONOO^-$, peroxynitrite; SVR, systemic vascular resistance. (From Hollenberg SM. Pathophysiology. In: Hochman JS, Ohman EM, eds. *Cardiogenic Shock*. Wiley-Blackwell; 2009. Copyright © 2009 American Heart Association. Reprinted by permission of John Wiley & Sons, Inc.)

A. Early signs of shock include **diminished urine output, compensatory tachycardia, and** tachypnea. Mental status of the patient is usually intact, though anxiety may be present due to fatigue and malaise. Nausea and/or dyspepsia commonly operate as bellwether symptoms of early CS.

B. Late signs of CS include **confusion and lethargy, respiratory distress, and cold and clammy extremities.**

C. Signs of congestion include rales or diminished breath sounds, elevated jugular venous pressure (JVP), S_3 on cardiac auscultation, abdominal distention, and pitting lower extremity edema. Those with predominant RV failure often present without respiratory symptoms.

Note that findings may be subtle in the early stages of CS—it is not unusual for patients to present with borderline blood pressure with low pulse pressures and tachycardia with an absence of overt symptoms.

III. DIAGNOSTIC STUDIES

A. Key diagnostic studies

1. Comprehensive transthoracic echocardiography (TTE) in all patients with CS is warranted. TTE is a key diagnostic tool for the initial assessment of ventricular function, helping to determine the extent of myocardial injury and

identify the primary cause of shock. This includes conditions such as RV failure, severe valvular regurgitation, pericardial effusion, or ventricular septal rupture (VSR), all of which can be complications of AMI. TTE is also an effective tool to assess for interval changes after initial intervention. If TTE is poor quality due to impairment of acoustic windows, transesophageal echocardiography (TEE) should be considered to rule out structural causes for CS, including mechanical complications of AMI that would require immediate surgical intervention.

2. **When suspicion for CS is high, we strongly advocate for invasive hemodynamic monitoring** with an **arterial line** and **pulmonary artery (PA) catheter (PAC).** Despite negative results with PAC use in acute decompensated HF, no clinical trial has been conducted on the PAC use in CS. Moreover, an increasing body of evidence links PAC use to improved outcomes in CS. Invasive hemodynamics are essential to assess filling pressures (eg, central venous pressure [CVP], pulmonary artery wedge pressure [PCW]), perfusion status (eg, CO/CI and cardiac power output [CPO]), as well as differentiate CS phenotype (ie, pulmonary artery pressure index [PAPi] <1.0, CVP/PCW <0.86 in post-MI RV failure). This information may rapidly guide selection of temporary mechanical circulatory support (tMCS), if necessary. Perhaps most importantly, a PAC allows for serial assessment of hemodynamic parameters to evaluate the efficacy of pharmacologic and/or mechanical intervention. Of note, **proper use of a PAC is crucial for fidelity of measurements to guide care**. Meticulous attention should be paid to zeroing and positioning transducer height at the level of right atrium. Signal quality must be carefully evaluated by a well-trained clinician to identify improper waveform due to damping and other artifact, especially when obtaining wedge pressures. Measurements should take place at end-expiration, regardless of the type of ventilation.

B. Additional studies

1. **Laboratory studies. Serum lactate, liver function tests, and blood urea nitrogen (BUN)/creatinine** are recommended to **assess degree of end-organ perfusion**, which **plays a pivotal role in deciding urgency of intervention**. Lactate may be trended serially to document the efficacy of intervention and resolution to end-organ malperfusion, as complete lactate clearance within 24 hours has been shown to be associated with improved outcomes. It should be noted that BUN/creatinine are often lagging indicators, manifesting several hours after the onset of acute tubular necrosis and resultant urine output decrease. Electrolyte abnormalities (calcium, potassium, magnesium) should be aggressively corrected to prevent additional risk of arrhythmias. Hematology and coagulopathy panels may reveal low hemoglobin, platelets, or elevated international normalized ratio (INR), which may require caution when considering implementation of tMCS.
2. **Electrocardiogram (ECG).** Patients with AMI-CS with resultant LV failure usually have extensive electrocardiographic abnormalities related to MI,

depending on the time from the index event (ST-segment changes, Q waves, conduction abnormalities). Otherwise, ECGs changes can be nonspecific, but can provide clues if there is concern for arrhythmia (eg, chronotropic incompetence, atrial fibrillation with rapid ventricular rate, ventricular tachycardia).

3. **Chest radiography** may reveal pulmonary congestion and enlarged cardiac silhouette and is necessary to ensure proper placement of PAC and tMCS devices.

IV. PROGNOSIS. Recently, professional associations including the Society for Cardiovascular Angiography and Interventions (SCAI), American Heart Association/American College of Cardiology (AHA/ACC), Society of Critical Care Medicine (SCCM), and Society of Thoracic Surgeons (STS) have adopted the following classifications for CS for the purposes of risk stratification and prognostication. **Table 4.1** provides a framework for identifying CS severity. The more severe the shock, the worse the prognosis. Emphasis should be placed on early hemodynamic and laboratory evaluation for those in early stages (SCAI B and SCAI C) prior to the onset of overt hypotension to implement treatment to reverse the course.

TABLE 4.1 SCAI Classifications of Cardiogenic Shock

Cardiogenic Shock Stage	Clinical Manifestations	Noninvasive Hemodynamics (w/o Intervention)	Invasive Hemodynamics	Labs	Interventions
A: "At risk"	No symptoms	Normotensive Nontachycardic	CI >2.5 L/min/m^2 MVO_2 >65%	Normal lactate No evidence of end-organ malperfusion +/− NT-proBNP elevation	None
B: "Preshock"	Rales Elevated JVP S_3	HR >100 SBP <90 OR SBP drop >30 from baseline HR: SBP ratio >1	Variable	Normal lactate No evidence of end-organ malperfusion NT-proBNP elevation	None
C: "Classic"	AMS Cold/clammy Rales Dusky Oliguria	Same as stage B, but requiring intervention to maintain perfusion	CI <2.2 L/min/m^2 MVO_2 <65% CPO <0.6	Lactate >2 >0.3 Increase in Cr OR 50% decrease in GFR Elevated LFTs	AT LEAST: 1 MCS device OR 1 vasoactive medication to maintain perfusion
D: "Deteriorating"	Same as stage C	Same as stage C, despite intervention	Same as stage C, despite intervention	Lactate >2 persistently, despite	AT LEAST: 1+ MCS device AND 1+

Cardiogenic Shock Stage	Clinical Manifestations	Noninvasive Hemodynamics (w/o Intervention)	Invasive Hemodynamics	Labs	Interventions
				initial intervention	vasoactive medication to maintain perfusion
E: "In extremis"	Multiorgan dysfunction, impending cardiac arrest	Hypotension despite maximal support, unconscious	CI ≪2.2 L/min/m^2 CPO ≪0.6	Lactate >8 pH <7.2 AND Renal and hepatic dysfunction	CPR, ECMO, 2+ MCS devices and 2+ vasoactive medications

AMS, altered mental status; CI, cardiac index; CPO, cardiac power output; CPR, cardiopulmonary resuscitation; Cr, creatine; ECMO, extracorporeal membrane oxygenation; GFR, glomerular filtration rate; HR, heart rate; JVP, jugular venous pressure, LFT, liver function test; MCS, mechanical circulatory support; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; SCAI, Society for Cardiovascular Angiography and Interventions.

In addition to assessing severity, phenotyping CS profiles by perfusion, congestion, and ventricles involved is recommended. Late and extreme presentations warrant immediate intervention, and rapid consultation with a multidisciplinary team for possible tMCS. CS phenotyping does inform prognosis, as patients with biventricular failure have been shown to have worse outcomes. In addition, the presence of RV failure plays a role in the decision of MCS for RV, that is, extracorporeal membrane oxygenation (ECMO) or temporary right-sided ventricular assist devices (RVADs), such as Protek Duo or Impella RP.

With regard to AMI-CS, despite advancements in coronary reperfusion, **contemporary mortality rates of AMI-CS remain high at 40% to 70%**. Prior infarct, older age, female sex, diabetes, and anterior infarction are risk factors for the development of CS after MI. Mortality with CS has decreased significantly in younger patients undergoing primary PCI (30%-40%) but remains high (60%-70%) among the older patients (age >75 years), regardless of revascularization. The only proven intervention to definitively reduce mortality in this setting is **early revascularization**.

V. ETIOLOGY AND PATHOGENESIS

A. Etiology. **Table 4.2** outlines the various etiologies of CS. HF-CS consists of acute-on-chronic decompensated HF and de novo myocardial failure, and overall has surpassed AMI-CS in incidence. AMI-CS usually occurs in the setting of an extensive MI, affecting at least 40% of the LV myocardium, according to autopsy studies. Up to 40% of patients have a history of prior MI. Patients typically have significant **left main** or **severe three-vessel coronary artery disease (CAD)** (16% and 53%, respectively, in the SHOCK trial), and the majority have proximal involvement of the **left anterior descending artery (LAD)**, though occasionally, in

the setting of an ischemic cardiomyopathy, a small acute MI in a nonanterior location may precipitate shock. In addition, severe valvular disease, incessant arrhythmias, and other conditions such as tamponade and massive pulmonary embolism (PE) also need to be ruled out.

TABLE 4.2 Etiologies of Cardiogenic Shock

Myocardial	Valvular	Electrical	Obstructive	Systemic
Myocardial infarction +/− complications	Valvular stenosis	Atrial tachyarrhythmias	Tamponade	Toxins
Nonischemic CM (all causes)	Valvular regurgitation	Ventricular tachyarrhythmia	Constriction	Hypothermia/drowning
Acute-on-chronic HF	Endocarditis	Conduction abnormalities and bradyarrhythmia	Pulmonary embolism	Endocrinopathy
Myocarditis/inflammatory myopathies	Prosthetic valve disorders			Autoimmune
Post–cardiotomy shock				
Sepsis-induced CM				
Outflow tract obstruction				

CM, cardiomyopathy; HF, heart failure.

B. Pathophysiology. Ineffective LV stroke volume results in hypotension with compensatory tachycardia. In the setting of extensive CAD, hypotension and rising LV end-diastolic pressures compromise coronary perfusion and precipitate ischemia in both the infarct-related artery territory and the rest of the myocardium. As a result, a vicious cycle ensues, culminating in circulatory collapse, irreversible end-organ injury, and death. Hypotension typically leads to compensatory peripheral vasoconstriction and an increase in systemic vascular resistance. However, many patients with CS were noted to have a low systemic resistance, noted as hemometabolic shock. This vasodilatory response, often occurring later in the shock process, is likely a result of significant end-organ injury, which, in turn, induces a systemic inflammatory response–like syndrome and resultant vasodilatory or mixed hemodynamic picture. Up to one-fifth of patients with CS may present in this manner.

VI. MANAGEMENT. In CS, immediate management should fulfill the dual mandate of **improving end-organ perfusion** and **offloading myocardial work**. The purpose of immediate management is the stabilization of patient in order to treat underlying physiology (ie, AMI-CS, severe valvular disease, refractory tachyarrhythmias, decompensated cardiomyopathy). In severe cases, the first goal, preserving organ

function, may involve correcting hypotension (ie, with vasopressors) initially, at the expense of increased cardiac demand. For SCAI stage C or greater, consideration should be given to utilizing mechanical support devices. Specifically, patients in SCAI stage D or greater (ie, deteriorating or in extremis) may warrant upfront aggressive measures, though there are no explicit studies with regard to the timing of MCS intervention on survival. Concurrently, the underlying pathophysiology (ie, MI, tachyarrhythmia, volume overload) must be addressed in an expedited manner.

A. For AMI-CS, successful early revascularization limits infarct size and translates into improved mortality. Thus, every effort should be made to facilitate prompt angiography to define coronary anatomy in the patient with acute MI and CS. In the SHOCK trial, early revascularization saved **13 lives per 100 treated at 1 year** compared with a strategy of medical stabilization and delayed revascularization. This strategy should be strongly considered in all patients aged <75 years in the absence of contraindications; select older patients with good premorbid functional status also derived a similar benefit from this approach. PCI is the dominant and preferred modality of revascularization for occluded culprit vessels, but in select cases of multivessel disease, surgery can be considered, guided mainly by the extent and location of disease and presence of other surgical indications, such as concomitant structural heart disease.

1. **Primary PCI** of the presumed culprit vessel remains the preferred method of revascularization in shock. However, in contrast to STEMI without CS, the CULPRIT SHOCK trial showed that in multivessel CAD and STEMI with CS, PCI of additional non–infarct-related arteries during the index procedure was associated with increased mortality compared with PCI of culprit vessel alone.
2. In AMI-CS with multivessel disease, in the absence of an occluded culprit vessel on coronary angiogram (ie, TIMI 3 flow), implementation of **percutaneous MCS bridge to coronary artery bypass grafting** (CABG) as the revascularization strategy can be considered in select patients.
3. In STEMI with CS and a non-LAD culprit vessel in the setting of multivessel disease, immediate PCI is warranted for the culprit vessel, but a Heart Team discussion to discuss CABG using intravenous (IV) antiplatelet bridge may be considered in expert centers.
4. **Fibrinolysis** should be administered to patients who present initially with STEMI, including those in CS, to a facility **without PCI capability and are unable to transfer to a PCI-capable facility in <120 minutes**, in the absence of contraindications to lytics. Fibrinolytics should preferably be administered within 3 hours from symptom onset but may be acceptable up to 12 hours. A reduction in mortality was observed in several studies using this approach including a post hoc analysis from the SHOCK trial. Following the administration of fibrinolysis, patients require transport to a PCI-capable center as soon as possible for routine angiography or rescue PCI in the setting of reperfusion failure. Therapeutic anticoagulation must be administered following fibrinolysis to prevent recurrent

thrombosis, with strict monitoring of activated clotting time (ACT) or activated partial thromboplastin time (aPTT) levels to minimize risk.

5. **Antiplatelet and anticoagulation.** Aspirin and therapeutic heparin should be administered to all patients at the time of diagnosis of MI barring any contraindication. In the setting of immediate cardiac catheterization, oral $P2Y_{12}$ inhibitor may be deferred until coronary anatomy is defined, given the prevalence of left main or severe multivessel disease in patients who present with shock. In the setting of delayed administration, or concern with absorption of oral $P2Y_{12}$ inhibitors, bridging with IV cangrelor or glycoprotein IIb/IIIa inhibitor (eg, eptifibatide, tirofiban) should be strongly considered adjunctive to PCI. Crushed oral $P2Y_{12}$ inhibitor may be administered to facilitate absorption when indicated.

B. Medical therapy. In the setting of circulatory collapse, pharmacologic agents are initially utilized to maintain hemodynamics while supportive mechanical devices are being considered. **Table 4.3** summarizes the hemodynamic effects of vasoactive medications used in the management of CS. In general, pharmacologic therapies should be initiated at the onset of SCAI stage B shock, tailored according to the invasive hemodynamic profile of the patient, which can be broadly categorized as follows:

TABLE 4.3 Hemodynamic Effects of Medications Used to Manage Cardiogenic Shock

Medication	Preload	Afterload	Inotropy	Chronotropy
Dopamine (3-10 mcg/kg/min)	0	−	++++	++
Dopamine (>10 mcg/kg/min)	0	+++	+++	+++
Norepinephrine (2-300 mcg/min)	0	++++	+	++
Epinephrine (0.05-1 mcg/kg/min)	0	+++	+++	+++
Phenylephrine (0.5-15 mcg/kg/min)	0	++++	0	−
Dobutamine (2.5-25 mcg/kg/min)	−	−	++++	+++
Milrinone (0.375-0.75 mcg/kg/min)	− −	− −	+++	+
Nitroglycerin (2.5-300 mcg/min)	− − −	−	0	+
Nitroprusside (0.3-10 mcg/kg/min)	− − −	− − −	0	+

0, no effect; −, decrease; +, increase.

- **Warm/wet profile (normal mean arterial pressure [MAP], low CI, high filling pressures, low urine output with diuretics alone)**: vasodilator for target SVR ~1,000 dynes, then diuretics
- **Cold/wet "classic" profile (low/borderline MAP, low CI, high filling pressures)**: upfront vasopressors to maintain MAP, then inotropes and diuretics

- **Vasodilatory and hypotensive profile (low MAP, low CI, low SVR):** norepinephrine with diuresis, then consider inotropic agents

1. **Vasodilators** such as nitroglycerin and **sodium nitroprusside** play an important role in the management of LV systolic failure by means of preload and afterload reduction. Sodium nitroprusside, in particular, can be particularly helpful in weaning inotropic agents or tMCS after optimization of volume status. Notably, the use of vasodilators may be limited by refractory hypotension.
2. **Vasopressors.** In the setting of hypotension, the initial pressor of choice is **norepinephrine** started at 2 to 5 mcg/min and titrated to a maximal dose of 30 mcg/min. In the setting of chronotropic incompetence, if transvenous pacing is not feasible, **dopamine** may be helpful and is started at 3 mcg/kg/min and titrated to a maximal dose of 20 mcg/kg/min. Dopamine may be associated with higher mortality than norepinephrine when titrated to maintain an effective mean arterial pressure.
3. **Inotropic agents** can be used to augment contractility and cardiac indices to maintain perfusion pressure. However, inotropes generally increase myocardial work and theoretically worsen ischemia and provoke arrhythmias. These agents should be avoided in AMI-CS if possible or used sparingly as a bridge to MCS device.
    a. **Dobutamine** has a positive inotropic action comparable to that of dopamine and may decrease afterload. Dobutamine is started at a dose of 2.5 mcg/kg/min and increased to a maximal dose of 40 mcg/kg/min, with typical doses around 5 to 10 mcg/kg/min. In our clinical experience, dobutamine has a neutral effect on blood pressure, provided filling pressures are adequate, and can be used when MAPs are borderline.
    b. **Milrinone**, a phosphodiesterase inhibitor with inotropic and vasodilator action, may be beneficial in some patients, especially those with RV dysfunction. Milrinone is given as a 50-mcg/kg bolus over 10 minutes, followed by an infusion of 0.375 to 0.75 mcg/kg/min. The bolus may be omitted in the care of patients with low blood pressure. Patients without adequate blood pressure may not tolerate milrinone. This agent should be used with caution in patients with hemodynamic instability because of the long half-life and renal clearance of this agent.
4. **Diuretics** should be initiated for volume overload after implementation of measures to improve CO. Optimization of filling pressures maximizes contractility in patients with decreased systolic function. **Ultrafiltration** via hemodialysis should be implemented if acute renal failure renders diuresis ineffective. With invasive hemodynamics, **optimal CVP target in AMI-CS is 8 to 12 mm Hg; optimal PCWP target is 12 to 17 mm Hg**. If filling pressures are lower due to overdiuresis with persistently low indices, consideration should be given toward replacing with IV fluids. In HF-CS, targets typically range higher

(10-15 mm Hg CVP, 15-20 mm Hg for PCWP) due to long-standing cardiomyopathy.

5. **β-Blockers and calcium channel blockers should be avoided in CS,** given their negative inotropic properties. Alternatively, **digoxin** can be considered if atrioventricular (AV) nodal blocking agents are required.

C. Transvenous pacing. Patients with significant heart block or chronotropic incompetence may require temporary pacing to increase the heart rate and augment CO. Once placed, **baseline rates may be increased to augment CO, usually between 80 and 100 beats/min**. If AV conduction remains intact, atrial pacing maintains AV synchrony and normal LV contraction and may be preferable to ventricular pacing. However, placement of an atrial wire requires technical experience in active fixation screw-in leads.

D. tMCS. Improvements in tMCS have revolutionized the management of CS, enabling a strategy of **a bridge to decision to be adopted in patients with refractory shock**. tMCS allows for recovery of end-organ injury while also providing time to address reversible causes and assess candidacy for advanced support with a durable ventricular assist device (VAD) or transplantation. **MCS consideration is warranted in the setting of SCAI stage C shock or greater, and MCS implementation should be expedited for those in SCAI D/E**. Patients who improve can then be weaned off support, whereas eligible patients in refractory shock may be considered for VAD or transplantation. As a general rule, all tMCS devices require therapeutic anticoagulation during their use; active bleeding and coagulopathy are absolute and relative contraindications, respectively. A comprehensive profile of short-term tMCS devices can be found in Chapter 62.

When ***considering escalation to temporary MCS, the following questions need to be considered***:

- Is the CS LV predominant, RV predominant, or both?
- Is there concomitant respiratory failure?
- Is there an adequate access site for device insertion?
- What is the exit strategy?
  - Identify treatments available to reverse the underlying cause.
  - If not, consider candidacy for advanced therapy options.
  - In patients with refractory shock without further treatment options, withdrawal of care in a controlled manner may be appropriate.
- Is there a reasonable chance of recovery with MCS intervention?
  - If neurologic status is poor, confer with consultants regarding recovery potential.
  - Rule out for the presence of irreversible end-organ injury (eg, severe gut ischemia, refractory liver failure or disseminated intravascular coagulation [DIC]).

- Consider baseline rehabilitative potential of patient.
- Assess the desires of the patient to undergo heroic treatment and rehabilitation.

1. **Intra-aortic balloon pump (IABP) counterpulsation.** This is the most widely available and traditional support device. IABP counterpulsation reduces afterload, improves coronary and peripheral perfusion, and decreases the myocardial oxygen requirement via reduction in wall stress. Contraindications to placement include the presence of significant peripheral vascular disease, aortic dissection, and moderate-severe or greater aortic insufficiency. The largest-sized balloon appropriate for the patient's height should be selected. At 30 days and 1 year, the IABP-SHOCK II trial failed to show a significant difference in rates of all-cause mortality or secondary end points (eg, length of stay, renal function) in patients receiving IABP support compared with those who did not. As a result, the ACC/AHA guidelines give a class IIa recommendation for the use of IABP support for patients who do not stabilize with pharmacologic therapies. Nevertheless, we feel that in select patients, ***early rapid IABP insertion*** can stabilize hemodynamics, particularly in patients with severe mitral regurgitation and/or VSR. Femoral IABPs may remain in place for up to 7 to 14 days. An axillary IABP may be considered for a more durable bridge, such as when awaiting advanced therapies.
2. **Venoarterial ECMO (VA-ECMO)** is an established therapy that **can be implemented expeditiously** in a percutaneous (or surgical) manner in experienced hands, even during cardiac arrest (extracorporeal cardiopulmonary resuscitation [E-CPR]). ECMO uses an extracorporeal centrifugal pump to provide **full hemodynamic support** and **can support oxygenation if lung function is compromised**. Peripheral ECMO requires adequate vasculature for cannulation of the femoral artery (16-18 French) and vein (24 French) with large-bore catheters. As a result, **a femoral artery lumen of at least 6 mm is required to prevent limb ischemia**. Limb ischemia can also be prevented with the antegrade reperfusion catheter, placed in the superficial femoral artery, which requires expertise with ultrasound-guided access. ECMO can also markedly increase LV afterload, and unloading strategies should be adopted to avoid LV distension (ie, Impella or IABP). ECMO typically offers a bridge of 7 to 14 days, in the absence of immediate complications.
3. Percutaneous microaxial pump devices such as the **Impella CP** can provide **3.5 L/min** hemodynamic support, directly unload the LV, and be placed before or after revascularization. The DanGer Shock Trial demonstrated that routine use of the Impella CP demonstrates a small mortality benefit in STEMI with AMI-CS at 180 days as compared to standard care. **More robust and durable circulatory support (5.5 L/min) can be provided by the Impella 5.5 device** but necessitates surgical cut-down for cannulation in the axillary position.

4. In cases of severe RV failure, an RVAD device such as a **Protek Duo** or **Impella RP** can be considered. The Impella RP is a percutaneous microaxial pump placed into the PA via the femoral vein. A Protek Duo is a dual-lumen cannula connected via an extracorporeal centrifugal pump that delivers blood from the inflow in the right atrium to the outflow in the PA. In addition, the Protek Duo can support oxygenation in the setting of respiratory compromise.
5. The **TandemHeart** (**Figure 4.2**) device provides percutaneous left atrial to femoral artery bypass flow at rates of up to 5.0 L/min with percutaneous access and can serve as a bridge to recovery or more definitive therapy. The device unloads the LV by decompressing the left atrium and may be especially useful when considering support in the setting of a VSR. However, placement requires technical expertise in a transseptal puncture.

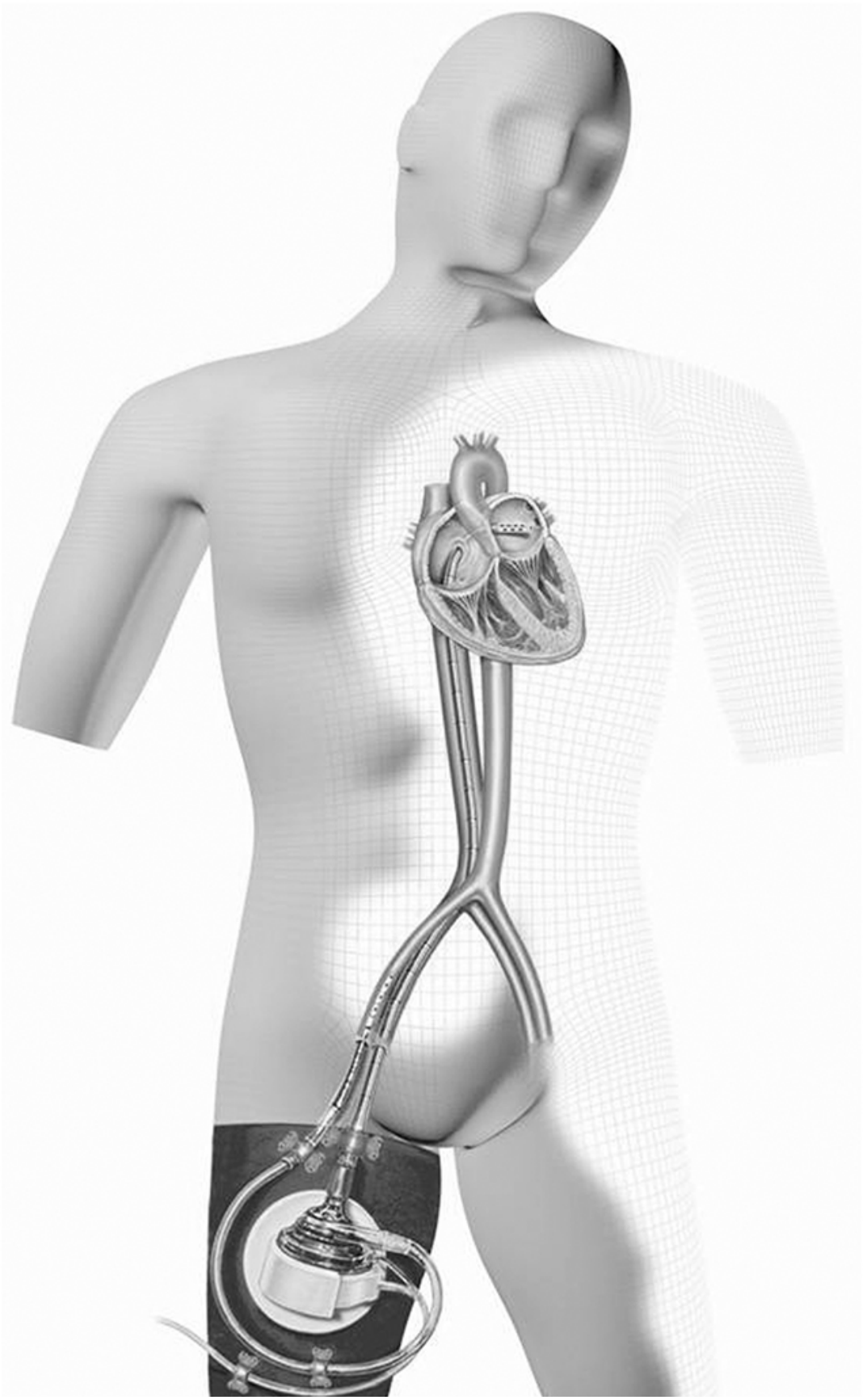

FIGURE 4.2 The TandemHeart percutaneous left ventricular assist device. (Courtesy of CardiacAssist, Inc, a subsidiary of LivaNova USA, Inc.)

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CHAPTER 5

Chronic Coronary Artery Disease

Trent L. Wei and Khaled Ziada

I. INTRODUCTION. Chronic coronary artery disease (CAD), also known as stable CAD and stable ischemic heart disease (SIHD), refers to a supply-demand mismatch in myocardial oxygen delivery caused by coronary disease, typically resulting from large-vessel atherosclerotic obstructive lesions. *Stable angina pectoris* (often abbreviated to angina) is the term used to describe the syndrome of chest discomfort resulting from myocardial ischemia.

Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque.

Unstable angina is defined as symptoms that worsen abruptly (increase in frequency and duration) without an obvious cause of increased myocardial oxygen consumption. Similarly, the onset of rest angina in a patient for whom angina was previously provoked by some degree of exertion may signal an unstable syndrome.

In this chapter, we review the clinical presentation, diagnostic testing, and management of stable CAD.

II. CLINICAL PRESENTATION. The 2021 American College of Cardiology/American Heart Association/American Society of Echocardiography/American College of Chest Physicians/Society for Academic Emergency Medicine/Society of Cardiovascular Computed Tomography/Society for Cardiovascular Magnetic Resonance (AHA/ACC/ASE/CHEST/SAEM/SCCT/SCMR) Chest Pain Guidelines is a comprehensive guideline for the evaluation and diagnosis of chest pain. Typical angina is a retrosternal pressure-like sensation precipitated by exertion and relieved by rest. Although typical angina is the hallmark of CAD, it is important to understand that angina and angina-equivalent presentations can vary, with symptoms encompassing pain, pressure, tightness, or discomfort in the chest, shoulders, arms, neck, back, upper abdomen, or jaw as well as dyspnea and fatigue. “Atypical angina” is no longer a preferred terminology, as it is potentially a misleading descriptor. If heart disease is not suspected, “noncardiac chest pain” is the preferred terminology.

A. Symptoms. The constellation of symptoms characteristic of angina pectoris includes the following four cardinal features:

1. **Location.** Discomfort is commonly located in the retrosternal area with radiation to the neck, shoulders, arms, jaws, epigastrium, or back. In some instances, it involves these areas without affecting the retrosternal area.
2. **Relation to a trigger.** Symptoms are typically triggered by physical activity, emotional stress, exposure to cold, consumption of a heavy meal, or smoking.
3. **Character.** Most patients describe angina as a vague chest discomfort. They describe it as a squeezing, burning, tight, choking, heavy, and, occasionally, hot or cold sensation. Many patients do not perceive angina as pain, per se. Some patients may experience dyspnea, profound fatigue, weakness, lightheadedness, nausea, diaphoresis, altered mental status, or syncope in the absence of any chest discomfort. These symptoms are often referred to as "anginal equivalents." Noncardiac causes of chest pain (gastrointestinal [GI], respiratory, musculoskeletal, etc) may be indicated by fleeting chest pain, unrelenting chest pain not affected by activity, antecedent chest trauma, association with food intake, location inferior to the umbilicus, and pleurisy.
4. **Duration.** The chest pain associated with ischemia typically lasts 3 to 5 minutes. Ischemic pain usually does not last more than 30 minutes without causing myocardial injury.
5. **Classification.** Various classifications are available to assess the severity and to predict the outcome among patients with angina. The Canadian Cardiovascular Society classification is the most popular (**Table 5.1**). Other classification systems include the Specific Activity Scale, the Duke Activity Status Index, and the Braunwald classification.

TABLE 5.1 Classification of Angina

CCS Class	Definition	Comment
I	Ordinary physical activity does not cause angina.	Angina only with extraordinary exertion at work or recreation
II	Slight limitation of ordinary activity	Angina with walking more than two blocks on a level surface or climbing more than one flight of stairs at a normal pace
III	Marked limitation of ordinary physical activity	Walking one to two blocks on a level surface or climbing one flight of stairs at a normal pace
IV	Inability to carry on any activity without discomfort	Angina at rest or with minimal activity or stress

CCS, Canadian Cardiovascular Society.

6. **Symptoms of associated conditions.** Evidence of peripheral arterial disease (claudication or history of peripheral revascularization) or cerebrovascular

disease (stroke, transient ischemic attacks, or carotid revascularization) indicate a high risk of having CAD and are also associated with worse prognosis than compared to CAD alone.

B. Physical findings. For patients with a history of chest pain, physical examination helps identify risk factors for CAD and occult cardiac abnormalities.

1. **The signs associated with a high risk for CAD** include elevated blood pressure or manifestations of hypertensive vascular disease such as retinal arteriopathy, signs of hyperlipidemic conditions including corneal arcus or xanthelasma, and evidence of carotid or other peripheral vascular disease.
2. **Physical examination** performed during an episode of chest pain may reveal rales, tachycardia, hypertension, an S_3 or S_4 gallop, or a systolic murmur from ischemic mitral regurgitation, all of which generally disappear with resolution of symptoms.

C. Baseline electrocardiogram (ECG)

1. A baseline ECG is useful for the initial screening of CAD, although the majority of patients with chest pain have a normal ECG in-between episodes of pain. The presence of pathologic Q waves or persistent ST depression is associated with an unfavorable outcome. The ECG can also demonstrate other abnormalities, such as left ventricular (LV) hypertrophy, bundle branch block, and preexcitation syndromes.
2. ECG at the time of chest pain can also help identify the cause of the chest pain. Transient changes in the T-wave, ST-segment, or conduction patterns point toward a cardiac source of chest pain; however, a normal ECG does not exclude ischemia as being the etiology of chest pain.

III. DIAGNOSTIC TESTING. For a patient with stable symptomatic CAD, investigations are aimed at risk stratification and management of symptoms and unfavorable outcomes.

A. Stress testing. The basic principle of stress testing is to provoke a supply-demand mismatch in coronary flow, followed by functional assessment with different modalities to detect ischemia. Stress tests can be categorized according to the methods used to provoke and detect myocardial ischemia. The sensitivity and specificity of each test to identify coronary stenosis vary according to the study population, definition of disease, definition of a positive test result, protocol used for the stress testing, and experience of the interpreter. The following is a brief overview of noninvasive cardiac testing. **For a thorough discussion on noninvasive imaging and stress modalities, refer to the dedicated** Chapters 46 and 47.

1. **Methods to induce supply-demand mismatch.** Exercise is the most physiologic method for inducing ischemia by increasing myocardial oxygen demand. An exercise test is considered adequate if 85% or more of age-

predicted maximum heart rate (220 minus age) is achieved. Exercise testing provides an objective assessment of functional capacity, which provides useful prognostic information. Pharmacologic testing with inotropic or vasodilator agents mimics exercise and increases blood flow through the coronary vasculature. Historically, the most common inotropic agent used is dobutamine. Vasodilator agents used are adenosine, adenosine derivatives (ie, dipyridamole), and regadenoson. Vasodilators create a coronary steal phenomenon by temporarily diverting blood flow from diseased vessels to nondiseased vessels, leading to a perfusion mismatch that can be identified by imaging modalities.

2. **Methods to assess ischemia**
   a. **Stress ECG.** Exercise ECG provides useful diagnostic information about the patients with normal baseline ECGs who are at intermediate risk for CAD. Stress ECG is also used to create an exercise prescription in patients with stable angina. The sensitivity and specificity of stress ECG are poor among patients with an abnormal baseline ECG, LV hypertrophy, ventricular pacing, left bundle branch block (LBBB), or intraventricular conduction disturbance and among patients taking digitalis or other medications that affect conduction and repolarization. Ischemic electrocardiographic changes during vasodilator testing have high specificity but poor sensitivity. Electrocardiographic changes during dobutamine infusion have sensitivity and specificity similar to those of exercise ECG.
   b. **Echocardiographic imaging.** Stress echocardiography is an economical test with good specificity for identifying the location and extent of ischemic territories. This is assessed by the induction of regional wall motion abnormalities with stress or dilation of the LV cavity with stress (which may indicate global ischemia). Exercise is preferred in patients with intermediate or high pretest probability who are able to exercise. If the patient is unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Augmentation of contractility in hypokinetic segments may indicate the presence of hibernating myocardium in a specific coronary distribution. Dipyridamole and adenosine stress tests can be performed with echocardiographic imaging, though this approach is not commonly utilized. Results of stress echocardiography are difficult to interpret in some patients with a hypertensive response to exercise and in some patients with severe mitral or aortic regurgitation. Preexisting wall motion abnormalities may further complicate image interpretation.

c. **Radionuclide imaging.** Single-positron emission computed tomography (SPECT) can be performed after injection with thallium-201 or technetium (Tc) 99m–labeled radiopharmaceuticals. Positron emission tomography (PET) can be performed utilizing rubidium-82 or ^{13}N ammonia tracers. PET imaging provides greater spatial resolution and diagnostic accuracy in comparison with SPECT imaging. In addition, PET enables quantification of coronary blood flow and assessment of coronary flow reserve. Injection of fluorine-18–labeled deoxyglucose allows assessment of myocardial viability in patients with resting perfusion defects. The sensitivity and specificity of SPECT nuclear testing are decreased among patients with severe obesity, balanced three-vessel disease, and LBBB.

B. Resting echocardiography provides useful information in the overall assessment of suspected stable angina.

1. Regional wall motion abnormalities involving the LV are commonly caused by CAD and may represent resting ischemia or prior myocardial infarction (MI).
2. Any impairment in LV systolic function, LV hypertrophy, and/or presence of substantial mitral regurgitation are associated with heightened clinical risk and poorer outcome. LV systolic function may guide the choice of medical therapy versus revascularization.

C. Magnetic resonance imaging (MRI) provides high accuracy due to improved spatial resolution; however, quantitative assessment remains nonstandardized.

1. Ischemic evaluation using pharmacologic stress (dobutamine or adenosine) and cardiovascular magnetic resonance can be used to evaluate myocardium in jeopardy.
2. MRI uses gadolinium as a contrast medium to evaluate regional wall motion abnormalities and ejection fraction as well as segmental myocardial perfusion (when using adenosine).
3. MRI can also provide direct visualization of the coronary arteries, although computed tomography angiography (CTA) is much better for this application.
4. Delayed-phase gadolinium imaging also provides information about myocardial viability, presence, location, and transmurality of myocardial scar.
5. The limitations of cardiac MRI include high cost, lack of portability, and unsuitability for use in many patients with pacemakers and defibrillators.

D. Electron beam computed tomography (EBCT)

1. EBCT is a noninvasive method that allows quantification of coronary artery calcification. The test is rapid and provides a “calcium score.” This test is not intended to identify or quantify the severity of stenosis because of atherosclerotic lesions.

2. An increasing calcium score indicates higher plaque burden, which correlates strongly with heightened risk of cardiovascular events, and abnormal findings should lead to further risk factor modification and cardiovascular risk assessment.

E. Multidetector computed tomography (MDCT)

1. Coronary computed tomography angiography (CCTA) allows for the evaluation of the epicardial coronary tree using a noninvasive approach.
2. The sensitivity of CCTA for assessing coronary stenosis approaches 97% with a specificity of 86% when using 64-slice technology. Importantly, the negative predictive value of CCTA is 99%, with an optimal study and appropriate patient selection.
3. Severe coronary artery calcification or previous coronary stent placement may significantly detract from image quality, rendering the specific coronary segments uninterpretable. Larger stents may be grossly evaluated for patency but accurate quantification for in-stent restenosis in anatomic locations distal to the left main coronary artery (LMCA) is not always feasible.

F. Coronary angiography

1. **Strengths.** Coronary angiography is the standard for anatomic assessment of coronary arterial stenosis and provides important prognostic information.
   a. Patients with >75% stenosis involving at least one coronary artery have a lower survival rate than patients with 25% to 50% or <25% stenosis. Even for mild stenosis, the risk for MI is markedly higher than for no stenosis.
   b. The severity of lesions demonstrated with angiography is not predictive of plaque stability; two-thirds of patients with acute MI have stenosis of >50% diameter at the site of plaque rupture before MI. It is possible, however, to assess plaque instability on the basis of angiographic characteristics or morphologic features of the lesion.
      (1) Eccentric lesions with narrow necks, overhanging edges, or scalloped borders (type II plaques) are more unstable than concentric lesions with smooth borders (type I plaques).
      (2) Lesion contour (ie, irregular borders) is predictive of plaque instability and heightens the risk of future infarction.
      (3) The morphologic characteristics of the plaque help in judging the feasibility and risk of percutaneous or surgical intervention.
2. **Indications.** In the management of stable angina, the use of angiography is variable. An ACC/AHA task force classified the indications for coronary angiography into three categories. The relevant indications in the context of stable angina are presented in **Table 5.2**.

TABLE 5.2 Indications for Coronary Angiography in Stable Angina
Class I (general agreement among cardiologists)
Severe anginal symptoms (CCS class III or IV) with OMT (LOE C)
Noninvasive testing indicates high risk of coronary disease (LOE C)
Survivors of sudden cardiac death or potentially fatal ventricular tachyarrhythmia (LOE B)
Symptoms of congestive heart failure with angina (LOE B)
Class II (frequently used but controversial)
Symptoms of angina and an LV ejection fraction <50% with intermediate risk/demonstrable ischemia (IIa, LOE C)
Symptoms of angina and positive stress test (IIa, LOE C)
Inadequate information from noninvasive testing (IIa, LOE C)
Severe angina with preserved ventricular function and intermediate risk noninvasive testing (IIa, LOE C)
Patients who are unable to be evaluated noninvasively (IIa, LOE C)
Patients who cannot undergo stress testing with a high pretest probability of coronary disease (IIa, LOE C)
Suspicion of left main or three-vessel coronary disease (IIa, LOE C)
Class III (unjustified use of angiography)
Low-risk patients who have not had noninvasive testing (LOE C)
Patients with a preserved LV ejection fraction (>50%) and low risk (LOE B)
Mild symptoms that resolve with medical therapy (LOE C)
Patients who would not or cannot undergo revascularization (LOE B)

CCS, Canadian Cardiovascular Society; LOE, level of evidence; LV, left ventricular; OMT, optimal medical therapy.

3. **Limitations.** Coronary angiography is, in essence, a two-dimensional contrast luminogram, thus giving little information about the arterial wall. Interpretation is typically regional, that is, segments are compared to adjacent segments with less luminal compromise. This leads to underestimation of plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease. Interpretation of angiograms is notoriously variable, with high inter- and intraobserver variability, particularly when diameter stenosis is in an intermediate range. Adjunctive imaging and functional testing facilitate the investigation of hazy areas on coronary angiograms, which may be caused by calcium, thrombus, severe eccentric lesion, or dissection.

G. Intravascular ultrasound (IVUS) allows visualization of the cross-sectional image of coronary arteries, as an adjunct to a coronary angiography procedure. It provides a tomographic perspective and direct imaging of the arterial wall. This

allows quantification of artery size, plaque area, lumen area, and luminal stenosis; assessment of hazy areas on coronary angiograms, questionable areas of stenosis, and extent of stenosis; and sometimes determination of the calcium content and morphology of a plaque. Hypodense areas in a plaque correlate with high-lipid content, which may indicate fast-growing or potentially unstable plaque. This information can help assess the need for and options of therapy. This modality does not, however, have a defined role in the routine evaluation of patients with stable angina because of the invasive nature of the test and the need for coronary artery instrumentation.

H. Optical coherence tomography (OCT) is another intracoronary imaging modality that has better resolution than IVUS but provides less depth. Benefits of OCT include visualization of thrombus and thin-cap atheroma, identification of plaque rupture or erosion, and better understanding of stent procedural results (degree of apposition and stent endothelialization, etc). Similar to IVUS imaging, this technique also requires coronary instrumentation. It also requires injection of contrast medium during imaging (usually totaling 8-15 cc per run) and is relatively contraindicated in patients with chronic kidney disease.

I. Invasive functional assessment. Invasive assessment of the functional significance of an intermediate stenosis can be made by measuring the pressure gradient across a stenosis at rest and/or during maximal hyperemia. The measurement relies on a standard 0.014-in angioplasty wire, mounted with a solid-state pressure transducer near its tip. In patients with angina or angina equivalent, the use of coronary physiology to guide revascularization with percutaneous coronary intervention (PCI) is recommended (class I, level of evidence [LOE] A).

1. Fractional flow reserve (FFR) is a ratio of mean pressure distal and proximal to the lesion after maximum hyperemia. Maximum hyperemia is typically achieved using intravenous infusion or intracoronary injection of adenosine. An FFR of <0.80 indicates a hemodynamically significant lesion. In patients with angiographically intermediate stenoses, the **Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) investigators** demonstrated lower rates of major adverse cardiac events (MACE) following coronary stenting using a strategy of FFR-guided versus angiography-guided lesion selection (8.4% vs 23.9%, $P = .02$). A subsequent trial, **Fractional Flow Reserve Versus Angiography for Multi-vessel Evaluation 2 (FAME-2)**, demonstrated that for patients with one-vessel or multivessel disease, and with FFR <0.8, PCI resulted in significantly lower rates of MACE compared to medical therapy alone (odds ratio [OR] 0.39; 95% confidence Interval [CI] 0.26-0.57; $P < .001$).
2. Instantaneous wave-free ratio (iFR) also measures physiologic impact of a coronary stenosis using a pressure wire, but without the use of adenosine (non–hyperemic index). In this case, the ratio of the mean distal pressure to proximal

pressure is calculated, where the mean distal pressure is measured during the wave-free period of diastole. An iFR of <0.89 indicates a hemodynamically significant lesion. Based on **Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) trial** and **Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI (iFR-SWEDEHEART) trial**, iFR was found to be noninferior to FFR assessment and lesion selection for PCI.

IV. THERAPY. The goals of therapy in stable CAD are to prevent cardiovascular morbidity and mortality and to improve quality of life.

Medical therapy, PCI, and coronary artery bypass grafting (CABG) have all been shown to control symptoms and improve exercise time to ischemia. CABG had been proven to decrease cardiovascular mortality in specific patient subsets, although the medical therapy used for control groups in these investigations was much less effective than contemporary regimens. Although PCI has been shown to improve stable anginal symptoms and improve quality of life, a decrease in mortality has not been proven in randomized controlled trials (RCTs).

A. Lifestyle modification

1. Exercise

a. Rationale. Exercise conditions the skeletal muscles, which decreases total body oxygen consumption for the same amount of workload. Exercise training also lowers heart rate for any level of exertion, which decreases the oxygen demand on the myocardium for any workload. Some evidence shows that higher physical activity and exercise can decrease cardiovascular morbidity and mortality.

b. Recommendation. For secondary prevention, aerobic and isotonic exercises with a goal of achieving a sustained heart rate of approximately 70% to 85% of the maximum predicted heart rate for at least 30 to 60 minutes at least 5 times per week have been shown to improve survival and carries a class I, LOE B, recommendation. For beginners, a supervised exercise or rehabilitative program, in which 50% to 70% of maximal predicted heart rate is achieved, is also helpful. Isometric exercises are not recommended because they increase myocardial oxygen demand substantially.

2. Diet. A low-fat diet that includes cereals and grains, skimmed dairy products, fruits and vegetables, fish, and lean meats should be recommended, and this is effective in providing cardiovascular risk reduction in patients with CAD. These are integral components of the "Mediterranean Diet," which has been shown to reduce cardiovascular risk. Consumption of one (for nonpregnant women) or one to two (for men) standard alcoholic beverages per day is reasonable if not contraindicated (ie, because of liver disease or alcoholism).

This is a class IIb, LOE C, recommendation. A multidisciplinary approach to the care of patients with CAD that includes a nutritionist/dietician can be quite helpful in personalizing patients' eating habits.

3. **Smoking cessation.** Cigarette smoking is associated with progression of atherosclerosis, increased myocardial demand because of an alpha-adrenergic increase in coronary tone, and adverse effects on hemostatic values, all of which can lead to worsening of stable angina. Smoking cessation decreases cardiovascular risk among patients with established CAD, including patients who have undergone CABG. Physician counseling is the best approach to achieve this goal, and adjunctive therapies include nicotine replacement patches, gum, or sprays, or medications such as bupropion and varenicline.
4. **Psychological factors.** Anger, hostility, depression, and stress are shown to adversely affect CAD. Results of small, nonrandomized trials show that biofeedback and various relaxation techniques can help modify these factors.

B. Antianginal medication. There are three main classes in the medical management of angina: beta-blockers, calcium channel blockers, and nitrates. Adjunctive medical therapies include angiotensin-converting enzyme (ACE) inhibitors and ranolazine.

1. **Beta-Blockers** (**Table 5.3**)

TABLE 5.3 Beta-Blockers

Compound	Daily Dose (mg)	Frequency	Excretion	Lipid Solubility	Intrinsic Sympathomimetic Activity	Membrane Stabilization
Selective Beta-Blockers						
Metoprolol						
Short acting	50-400	Every 12 h	Liver	Moderate		
Long acting		Every 24 h			None	Possible
Atenolol	25-200	Every 24 h	Kidney	None	None	None
Acebutolol	200-600	Every 12 h	Kidney	Moderate	Low	Low
Nebivolol	5-40	Every 24 h	Kidney	High	None	
Betaxolol	20-40	Every 24 h	Kidney		Low	
Nonselective Beta (Beta$_1$ + Beta$_2$)-Blockers						
Propranolol	80-320	Every 4-6 h	Liver			
Long acting		Every 12 h		High	None	Moderate

Compound	Daily Dose (mg)	Frequency	Excretion	Lipid Solubility	Intrinsic Sympathomimetic Activity	Membrane Stabilization
Nadolol	80-240	Every 24 h	Kidney	Low	None	None
Timolol	15-45	Every 12 h	Liver	Moderate	None	None
Pindolol	15-45	Every 8-12 h	Kidney	Moderate	Moderate	Possible
Labetalol[a]	600-2,400	Every 6-8 h	Liver	None	None	Possible
Carvedilol[a]						
Short acting	25-50	Every 12 h	Liver	Moderate	None	Possible
Long acting	10-80	Every 24 h				

[a]Also a potent **alpha$_1$**-antagonist.

a. Mechanism of action. Blocking the **beta$_1$**-adrenergic receptors in the heart decreases the rate-pressure product and myocardial oxygen demand. Decreased tension in the LV wall allows favorable redistribution of blood flow from the epicardium to the endocardium.

(1) Coronary vasospasm is rare from the **beta$_2$**-receptor blocking effect, but the use of nonselective **beta**-blockers should be avoided among patients with known, active vasospasm.

(2) **Beta**-blockers have a variable degree of membrane-stabilizing effect.

b. Evidence for effectiveness. Beta-blockers decrease mortality after MI. The mortality benefit is not proven among patients with stable angina without prior MI or heart failure, although symptomatic improvement is well documented with multiple agents. Initiation of **beta**-blockers carries a class I, LOE B, recommendation as the initial therapy for relief of symptoms in patients with stable angina.

c. Side effects. The most important side effects are related to blockade of **beta$_2$**-receptors. However, data show that some of the side effects may occur less frequently than previously believed, and potentially lifesaving therapy should be offered to those at greatest risk for adverse events.

(1) Bronchoconstriction, masking of symptoms caused by hypoglycemic reaction among patients with diabetes, exacerbation of symptoms of peripheral vascular disease, and central nervous system (CNS) side effects such as somnolence, lethargy, depression, and vivid dreaming

are well documented. The CNS side effects are thought to be related to the lipid solubility of these compounds.

(2) Symptomatic bradycardia and precipitation of heart failure are concerns for patients with a diseased conduction system and preexisting heart failure, respectively.

(3) Decreased libido, impotence, and reversible alopecia can be a problem for some patients.

d. Drug interactions. Severe bradycardia and hypotension can occur with concomitant use of some calcium channel blockers.

e. Selection of preparations. Cardioselectivity, lipid solubility, mode of excretion, and frequency of dosing are the main considerations when selecting a particular agent. The major cardiospecific agents (ie, **beta$_1$**-blockade) include metoprolol, atenolol, bisoprolol, and nebivolol. Of note, nebivolol also induces the endothelial NO pathway and contributes to vasodilation. Intrinsic sympathomimetic activity (ISA) is not a clinically important factor in the choice of a medication, although benefits in patients with CAD have been decreased with agents having ISA, such as pindolol and acebutolol.

2. Calcium channel blockers (Table 5.4)

TABLE 5.4 Calcium Channel Blockers

Compound	Each Dose (mg)	Frequency	Vasodilation	Sinoatrial Node Inhibition	Atrioventricular Node Inhibition	Negative Inotrope
Nifedipine	30-120	Every 8 h	5	1	0	1
Nifedipine (Procardia XL)	30-180	Every 24 h				
Diltiazem	30-90	Every 6-8 h	3	5	4	2
Diltiazem (Cardizem CD)	120-300	Every 24 h				
Verapamil	40-120	Every 6-8 h	4	5	5	4
Verapamil (Calan SR and Isoptin SR)	120-240	Every 12 h				
Amlodipine	2.5-10	Every 24 h	4	1	0	1

Compound	Each Dose (mg)	Frequency	Vasodilation	Sinoatrial Node Inhibition	Atrioventricular Node Inhibition	Negative Inotrope
(Norvasc)						
Felodipine (Plendil)	5-20	Every 24 h	5	1	0	0
Bepridil (Vascor)	200-400	Every 24 h	4	4	4	5
Isradipine (DynaCirc)	2.5-10	Every 24 h	4	4	0	0
Nicardipine (Cardene)	10-20	Every 8 h	5	1	0	0

0, no activity; 5, most potent effect. Intermediate numbers suggest intermediate potency of effects.

a. Mechanism of action. These agents block calcium entry into vascular smooth muscle cells and cardiac cells by inhibiting calcium channels, but they do not affect the regulation of intracellular calcium release. The result is decreased contraction of muscle cells.

(1) The four types of calcium channels are L, T, N, and P.

(2) The T-type calcium channels are located in the atria and sinoatrial node and affect the phase I of depolarization.

(3) The L-type channels contribute to entrance of calcium into the cell during phase III of the action potential.

(4) The N and P types of channels are present mainly in the nervous system.

(5) The three main groups of calcium channel blockers are dihydropyridines (eg, nifedipine), benzothiazepines (eg, diltiazem), and phenylalkylamines (eg, verapamil).

(6) The dihydropyridines bind to the extracellular portion of the L channels at a specific site. They do not bind to the T channels and do not have a negative chronotropic effect. Because of their extracellular site of action, dihydropyridines do not inhibit receptor-induced intracellular calcium release.

(7) Verapamil binds to the intracellular part of the L channel and inhibits the T channel. Intracellular calcium release is inhibited by verapamil because of its intracellular binding site and reflex sympathetic activation is less effective. Use dependence occurs with verapamil because open channels are needed for transport of the drug into the intracellular binding site. In stable angina, verapamil helps by improving rate-pressure product and by increasing oxygen delivery from coronary vasodilation.

b. Evidence of effectiveness. Numerous placebo-controlled, double-blind trials have shown that calcium channel blockers decrease the number of anginal attacks and attenuate exercise-induced depression of ST segments. Calcium channel blockers are either started in patients who are **beta**-blocker intolerant (class I, LOE B) or as an adjunct in those for whom **beta**-blockers have not provided symptomatic relief (class I, LOE B).

(1) Studies comparing the efficacy of **beta**-blockers and calcium channel blockers in the management of stable angina in which death, infarction, and unstable angina were used as end points showed calcium channel blockers to be as effective as **beta**-blockers.

(2) Increased mortality caused by short-acting nifedipine among patients with CAD has been demonstrated. If the use of nifedipine is contemplated, a long-acting preparation in conjunction with **beta**-blocker therapy is the safer approach. The mechanism of increased mortality is unclear, but reflex tachycardia and coronary steal phenomenon are potential explanations.

c. Side effects. The most common side effects are lower extremity edema, hypotension, flushing, dizziness, bradycardia, and headache. Because a negative inotropic effect can precipitate heart failure, the use of calcium channel blockers to treat patients with impaired LV function is relatively contraindicated. Conduction disturbances and symptomatic bradycardia occur with the use of compounds that have a marked inhibitory effect on the sinoatrial and atrioventricular nodes. Bepridil is known to prolong QTc, and QT monitoring is necessary when this medication is used. Lower extremity edema is often seen with the use of dihydropyridine calcium channel blockers, which may necessitate lowering the dose or discontinuing the medication. The nondihydropyridine calcium channel blockers are known to cause constipation.

d. Drug interactions. Digitalis levels are increased by the nondihydropyridine calcium channel blockers verapamil and diltiazem. The use of these drugs is contraindicated in the presence of digitalis toxicity.

e. Selection of preparations. Calcium channel blockers have a variable negative inotropic effect.

(1) Amlodipine is most likely to be tolerated by patients with compensated heart failure. In decompensated heart failure, all calcium channel blockers should be avoided.

(2) Amlodipine, diltiazem, nifedipine, and verapamil are the only calcium channel blockers approved for angina by the U.S. Food and Drug Administration.

(3) Patients with conduction disturbances should take agents with minimal effects on the conduction system. Longer acting preparations minimize the risk for precipitation of angina caused by reflex tachycardia.

3. Nitrates (Table 5.5)

TABLE 5.5 Nitrates

Medication	Route of Administration	Each Dose	Frequency
Nitroglycerin (glyceryl trinitrate, Nitro-Bid, Nitrostat, and Nitro-Dur)	Sublingual tablet	0.15-0.6 mg	As needed
	Sublingual spray	0.4 mg	As needed
	Sustained-release capsule	2.5-9.0 mg	Every 6-12 h
	Ointment (topical)	0.5-2 in (1.25-5 cm)	Every 4-8 h
	Disk (patch)	1 disk (2.5-15 mg)	Every 24 h
	Intravenous		Continuous
	Buccal tablet	5-400 mcg/min	Every 3-5 h
		1 mg	
Isosorbide dinitrate (Isordil, Sorbitrate, and Dilatrate SR)	Sublingual tablet	2.5-10 mg	Every 2-3 h
	Chewable tablet	5-10 mg	Every 2-3 h
	Oral tablet	10-40 mg	Every 6 h
	Sustained-release tablet	40-80 mg	Every 8-12 h
Isosorbide-5-mononitrate (Imdur and Ismo)	Sublingual tablet	10-40 mg	Every 12 h
	Sustained release	60 mg	Every 24 h
Erythrityl tetranitrate (Cardilate)	Sublingual tablet	5-10 mg	As needed
		10 mg	Every 8 h

a. Mechanism of action. Nitrates decrease cardiac workload and oxygen demand by means of reducing preload and afterload of the LV. They also redistribute blood flow to the ischemic subendocardium by means of decreasing LV end-diastolic pressure, vasodilation of epicardial vessels, and improvement of collateral blood flow to ischemic tissue. Nitrates may also be weak inhibitors of platelet aggregation, although the clinical relevance of this is unclear.

b. Evidence for effectiveness. Nitrates can decrease exercise-induced myocardial ischemia, alleviate symptoms, and increase exercise tolerance in patients with stable angina.

(1) Adding nitrates to an optimal beta-blocker regimen does not improve the frequency of anginal episodes, glyceryl trinitrate consumption, exercise duration, or duration of silent ischemia.

(2) In some small studies, the efficacy of nitrates in reducing anginal episodes was increased with concomitant use of ACE inhibitors.

(3) No study has shown survival benefit with the use of nitrates to treat patients with chronic stable angina.

c. **Selection of preparations.** Because nitrates have a fast onset of action, a sublingual tablet or oral spray offers immediate relief of an anginal episode. For short-term prophylaxis (up to 30 minutes), nitroglycerin tablets can be used when activities known to precipitate angina are anticipated. Timing and frequency of the doses can be individualized according to the diurnal rhythm of anginal episodes. A nitrate-free interval of about 8 hours is adequate to prevent tolerance. The use of long-acting medications and transcutaneous delivery systems improves compliance but still necessitates a nitrate-free interval.

d. **Side effects.** Oral nitrates should be taken with meals to prevent heartburn.

(1) Headache is common and can be severe. Severity usually decreases with continued use and often can be controlled by decreasing the dose.

(2) Transient episodes of flushing, dizziness, weakness, and postural hypotension can occur, but these effects are usually abrogated by positioning, adequate hydration and by other procedures that facilitate venous return.

e. **Drug interactions.** Hypotension can occur with the use of other vasodilators, such as ACE inhibitors, hydralazine, or calcium channel blockers. **Concurrent use of phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil (Viagra) and nitrates can lead to severe hypotension and, therefore, is absolutely contraindicated.**

f. **Controversies**

(1) **Tolerance.** Sustained therapy attenuates the vascular and antiplatelet effects of nitrates. Although the basis for this phenomenon of nitrate tolerance is not completely understood, sulfhydryl depletion, neurohormonal activation, and increased plasma volume are likely involved. Intermittent therapy with a nitrate-free period of about 8 to 12 hours daily is the only practical way to avoid nitrate tolerance.

(2) **Rebound angina.** Intermittent use of nitrates is not associated with serious rebound of angina among patients taking maintenance therapy with **beta**-blockers. Dosing to allow for a longer nitrate-free interval is also not associated with rebound.

4. **Ranolazine**

a. **Mechanism.** Ranolazine has been shown to work by inhibiting the late sodium channel in myocytes, which can otherwise remain open in pathologic states, such as ischemia and heart failure. By reducing the late sodium entry into myocytes, ranolazine causes reduced sodium-dependent calcium entry into the cytosol. This downstream reduction in intracellular

calcium levels is thought to reduce diastolic stiffness, thereby improving diastolic blood flow and reducing ischemia and angina. Earlier studies had suggested that the effects of ranolazine were primarily through its impact on fatty acid metabolism; however, the weight of evidence now suggests that late sodium channel inhibition is its primary mechanism.

b. **Efficacy.** Numerous randomized studies of ranolazine, with or without background antianginal therapy, have shown a benefit in patients with stable angina with respect to the frequency of anginal attacks, exercise duration, time to ST-segment depression on treadmill testing, and use of sublingual nitroglycerin. The most recent ACC/AHA guidelines suggest that ranolazine can be used either in combination with **beta**-blockers when symptoms are uncontrolled (class IIa, LOE B) or in place of **beta**-blockers if the patient does not tolerate **beta**-blockers or if **beta**-blockers are ineffective (class IIa, LOE B).

c. **Side effects.** Dizziness, headache, and GI intolerance are the most common side effects noted. Prolongation of the QT interval has been reported, especially in patients with hepatic or liver dysfunction because of decreased metabolism. **Prolonged QT interval** at baseline or during treatment follow-up **is a contraindication** to its use.

d. **Drug interactions.** Inhibitors of CYP3A4, such as azole antifungals, nondihydropyridine calcium channel blockers, macrolide antibiotics, protease inhibitors, and grapefruit juice, should not be used concomitantly because of inhibition of ranolazine metabolism.

5. **ACE inhibitors.** The rationale for using ACE inhibitors to manage chronic stable angina comes from post-MI and heart failure trials that demonstrated a significant reduction in ischemic events with the use of ACE inhibitors.

   a. It is possible that ACE inhibitors, by decreasing mainly the preload and, to some extent, afterload, decrease myocardial oxygen demand and help in the management of chronic stable angina.

   b. **The Heart Outcomes Prevention Evaluation (HOPE) trial** in high-risk patients with CAD, stroke, diabetes, and peripheral vascular disease showed that ramipril was associated with a significant reduction in death, MI, and stroke in this population. A meta-analysis found that ACE inhibitors reduce the risk of these outcomes even in patients with atherosclerosis who do not have evidence of systolic dysfunction. It is notable that the randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition study evaluating the use of trandolapril in patients with preserved LV function did not find a benefit with respect to death, MI, angina, revascularization, or stroke. Numerous hypotheses to explain these divergent results, including

dose effects, difference in medication effects, and the risk level of enrolled patients, have been postulated.

c. The use of ACE inhibitors is recommended (class I) for patients with hypertension, diabetes, chronic kidney disease, or an LV ejection fraction of less than 40% and is considered reasonable (class IIa, LOE B) for patients without class I indications but who have both stable angina and other vascular disease.

d. Serious side effects of ACE inhibitors include cough, hyperkalemia, and decreased glomerular filtration rate. They are contraindicated in the care of patients with hereditary angioedema or bilateral renal artery stenosis. Angiotensin receptor blockers may be substituted in this population.

C. Platelet inhibitors

1. Aspirin

a. **The Antiplatelet Trialists' Collaboration** was a meta-analysis that included approximately 100,000 patients from 174 trials involving antiplatelet therapy. This data set showed that aspirin (acetylsalicylic acid [ASA]) reduced the rate of stroke, MI, and death among high-risk patients, including those with stable angina without previous MI.

b. **Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness (ADAPTABLE) trial** showed that low-dose ASA 81 mg daily had no significant difference in cardiovascular events or major bleeding compared to high-dose ASA 325 mg.

2. Clopidogrel

a. In the initial analysis of the **Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial**, performed on a large group of patients included with either prior cardiovascular events or multiple cardiovascular risk factors, there was no benefit from the use of dual-antiplatelet therapy (DAPT) over aspirin alone in preventing MI or death.

b. A prespecified analysis of higher risk patients only (such as those with prior MI) did show a decrease in cardiovascular events for the group receiving clopidogrel in addition to aspirin. This suggests that an appropriate group of patients may benefit from prolonged DAPT.

c. Can be used as an alternative for those with true aspirin allergy

3. Ticagrelor

a. The benefits of prolonged DAPT in secondary prevention observed in CHARISMA were confirmed in the **Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to**

Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction (TIMI) 54 trial.

b. In patients who had an MI 1 to 3 years prior, both ticagrelor dosages at 90 and 60 mg twice daily with aspirin reduced the risk of death, MI, and stroke by approximately 15% compared with low-dose aspirin alone. This strategy came with a significantly increased risk ($P < .001$) of TIMI major bleeding (2.6% and 2.3% with ticagrelor 90 and 60 mg, respectively, compared with 1.06% with aspirin alone).

D. PCI. Numerous historic and contemporary trials have demonstrated that the role of PCI in chronic stable disease is to primarily control symptoms when medical therapy is not adequate. The effectiveness of PCI compared to medical therapy or CABG has been extensively studied.

1. PCI compared with medical treatment

a. The Medicine, Angioplasty, or Surgery Study (MASS) trial randomized approximately 200 patients with proximal left anterior descending (LAD) artery disease to medical therapy, PCI, or CABG. This study demonstrated no difference in the primary end point (ie, death, MI, or refractory angina necessitating revascularization) at 3 years. Patients randomized to CABG had a lower incidence of medium-term events compared with the other two groups, driven by a decrease in repeat revascularization procedures.

b. The Randomized Intervention Treatment of Angina-2 (RITA-2) trial randomized more than 1,000 patients with stable angina to medical therapy or PCI. After 2.7 years of follow-up, the primary end point (ie, death or MI) was lower in the medically treated group. There was also a higher incidence of revascularization in the medically treated group. There was an improvement in angina, exercise capacity, and perceived quality of life in patients who underwent PCI.

c. The study on Optimal Medical Therapy (OMT) with or without PCI for Stable Coronary Disease (by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] Trial Research group) evaluated patients with severe angiographic disease of one or more vessels, and either classic symptoms or documented ischemia on provocative testing. Compared with aggressive medical therapy, an initial strategy of PCI with bare-metal stent (BMS) did not reduce the primary end point of death or major adverse cardiovascular events, including symptom relief.

(1) Notable limitations to the interpretation of this study include the fact that the OMT group had stringent follow-up to achieve the high rates of medical adherence, one-third of patients in the medical therapy group crossed over to PCI (but were included in the OMT group as intention-

to-treat analysis), and almost 80% of patients had no or minimal angina. Furthermore, it should be stressed that all patients were enrolled after angiography had been performed.

(2) In a substudy of patients enrolled in COURAGE on the basis of positive stress imaging, investigators found that PCI in addition to OMT was superior in reducing ischemia than OMT alone. Furthermore, the degree of residual ischemia was related to the future risk of death or MI.

2. **The FAME-2 trial** randomized 888 patients with functionally significant stenosis, defined by an FFR of less than 0.8, to either stenting with a drug-eluting stent (DES) or OMT. At 12 months, stented patients had a lower need for future urgent revascularization but no difference in all-cause mortality or MI.
3. **The Percutaneous Coronary Intervention in Stable Angina (ORBITA) trial** randomized 200 patients with severe single-vessel stenosis and medically treated stable angina to PCI versus sham-procedure placebo. There was no significant difference in the primary end point of exercise time increment between groups (PCI minus placebo 16.6 seconds; 95% CI 8.9-42 seconds, P = .20).
4. **The International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial** randomized 5,179 patients with stable coronary disease and moderate or severe ischemia. At median 3.2 years, initial invasive strategy (angiography and revascularization when feasible) did not reduce the risk of ischemic cardiovascular events or death from any cause compared to initial conservative strategy of medical therapy alone (16.4% vs 18.2%).
   a. Notable limitations to the interpretation include the fact that more than one-third of patients had not had angina in the 4 weeks preceding enrollment and 21% of the patients in the conservative strategy group underwent revascularization.
   b. Patients who had angina at baseline who were randomized to initial invasive strategy had greater improvement in angina compared to initial conservative strategy.
   c. The risk of adverse events was not associated with the extent of ischemia on functional testing, but much more so on the extent of disease based on anatomic classification.
5. **Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction (REVIVED-BCIS2) trial** randomized 700 patients with LV ejection fraction of 35% or less with extensive CAD and demonstrable myocardial viability to either PCI plus OMT versus OMT alone. Over a median of 41 months, a primary outcome event occurred in 37.2% patients in the PCI group and in

38.0% patients in the OMT group (hazard ratio [HR] 0.99; 95% CI 0.78-1.27, *P* = .96).

6. PCI compared with CABG
   a. **The Emory Angioplasty versus Surgery (EAST) trial** randomized approximately 400 patients with multivessel disease to PCI or CABG. After 8 years of follow-up, there was no difference in the combined end point of mortality, Q-wave MI, and large thallium perfusion defect. In patients with proximal LAD artery disease or diabetes, there was a nonsignificant trend toward improved survival with CABG.
   b. **The Bypass Angioplasty Revascularization Investigators (BARI)** compared PCI with CABG in the management of multivessel disease. In this trial, there was no difference in survival between patients randomized to PCI or CABG at 7 years of follow-up (80.9% for PCI and 84.4% for CABG, *P* = .043), although the subgroup of patients with diabetes had a better survival rate with CABG than with PCI (76.4% vs 55.7%, *P* = .0011).
   c. **The Arterial Revascularization Therapies Study (ARTS)** randomized 1,200 patients with multivessel disease to CABG or BMS placement. After 1 and 5 years of follow-up, there was no difference in mortality, MI, or stroke. Outcomes were similar for patients with stable and unstable angina. Among patients with diabetes, however, mortality was greater for those who received PCI. There was a greater incidence of repeat revascularization in the PCI group, although the use of DES in **ARTS 2** (compared with the historic CABG group from **ARTS 1**) shows a similar 1-year rate of revascularization between PCI and CABG groups.
   d. In the **BARI 2 Diabetes (BARI 2D) trial**, investigators compared prompt revascularization (PCI or CABG as deemed appropriate) versus OMT in a group of patients with type 2 diabetes mellitus and CAD. The primary outcome of death was not significantly different in the two groups, nor was the rate of major cardiovascular events (the major secondary end point including death, MI, and stroke). When stratified by revascularization strategy, patients in the CABG group had greater freedom from major cardiovascular events (77.6% vs 69.5%, *P* = .01); this finding was not significant in patients undergoing PCI. Notably, however, this trial was not designed to compare CABG and PCI as revascularization strategies.
   e. **The SYNergy between PCI with TAXus and cardiac surgery (SYNTAX) trial** was a pivotal trial randomizing patients with three-vessel disease or left main trunk (LMT) stenosis to multivessel PCI versus CABG. The primary end point of death, stroke, MI, and repeat revascularization favored CABG (12.3% vs 17.6%, *P* = .002). The secondary end point, which included death, stroke, and MI, was not different between the two groups

(7.7% vs 7.6%, $P = .98$). The primary end point favoring CABG was, therefore, driven primarily by increased rates of repeat revascularization in the PCI group (13.5% vs 5.9%, $P < .001$), although, notably, the rate of stroke was also significantly lower in the PCI group (2.2% vs 0.6%, $P = .003$).

f. The other major take-home point of the **SYNTAX** trial was the formulation of the SYNTAX score, which received a class I indication for evaluation of LMT or multivessel disease in the ACC/AHA PCI guidelines. The SYNTAX score grades coronary anatomy on the basis of lesion location, complexity, and functional impact and is a helpful tool for assessing patients at the individual level when discussing CABG versus PCI. In the trial, outcomes were assessed by SYNTAX score tertile: Patients with a low (0-22) or intermediate (23-32) score had no difference between the two modes of revascularization for the primary outcome. In patients with a score >32, however, CABG was favored for the primary outcome (10.9% vs 23.4%, $P < .001$).

g. **The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial** enrolled 1,900 patients with stenoses of greater than 70% in two or more epicardial vessels, randomizing them to DES placement or CABG. At 1 year, the risk of MI (5.8% vs 3.4%, $P = .02$) and the combined outcome of death, MI, or stroke (16.8% vs 11.8%, $P = .004$) were significantly higher for patients in the PCI arm of the trial. The risk of stroke was higher with CABG than with PCI (1.9% vs 0.9%, $P = .06$), and there was no difference in death (4.2% vs 3.4%, $P = .35$) between the two groups. The benefit of CABG over PCI was maintained for patients of all SYNTAX scores.

h. **Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease (EXCEL) trial** randomly assigned 1,905 patients with LMT disease of low or intermediate anatomic complexity to undergo either PCI DES or CABG. At 3 years, PCI was noninferior to CABG for the primary end point of composite of death from any cause, stroke, or MI (15.4% vs 14.7%, $P = .02$). Similar findings of noninferiority were found at 5 years (22.0% vs 19.2%, $P = .13$).

i. **Long-Term Survival After Surgical or Percutaneous Revascularization in Patients With Diabetes and Multivessel Coronary Disease** was a retrospective observational study evaluating patients with diabetes and multivessel CAD. The Ontario, Canada, database compiled a total of 4,519 patients who underwent PCI and 9,716 patients who underwent CABG. All-cause mortality (HR 1.39; 95% CI 1.28-1.51, $P < .0001$) and overall major adverse cardiac and cerebrovascular events (MACCE) (HR 1.99; 95% CI 1.86-2.12, $P < .0001$) were significantly higher with PCI compared with

CABG. The ACC/AHA guidelines indicate that in patients with three-vessel CAD or with severe stenosis of the proximal LAD and another vessel, CABG should be pursued (class I, LOE B). For patients who are able to undergo either of the treatments, an educated decision should be made by the patient, the cardiologist, and a cardiac surgeon using a heart team approach.

j. Revascularization methods. For details of PCI strategy and equipment, see Chapter 63.

E. CABG. In patients who are being considered for CABG, calculation of the Society of Thoracic Surgeons (STS) risk score is recommended to help stratify patient risk (Class I, LOE B-NR).

1. Compared with medical treatment. Compared with medical treatment, CABG improves the survival rate among patients with high-risk stable angina. The benefit is most profound in patients with three-vessel CAD, impaired LV function, or substantial LMCA stenosis.

a. This information is derived from the Coronary Artery Surgery Study, European Coronary Surgery Study, and Veterans Administration Cooperative Study. These trials were completed before generalized awareness grew regarding the benefits of medical management with **beta**-blockers, ACE inhibitors, antiplatelet agents, or lipid-lowering medications.

b. Surgical techniques have also changed significantly, with greater use of arterial conduits including internal mammary artery (IMA) grafts, minimally invasive surgery, and improved techniques of cardiac tissue preservation and anesthesia.

2. Venous or arterial grafts. With open sternotomy, in which the use of left internal mammary artery (LIMA) is well studied, internal mammary artery grafts have better long-term outcome compared with vein graft conduits. Given the success of the LIMA graft, other arterial conduits have been used, such as the right internal mammary artery (RIMA), the radial artery, and the right gastroepiploic artery.

a. Twenty percent of venous grafts are nonfunctional at 5 years, and only 60% to 70% are functional after 10 years. In contrast, >90% of LIMA-to-LAD artery grafts are patent 20 years after the operation.

b. IMA grafts have a better patency rate at 10 years when used for LAD lesions (95%) than for circumflex (88%) or right coronary artery (76%) lesions. The patency rates are higher for LIMA compared with RIMA and for in situ grafts compared with free grafts.

c. Patient survival is better with an IMA graft than when only saphenous venous grafts (SVGs) are used. This survival benefit persists for up to 20 years.

d. The radial artery graft was introduced into clinical practice around the year 1970. At approximately 1 year, 92% of the grafts are patent, and at 5 years, 80% to 85% of grafts are open. The patency rates of radial grafts are superior to those of SVG and RIMA grafts.

e. Bilateral internal mammary artery (BIMA) grafts are associated with superior overall long-term outcomes compared with LIMA + SVG grafting (HR 0.78; CI 0.72-0.84; $P < .00001$).

3. Previous CABG. Little information is available on the treatment of patients with stable angina who have already undergone bypass surgery. Although another bypass operation may be offered to these patients, it is important to understand that the risk of adverse events is higher with redo CABG. There is no direct comparison with medical treatment in this patient population that has not been made. The most recent ACC/AHA guidelines recommend PCI in patients with prior CABG who have one or more significant (greater than 70%) stenoses who have angina despite OMT.

4. Compared with PCI. This is discussed in the previous section.

F. Hybrid coronary revascularization. In some patients, in whom the aorta is calcified or who possess poor targets for full surgical revascularization, hybrid revascularization is an option. In this procedure, a combination of bypasses (almost always including the LIMA anastomosed to the LAD) and PCI (to lesions unable to be bypassed) is performed. The procedure may be performed simultaneously, in a hybrid operating room, or, sequentially, with PCI occurring hours to days after CABG. Although no published randomized trials have assessed the efficacy and outcomes of this approach in comparison to traditional PCI or CABG, this procedure carries a class IIa, LOE B, recommendation in the most recent ACC/AHA guidelines.

V. RECOMMENDED APPROACH TO STABLE ANGINA

A. The following approach is suggested for the treatment of patients with stable angina.

1. It is reasonable to risk-stratify patients with stable angina using coronary CTA or, possibly, with stress testing with imaging, such as nuclear isotope imaging or echocardiography.

a. LV systolic function should be assessed with echocardiography to guide therapy and to identify patients with LV systolic dysfunction.

b. Patients with lower plaque burden, small perfusion defects or small wall motion abnormalities, high threshold for ischemia, normal LV systolic function, and clear symptoms should be treated with medication.

2. If symptoms continue after medical therapy is maximized, angiography should be planned. Coronary angiography should also be performed for patients with

evidence of impaired perfusion involving multiple territories, a low threshold for ischemia, and LV systolic dysfunction.

3. **Single-vessel disease.** If a patient has single-vessel CAD that does not involve the LMT or supply a large myocardial territory, medical management with risk factor modification is the appropriate first step.
   - **a.** Revascularization should be offered if patient cannot tolerate medical treatment or if patient has symptoms despite maximum medical therapy.
   - **b.** For single-vessel disease, PCI would be preferable to CABG.
4. **Multivessel disease.** If a patient has multivessel disease, medical treatment remains an alternative for patients who have normal LV systolic function, mild symptoms, and relatively smaller areas of myocardium at risk. However, there is a low threshold for referral for revascularization if patient has persistent symptoms.
   - **a.** The decision for multivessel PCI versus CABG in this group of patients should be made on an individual basis, taking into consideration the angiographic anatomy, LV function, patient comorbidities (especially diabetes), surgical risk, and patient preference.
     - **(1)** For patients with multivessel disease and diabetes, CABG would be preferable to PCI.
     - **(2)** For patients with multivessel disease and diabetes but are poor surgical candidates, PCI could be useful to reduce symptoms.
     - **(3)** For patients with multivessel disease, low complexity coronary anatomy, and no diabetes, patient-centered discussion regarding risks versus benefits of PCI and CABG should be discussed.
     - **(4)** For patients with multivessel disease, complex CAD, and elevated SYNTAX score >33, CABG would be preferable to PCI for survival advantage.
5. In patients with "unprotected" LMT stenosis, the previous recommendations of CABG in all patients who are able to undergo surgery have been revised. PCI for severe LMT disease may be appropriate in select patients.
6. Regardless of treatment strategy, aggressive risk factor modification, including use of lipid-lowering agents, lifestyle modification, and aspirin therapy, is an essential component of management.

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CHAPTER 6

Other Ischemic Syndromes: Spontaneous Coronary Artery Dissection, Coronary Microvascular Dysfunction, and Takotsubo Cardiomyopathy

Mohammad Zmaili and Claire Raphael

I. SPONTANEOUS CORONARY ARTERY DISSECTION

A. Introduction. Spontaneous coronary artery dissection (SCAD) is defined as noniatrogenic separation (dissection) of the layers of the coronary artery, not associated with atheroma or trauma. The space between the separated layers fills with blood, known as intramural hematoma (IMH). Disruption of coronary artery flow may occur due to the intimal dissection flap impeding coronary flow or IMH impinging on the true lumen. Patients are usually younger and female compared to atherosclerotic myocardial infarction (MI), with a mean age at presentation of 47 to 53 years old. SCAD accounts for approximately 20% of MI in women under 50 years old, and about 20% of MI during gestation or in the peripartum period.

B. Presentation. SCAD manifestations are similar to atherosclerotic acute coronary syndrome (ACS), with chest pain being the most commonly reported symptom. Patients usually have a lower burden of cardiovascular risk factors compared to those with atherosclerotic MI and are usually younger, making under-investigation more common. Up to half of patients present with ST-elevation myocardial infarction (STEMI), and a small percentage have malignant ventricular arrhythmias or cardiogenic shock upon presentation. There may be an inciting emotional or physical stressor.

C. Mechanisms. Initially, it was thought that SCAD began with an intimal dissection flap; however, most recently, the inciting event is thought to be development of spontaneous IMH. IMH has been visualized in the absence of a visible dissection flap using intracoronary imaging.

SCAD is classified into three main types based on the angiographic appearance of the coronary vasculature:

1. **Type I:** Dual- or multiple-lumen appearance with delayed contrast clearance signifying the presence of true and false lumens
2. **Type II (most common)**: Smooth stenosis in a long (typically >20 mm) coronary arterial segment due to compressed true lumen. The affected segment can either be interposed between normal-appearing segments (type IIA) or extend all the way to the distal vessel (type IIB).
3. **Type III (rare):** A focal or tubular stenosis that mimics an atherosclerotic lesion. Usually requires intracoronary imaging to establish the diagnosis

   A fourth type has been proposed in which the vessel is totally occluded. The diagnosis in this case can be made after the exclusion of embolic etiologies and after restoration of coronary flow.

D. Diagnosis. The diagnosis of SCAD is usually made with invasive coronary angiography. Computed tomographic coronary angiogram (CTCA) may be diagnostic, but a normal CTCA cannot rule out SCAD due to the limited spatial resolution, particularly of the distal vessels. ACS or cardiac arrest in a young female patient who has low cardiovascular risk profile should raise a concern for SCAD. Patients with SCAD are at risk of missed diagnosis due to their young age and lack of atherosclerotic risk factors. The classic angiographic appearance that is characteristic of SCAD (type I) is seen in less than one-third of cases. If type II SCAD is suspected based on the angiographic appearance, intracoronary nitroglycerin is recommended to eliminate any vasospastic component to the stenotic segment. Coronary vasculature that is tortuous and free from atherosclerotic features can be suggestive of SCAD. When diagnosis

is in doubt, intracoronary imaging, either intravascular ultrasound (IVUS) or optical coherence tomography (OCT), is very helpful. Repeat coronary imaging (angiography or CT) in 6 to 8 weeks may be helpful in the case of diagnostic uncertainty or recurrent symptoms.

Patients who present with SCAD should be followed up in a specialist clinic. As there is a strong association between SCAD and fibromuscular dysplasia (FMD)/vascular abnormalities, patients should be thoroughly examined, especially peripheral pulses and auscultation for bruits. Imaging of the arteries from the brain to pelvis, usually with CT, may be performed to assess for FMD. FMD most commonly affects the renal arteries and extracranial carotid arteries, while 20% of persons with SCAD may also have intracranial aneurysm.

E. Therapy. Most SCAD cases are managed conservatively and most SCAD lesions demonstrate angiographic healing when reimaged 30 days or more after the index event. Coronary revascularization should be considered in situations where there is ischemia due to impaired coronary flow, hemodynamic instability, or high-risk anatomic findings, such as left main or proximal multivessel dissections. In these cases, balloon angioplasty or stent placement (percutaneous coronary intervention [PCI]) to restore flow in the coronary artery may be performed. In left main SCAD or SCAD where PCI has failed, emergency coronary artery bypass grafting (CABG) may be required. The major risk with either PCI or surgical intervention is extension of the original IMH/dissection and inadvertent wiring of the false rather than the true lumen, both of which may lead to worsening ischemia.

In clinically stable patients without high-risk features who are being managed conservatively, inpatient monitoring for at least 2 or 3 days is recommended. Fifteen percent of patients initially managed medically go on to deteriorate and need emergency revascularization. Randomized clinical trials for the role of pharmacotherapy in SCAD are ongoing, and there is scarce data to support SCAD-specific pharmacologic interventions. Nonetheless, recommendations based

on expert opinion and some retrospective observational data are briefly summarized as follows:

1. **Antiplatelet therapy**. Patients who receive PCI should be provided with guideline-based antiplatelet therapy with aspirin and P2Y12 inhibitor for 1 to 6 months depending on stent platform used. Patients who are managed conservatively are recommended aspirin therapy for at least 1 year based on expert opinion. Some experts recommend a short dual antiplatelet therapy course for up to 1 month following SCAD without PCI if bleeding risk is low.
2. **Beta-blockers**. Beta-blockers have been shown in an observational study to reduce the risk of recurrence, and their use is justified especially if there is concomitant hypertension. Beta-blockers may also help with angina as the SCAD heals.
3. **Statins**. There is no evidence-based data for routine statin use in patients with SCAD. Use should be limited to patients who have appropriate indication for statin therapy.
4. **Heart failure (HF) medical therapy.** Patients with left ventricular (LV) systolic dysfunction should be managed with guideline-directed medical therapy. Similarly, concurrent cardiovascular risk factors should be controlled and optimized.
5. **Antianginal therapy.** This can be provided for post-SCAD chest pain syndrome for symptomatic relief.
6. **Lifestyle changes.** Counseling on the avoidance of isometric and high-intensity endurance exercise is advisable to reduce the risk of recurrence.
7. **Referral to cardiac rehabilitation**

F. **Prognosis**. In-hospital mortality due to SCAD is low. Recurrent SCAD occurs in ~15% to 20% of cases over 3-year follow-up and may affect the same or a different coronary artery. Predictors of recurrent SCAD include severe coronary artery tortuosity, hypertension, migraine, and the presence of underlying FMD. Pregnant females who develop SCAD tend to have worse prognosis than nonpregnant patients. Preconception counseling and

multidisciplinary approach is recommended in female patients who wish to become pregnant after SCAD.

II. CORONARY MICROVASCULAR DYSFUNCTION

A. Introduction. Approximately 50% of patients referred for coronary angiography in the setting of chest pain do not have obstructive coronary artery disease (CAD) by angiography. About half of these patients have coronary microvascular dysfunction (CMD). CMD results from structural and/or functional abnormalities of the coronary microcirculation, characterized by reduced coronary blood flow and/or increased microvascular resistance under conditions of increased myocardial oxygen demand. Microvascular angina (MVA) is the clinical manifestation of CMD that results from myocardial ischemia. CMD is associated with an increased risk of cardiac events, hospitalization, MI, and coronary revascularization, and the primary goal of treatment is cardiac risk factor modification.

B. Presentation. Angina in the absence of obstructive CAD was previously referred to as Syndrome X. However, these patients constitute a heterogeneous group, including coronary spasm and noncardiac chest pain; therefore, this terminology has been largely abandoned. In contemporary practice, the term *ischemia with nonobstructive coronary arteries* (INOCA) or *angina with nonobstructive coronary arteries* (ANOCA) is used to refer to the subset of patients with suspected cardiac chest pain in the absence of obstructive CAD. INOCA is more common in female patients. Patients with INOCA and CMD have higher rates of traditional atherosclerotic risk factors such as diabetes mellitus and hypertension compared with healthy controls. Chronic inflammatory diseases have also been associated with higher rates of CMD.

C. Mechanisms. Angina in obstructive CAD arises from a fixed epicardial stenosis, leading to inadequate myocardial oxygen supply during periods of increased demand. Similarly, INOCA results from an imbalance between oxygen supply and demand, which in this context can be caused by CMD, vasospastic angina (VSA), or a combination of both.

CMD arises from structural changes (e.g., vessel wall thickening, medial smooth muscle hypertrophy), functional impairments (e.g., disrupted vasomotor regulation), or a combination of both. CMD is defined by low coronary flow reserve (CFR) and/or high microcirculatory resistance. **CFR** is the **ratio of myocardial blood flow (MBF) during peak stress or vasodilation to MBF at rest**. CFR and microcirculatory resistance can be measured during induced hyperemia.

CMD can be further categorized into two types:

1. **Endothelial-dependent CMD:** Characterized by impaired microvascular vasodilation or paradoxical vasoconstriction in response to intracoronary acetylcholine.
2. **Nonendothelial-dependent CMD:** Diagnosed when CFR is reduced (<2.0) during maximal hyperemia, usually induced by adenosine.

D. Diagnosis. Whereas epicardial CAD can be reliably detected by both functional (nuclear myocardial perfusion imaging [MPI], exercise electrocardiogram [ECG], stress echocardiography) and anatomic (coronary angiography, CT) imaging strategies, CMD is diagnosed via functional testing, with demonstration of reduced CFR, high microvascular resistance, or abnormal response to acetylcholine.

1. CFR can be measured **invasively** in the cardiac catheterization lab using Doppler flow wire or thermodilution wire with intracoronary measurements.
2. CFR can be measured **noninvasively** by positron emission tomography (PET) or cardiovascular magnetic resonance assessment of myocardial perfusion at rest and during adenosine hyperemia. Doppler echocardiography can be used to measure CFR but requires a special probe. The American Health Association (AHA) defines CMD as a CFR ≤2.0, although values between 2.0 and 2.5 are often also considered to represent CMD, particularly in the presence of abnormal microvascular resistance.

E. Therapy. There is a paucity of evidence-based therapies for CMD and INOCA because of a lack of randomized trials in this area. General measures include lifestyle modifications and risk factor

optimization. Statins, angiotensin-converting enzyme (ACE) inhibitors, and weight loss in bariatric patients have been shown to improve endothelial function in small studies. Improvement in blood pressure and blood sugar control in hypertension and diabetes will improve microvascular function. L-Arginine has been shown to improve symptoms and coronary blood flow in endothelium-dependent CMD. Antianginal agents include calcium channel blockers, beta-blockers, ACE inhibitors, and ranolazine. Patients with VSA should be managed with calcium channel blockers (often requiring high doses) and sublingual nitrates for acute attacks.

F. Prognosis. Historically, the prognosis for patients with angina and normal coronary arteriograms was generally thought to be favorable with good long-term outcomes. However, it is now recognized that **CMD is associated with increased rates of major adverse cardiac events, stroke, HF, and death.** Therefore, a low CFR can have an incremental prognostic value when incorporated into patient's overall risk profile, with the lowest values being associated with the worst outcomes.

III. TAKOTSUBO (STRESS) CARDIOMYOPATHY

A. Introduction. Takotsubo or stress cardiomyopathy is a syndrome of **transient LV dysfunction, which occurs in the setting of intense physical or emotional distress**. The term *takotsubo* is derived from the Japanese word for octopus trap, and it was chosen due to the classic appearance of apical ballooning with preserved basal LV systolic function. The pathophysiology of this syndrome includes catecholamine-induced myocardial dysfunction and CMD. Takotsubo cardiomyopathy is most prevalent among postmenopausal women, and the presentation can often mimic acute MI with chest pain, abnormal ECG findings, and positive cardiac biomarkers. Therefore, the diagnosis is often confirmed only at the time of coronary angiography when no obstructive CAD is identified.

B. Presentation. Takotsubo cardiomyopathy is relatively infrequent, affecting only 2% of patients presenting with suspected ACS. An overwhelming majority (90%) are women and 90% are older than 50

years of age. Physical stress such as acute intercurrent illness is the most common precipitant, but emotional stress is also a common trigger. In one-third of cases, no trigger is identified. Physical stress is a more prevalent trigger among men, whereas emotional stress is more prevalent among women. Chest pain and dyspnea are the most common presenting symptoms, with 5% to 10% of patients presenting with cardiogenic shock.

C. **Mechanisms.** The underlying pathophysiology of stress cardiomyopathy is thought to be **catecholamine excess due to activation of the hypothalamic-pituitary-adrenal axis under a condition of extreme physical or emotional stress**. Similar LV dysfunction has been described in the setting of exogenous catecholamine use and other states of excess endogenous catecholamine production, such as pheochromocytoma. Supraphysiologic catecholamine levels have deleterious effects on the cardiac myocyte, including myocyte hypertrophy, damage to key structural and contractile proteins, and calcium excess. Stress cardiomyopathy is also associated with coronary vasomotor dysfunction at the epicardial and microvascular level, with increased vasoconstriction resulting in vasospasm and transient myocardial ischemia. In addition, systemic response to catecholamine surges includes peripheral vasoconstriction resulting in an acute increase in LV afterload, which may further contribute to LV systolic dysfunction. **The apex of the LV has a higher proportion of beta-adrenergic receptors**, which may account for the vulnerability of the LV apex to stress cardiomyopathy.

D. **Diagnosis.** Takotsubo **cardiomyopathy is diagnosed on clinical grounds** with characteristic findings of new or transient LV systolic dysfunction, absence of an alternative myopathic process (acute MI, myocarditis, tachycardia, pheochromocytoma), and a history of intense physical or emotional distress. This may include acute systemic illness. The vast majority of patients have elevated cardiac troponin levels, but the elevation in cardiac troponin is typically mild. ECG findings include dynamic ST-segment elevation and T-wave

inversion. **The ECG findings during stress cardiomyopathy can mimic those of an acute MI.**

1. **Echocardiography.** The characteristic echocardiographic finding is that of severe apical hypokinesis or akinesis with relatively preserved function of the LV base. **However, nonapical variants, including mid-ventricular, basal, focal, and global hypokinesis, have been reported with less frequency, as has involvement of the right ventricle.** LV ejection fraction is typically severely reduced during the acute phase of takotsubo cardiomyopathy, but in **most patients, LV systolic function recovers within 4 to 6 weeks after the acute presentation.**
2. **Cardiac magnetic resonance imaging (MRI).** In patients with an abnormal ECG, new LV dysfunction, and positive cardiac biomarkers, cardiac MRI is useful for discriminating takotsubo cardiomyopathy from other syndromes with similar presentation such as myocarditis or ACS with a recanalized coronary obstruction. In patients with takotsubo cardiomyopathy, **cardiac MRI shows no perfusion abnormalities and no evidence of delayed gadolinium enhancement suggestive of scar.** Acute myocarditis may be seen on short tau inversion recovery (STIR) or early gadolinium imaging, while recanalized coronary obstruction would usually result in early or late gadolinium subendocardial enhancement in a coronary distribution.
3. **Cardiac catheterization.** Because there is near-complete overlap between the clinical presentation of acute MI and takotsubo cardiomyopathy, **a coronary angiogram is required in almost all cases to exclude a culprit coronary lesion** that might account for the clinical findings.

E. Therapy. Treatment of takotsubo cardiomyopathy is multifaceted. The underlying physical or emotional trigger should be identified and mitigated if possible to try to prevent future episodes. In the acute phase, treatment is targeted at prevention and management of electrical and mechanical complications resulting from acute LV dysfunction such as ventricular tachycardia or cardiogenic shock, using conventional therapies for these complications. Medical

therapy for LV dysfunction is commonly prescribed, particularly ACE inhibitors/angiotensin receptor blockers and beta-blockers, which may help with ongoing sympathetic overactivation. There is no proven therapy to prevent recurrence of takotsubo cardiomyopathy.

F. Prognosis. Historically, the prognosis of takotsubo cardiomyopathy was felt to be favorable when compared with acute MI. However, some series reported **in-hospital mortality of 2% to 7%, which is similar to the in-hospital mortality of patients with STEMI**. The relatively high in-hospital mortality may reflect that it is often associated with other noncardiac acute comorbid illnesses. Although LV dysfunction is typically transient, it can be associated with lethal dysrhythmias and mechanical failure, such as cardiogenic shock or LV outflow tract obstruction. The annual rate of recurrence of takotsubo cardiomyopathy is about 1% to 3% per year with recurrences more common in patients younger than 50 years of age.

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SECTION II

Heart Failure and Transplant

EDITOR: W. H. Wilson Tang

CHAPTER 7

Heart Failure With Systolic Dysfunction

Alejandro Duran Crane and Chonyang Albert

I. INTRODUCTION. Heart failure (HF) is a complex clinical syndrome characterized by impaired myocardial performance and progressive maladaptive neurohormonal activation of the cardiovascular and renal systems, leading to circulatory insufficiency and congestion. Currently, acutely decompensated heart failure (ADHF) constitute the most common indication for hospitalization in adults over age 65. In 2012, age-adjusted death rate per capita for HF increased for the first time in the United States, and U.S. hospitalizations for HF as well as deaths attributed from HF have increased in the United States over the past decade. With the increasing age of the population, improved patient survival with acute coronary syndrome, and reduced mortality from other diseases, the prevalence and attendant cost of managing patients with HF will inevitably continue to increase.

A. Terminology

1. Based on the hemodynamic model, systolic HF has been defined by the presence of impaired contractility of the left ventricle (LV), commonly conveyed by an impaired left ventricular ejection fraction (LVEF). This drop in contractility may be associated with chamber dilation and decreased stroke volume (**Figure 7.1**). The universal definition of HF was published in 2021, categorizing HF into four categories: (1) **HF with reduced ejection fraction (HFrEF**, defined as LVEF ≤40%); (2) **HF with mildly reduced ejection fraction** (HFmrEF, defined as LVEF 41%-49%); (3) **HF with preserved ejection fraction** (HFpEF), defined as LVEF ≥50% (see Chapter 8); and (4) **HF with improved ejection**

fraction (HFimpEF, defined as prior HFrEF but improved to LVEF >40%).

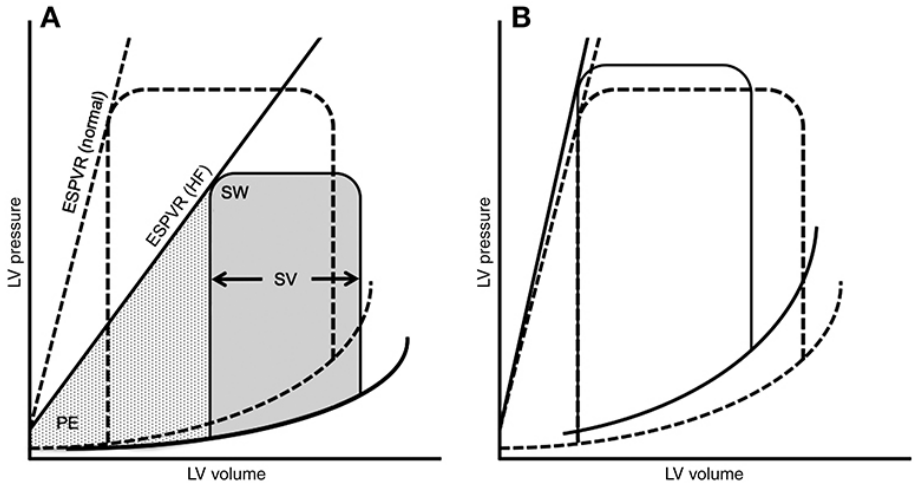

FIGURE 7.1 Pressure-volume loops in patients with normal heart (dashed line) and those with heart failure (HF; solid line). **A.** Pressure-volume loops in HF with impaired ejection fraction typically demonstrate a reduction in the end-systolic pressure-volume relationship (ESPVR; ie, the end-systolic elastance), a representation of contractility. This is typically accompanied by an increase in end-diastolic volume and a reduction in stroke volume (SV) and stroke work (SW; shaded area). At a given ESPVR, a reduction in end-systolic pressure results in an increased SV and reduction in the left ventricular (LV) elastic potential energy (PE; speckled area). **B.** In contrast, patients with HF with preserved ejection fraction have a normal or elevated ESPVR with a left and upward shift in the end-diastolic pressure-volume relationship reflecting decreased myocardial compliance.

2. Diagnosis of HFmrEF and HFpEF requires evidence of spontaneous or provokable increased LV filling pressures by noninvasive or invasive methods (ie, elevated natriuretic peptide, evidence of diastolic dysfunction on echocardiography, or increased filling pressures on invasive hemodynamic testing).
3. There is a growing appreciation for the limitations of this classification. The threshold for systolic dysfunction is arbitrary, and it is now clear that patients with HFpEF may suffer similar morbidity and mortality.

4. In practice, HF is a bedside diagnosis that is defined by clinical assessment. Patients may have cardiac dysfunction without symptoms, often referred to as **asymptomatic LV dysfunction**. It is important to emphasize that patients may not complain about signs and symptoms of HF, yet they may experience them upon exertion.
5. The major pathophysiologic process in the progression of HF is **cardiac remodeling**, progressive chamber enlargement with an obligatory reduction in EF. From a histopathologic standpoint, this is associated with myocyte hypertrophy, fibrosis, apoptosis, and necrosis. Molecular alterations including reexpression of a fetal gene program and alterations in excitation-contraction coupling, and regulatory proteins occur.
6. **Myocardial recovery** or **reverse remodeling** is possible with pharmacologic and device therapy.
7. The term **congestive HF** is often being applied to states of hypervolemia unrelated to cardiac dysfunction. Conversely, not all patients with HF have signs and symptoms of congestion or impaired perfusion (low cardiac output).
8. The term **right-sided HF** is used to describe patients with predominantly peripheral signs and symptoms of peripheral or tissue congestion with a relative paucity of central or pulmonary congestion.
9. **Acutely decompensated heart failure (ADHF)** refers to an episode of acute or subacute deterioration because of a wide range of precipitants. Most of these events are marked by systemic and/or pulmonary congestion (**Table 7.1**).

TABLE 7.1 Classification of Heart Failure by LVEF

Type of Heart Failure Depending on LVEF	Criteria
HFrEF (HF with reduced EF)	LVEF ≤40%

Type of Heart Failure Depending on LVEF	Criteria
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%-49% and evidence of spontaneous or provokable increased LV filling pressures (ie, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% and evidence of spontaneous or provokable increased LV filling pressures (ie, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

EF, ejection fraction; HF, heart failure; HFimpEF, HF with improved ejection fraction; HFmrEF, HF with mildly reduced ejection fraction; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LV; left ventricle; LVEF, left ventricular ejection fraction.

II. PATHOGENESIS. HF is a progressive disorder initiated by some form of injury or inciting event. This injury may range from acute disruptions in myocardial function to one of several chronic derangements, including familial, infiltrative, metabolic cardiomyopathies, or chronic volume or pressure overloading states related to valvulopathies, intracardiac shunts, systemic/pulmonary hypertension, or conduction abnormalities. Regardless of the initial insult, the acute beneficial compensatory mechanisms ultimately become maladaptive.

A. Neurohormonal activation

1. Activation of the sympathetic nervous system. Chronic activation of the sympathetic nervous system ultimately results in decreased beta-adrenergic receptor responsiveness, decreased norepinephrine stores, and sympathetic innervation of the myocardium. Chronically, these changes contribute to myocyte hypertrophy, fibrosis, and necrosis. Extracardiac effects include increased tubular reabsorption of sodium, activation of the renin-angiotensin-aldosterone system (RAAS), neurogenic and systemic vasoconstriction, and vascular hypertrophy.

2. **Activation of the RAAS.** As HF progresses, renal hypoperfusion and sympathetic stimulation of the kidneys result in increased production of renin by the juxtaglomerular apparatus. Renin cleaves circulating angiotensinogen into the biologically inactive angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to the biologically active angiotensin II. Importantly, renin and ACE-independent pathways can generate angiotensin II. In addition to direct cardiovascular effects, angiotensin II stimulates aldosterone production by the zona glomerulosa within the adrenal cortex, which, in turn, promotes reabsorption of sodium in exchange for potassium in the distal tubule and collecting ducts of the nephron. Over time, increased aldosterone levels result in the promotion of vascular and myocardial hypertrophy and fibrosis, endothelial dysfunction, and inhibition of norepinephrine uptake.
3. **Other neurohormonal derangements.** Inappropriate production of arginine vasopressin has an antidiuretic effect and augments systemic vasoconstriction. Endothelin, neuropeptide Y, and other peripheral vasoconstrictors further enhance vascular tone.

III. CLASSIFICATION

A. The American College of Cardiology/American Heart Association (ACC/AHA) guidelines currently classify HF on the basis of the evolution of the disease across a continuum (always progressive, no reversal):

1. **Stage A.** Patients at high risk for developing HF without structural heart disease or symptomatic HF
2. **Stage B.** Patients with structural heart disease who have not yet developed symptoms of HF. Recent universal definition has also defined elevated natriuretic peptide levels (N-terminal pro–B-type natriuretic peptide [NT-proBNP] >125 pg/mL or B-type natriuretic peptide [BNP] ≥35 pg/mL) in the absence of overt HF signs and symptoms as a defining criterion for stage B HF.
3. **Stage C.** Patients with structural heart disease with prior or current symptoms of HF

4. **Stage D.** Patients with refractory end-stage HF who require specialized advanced treatment

B. The **New York Heart Association (NYHA) functional classification**, although subjective and vague, remains the most commonly used standard by which the severity of functional impairment is graded (**Table 7.2**).

TABLE 7.2 New York Heart Association Functional Classification of Heart Failure

Class	Description
I	Patients have cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in an inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

C. The **Killip classification** grades the severity of acute decompensated HF in the post–acute coronary syndrome setting and is predictive of 30-day mortality.

1. **Killip I.** Patients with no clinical evidence of HF
2. **Killip II.** Patients with mild signs of HF: S_3, elevated jugular venous pressure (JVP), or pulmonary crackles
3. **Killip III.** Patients with acute pulmonary edema
4. **Killip IV.** Patients with cardiogenic shock

IV. ETIOLOGY. It is essential to make every effort to identify the specific etiology of HF because it may have implications for management and prognosis. Whereas ischemic cardiomyopathy is by far the most

common cause of systolic HF, a diverse array of disease states can culminate in this phenotype (**Table 7.3**).

TABLE 7.3 Etiologies of Heart Failure

Ischemic cardiomyopathy
Idiopathic cardiomyopathy
Familial cardiomyopathy
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Arrhythmogenic heart disease
Valvular heart disease
Hypertension
Inflammatory (lymphocytic, eosinophilic, giant cell myocarditis)
Amyloidosis
Sarcoidosis
Infectious (Chagas disease, Lyme disease, HIV, enterovirus, adenovirus, CMV, bacterial or fungal infections)
Toxins (alcohol, catecholamines, cocaine, anthracyclines, chloroquine, and other chemotherapeutics, radiation)
Endocrine (thyroid diseases, adrenal insufficiency, pheochromocytoma, acromegaly, diabetes mellitus)
Stress-induced (Takotsubo) cardiomyopathy
Peripartum cardiomyopathy
LV noncompaction
Mitochondrial cardiomyopathy
Fibroelastosis
Familial storage disease (hemochromatosis, glycogen storage disease, Hurler syndrome, Anderson-Fabry disease)
Electrolyte deficiency syndromes (hypokalemia, hypomagnesemia)
Nutritional deficiencies (L-carnitine, iron, thiamine, and selenium deficiency)

Familial Mediterranean fever
Systemic diseases
Connective tissue disorders (SLE, polyarteritis nodosa, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis, sarcoidosis)
Muscular dystrophies (Duchenne, Becker, myotonic, limb girdle)
Neuromuscular (Friedreich ataxia, Noonan disease)

CMV, cytomegalovirus; HIV, human immunodeficiency virus; LV, left ventricular; SLE, systemic lupus erythematosus.

A. **Ischemic cardiomyopathy** accounts for almost half of the cases of systolic HF in industrialized countries. It is defined as **cardiomyopathy in the presence of prior extensive myocardial infarction, hibernating myocardium, or severe coronary artery disease (CAD)**. However, the mere **presence of obstructive CAD does not equal ischemic cardiomyopathy because it is possible to have CAD superimposed with a nonischemic etiology of HF**. A careful assessment of the coronary anatomy, ischemic burden, and the presence of infarcted and viable myocardium must be made, and an assessment of the proportionality of these findings to the degree of myocardial dysfunction should be determined. The risks and benefits of percutaneous or surgical revascularization should be assessed in all patients with ischemic cardiomyopathy. Extensive observational data have suggested a benefit for coronary artery bypass grafting (CABG) compared with medical therapy alone in moderate-to-severe LV systolic dysfunction. Registry data suggest that CABG is superior to percutaneous coronary intervention (PCI) in patients with reduced LVEF, especially in patients with diabetes mellitus. The Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated a significant reduction in all-cause mortality, cardiovascular death, and HF hospitalization in the CABG plus medical therapy cohort compared with the medical therapy alone in patients with an EF <35%. Notably, patients with left main trunk disease and severe angina were excluded from the study, and these patients should continue to be treated aggressively with revascularization. In the Revascularization for Ischemic Ventricular Dysfunction trial,

percutaneous intervention in patients with severe LV dysfunction, treated with optimal medical therapy, was not associated with a lower rate of death or hospitalization for HF.

B. **Nonischemic cardiomyopathy** represents a heterogeneous cohort of patients with systolic dysfunction not related to underlying CAD. Patients with **dilated cardiomyopathy typically have a better prognosis than their ischemic counterparts**. The following are some common etiologies of nonischemic cardiomyopathy:

1. **Subclinical viral myocarditis** can progress to dilated cardiomyopathy. Endomyocardial biopsy sensitivity remains poor, but molecular techniques such as reverse transcription polymerase chain reaction analysis demonstrate amplification of viral genomes in approximately two-thirds of cases and should be considered when the benefits outweigh the risks (see Chapter 11). Any virus can cause myocarditis, but coxsackie B virus and parvovirus B_{19} are the most epidemiologically important.
2. **Familial dilated cardiomyopathy.** It is now recognized that 25% to 50% of cases of dilated cardiomyopathy may have a genetic etiology. Conditions are typically autosomal dominant and show variable penetrance. A detailed **four-generation** family history is essential at the time of initial evaluation. If the family history suggests a genetic predisposition, or in young patients presenting with de novo HF, clinical screening of family members is appropriate, and genetic testing can be performed following referral to a genetic counselor. Importantly, only 40% of presumed familial dilated cardiomyopathies have identifiable genetic alterations.
3. **Hypertensive and diabetic cardiomyopathy** are seldom considered stand-alone diagnoses. Progression from LV hypertrophy to overt dysfunction in patients with hypertension (the so-called burnt-out hypertensive heart) most likely results from progressive microvascular ischemia. Hypertension and diabetes mellitus also contribute significantly to the development of CAD and ischemic cardiomyopathy.

4. **Cardiotoxic agents.** The list of toxins that can produce cardiomyopathy is extensive. Identification of the toxin and removal of the offending agent may halt the progression of or even reverse LV dysfunction.
   a. **Chemotherapeutic agents. Anthracycline** (doxorubicin, epirubicin, mitoxantrone) toxicity can cause myocyte destruction and cardiomyopathy in a dose-dependent manner. Patients who receive a cumulative doxorubicin equivalent dose of <400 mg/m^2 are at low risk for this syndrome, whereas those receiving a cumulative dose >700 mg/m^2 have an approximately 20% lifetime risk of developing cardiomyopathy. However, **cardiotoxicity can occur at any dose**. Doxorubicin is the most cardiotoxic. To minimize doxorubicin cardiotoxicity, the agent should be administered via a continuous infusion, not bolus, as a means to lower the peak plasma level and via a liposomal formulation to minimize cardiotoxicity. Alongside standard cardioprotective HF medications, **dexrazoxane** has been approved for patients receiving doxorubicin therapy to minimize cardiotoxicity. Other cardiotoxic drugs that require careful cardiac monitoring include **cyclophosphamide** and **trastuzumab**. Trastuzumab (Herceptin) is now frequently used in the treatment of human epidermal growth factor receptor 2–positive breast cancer and has been associated with cardiotoxicity in 8% to 30% of cases, which is reversible following drug cessation in approximately 60% of cases and can be rechallenged with close monitoring. Cardiotoxicity associated with trastuzumab is less frequent now when used without doxorubicin. Antiangiogenic drugs such as **sunitinib** can also cause cardiotoxicity and uncontrolled hypertension. **5-Fluorouracil** has been associated with both cardiomyopathy and severe coronary vasospasm. Immune checkpoint inhibitors can cause acute (and sometimes fulminant) myocarditis, although the majority of transient cardiac dysfunction following chemotherapy or radiation

therapy may also be attributed to acute myocarditis. See Chapter 42 for more detailed information.

b. **Alcohol** consumption (>5 drinks per day) is thought to represent a common cause of toxin-mediated cardiomyopathy. However, there is limited observational data on the actual incidence of cardiomyopathy or the volume of alcohol consumption necessary to induce it. Total abstinence from alcohol may result in complete resolution, whereas continued use is associated with a 3- to 6-year mortality exceeding 50%.

c. **Stimulant drugs** including cocaine and methamphetamines may result in the development of HF via multiple derangements, including progressive concentric hypertrophy and recurrent myocardial infarction. There have been considerations that therapeutic stimulants (such as amphetamine or ephedrine) can also cause HF, especially when misused.

d. **Toxin exposures** including lead, arsenic, and cobalt can result in progressive myocardial dysfunction. **Iron overload** from primary or secondary **hemochromatosis** may present with restrictive cardiomyopathy; it typically progresses to a mixed or dilated form. Treatment with chelating agents or phlebotomy may improve cardiac function in both primary and secondary forms.

5. **Inflammatory cardiomyopathy** (ie, myocarditis) is discussed in detail in Chapter 11.

6. **Tachyarrhythmia-induced cardiomyopathy** can complicate the course of atrial fibrillation, atrial flutter, ectopic atrial tachycardia, and even occult sustained ventricular tachycardia and frequent premature ventricular contractions (>10%-20% of beats). In general, it is thought that persistent tachycardia in excess of 110 beats/min is required to induce LV dysfunction. This is a critical diagnosis to make because treatment of the underlying tachyarrhythmia generally results in complete resolution of the cardiomyopathy.

7. **Peripartum cardiomyopathy** is defined as a dilated cardiomyopathy occurring between the last month of pregnancy and up to 5 months postpartum. Approximately 50% of peripartum cardiomyopathy patients improve with standard HF pharmacotherapy, but the morbidity and mortality continue to be high for those patients who do not demonstrate myocardial recovery. Risk factors include age >30, multiparity, African American, and hypertension or history of preeclampsia.
8. **Valvular disorders** are common causes of HF secondary to volume overload, pressure overload, or both. Aortic and mitral valve pathology can lead to progressive LV dysfunction (see Chapters 15 and 16). When appropriate, surgical correction is the preferred management of severe valvular lesions, or high-risk candidates could consider a percutaneous approach, for example, transcatheter aortic valve replacement, balloon valvuloplasty, or MitraClip.
9. **Stress (Takotsubo) cardiomyopathy** is an acute and transient condition characterized by decreased LF function with classic findings of apical ballooning on echocardiogram and can occur after acute emotional or physical stressors. ST elevations in precordial leads can be seen as well as subsequent T-wave inversions and Q waves. It is a diagnosis of exclusion; therefore, ischemic injury must usually be ruled out with coronary angiography.
10. **Thyroid disorders** can cause or worsen HFrEF. **Hypothyroidism** is common in patients with HF. Severe hypothyroidism (ie, myxedema) may cause decreased cardiac output and HF. Bradycardia and pericardial effusion can develop in extreme cases of hypothyroidism. LVEF may improve after weeks to months of adequate thyroid hormone supplementation. **Hyperthyroidism** can also lead to ADHF, which can be especially problematic in older patients with low ventricular reserve. Atrial fibrillation is a common accompanying arrhythmia, occurring in 9% to 22% of patients with thyrotoxicosis. Nonspecific symptoms such as fatigue, weight loss, and insomnia may predominate. Previously

stable angina may also become unstable. Patients treated with amiodarone may develop a wide range of thyroid disorders ranging from abnormal thyroid function tests to overt amiodarone-induced thyrotoxicosis or hypothyroidism. Both conditions can occur in otherwise normal thyroid glands.

11. **Thiamine deficiency (beriberi).** Although rare in industrialized countries, thiamine deficiency is still prevalent in the developing world. It can also occur in those with alcohol use disorder or individuals observing fad diets. *Wet beriberi* includes features of **high-output cardiac failure,** such as marked edema, peripheral vasodilatation, and pulmonary congestion. The signs and symptoms of *dry beriberi* include **glossitis, hyperkeratosis, and peripheral neuropathy**. The laboratory diagnosis is made by assessing erythrocyte transketolase and 24-hour urine thiamine levels. Severe cases can present with lactic acidosis. Intravenous (IV) therapy with 100 mg of thiamine followed by daily oral supplementation can result in dramatic clinical improvement. Chronic use of high-dose diuretics may be complicated by subclinical thiamine deficiency of unknown significance.
12. **Other nutritional deficiencies.** Carnitine and selenium deficiency may result in dilated cardiomyopathy complicating chronic parenteral nutrition.
13. **Anemia and iron deficiency.** Acute anemia caused by rapid blood loss is associated with decreased cardiac output because of hypovolemic shock. In contrast, chronic anemia can be associated with symptoms of HF because of compensatory mechanisms. These include fluid retention, increased cardiac output, decreased systemic vascular resistance, and increased 2,3-diphosphoglycerate with a resultant rightward shift in the oxyhemoglobin dissociation curve. Chronic anemia (hemoglobin <9 g/dL) may exacerbate or augment HF symptoms in patients with preexisting disease. Chronic anemia of severe proportion (hemoglobin <7 g/dL) may result in high-output HF, even in individuals with normal cardiac anatomy. Evaluation and management of the underlying cause and supportive care are

advised. Thresholds for transfusion depend on the clinical context and rapidity of blood loss. More than 50% of patients with chronic HF present with iron deficiency, and iron repletion should be considered in iron-deficient patients with IV iron with or without anemia. (See Section VII for current guideline recommendations regarding the management of iron deficiency anemia in stage C HF.)

14. **Inherited myopathies** such as Becker or Duchenne muscular dystrophy and myotonic dystrophy represent a group of dystrophinopathies that can be associated with a dilated cardiomyopathy. Friedreich ataxia is most commonly associated with hypertrophic cardiomyopathy but, in rare instances, can present with a dilated phenotype. Fabry disease can appear as hypertrophic cardiomyopathy. It is an X-linked, lysosomal storage disease and will have systemic manifestations, including acroparesthesias, renal dysfunction, and angiokeratomas. Mitochondrial cardiomyopathies may also present with dilated cardiomyopathy. Danon disease is an X-linked, glycogen storage disorder associated with a lysosomal-associated membrane protein-2 mutation. Dilated cardiomyopathies without conduction disease may be associated with a titin (TTN) mutation. Dilated cardiomyopathies with conduction disease may be associated with Lamin A/C mutations (see Chapter 39 for genetic cardiomyopathies).
15. **Cardiac sarcoidosis** can present with LV dysfunction with regional hypokinesis or aneurysmal dilatation. It is frequently associated with conduction abnormalities and ventricular tachyarrhythmias. Elevated sedimentation rate may be present but is nonspecific, as are elevated immunoglobulins, ACE levels, or hypercalcemia. Classic basal septal thinning can be appreciated in echocardiography. The diagnosis can be supported with stereotypical findings on cardiac magnetic resonance (CMR) imaging or positron emission tomography (PET). The diagnosis is relatively rare in the absence of extracardiac manifestations.

16. **Amyloidosis** can impact cardiac function secondary to the deposition of insoluble proteins within the myocardial matrix. In the early stages, it may be present as HFpEF, but in the late stages, it may present as HFrEF and can have both a dilated and nondilated appearance. Cardiac amyloidosis is primarily due to either transthyretin (TTR)—senile/wild-type versus mutant—or primary amyloidosis, which is secondary to a light chain dyscrasia: κ or λ (see Chapter 9).
17. **Chagas disease** caused by the flagellate protozoan *Trypanosoma cruzi*, this entity remains a common cause of HF in patients from Latin America. In the chronic symptomatic phase, patients typically present with a syndrome of ventricular dysfunction with regional wall motion abnormalities in the absence of obstructive CAD. Ventricular arrhythmias are often present. Late gadolinium enhancement (LGE) can be seen in MRI, usually compromising apical and inferolateral walls, and apical aneurysms can be seen. This pattern should prompt *T. cruzi* titers in patients from endemic regions.

V. SIGNS AND SYMPTOMS

A. There is a wide spectrum of signs and symptoms in patients with HF. Subjective changes in signs and symptoms are often difficult to elicit and frequently leave insufficient time lag for therapeutic interventions prior to hospitalization.

1. The most common and earliest presenting symptom is **dyspnea**, typically with exertion. **Orthopnea** is typical with more advanced disease. It is among the most sensitive (90%) and specific (90%) signs of decompensated HF. With further decompensation, paroxysmal nocturnal dyspnea and Cheyne-Stokes respiration may occur. **Bendopnea** (increased shortness of breath with prolonged bending over) is a recently described sign of elevated intracardiac filling pressures.
2. **Fatigue** and **exercise intolerance** are common complaints in patients with HF and may reflect diminished cardiac output.

Seldom considered but highly prevalent symptoms include anorexia, **nocturnal cough, insomnia, and depressed mood**.

3. **Syncope** may occur in patients with underlying arrhythmia, severe cardiac dysfunction, or pulmonary arterial hypertension and requires prompt evaluation.
4. **Anorexia**, **abdominal pain**, and **bloating** are common in advanced right HF. Unexplained weight loss and sarcopenia are poor prognostic signs associated with cardiac cachexia.

B. **Physical examination** of patients with significant but well-compensated systolic HF may reveal no abnormalities. Physical signs vary according to the degree of compensation, chronicity, and chamber involvement.

1. **Volume overload** is the hallmark of HF. Typical signs of volume overload include the following:
   a. **Weight gain** is a sensitive indicator of congestion.
   b. **Pulmonary rales** because of accumulation of fluid in the pulmonary interstitium and alveoli secondary to high left atrial pressure are commonly referred to as **acute cardiogenic pulmonary edema**. Importantly, rales may be absent in patients with chronic systolic HF who develop compensatory perivascular and lymphatic changes.
   c. **Jugular venous distention or elevated JVP,** although not directly reflecting left-sided filling pressures, can track these with a reasonable sensitivity (70%) and specificity (79%). JVP should be assessed at a 45° incline with the neck fully exposed. In cases of extreme JVP elevation, the patient may need to be seated upright to facilitate visualization. Five centimeters of water should be added to the vertical distance from the sternal angle to the meniscus of the JVP to account for the distance to the midpoint of the right atrium (RA). Compression of the right upper quadrant and a resultant positive **hepatojugular reflex** (defined as a sustained increase in JVP of ≥4 cm) increase the sensitivity of the JVP for detecting congestion.

d. **Pedal edema** by some estimates is only present in 30% of patients with decompensated HF and is somewhat nonspecific, because it may reflect venous insufficiency, nephrotic syndrome, hepatic dysfunction, or concomitant treatment with specific medications, such as calcium channel blockers or thiazolidinediones.

2. **Ascites and hepatomegaly** may occur. Severe tricuspid regurgitation may be present in the setting of a palpable, pulsatile liver.
3. A holosystolic murmur of mitral regurgitation (MR) is often present in the setting of LV dilatation.
4. **A third heart sound** (S_3 gallop) is best heard with the bell of the stethoscope in the left lateral position and signifies increased LV end-diastolic pressure. Often neglected are the subtle signs of **peripheral hypoperfusion**.
5. **Pulsus alternans** or a low-amplitude pulse in the absence of alternative explanations reflects severely impaired cardiac output.
6. Tachycardia and narrow pulse pressure also suggest diminished cardiac output.
7. Lethargy, pallor, mottled skin, cool extremities, and poor capillary refill are typical signs.
8. **Hypotension** itself may be one of the most important clinical findings in HF. Several studies have demonstrated that a systolic blood pressure <90 mm Hg is a strong predictor of morbidity and mortality.

VI. DIAGNOSTIC EVALUATION

A. **Laboratory work** is used to diagnose potentially reversible causes, identify comorbidities, monitor and correct abnormalities before or during treatment, and assess the disease severity.

1. A **comprehensive metabolic panel** should be assessed on initial evaluation and then subsequently based on clinical judgment. Particular attention should be paid to the presence of hyponatremia, which portends a worse prognosis. **Hypokalemia** is

common in the setting of ongoing diuretic therapy. **Hyperkalemia** can be seen in the context of overaggressive potassium repletion and ongoing treatment with renin-angiotensin-aldosterone antagonists, or K-sparing diuretics, or in patients with diabetes with associated type IV renal tubular acidosis. Aside from the pragmatic considerations, many real-world registries have identified elevated blood urea nitrogen (BUN) and creatinine as powerful predictors of outcome. Renal function must also be taken into account when considering therapy. In the context of chronic, congestive right HF, liver function testing abnormalities are most consistent with cholestasis.

2. **Anemia** is present in up to 40% of patients with HF and is associated with increased mortality and functional impairment. Although frequently because of anemia of chronic disease, a thorough diagnostic evaluation should be performed. Iron deficiency (in the absence of anemia) is also common. **Iron, total iron binding capacity (TIBC), and ferritin** should be ordered to determine if patient is a candidate for iron supplementation with or without underlying anemia.
3. The natriuretic peptides **BNP and NT-proBNP** are released in the setting of increased ventricular dilation or wall stress. Normal ranges (BNP <100 pg/mL; NT-proBNP <125 pg/mL if age <75 years and <450 pg/mL if age ≥75 years) must be interpreted in the context of associated conditions known to alter levels. **Increasing age, female sex, anemia, and worsening renal function are associated with increased levels.**
    a. **Screening for HF.** Although cardiac dysfunction has been associated with elevated natriuretic peptide levels, the sensitivity is relatively low in asymptomatic patients and is highly dependent on the cutoff levels chosen. In general, routine assessment of natriuretic peptide is not recommended as a general screening test for structural heart disease in asymptomatic patients, although there is evolving clinical evidence and guideline recommendations supporting natriuretic

peptide testing for at-risk patients (eg, history of CAD, diabetes mellitus).

b. **Diagnosing HF.** The primary use of natriuretic peptides remains the diagnosis of HF in symptomatic patients, particularly when the diagnosis is unclear. The high negative predictive value (up to 90%) in this setting allows BNP testing to be useful to rule out a cardiac cause of symptoms. With the growing obesity epidemic, it is important to remember that ***normal natriuretic peptide levels may be present in patients who are morbidly obese with decompensated HF***. Other noncardiac causes of elevated natriuretic peptides include sepsis, pulmonary disease, pulmonary hypertension, and critical illness.

c. **Management of HF.** Although controversial, there is emerging evidence that serial measurements of natriuretic peptides may be beneficial in guiding outpatient HF management and may result in decreased HF-related mortality versus usual care. Post-HF hospitalization assessment or predischarge natriuretic assessment can aid in additional prognostic information. Of note, BNP is a substrate for neprilysin; therefore, if a patient is on an angiotensin receptor neprilysin inhibitor (ARNI), it cannot be used to follow a patient's clinical course. However, NT-proBNP levels will not be impacted.

d. **Determining prognosis of HF.** Natriuretic peptide levels correlate with morbidity and mortality in patients with both established HF and other cardiovascular diagnoses (eg, stable CAD, acute coronary syndromes, pulmonary hypertension, and atrial fibrillation).

4. **Other biomarkers.** Cardiac troponin T or I may be elevated in chronic HF and demonstrate ongoing myocyte injury. Alongside natriuretic peptides and troponins, a growing list of biomarkers assessing systemic inflammation, oxidative stress, extracellular matrix remodeling, myocardial fibrosis, and myocyte injury is commercially available or in development (eg, soluble ST2, cystatin C, galectin-3). Whereas some of these provide useful

prognostic information, it remains unclear on how to best integrate into the routine diagnosis and management of HF.

5. **Thyroid function testing** is warranted for all patients with a new diagnosis of HF.
6. Iron studies including ferritin, serum iron, and TIBC (with calculation of percent transferrin saturation) should be performed to screen for hemochromatosis and occult iron deficiency.
7. Standard laboratory screening for **modifiable cardiovascular risk factors** including fasting lipid panel and serum glucose should also be obtained. When clinical suspicion is heightened, consider additional screening for human immunodeficiency virus, rheumatologic processes, and amyloidosis.

B. The electrocardiogram (ECG) provides important information pertaining to the cause and management of HF and is a recommended component of the evaluation of any patient with a clinical diagnosis of HF and change in clinical status.

1. It is important to look for evidence of prior myocardial infarction, chamber enlargement and hypertrophy, conduction disease, and supraventricular or ventricular arrhythmias.
2. Specific diagnoses can be suggested utilizing the ECG. Cardiac amyloidosis may classically present with low voltage and a pseudoinfarction pattern in the anterior leads in stark contrast to thickened walls observed on echo. Arrhythmogenic right ventricular (RV) dysplasia may present with epsilon waves or localized prolongation (>110 ms) of the QRS complex in the right precordial leads.
3. The ECG is an important means of assessing **dyssynchrony**. Marked first-degree atrioventricular (AV) block or very short AV delays in the presence of paced rhythms may contribute to AV dyssynchrony. The presence of QRS prolongation >120 ms (particularly left bundle branch block) suggests interventricular dyssynchrony and remains the most important predictor of response to cardiac resynchronization therapy (CRT-D).

4. **Holter or event monitors** are often useful in identifying occult arrhythmia, arrhythmia burden, and conduction abnormalities.

C. Examination of the **chest radiograph** should include an assessment of the heart size, pleura, and the condition of the pulmonary parenchyma. Determination of cardiac size is best restricted to standard posteroanterior projection, because "portable" anteroposterior projection will magnify the cardiac silhouette. The lateral projection is useful to assess for RV enlargement with associated filling of the retrosternal space and pleural effusion(s). A normal cardiac silhouette does not exclude systolic or diastolic dysfunction. The lung field abnormalities may range from mild engorgement of the perihilar vessels to bilateral pleural effusions, Kerley B lines, and frank pulmonary edema.

D. Echocardiography is perhaps the most useful diagnostic test in the evaluation of patients with HF. It can provide useful information pertaining to the etiology and prognosis of HF. As described in later sections, echocardiography also plays a key role in guiding HF therapy.

1. **Etiology of HF.** Regional wall motion abnormalities occurring in an anatomic coronary artery distribution are suggestive of ischemic cardiomyopathy. However, regional wall motion abnormalities can also be seen in the context of nonischemic dilated cardiomyopathy, stress-induced cardiomyopathy, and infiltrative cardiomyopathies (with inferobasal wall motion abnormalities classically seen in the setting of cardiac sarcoidosis). The presence and severity of valvular stenosis or insufficiency can be assessed as can the relative dysfunction of the RV and LV.
2. **Prognosis in HF.** The following parameters are useful in assessing the risk of HF-associated morbidity and mortality:
   a. **LVEF and LV dimensions** may not correlate with HF symptoms. However, exercise capacity, oxygen consumption, and EF provide valuable prognostic information. Morbidity and mortality are linked to EF and LV volumes. The American

Society of Echocardiography recommends EF and LV volume assessment by Simpson biplane method.

b. **LV mass.** Cardiac remodeling results in increased LV mass because of eccentric hypertrophy, which worsens prognosis. Eccentric hypertrophy is defined echocardiographically as an LV mass >95 g/m^2 in women and >115 g/m^2 in men with a regional wall thickness (2 × posterior wall thickness/LV end-diastolic dimension) of ≤0.42.

c. **The myocardial performance index (Tei index)** provides a useful assessment of systolic and diastolic function and is equal to the (isovolumic contraction time + the isovolumic relaxation time)/the ejection time. All dimensions are obtained via pulsed wave or tissue Doppler. A Tei index of >0.77 in patients with dilated cardiomyopathy is highly predictive of cardiovascular morbidity and mortality.

d. **Measures of diastolic dysfunction.** Many of the measures of diastolic dysfunction detailed in Chapter 9 have powerful prognostic ability in patients with systolic HF. The presence of a restrictive filling pattern (*E*/*A* >2, deceleration time <115-150 ms) persisting despite Valsalva maneuver is a particularly ominous finding.

E. Other imaging modalities

1. **CMR imaging** (Chapter 52). CMR offers unparalleled myocardial tissue characterization and allows for myocardial viability assessment. It is an increasingly useful tool in the diagnosis of specific cardiomyopathies (eg, LV noncompaction, cardiac sarcoidosis, and amyloidosis). The distribution of late gadolinium hyperenhancement representing scar can effectively discriminate between ischemic and nonischemic causes of fibrosis. Cine MRI provides accurate assessments of chamber volumes and LV and RV systolic function that can be performed in arbitrary tomographic views. Major limitations are incompatibility with implanted electronic cardiovascular devices and the potential for nephrogenic sclerosing fibrosis in patients with preexisting renal insufficiency.

2. **Nuclear imaging.** Single-photon emission computed tomography (SPECT) and PET imaging are primarily of use in ruling out myocardial ischemia and/or viability as well as metabolic activity. **Viability assessment** (ie, discriminating between scarred and hibernating myocardium) is critical in the assessment of patients with HF and CAD and the potential for myocardial recovery with revascularization. This can be achieved with PET using concomitant flow and metabolism tracers (typically [^{18}F] fluorodeoxyglucose) or thallium-201 versus technetium-99m SPECT redistribution imaging (see Chapter 49). There is growing evidence that PET is superior to SPECT in patients with systolic dysfunction, and when available, it should be used preferentially in patients with an LVEF <35%. Dobutamine stress echocardiography and CMR are alternative means of assessing viability. Radionuclide ventriculography using multiple-gated acquisition scanning has long served as the gold standard for precise serial measurements of the LVEF (classically in the evaluation of patients receiving cardiotoxic chemotherapeutics). Increasingly, however, it is being surpassed by CMR and three-dimensional echocardiography. A **technetium pyrophosphate scan** is an additional nuclear modality that can be used to assess for TTR (wild-type or mutant) amyloidosis with high specificity and sensitivity.

F. Right heart catheterization (see Chapter 60). Invasive hemodynamic monitoring is often helpful in the diagnosis and inpatient management of HF. Right heart catheterization can be combined with exercise testing or addition of inotropic or vasodilatory agents to evaluate the impact on hemodynamics. Indications for right heart catheterization include short-term management of acute cardiogenic shock, evaluation of patients for cardiac transplantation or mechanical circulatory support, clarification of hemodynamics in the context-specific comorbidities (eg, suspected RV infarction or mechanical complications of myocardial infarction), and clarification and optimization of medical therapy in patients with recurrent or refractory symptoms.

1. **Cardiac output/index** can be determined by thermodilution or the Fick method using estimated or measured oxygen consumption and a directly measured mixed venous oxygen saturation (MVO_2).
2. **Pulmonary capillary wedge pressure (PCWP)** should be measured in all cases. An inability to normalize the PCWP (<16 mm Hg) with pharmacotherapy was shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial to confer a 2-fold increased risk of mortality.
3. **RA pressure** is an important indicator of volume status and right heart function. An elevated central venous pressure has been shown to be the most important predictor of worsening renal function during hospitalizations for acute decompensated HF. RA pressure-to-PCWP ratio >0.63 or an RV stroke work index <400 portends RV dysfunction.

G. Coronary angiography (see Chapter 63). There are many approaches to determining which patients with systolic HF warrant evaluation by coronary angiography. The Heart Failure Society of America, American College of Cardiology Foundation, and AHA recommend performing coronary angiography in patients with a high pretest probability of underlying ischemic cardiomyopathy and who are candidates for percutaneous or surgical revascularization. At a minimum, patients meeting this description should undergo some form of noninvasive stress testing. Some centers advocate for a baseline coronary angiogram in all patients with newly established systolic HF, regardless of risk factors or presentation.

H. Endomyocardial biopsy (see Chapter 61) is indicated only when a specific primary myocardial disease is suspected and other causes of decompensation have been ruled out. The AHA/ACC/European Society of Cardiology 2007 writing group identified 14 clinical scenarios in which there is an incremental diagnostic, prognostic (eg, amyloidosis), or therapeutic (eg, giant cell myocarditis) value to biopsy that can be weighed against the procedural risk.

I. Cardiopulmonary exercise testing (metabolic stress testing), although not recommended as part of the routine evaluation of

patients with HF, should be considered in the context of symptoms out of proportion to clinical examination as an objective measure of disease severity, discriminating between cardiac and pulmonary etiologies of dyspnea, or assessing candidacy for advanced HF therapies: cardiac transplantation or mechanical circulatory support. The following parameters along with inappropriate blood pressure response to exercise are highly predictive of prognosis in patients with established HF:

1. **Peak oxygen consumption (Vo_2)** is perhaps the most important parameter in objectively describing functional capacity and prognostication. Normal values based on age and sex are indexed to body weight, with a normal value being >84% predicted. Patients being considered for heart transplantation undergo risk stratification with a metabolic stress test. Patients with a peak VO_2 <14 mL/kg/min or <50% predicted are at increased risk for adverse cardiovascular events and, if the limitation is deemed to be cardiac, should be considered for transplantation. Interpretation of the peak VO_2 is highly dependent on the adequacy of effort as assessed by the respiratory exchange ratio (RER). The RER is the ratio of VCO_2/VO_2 and is, at steady state, an estimate of the respiratory quotient. It signifies the **conversion to anaerobic metabolism** and the sudden rise in cO_2 production occurring with the onset of metabolic acidosis. Failure to achieve an RER >1.05 suggests insufficient effort or premature termination of the study. Up to 50% of patients with HF are incapable of achieving an adequate RER, with a modified Bruce treadmill protocol necessitating the use of alternative protocols.
2. **Ventilatory anaerobic threshold** is another means of assessing the adequacy of effort and represents the point at which minute ventilation (VE) increases out of proportion with VO_2 (typically occurring at 60%-70% of peak VO_2).
3. **VE/Vco_2 slope** is a dimensionless ratio indicating the relationship between minute ventilation and CO_2 production. The slope is elevated in most patients with HF and is inversely related to

cardiac output at peak exercise. A slope >45 identifies higher risk individuals, independently of peak VO_2.

J. Sleep study. Central and obstructive sleep apnea is common in patients with chronic HF, with up to 50% of patients experiencing sleep-disordered breathing. A formal sleep study should be considered in all patients with NYHA II-IV HF. **Continuous positive airway pressure (CPAP)** in patients with obstructive sleep apnea improves oxygenation and sleep quality and reduces the apnea-hypopnea index.

III. TREATMENT. The effective management of HF relies on appreciating the distinction between acute and chronic therapies.

A. ADHFs. In the United States, ADHFs continue to constitute the most common indication for hospital admission in adults over the age of 65 years. These hospitalizations represent an inflection point in the course and prognosis of the chronic disease, with 90-day and 1-year postdischarge mortality as high as 14% and 37%, respectively. Only 20% of ADHF represent patients with de novo HF. The majority are patients with worsening chronic HF. The initial management goals include symptom improvement, decongestion, and hemodynamic stabilization with optimization of tissue perfusion. It is important to identify and correct any precipitating factors (**Table 7.4**). Acute HF decompensation can be classified based on hemodynamic and fluid status as described by Stevenson and colleagues (see **Table 7.5**)

TABLE 7.4 Common Precipitants of Acute Decompensated Heart Failure

Medication nonadherence
Acute myocardial ischemia, infarction, and associated complications: ventricular septal rupture, papillary muscle rupture, free wall rupture, and cardiogenic shock
Arrhythmias (tachyarrhythmias, bradycardia)
Pulmonary embolus
Infections (eg, pneumonia, urinary tract infection, bacteremia, viremia, endocarditis)
Alcohol consumption or illicit drug use

Uncontrolled hypertension
Acute cardiovascular compromise: myocarditis, aortic dissection, valvular pathology
Drugs that can acutely worsen HF symptoms (eg, calcium channel blockers, nonsteroidal anti-inflammatory drugs, thiazolidinediones, steroids)
Beta-blocker initiation in decompensated state

HF, heart failure.

TABLE 7.5 Stratification and Treatment of Patients With Acutely Decompensated Heart Failure Based on Initial Clinical Presentation

	No Fluid Overload (PCWP <18 mm Hg)	Presence of Fluid Overload (PCWP >18 mm Hg)
Warm extremities	**Warm-dry**	**Warm-wet**
(CI >2.2 L/min/m^2)	Therapy: Adjust oral therapy.	Therapy: Vasodilators and diuretics as tolerated by blood pressure, consider ultrafiltration (if diuretic resistant).
Cold extremities (CI<2.2 L/min/m^2)	**Cold-dry** Therapy: Consider fluid challenge, consider inotropic agents if still hypoperfused.	**Cold-wet** Therapy: If SBP <90 mm Hg, inotropic agents and vasopressors (in refractory hypotension), diuretics and mechanical circulatory support (if drug refractory therapy). If SBP>90 mm Hg: Vasodilators, diuretics and inotropes (in refractory cases)

CI, cardiac index; PCWP, pulmonary capillary wedge pressure.

1. Invasive hemodynamic monitoring

a. Pulmonary artery catheter. The **ESCAPE** trial demonstrated that routine use of pulmonary artery catheters did not result in a reduction in subsequent hospitalizations or mortality in patients with ADHF but did result in increased, anticipated adverse events. Invasive hemodynamic guided management should be restricted to scenarios outlined above or where there is a need for clarification of cardiac indices and/or filling pressures in

critically ill patients. A PCWP of >18 mm Hg suggests cardiogenic pulmonary edema, and a cardiac index of <2.0 L/min/m^2 is consistent with cardiogenic shock.

b. **Arterial catheter.** Continuous blood pressure monitoring with an arterial catheter can be useful in cases with marginal blood pressure and optimizes titration of IV vasodilators.

2. **Maximizing oxygenation** is vital. All patients with acute cardiogenic pulmonary edema should be positioned upright and receive supplemental oxygen. **Noninvasive positive pressure ventilation (NIPPV)** should be considered in those with ongoing increased work of breathing, respiratory acidosis, or persistent hypoxemia. The Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema trial demonstrated that NIPPV results in a more rapid resolution of symptoms and metabolic derangements than CPAP ventilation or standard oxygen therapy. Although there was no evidence of a reduction in short-term mortality, this can be an invaluable tool often forestalling intubation. Patients who fail to respond to NIPPV should be promptly intubated. The use of positive end-expiratory pressure (PEEP) can be effective in improving oxygenation and decreasing cardiac afterload, but high levels of PEEP come at the cost of reduced systemic venous return and subsequently cardiac output, particularly in individuals with RV dysfunction.

3. **Vasodilators.** In the absence of symptomatic hypotension, IV vasodilators are the first-line therapy for the management of cardiogenic pulmonary edema.

a. **Nitroglycerin** reduces LV filling pressures via venodilation and, to a lesser extent, systemic afterload reduction. It may be given rapidly in the emergency setting (0.4-0.8 mg, given sublingually every 3-5 minutes) and by means of IV infusion in the subacute setting (starting dosage of 0.2-0.4 mcg/kg/min), with titration every 5 minutes on the basis of symptoms or mean arterial pressure (MAP). Although there is no maximal dose, increasing beyond 300 to 400 mcg/min likely yields no additional benefit and should prompt the addition of another

vasodilator. Tachyphylaxis can occur with high-dose infusions. Headache is the most common side effect, and its use is contraindicated in the setting of recent use of phosphodiesterase-5 (PDE-5) inhibitors.

b. **Sodium nitroprusside (Nipride)** is a potent vasodilator with balanced venous and arteriolar effects. It requires careful hemodynamic monitoring. A starting dosage of 0.1 to 0.2 mcg/kg/min is used and titrated every 5 minutes to achieve a clinical response while maintaining an MAP >65 mm Hg. Nipride is particularly useful in instances where a rapid and large reduction in afterload is desired (eg, cardiogenic shock, acute aortic regurgitation, or acute MR). Whereas cyanide and thiocyanate toxicity are rare with short durations of therapy, Nipride should be used with caution in patients with severe renal dysfunction, and long-term, high-dose infusions should be avoided. In patients with myocardial ischemia, nitroglycerin or a combination of nitroglycerin and Nipride is preferred to avoid the theoretical risk of coronary steal syndrome.

4. **Diuretics.** In addition to their ability to gradually reduce intravascular volume, diuretics have an immediate vasodilatory effect, which may be responsible for their prompt symptom relief. Reductions in filling pressures may be associated with augmented forward flow because of the optimization of LV and RV mechanics. Because many patients with acute cardiogenic pulmonary edema do not have total body salt and water excess, the judicious use of diuretics is recommended. Often, filling pressures normalize with the use of vasodilators alone. Patients without chronic exposure to loop diuretics usually respond to 20 to 40 mg of IV furosemide. Patients undergoing long-term loop diuretic therapy typically need an IV bolus dose at least equivalent to their oral dose (Diuretic Optimization Strategies Evaluation [DOSE] trial). Rather than an arbitrary therapeutic goal of net fluid balance or an estimated dry weight, frequent clinical assessments of volume status should guide therapy and define the point at which conversion to an oral maintenance regimen should occur.

Nevertheless, up to 30% of patients with ADHF continue to have symptoms of congestion at the time of discharge. Important adverse effects include hypotension, hypokalemia, hypomagnesemia, and hypocalcemia. There is also extensive evidence suggesting that IV diuretics may result in at least transient neurohormonal activation, which is theoretically disadvantageous. Electrolyte repletion is best achieved with scheduled doses of potassium and magnesium supplements to prevent severe deficits. DOSE demonstrated no benefit of continuous or bolus dose IV diuretic administration and no detriment from high doses (an IV dose 2.5 times the patients' chronic oral dose of furosemide). If a continuous diuretic infusion is opted for, it should be preceded by a bolus dose to achieve therapeutic threshold, as should any subsequent continuous dose titration. Escalating diuretic dose requirement should raise suspicion of resistance and can be addressed with the addition of sequential nephron blockade with a thiazide diuretic (hydrochlorothiazide, metolazone, or chlorothiazide) for synergistic effect. Some degree of worsening renal function must often be tolerated in order to achieve adequate decongestion. However, if progressive renal failure occurs despite persistent congestion, ultrafiltration (UF) or additional pharmacologic intervention(s) may be warranted. The Acetazolamide in Acute Decompensated Heart Failure with Volume Overload (ADVOR trial) showed that the addition of IV acetazolamide (500 mg daily) together with magnesium supplementation to standard diuretic therapy in patients with acutely decompensated HF and elevated natriuretic peptide improved the rate of successful decongestion during a hospital admission. Adequate diuresis is commonly defined as urine sodium excretion >50 to 70 mEq/L within 2 hours or urine output >100 mL/h within 6 hours of IV diuretics, with daily urine output goal of 3 to 5 L/day.

5. **Inotropic therapy.** When signs and symptoms of decompensated HF persist despite administration of vasodilators and diuretics, IV inotropes may be considered. Their use should be restricted to

patients with clear clinical or direct hemodynamic evidence of refractory elevated filling pressures and reduced cardiac indices. For patients without significant hypotension, dobutamine or milrinone can be used to augment cardiac output. Both drugs are associated with increased myocardial oxygen demand and cardiac arrhythmias and should be used with extreme caution in patients with ischemia and preexisting arrhythmias. Both drugs may cause hypotension, although this is more common with loading doses of milrinone. **There is no evidence to support benefit with the use of chronic or intermittent infusion of inotropic agents, and in fact, there is extensive observational data suggesting a trend toward increased postdischarge mortality**. Use is typically confined to the acute care setting as a bridge to decision-making, transplant, or mechanical circulatory support or as definitive palliative therapy in patients who are not candidates for advanced therapies. In cases of severe hypotension (especially as a result of administration of vasodilators or **beta**-blockers [BBs]), temporary use of vasopressors such as dopamine or norepinephrine may be necessary. In contrast to the conventional wisdom, recent prospective data suggest that norepinephrine is not inferior to dopamine in the setting of cardiogenic shock.

a. **Dobutamine** acts on **beta**-1 and, to a lesser extent, on **beta**-2 and **alpha**-1 adrenergic receptors. It has a short half-life (~2 minutes). Infusions are usually started at 2.5 to 5.0 mcg/kg/min. Based on hemodynamic response, it may be titrated by 1 to 2 mcg/kg/min every 30 minutes until the desired effect or a dosage of 10 mcg/kg/min is reached.
b. **Milrinone** is a PDE-III inhibitor that acts as a potent inodilator with a longer half-life (~2 to 3 hours and is renally cleared). For patients who need an immediate inotropic response, a loading dose of 50 mcg/kg over 10 minutes is followed by an infusion of 0.125 to 0.75 mcg/kg/min. Because it does not target **beta**-receptors, milrinone may be more effective than dobutamine in the setting of recent or chronic BB use.

6. **UF** has been used as an alternative to pharmacologic diuresis in acute decompensated HF. The UF versus IV diuretics for patients hospitalized for acute decompensated congestive HF study demonstrated that UF was safe and resulted in a reduced need for IV diuretics and inotropes. However, **CARRESS-HF** demonstrated a stepped pharmacologic approach to ADHF with worsening renal function was superior to UF. Currently, the use of UF is reserved for patients who are refractory to IV diuretic therapy.
7. **Vasopressin antagonists.** The oral vasopressin receptor 2 antagonist tolvaptan was shown to be safe and results in short-term symptom improvement in patients hospitalized with acute decompensated HF. However, the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial failed to demonstrate an improvement in morbidity or mortality in patients with ADHF. Tolvaptan and the nonselective IV vasopressin receptor inhibitor conivaptan are both approved for the management of hypervolemic or euvolemic hyponatremia that can accompany decompensated HF, but neither has demonstrated benefit with regard to morbidity or mortality.
8. **Temporary mechanical circulatory support.** The use of temporary and permanent mechanical circulatory support is described in detail in Chapter 12. Patients with refractory cardiogenic shock and cardiogenic pulmonary edema may benefit from the temporary use of intra-aortic balloon counterpulsation, or an alternative temporary means of mechanical circulatory support (ie, venoarterial extracorporeal membrane oxygenation, Impella, or TandemHeart) may facilitate bridging to stabilization or durable advanced HF therapies such as left ventricular assist devices (LVADs) or heart transplantation.
9. **Transition to chronic pharmacotherapy** is implemented once clinical stability is achieved. Generally, vasodilators and neuromodulators such as ARNIs, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and mineralocorticoid receptor antagonists (MRAs) are reintroduced first in concert with weaning off IV

vasodilators. If BBs were held due to cardiogenic shock, they can be cautiously reintroduced in stable, euvolemic patients. The PIONEER-HF trial showed that the initiation of sacubitril/valsartan in patients with acute decompensated HF led to a greater reduction in the NT-proBNP concentration than enalapril therapy without an increase in adverse events. Although the clinical benefit of this approach is not yet understood, it is considered safe practice to initiate ARNIs in ADHF. Rapid titration of guideline-directed heart failure medical therapies (HF-GDMTs) in the STRONG-HF open-label randomized trial demonstrated the safety and efficacy of rapid uptitration of HF pharmacotherapies with a reduction in HF readmission and all-cause mortality. It is, therefore, prudent for all patients be prescribed quadruple therapy unless intolerant prior to discharge.

B. Chronic medical therapies. The goal of chronic medical therapy is to prolong survival and improve quality of life. In the 2022 ACC/AHA HF guidelines, there are four classes of medications with class I indication in patients with systolic HF: ARNIs, ACE inhibitors (ACEis), angiotensin receptor blockers (ARBs), BBs, MRAs, and SGLT2 inhibitors. Altogether, these are referred to as the "four pillars" of HF-GDMT and, when combined, are referred to as quadruple therapy for patients with HFrEF.

1. **Renin-angiotensin system (RAS) inhibition** is crucial to reduce morbidity and mortality in patients with HFrEF. In addition to providing afterload reduction, RAS-blocking agents provide neurohormonal blockade and prevent cardiac remodeling.
   a. **Sacubitril/valsartan** is a combination pill that consists of a neprilysin inhibitor with ARB. Inhibition of neprilysin leads to the inhibition of natriuretic peptides and additional vasoactive peptides, subsequently augmenting natriuresis and decreasing sympathetic tone, aldosterone, and cardiac fibrosis/hypertrophy. ARNIs have demonstrated superiority to ACEis in the Paradigm-HF trial. **Sacubitril/valsartan is the first-line therapy for symptomatic HFrEF.** PARADIGM-HF demonstrated a 20% reduction in cardiovascular death or first

HF hospitalization (see **Table 7.6** for dosing) when comparing sacubitril/valsartan against enalapril. When transitioning from ACEi to ARNIs, there should be a minimum 36-hour washout period between discontinuation of ACEi and administration of ARNI to avoid angioedema. If ARNIs cannot be used due to hypotension or intolerance, ACEis and ARBs can be used instead.

TABLE 7.6 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

Drug	Start (mg)	Target (mg)	Max (mg)
ACE Inhibitors			
Captopril (Capoten)	6.25-12.5 tid	50 tid	100 tid
Enalapril (Vasotec)	2.5-5 bid	10 bid	20 bid
Lisinopril (Prinivil, Zestril)	2.5-5 qd	20 qd	40 qd
Ramipril (Altace)	1.25-2.5 bid	5 bid	10 bid
Quinapril (Accupril)	5 bid	20 bid	20 bid
Fosinopril (Monopril)	2.5 or 5 bid	20 bid	20 bid
Benazepril (Lotensin)[a]	2.5 or 5 bid	20 bid	20 bid
Moexipril (Univasc)[a]	7.5 qd	30 qd	30 qd
Trandolapril (Mavik)	1 qd	4 qd	4 qd
Angiotensin Receptor Blockers			
Candesartan (Atacand)	16 qd	32 qd	32 qd
Valsartan (Diovan)	80 qd	160 qd	320 qd
Losartan (Cozaar)[a]	12.5-25 qd	50 qd	100 qd
Irbesartan (Avapro)[a]	150 qd	300 qd	300 qd
Telmisartan (Micardis)[a]	40 qd	80 qd	80 qd
Hydralazine/Isosorbide Dinitrate			
Hydralazine	25 qid	50-75 qid	100 qid

Drug	Start (mg)	Target (mg)	Max (mg)
Isosorbide dinitrate	10-20 tid	20-80 tid	80 tid
Hydralazine-isosorbide dinitrate (BiDil)	25/37.5 tid	50/75 tid	50/75 tid
Aldosterone Antagonists			
Spironolactone (Aldactone)	12.5-25 qd	25 qd	50 bid
Eplerenone (Inspra)	25 qd	50 qd	100 qd
Loop Diuretics[c]			
Furosemide (Lasix)	10 qd (IV)	As required	1,000 qd (IV)
	20 qd (PO)	As required	240 bid (PO)
Bumetanide (Bumex)	1 qd	As required	10 qd
Torsemide (Demadex)	10 qd	As required	200 qd
Ethacrynic acid (Edecrin)	50 qd	As required	200 bid
Thiazide Diuretics			
Hydrochlorothiazide (HCTZ)	25 qd	As required	200 qd
Metolazone (Zaroxolyn)	2.5 qd	As required	10 qd
Chlorthalidone	12.5 qd	As required	100 qd
Chlorothiazide (PO or IV)	250-500 (PO) qd/bid 500-1,000 (IV)	As required NA	1,000 mg NA
Potassium-Sparing Diuretics			
Triamterene (Maxzide)	50 qd	As required	100 bid
Amiloride	5 qd	As required	20 qd
Beta-Blockers			
Carvedilol (Coreg)	3.125 bid	25 bid	50 bid
Carvedilol phosphate (Coreg CR)	10 qd	40 qd	80 qd

Drug	Start (mg)	Target (mg)	Max (mg)
Metoprolol succinate (Toprol XL)	25 qd	150-200 qd	200 qd
Bisoprolol (Zebeta)	1.25 qd	8.6 qd	10 qd
Nebivolol (Bystolic)[a,b]	1.25 qd	10 qd	40 qd
Neprilysin Inhibitor + Angiotensin Receptor Blockers			
Sacubitril/Valsartan (Entresto)	24/26 bid	97/103 bid	97/103 bid
Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors			
Empagliflozin	10 qd	10 qd	10 qd
Dapagliflozin	10 qd	10 qd	10 qd
If Current Inhibitor			
Ivabradine (Corlanor)	5 bid	As required	15 qd

ACE, angiotensin-converting enzyme; bid, twice daily; IV, intravenous; PO, orally; qd, everyday.

[a]Not yet approved by the Food and Drug Administration (FDA) for the management of heart failure.

[b]Approved in Europe, not yet approved by the FDA for the management of heart failure. SENIORS trial demonstrated all-cause mortality benefit in patients over 70 years of age.

[c]Oral to IV conversion for furosemide is approximately 2:1. Oral to IV conversion for all other loop diuretics is 1:1.

b. ACEis have been shown to reduce morbidity and mortality among patients with systolic HF. The mechanism of long-term benefit is related to attenuation of the RAS. In addition, ACEis improve symptoms, clinical status, and exercise capacity.

(1) The dose of the ACEis should be increased to the target doses demonstrating clinical benefits in trials (**Table 7.6**). Although there are theoretical benefits of using "tissue" inhibitors (eg, quinapril and ramipril), there are no data to support their preferential use. Relative contraindications include hyperkalemia (potassium >5.5 mEq/L), renal insufficiency (creatinine >3.0 mg/dL), and hypotension

(systolic blood pressure <90 mm Hg) and should be gauged on a case-by-case basis. It is not advisable to stop ACEis in patients with systolic HF, even when there is complete resolution of symptoms.

(2) After initiation, close monitoring for **hyperkalemia** and **renal insufficiency** is warranted. Renal insufficiency and hyperkalemia may occur when ACEis are given in the setting of volume depletion. It is crucial to discontinue other nephrotoxic agents (eg, nonsteroidal anti-inflammatory agents) and ensure adequate kidney perfusion. If BUN or creatinine levels increase by <50%, ACEis can be continued safely; if they increase by >50%, the ACEis dose should be halved; if they increase by >100%, ACEis should be held and switched to hydralazine and isosorbide dinitrate. In the case of hyperkalemia, discontinuation of potassium supplementation, K-sparing diuretic, and reducing the ACEi dose are usually effective. Potassium binders may reduce hyperkalemia, but currently, there are no data to support any incremental clinical benefit.

(3) **Hypotension** is common, especially with the first dose in a volume-depleted patient (eg, after aggressive diuresis). This may require downtitration of diuretic doses and other vasodilator therapy. Because of its short half-life, captopril is usually used in the acute setting (eg, after myocardial infarction).

(4) Unique side effects of ACEis are cough and angioedema. The **cough** associated with ACEis is related to increased levels of bradykinin and is seen in ~20% of patients. It tends to be nonproductive and involuntary, rarely resolving by altering the dose or specific agent. All attempts should be made to identify an alternative cause of cough before discontinuing ACEis. **Angioedema** is a rare complication of ACEis (0.4%). It involves soft tissue edema of the lips, face, tongue, and, occasionally, the oropharynx and

epiglottis. Angioedema typically begins within 2 weeks of initiation of ACEi therapy, but some patients present with this complication months to years after starting therapy. **Angioedema is an absolute contraindication to the use of any type of ACEis.**

c. **ARBs** are specific receptor antagonists to the angiotensin II type 1 receptors. Although they theoretically provide more complete inhibition of the deleterious effects of angiotensin II than do ACEis, clinical trials have not demonstrated superiority in patients with HF. In general, ARBs are used and monitored in the same manner as ACEis. These drugs are reserved for patients who are ACEi intolerant, although in practice, they are used extensively. ARBs have a similar side-effect profile to ACEis (eg, hypotension, renal insufficiency, and hyperkalemia). There appears to be a <10% incidence of cross-reactivity for ACEi-associated angioedema in patients receiving ARBs. However, consideration for the use of these agents must be weighed against the life-threatening nature of this complication. Whereas the addition of an ARB is reasonable in patients on target doses of ACEis and BBs with persistent symptoms, it is preferable to add an aldosterone antagonist first to get added morbidity and mortality benefits. ARBs should not be added to an ACEi in the post–myocardial infarction period. Valsartan and candesartan are the best-studied ARBs in patients with HF and should be used preferentially.

2. **BBs** should be included as first-line therapy for chronic symptomatic patients with HF (NYHA class I, II, III, or stable class IV) because of their consistent mortality and morbidity benefits.

   a. It is often customary to start ACEis before BBs. This, in part, reflects the fact that all major BB trials demonstrated their benefit on a background of therapy with ACE inhibition. Furthermore, whereas ACEis provide immediate beneficial hemodynamic effects, BBs may acutely result in diminished

LVEF and cardiac output, which may be poorly tolerated in decompensated patients. In some instances (eg, post–myocardial infarction and comorbid tachyarrhythmias), BBs may be particularly beneficial and should be started before or concurrently with ARNIs or ACEis. BBs should typically not be initiated or titrated in the setting of acutely decompensated HF.

b. The three evidence-based BBs to reduce mortality and morbidity in systolic HF are bisoprolol, carvedilol, and metoprolol succinate. Although atenolol and metoprolol tartrate are widely available and relatively inexpensive, there is no evidence to support their use. BBs with intrinsic sympathomimetic activity (pindolol and acebutolol) should be avoided.

c. Relative contraindications to BB therapy are a heart rate <60 beats/min, symptomatic hypotension, more than minimal pulmonary or systemic congestion, signs of peripheral hypoperfusion, a PR interval >0.24 seconds, second- or third-degree AV block, a history of severe reactive airway disease, and peripheral arterial disease with resting limb ischemia. It is important to note that these are relative contraindications, and particularly in the setting of reactive airway disease and peripheral arterial disease, the risks of BB therapy must be weighed against their known benefits.

d. Current recommendations are to start BBs in those who are clinically euvolemic. The initial dose is **slowly uptitrated every 2 to 4 weeks over 3 to 4 months to achieve target doses**, provided that the patient can tolerate side effects. It is imperative to maintain contact with the patient and adjust vasodilator or diuretic therapy during titration. It is not advisable to stop BBs in patients with a history of HF, even if there is complete resolution of symptoms and LV dysfunction.

e. Every effort should be made to achieve target doses, but it is clear that even low doses of these drugs provide mortality and morbidity benefits.

f. Side effects of BBs include **dizziness** and **lightheadedness**, which may be related to hypotension or heart block. Hypotension can be managed by staggering the timing of drug administration. In practice, carvedilol (with its nonselective, $beta_1$-blocking vasodilator effects) may have a greater blood pressure lowering than selective $beta_1$ agents, such as metoprolol succinate. **Significant bradycardia** mandates dose reduction of BBs and other rate-lowering agents, such as digoxin and amiodarone. **Advanced heart block** is a contraindication to BBs unless a permanent pacemaker is present. **Worsening HF** is still an important adverse effect of BBs. Intensification of diuretic therapy and dose reduction or slower titration may be necessary.

3. **MRAs** have long been used as weak, potassium-sparing diuretics in patients with HF. The concept of incomplete RAS blockade by ACE inhibition or ARB led to studies demonstrating significant pleiotropic effects of aldosterone antagonism in patients with advanced HF, including antifibrotic effects and reduction in sudden cardiac death. Results from the Randomized Aldactone Evaluation Study (**RALES**), Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (**EPHESUS**), and Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (**EMPHASIS-HF**) trials have demonstrated substantial mortality and morbidity benefit in stage C HF. MRAs are indicated in patients with HFrEF and NYHA class II-IV symptoms receiving ACEis/ARB/ARNI and BBs that do not have significant renal dysfunction (creatinine clearance >30 mL/min) or hyperkalemia (potassium <5 mEq/L). Their use is also indicated in patients with postinfarction LV dysfunction (LVEF ≤40%) with any HF symptoms or history of diabetes mellitus.

   a. In most cases, potassium supplementation should be reduced or discontinued. A basic metabolic panel should be checked within 1 week after initiation and monitored at regular intervals.

b. The most common and life-threatening side effect of aldosterone antagonists is hyperkalemia, which is particularly problematic in patients with concomitant renal insufficiency and diabetes mellitus (type IV renal tubular acidosis). Gynecomastia and galactorrhea may occur with spironolactone.

c. Whereas clinical trials used either spironolactone (RALES) or eplerenone (EPHESUS and EMPHASIS-HF), most experts believe that aldosterone inhibitors work via class effect. Our approach is to initiate treatment with spironolactone because of its low cost and transition to eplerenone only in the setting of significant gynecomastia.

4. **SGLT2 inhibitors** enhance natriuresis and glucosuria and reduce the progression of diabetic kidney disease. They have recently shown to improve mortality and HF events in patients with symptomatic diabetes and those without diabetes with HFpEF and HFmrEF. Dapagliflozin and empagliflozin have proved to be effective at fixed doses in reducing the composite of cardiovascular death or HF hospitalizations by approximately 25% in patients with EF ≤40% (DAPA-HF and EMPEROR-Reduced trials). Sotagliflozin (an SGLT1 and SGLT2 inhibitor) has also shown to reduce the composite of cardiovascular mortality and HF events by 29% in patients with type 2 diabetes and HF; however, it is not currently commercially available in the United States.

   a. These agents should not be prescribed in the presence of type 1 diabetes mellitus or type 2 diabetes with a history of diabetic ketoacidosis. They should not be used when the estimated glomerular filtration rate (eGFR) is <30 mL/min/1.73 m^2 for dapagliflozin and sotagliflozin or <20 mL/min/1.73 m^2 for empagliflozin. Caution should be used in patients with a history of frequent urinary tract or genitourinary infections.

   b. Common side effects of SGLT2 inhibitors include hypotension or volume depletion due to their diuretic effect and increased frequency of bacterial urinary infections or genitourinary yeast infections.

5. The combination of **hydralazine** and **isosorbide dinitrate** may provide a reduction in morbidity and mortality in African American patients on optimized four pillars of HF-GDMT and who still experience NYHA III HF symptoms. A fixed-dose combination of hydralazine and isosorbide dinitrate (BiDil) demonstrated a substantial reduction in mortality when added to African American patients on optimal medical therapy, including ACEis and BBs in the African-American Heart Failure Trial. This combination is also indicated in patients intolerant of ACEis, ARBs, or ARNI or in patients receiving maximal RAS inhibition therapy in need of additional vasodilator therapy. Side effects of hydralazine may include reflex tachycardia and, rarely, drug-induced lupus erythematosus.
6. **Diuretics** are used to maintain euvolemia and to improve symptoms, but their overuse can result in volume contraction, hypotension, resistance, and renal dysfunction.
    a. An effective and inexpensive initial regimen includes 20 to 120 mg of furosemide taken orally each day. If furosemide doses higher than 120 mg/d are needed, a second evening dose is typically prescribed. If this regimen fails, sequential nephron blockade with a thiazide diuretic can provide synergistic benefit.
    b. More expensive loop diuretics (eg, torsemide and bumetanide) have superior bioavailability and may be more effective in diuretic-resistant patients. Torsemide in particular may have unique benefits in the form of antifibrotic effects and minimization of the postdiuretic sodium retention that complicates the use of loop diuretics with shorter half-lives. However, in randomized clinical trial settings such as the Transform HF trial, torsemide was found to be nonsuperior to furosemide.
7. **Digoxin** is reasonable to use in patients with persistent HF symptoms despite appropriate, optimized GDMT and/or in patients with atrial fibrillation to control ventricular rate. It carries a class IIb recommendation in the 2022 ACC/AHA HF guidelines.

a. Despite a fairly narrow therapeutic window, digoxin is safe and significantly reduces HF hospitalizations. A typical starting dose of 0.125 mg of digoxin daily is appropriate in patients with normal renal function.

b. Whereas the **Digitalis Investigation Group trial** demonstrated the best clinical outcomes in patients with a serum digoxin concentration of 0.5 to 0.8 ng/mL, routine measurement of levels is not recommended in the absence of concern for toxicity.

8. **Ivabradine** is an I_f current inhibitor within the sinus node; inhibition leads to rate reduction and subsequently increases stroke volume while preserving AV nodal conduction and contractility. The addition should be considered in individuals with HFrEF, NYHA II-III receiving GDMT, including maximally tolerated dose of BB and having a sinus heart rate >70 beats/min. The SHIFT trial demonstrated an overall significant reduction in all-cause HF and cardiovascular admission in individuals with HFrEF and sinus rhythm with a rate over 75 beats/min (see **Table 7.6** for dosing). It has garnered a class 2A recommendation in the 2022 ACC/AHA guidelines.
9. **Vericiguat** is a soluble guanylate cyclase stimulator that enhances the cyclic guanosine monophosphate (GMP) pathway by directly stimulating soluble guanylate cyclase through a binding site independent of nitric oxide, and it sensitizes soluble guanylate cyclase to endogenous nitric oxide by stabilizing nitric oxide binding to the binding site. It has shown to reduce NT-proBNP levels in patients with HFrEF, and in the VICTORIA trial, it showed an absolute risk reduction of 3% in cardiovascular mortality or hospitalization in patients with symptomatic HF with an LVEF <45% who were already on GDMT. It has garnered a class 2B recommendation in the 2022 ACC/AHA HF guidelines.
10. **Statins** should be used in the secondary prevention of atherosclerotic cardiovascular disease without regard to the presence of HF. There is no evidence of benefit in patients with HF without CAD.

11. **Aspirin** clearly prevents reinfarction and other vascular events in patients with known CAD; there is growing evidence from observational and randomized studies that it may worsen outcomes in patients with HF via inhibition of prostaglandin synthesis and the resultant adverse hemodynamic and renal effects. This remains a controversial subject and the decision of whether to use aspirin should be made on a case-by-case basis. It should likely be avoided in patients without coronary disease who have refractory HF symptoms.
12. **Electrolyte supplementation** is among the most important and least emphasized areas in chronic HF management. Potassium depletion is common with diuretic therapy, whereas hyperkalemia can be caused by RAS inhibitors or worsening renal insufficiency. In general, oral potassium supplementation is necessary to maintain serum potassium level in the ideal range of 4.0 to 5.0 mEq/L. Magnesium, thiamine, and calcium depletion are also common with long-standing diuretic therapy.
13. **Iron supplementation.** Iron deficiency (defined as a ferritin level <100 mcg/L or a ferritin level of 100-299 mcg/L with a transferrin saturation <20%) is present in as much as 50% of patients with HF and is associated with worse outcomes. The FAIR-HF and CONFIRM-HF demonstrated functional improvement in symptoms, functional capacity, and quality of life with IV iron replacement maintained up to 24 and 52 weeks, respectively, with a good safety profile. The AFFIRM-HF trial showed that IV iron in iron-deficient patients with HF and LVEF <50% admitted for acute HF decompensation reduced the risk of readmission by 26%. IV ferric carboxymaltose should be given based on the patient's weight. Similar benefits have not been found with oral iron supplementation due to issues with poor absorption with oral repletion.
14. **Device therapy.** Chapters 55 and 56 provide detailed coverage of the indications, contraindications, and clinical issues related to implantable cardioverter-defibrillators (ICDs) and CRT-D.

15. **Device monitoring.** Currently, implanted electrical cardiovascular devices including ICD and CRT-D have the capability to remotely monitor a variety of electrophysiologic (eg, heart rate variability, atrial arrhythmia burden and rate, ventricular tachycardia, % biventricular pacing, and average heart rate) and physiologic (eg, patient activity and intrathoracic impedance) parameters with prognostic value. Ambulatory HF monitoring using implantable devices such as CardioMEMS or external patch-based wearable monitors present opportunities for hemodynamic guided outpatient monitoring. How to best integrate device monitoring into a comprehensive approach to HF disease management remains to be established.

16. **Management of comorbidities**

    a. **Sleep apnea** should be investigated in patients with HFrEF based on clinical judgment. Although it has not been shown to affect survival, treatment of sleep-disordered breathing with CPAP is associated with better sleep quality and nocturnal oxygenation, as well as improvement in BNP levels, blood pressure, and LVEF.

    b. **Atrial fibrillation** is common in patients with HFrEF. Guidelines recommend the use of anticoagulation for a CHA_2DS_s-VASc score of ≥2 (for men) or ≥3 (for women). Direct oral anticoagulants should be used over warfarin in eligible patients. The AATAC trial demonstrated that catheter ablation was superior to amiodarone in symptomatic select patients with HFrEF, persistent atrial fibrillation, and dual-chamber ICD or CRT, leading to a decrease in HF hospitalizations as well as improved mortality. If a cardiomyopathy resulting from rapid atrial fibrillation is suspected, rhythm control should be sought to maintain sinus rhythm, and if that fails, AV node ablation with placement of a CRT device should be considered.

    c. **MR.** Secondary MR is frequently seen in patients with HFrEF. While CRT, LVADs, and cardiac transplantation improve outcomes in patient with secondary MR and HFrEF, no

evidence suggests that mitral valve surgery improves outcomes in this population. However, transcatheter mitral therapies such as MitraClip in the appropriately selected patient do confer benefit. According to the COAPT trial, patients with symptomatic HFrEF and moderate-to-severe MR despite optimal medical therapy and CRT-D benefited from MitraClip procedure, which reduced the degree of MR as well as the number of HF hospitalizations and 2-year all-cause mortality. Patients with stage D HF, severe LV dilation >7 cm, or systolic pulmonary arterial pressure >70 mm Hg were excluded. In contrast, the MITRA-FR study in France showed reduction of MR after MitraClip in a majority of patients but showed no impact on HF hospitalizations on all-cause mortality or HF hospitalizations, although it had less strict inclusion and exclusion criteria. Careful patient selection based on the COAPT trial inclusion and exclusion criteria is suggested when considering patients for transcatheter mitral therapies.

d. **CAD** in conjunction with decreased EF is common, and noninvasive and functional testing, as well as clinical acumen and anatomic correlation to the area of disease myocardium, is required to determine if CAD is coincidental or responsible for LV dysfunction. The STITCH trial showed that, when compared to optimal medical management alone, CABG surgery plus GDMT resulted in significant reductions in all-cause mortality at 10 years in patients with LVEF <35% and ischemic cardiomyopathy. The same benefit was not evident at 56 months after intervention. However, the same results have not been elucidated for PCI. The REVIVED-BCIS2 trial randomized patients with LVEF <35%, CAD amenable to PCI, and demonstrable myocardial viability to PCI versus optimal medical therapy and failed to show improved outcomes or LVEF after revascularization in the PCI group after a median follow-up of 3.4 years.

C. Chronic nonmedical therapies

1. **Patient education and disease management programs** remain the most effective treatment strategy for patients with systolic HF. Sodium restriction (<2,000 mg daily) and medication compliance are crucial to reducing hospitalizations. Efforts should be made to carefully reconcile medications at each visit, as patients with HF may suffer from polypharmacy. Control of blood pressure, serum glucose, and lipid levels should be emphasized. Some highly motivated patients can perform self-monitoring (ie, daily weights and symptom assessment) and care (ie, titration of diuretics) analogous to the chronic management of diabetes.
2. **Exercise training.** There is a clear body of evidence supporting the fact that exercise training improves endothelial function and functional capacity in patients with chronic HF. HF-ACTION failed to demonstrate a reduction in all-cause mortality and hospitalization but demonstrated significant improvement in self-reported health status. A supervised cardiac rehabilitation program should be advised when available.

D. Advanced therapies. Mechanical circulatory support and orthotopic heart transplantation are therapies currently reserved for patients with ACC/AHA stage D HF refractory to other therapies. These are described in detail in Chapters 12 and 13, respectively.

III. PROGNOSIS. HF is associated with high rates of morbidity and mortality. In the Framingham Heart study, patients with HF had mortality rates 4 to 8 times those of age-matched controls. A patient with NYHA class IV HF has a 1-year survival between 30% and 50%—a mortality rate comparable to that of advanced malignancies. Several risk scores have been developed to characterize the risk of HF hospitalization and mortality. The Seattle Heart Failure Model is perhaps the most widely used of these and incorporates demographic, clinical, pharmacologic, and laboratory data to provide accurate 1-, 2-, and 3-year survival estimates. **Table 7.7** lists some common clinical predictors of poor survival in systolic HF.

TABLE 7.7 Common Clinical Predictors of Poor Prognosis in Systolic Heart

Failure
Increased age
Increased New York Heart Association functional class
Severely reduced LV ejection fraction (<25%), extensive cardiac remodeling (LVIDd >65 mm), or reduced cardiac index (<2.5)
Concomitant diastolic dysfunction (particularly irreversible restrictive filling, stage IV diastolic dysfunction)
Reduced RV function
Atrial fibrillation, elevated average heart rate, and reduced heart rate variability
Low peak VO_2 with maximal exercise (14 mL/min/kg), low heart rate response to exercise, increased peripheral chemosensitivity (ventilatory response to hypoxia), and high VE/VCO_2
High plasma BNP and NT-proBNP levels
High levels of other cardiac and neurohormonal biomarkers including norepinephrine, renin, arginine vasopressin, aldosterone, endothelin-1, tumor necrosis factor, cardiac troponin T and I, and C-reactive protein
Anemia
Low systolic blood pressure
Renal insufficiency (creatinine clearance <60 mL/min)
Attenuated response to diuretics and lack of hemodynamic and structural improvement (reverse remodeling) with medical therapy
Persistent signs of congestion and fluid retention or failure to normalize filling pressures (PCWP <16 mm Hg, CVP <8 mm Hg) with medical therapy
Serum sodium <135 mg/dL
Cardiac dyssynchrony (QRS >130 ms, left bundle branch block)
Depression
Nocturnal Cheyne-Stokes respiration and obstructive sleep apnea

BNP, B-type natriuretic peptide; CVP, central venous pressure; LV, left ventricular; LVIDd, left ventricular internal dimension at diastole; NT-proBNP, N-terminal pro–B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; RV, right ventricular; VE, ventilation.

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SUGGESTED READINGS

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HFSA Heart Failure Guidelines. http://www.hfsa.org/heart-failure-guidelines-2/

Seattle Heart Failure Model. http://depts.washington.edu/shfm/

CHAPTER 8

Heart Failure With Preserved Ejection Fraction

Robert A. Montgomery and Sanjeeb Bhattacharya

I. INTRODUCTION

A. Epidemiologic studies suggest that nearly half of patients with heart failure (HF) have a preserved ejection fraction (EF); the proportion in those hospitalized has been reported to range from one-quarter to half. The survival of patients with HF and preserved EF was once thought to be better than those with a decreased EF, but current evidence suggests similar mortality rates.

Heart failure with preserved ejection fraction (HFpEF) has become the preferred term in the literature to describe the diagnosis of HF in the setting of an EF measured in the normal range. This clinical entity historically has also been referred to as diastolic HF. In this chapter, we focus on HFpEF, including its diagnosis and treatment.

B. Definition. According to the 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) Guideline for the Management of Heart Failure, the diagnosis of HFpEF requires **evidence of increased left ventricular (LV) filling pressures at rest, exercise, or other provocations in conjunction with an EF of ≥50%. Evidence of elevated filling pressures can be supported by the presence of elevated natriuretic peptide levels, specific echocardiographic parameters, or direct evidence of elevated left-sided filling pressures at rest or with provocation** (**Table 8.1**). Imaging evidence of structural heart disease supports the diagnosis of HFpEF but is not diagnostic in and of itself.

TABLE 8.1 Diagnostic Criteria for Heart Failure With Preserved EF

Clinical Presentation	Signs and Symptoms of Congestive Heart Failure
Left ventricular function	LVEF >50%
Evidence suggesting diastolic dysfunction on diagnostic testing	
Laboratory	Elevated natriuretic peptide plasma levels[a] (NT-proBNP >125 pg/mL or BNP >35 pg/mL)
Echocardiographic	
Functional	• Unequivocal echocardiographic evidence of elevated LV filling pressure (*E*/*é* >15) • Abnormal mitral inflow Doppler pattern suggesting impaired relaxation (*E*/*A* <1) or *E*/*A* pseudonormalization or restrictive physiology (*E*/*A* >2) • Lateral *é* velocity <10 cm/s or septal *é* velocity <7 cm/s • TR velocity >2.8 m/s • Estimated PA systolic pressure >35 mm Hg • GLS <16%
Structural	• LAVI ≥29 mL/m^2 • LVMI >116/95 g/m^2 • RWT >0.42 • LV wall thickness ≥12 mm
Invasive cardiac catheterization	• Rest: PCWP >15 mm Hg • Fluid challenge: PCWP >18 mm Hg following 500 mL infusion of isotonic fluids given over 5 min • Passive leg raise: PCWP >15 mm Hg during 3 min following incline of legs greater than 50%. • Exercise: PCWP ≥25 mm Hg and/or ΔPCWP/ΔCO slope >2 mm Hg/L/min over serial measurements during exercise

AF, atrial fibrillation; BNP, brain natriuretic peptide; CKD, chronic kidney disease; GLS, global longitudinal strain; HF, heart failure; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass

index; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RWT, relative wall thickness; TR, tricuspid regurgitation.

[a]Cutoffs provided for natriuretic peptide levels may have lower specificity, especially in older patients or in patients with AF or CKD. Usually, higher cutoff values are recommended for the diagnosis of HF in these patients. Natriuretic peptide cutoffs selected for population screening for pre-HF (stage B HF) may be <99% reference limits and need to be defined according to the population at risk.

C. Pathophysiology. Most pathophysiologic abnormalities in patients with HFpEF are related to diastolic function. There are two major determinants of diastolic function: LV relaxation and LV stiffness. LV relaxation relates to the cellular mechanisms involved with actin-myosin cross-bridge detachment. This requires intracellular calcium uptake into the sarcoplasmic reticulum, an energy- or adenosine triphosphate (ATP)-dependent process. Thus, ischemia, which would decrease intracellular availability of ATP, would prolong the time required for ventricular relaxation. LV stiffness relates to the compliance of the myocardial tissue. One determinant of this is the extracellular matrix. For example, increase in fibrosis and collagen deposition, as in patients with hypertensive heart disease, leads to an increase in LV stiffness. Restrictive cardiomyopathies share a similar pathophysiology, with increased LV stiffness; however, these differ in the pathology underlying the change in ventricular compliance: extracellular amyloid deposition (cardiac amyloidosis), endocardial fibrosis from eosinophilic injury (Loeffler endocarditis and endomyocardial fibrosis), intracellular lysosomal engorgement with sphingolipids (Fabry disease), and others. A number of other pathophysiologic mechanisms have been implicated in patients with HFpEF, including arterial stiffness, the relationship between arterial and ventricular stiffness, and chronotropic incompetence. The implications and relative importance of these mechanisms are still unclear.

II. CLINICAL PRESENTATION

A. Demographics. When compared with patients with heart failure with reduced ejection fraction (HFrEF), those with HFpEF tend to be **older** and are more likely to be **female**. Associated comorbidities

include hypertension, diabetes, obesity, physical deconditioning, atrial fibrillation, chronic kidney disease, and advanced age.

B. Symptoms. Analogous to HFrEF, HFpEF spans the spectrum of asymptomatic or subclinical disease to chronic congestive HF. The symptoms of HFpEF are indistinguishable from those of HFrEF. Some patients present with only exertional fatigue or dyspnea. Other patients experience overt symptoms of left-sided (dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) and right-sided (edema and abdominal bloating) HF.

C. Signs. The signs of HFpEF are similar to those of HFrEF. Patients should be evaluated for typical signs of right-sided (elevated jugular venous pressure, hepatic congestion, ascites, and lower extremity edema) and left-sided (pulmonary edema and pleural effusion) congestion. The presence of an S_4 usually signifies a stiff LV. In contrast to patients with dilated cardiomyopathy, the location of the apical impulse is usually close to the midclavicular line, signifying a normal-sized ventricle. In addition, a hypertrophied ventricle will often have a stronger impulse than a ventricle of normal thickness. This may be appreciated on examination in patients who do not have thick chest walls. In patients with exertional symptoms alone, these signs may not be present as the manifestation of their diastolic dysfunction may occur only during exercise.

The presence of severe right-sided HF features, particularly ascites and hepatic congestion, should raise suspicion for restrictive cardiomyopathy, constrictive pericarditis, or both. In these patients, clinical findings of multiorgan disease may provide additional insights into the etiology of their cardiomyopathy. Kussmaul sign, a paradoxical elevation in the mean jugular venous pressure during inspiration, has been classically described in constrictive pericarditis. However, it can also be present in patients with restrictive cardiomyopathy as well as other pathologies involving the right heart (eg, severe right ventricular [RV] systolic dysfunction and dilatation with secondary tricuspid regurgitation).

III. BASIC INVESTIGATIONS

A. Electrocardiogram (ECG). ECG is an insensitive test for HFpEF. The most important finding is the amplitude of QRS voltage. The presence of elevated voltage and other criteria for left ventricular hypertrophy (LVH) can suggest a possible etiology of HFpEF. Conversely, in a patient who has increased wall thickness (typically identified by echocardiography) but has low voltage or infarction patterns on ECG ("pseudoinfarction"), infiltrative cardiomyopathy should be considered.

B. Chest radiograph. The chest x-ray has few specific findings for HFpEF. In a posterior-anterior film, a normal-sized heart (lateral heart width less than two-thirds of a hemithorax) may be a clue to a normal-sized LV. Otherwise, the findings are the same as in HFrEF: fluffy alveolar opacities (alveolar pulmonary edema), increased interstitial markings (increased interstitial fluid), pulmonary vascular redistribution (increased pulmonary venous pressure), and pleural effusions.

C. Specific laboratory investigations. Natriuretic peptide assessment can be helpful in establishing the diagnosis of HFpEF. When compared with patients with systolic HF, the elevation in brain natriuretic peptide (BNP) or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is generally lower. In patients with undifferentiated dyspnea, a normal BNP or NT-proBNP would argue against the presence of any HF syndrome; however, it does not fully exclude it, especially in the setting of obesity or increased LV wall thickness, which may decrease wall stress.

IV. DIFFERENTIAL DIAGNOSIS. The two most common clinical presentations of HFpEF are congestive HF and exertional dyspnea (without physical examination findings of decompensated HF). In a patient presenting primarily with exercise intolerance or exertional dyspnea, HFpEF should be considered in the absence of alternate etiologies (eg, coronary artery disease [CAD], primary lung disease, anemia).

In a patient who has an established clinical syndrome of HF, the differential diagnosis is typically narrowed following echocardiography. HFpEF is the most likely diagnosis in a patient with preserved EF and a

normal-sized LV. Other cardiac diagnoses to consider include restrictive cardiomyopathy, hypertrophic cardiomyopathy (HCM), valvular heart disease, and constrictive pericarditis (**Table 8.2**), which are discussed in other chapters.

TABLE 8.2 Disorders That May Mimic HFpEF

- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathies
  - Cardiac amyloidosis
  - Endomyocardial fibrosis
  - Loeffler (eosinophilic) endocarditis
  - Idiopathic restrictive cardiomyopathy
  - Sarcoidosis
  - Radiation carditis
  - Metabolic storage diseases
    - Hemochromatosis
    - Glycogen storage diseases
    - Gaucher disease
    - Fabry disease
- Constrictive pericarditis
- Noncompaction cardiomyopathy
- Uncorrected valvular heart disease
- Isolated right-sided heart failure
- High-output states (anemia, arteriovenous fistula, thyroid disease)
- Fluid overload from kidney, pulmonary, or liver disease

HFpEF, heart failure with preserved ejection fraction.

A. HFpEF. HF without another obvious cause, particularly in the context of advanced age, hypertension, obesity, chronic kidney disease, and diabetes, should lead to an early consideration for HFpEF. To assist in the diagnosis, there are **two established clinical scoring systems that integrate clinical and imaging characteristics**: the H_2FPEF and HFA-PEFF scores.

1. The **H2FPEF score** uses six variables (contained in the acronym): **H**eavy (body mass index [BMI] >30) = 2 points; **H**ypertensive (use of one or more antihypertensives) = 1 point; atrial **F**ibrillation = 3 points; **P**ulmonary hypertension (estimated pulmonary artery systolic pressure >35 mm Hg by Doppler) = 1 point; **E**lder (age >60 years) = 1 point; **F**illing pressure (Doppler echocardiographic *E*/*é* >9) = 1 point. A score of ≥6 is considered diagnostic for HFpEF, and a score of 0 to 1 effectively rules out HFpEF. Scores in between require further assessment.
2. The Heart Failure Association of the European Society of Cardiology recommends an alternate stepwise diagnostic algorithm. The decision aid requires that if clinical characteristics are concerning for HFpEF (accounting for age and comorbidities), the clinician should calculate the **HFA-PEFF score**, which aggregates echocardiographic and natriuretic peptide findings to provide a likelihood of HFpEF diagnosis. Across functional, morphologic, and natriuretic peptide levels, the tool provides major criteria adding 2 points and minor criteria adding 1 point to the final composite score. An HFA-PEFF ≥5 points is considered to establish the HFpEF diagnosis in the absence of other clearly identified causes, and a score of 0 to 1 should prompt further evaluation for noncardiac etiology to the patient's symptoms. The society recommends exercise imaging or invasive right heart catheterization where the score is between 2 and 4.

V. DIAGNOSTIC TESTING

A. Echocardiography is the primary imaging modality for evaluating a patient with a clinical syndrome of congestive HF. It is the modality of choice when evaluating LV diastolic function. The most commonly

used parameter in clinical practice is the Doppler interrogation of the transmitral flow pattern and tissue Doppler evaluation of annular velocity to determine the *E*/*é* ratio. There are numerous other 2D and Doppler findings that are critical to diagnosis, including chamber size and wall thickness.

1. **Transmitral flow pattern.** In sinus rhythm, using pulsed-wave Doppler across the mitral inflow tract generates two waves: the early E wave, corresponding to rapid ventricular filling as the mitral valve opens, and the A wave, which reflects atrial contraction. The E-wave deceleration time is the time from peak E inflow velocity to decay to zero. With age, hypertension, or ischemia, the viscoelastic properties of the ventricle decrease, and the E wave decreases in amplitude, has a gentler slope, and has a longer deceleration time. The atrial kick is proportionately greater, and E-A reversal may occur. However, multiple other factors can impact the *E*/*A* ratio, and recent guidelines have abandoned this as a sensitive measure of diastolic dysfunction. Recent guidelines advocate using left atrial (LA) size, septal and lateral mitral annular velocity (*É*), and tricuspid regurgitant velocity to identify those with grade 1 diastolic dysfunction. With progression of diastolic dysfunction, LA pressure rises further to compensate, and the E wave becomes more prominent than the A wave (ie, pseudonormalization or grade 2 diastolic dysfunction). As diastolic dysfunction progresses, the LV stiffness increases and the deceleration time shortens, reflecting rapid equilibration of LA/LV pressures during early diastole. When the deceleration time is <160 ms and the *E*/*A* ratio is >2, the patient is considered to have grade 3 diastolic dysfunction.

   Although the transmitral flow pattern is one of the primary ways of evaluating diastolic function, it has several limitations. It can be difficult to differentiate normal diastolic function from the "pseudonormal" pattern of grade 2 diastolic dysfunction, as they both have *E*/*A* ratios >1. Also, the transmitral flow pattern can often be difficult to interpret or is uninterpretable in common scenarios, including atrial fibrillation, tachycardia (fusion of E and

A waves), and mitral valve disease (mitral regurgitation [MR] ≥3+, mitral stenosis, and mitral prosthesis).

2. **Tissue Doppler imaging (TDI) of the mitral annular velocity.** In the evaluation of LV diastolic function, TDI is used to measure the velocity of movement of the septal and lateral aspects of the mitral annulus. The myocardial velocities have three main components: systolic wave (*ś*), early diastolic wave (*é*), and late diastolic wave (*á*). In the earliest stages of diastolic dysfunction, the diastolic velocities of annular motion decrease. Normally, the lateral annulus tends to have higher velocities than the septal mitral annulus. Septal *é* <7 cm/s and/or lateral *é* <10 cm/s suggest the presence of diastolic dysfunction. The mitral annular TDI should be used with caution when other conditions that may affect annular velocity independent of ventricular relaxation coexist, such as infarction of the septum or lateral wall or constriction with pericardial adhesion of the lateral wall.
3. ***E/é.*** The ratio of the *E* velocity (obtained from the transmitral flow pattern) and the *é* (obtained from TDI, primarily of the lateral mitral annulus) can be used to estimate filling pressure, as there is a rough correlation with invasive hemodynamics (pulmonary capillary wedge pressure [PCWP]). This correlation is better with patients with depressed EF but is reasonable in patients with normal EF. Extreme values are most helpful. *E*/*é* <8 correlates with normal LV filling pressures. *E*/*é* >15 correlates with PCWP >12 mm Hg; higher values are more specific for this. There are many patients who fall into the intermediate zone, where *E*/*é* >8 but <15. For these patients, the presence of elevated filling pressure cannot be determined by this method alone. Echocardiographic guidelines suggest using the presence of LA enlargement (LA volume index >34 mL/m^2) as providing additional support for elevated filling pressures. Plasma BNP or NT-proBNP can be helpful in equivocal cases to determine whether there is corroborating evidence for elevated pressures.
4. In patients with predominantly exertional symptoms, it may be useful to perform **exercise echocardiography** to assess for

diastolic dysfunction during exercise, particularly when this is not evident at rest. Exercise provides additional valuable information, such as exercise capacity, heart rate, and blood pressure response to stress. Abnormalities in these parameters are common in patients. When obtaining exercise echocardiographic assessments, the sonographer should obtain LV images in multiple views following stress. Once the 2D information has been acquired, Doppler studies, including the transmitral flow pattern and the TDI of the septal and lateral mitral annulus, should be recorded. The diastolic abnormalities usually persist after tachycardia subsides. Therefore, Doppler data should be recorded for a period following stress to reduce the likelihood of E- and A-wave fusion, which can make the E-wave velocity difficult to interpret. If *E*/*é* following stress is >15, exertional increase in LV filling pressures is likely.

B. Invasive hemodynamic assessment. Invasive hemodynamic assessment is not routinely performed as part of the initial evaluation of HFpEF but is indicated when noninvasive studies cannot adequately assess filling pressures. The PCWP or left ventricular end-diastolic pressure (LVEDP) should be measured. Other diastolic parameters, including tau (τ), the time constant of isovolumic relaxation, are rarely measured in clinical practice.

When restrictive cardiomyopathy is considered, detailed hemodynamics may be of greatest value in directing management but are often less helpful in differentiating between possible diagnoses. Findings such as elevated and equalized diastolic pressures in four chambers (within 5 mm Hg), M pattern of the right atrial pressure waveform, "dip and plateau" of the ventricular diastolic pressures, equalization of LVEDP/RVEDP (right ventricular end-diastolic pressure), and Kussmaul sign occur in a number of pathologies, including restrictive cardiomyopathy, constrictive pericarditis, severe RV failure, and severe tricuspid regurgitation.

In the presence of normal resting hemodynamics and a high concern of HFpEF, **several abnormal hemodynamic responses to provocation may reveal occult HFpEF**. These should be performed

especially in the setting of exertional intolerance. A safe and simple exercise is to rapidly infuse 500 mL of isotonic crystalloid solution intravenously over 5 minutes. A rise in PCWP to >18 mm Hg supports an HFpEF diagnosis. Alternatively, transiently increasing venous return with a passive leg raise can also provoke an abnormal rise in LV filling pressures. Within 3 minutes after a passive leg raise, a rise in PCWP to >19 mm Hg strongly supports an HFpEF diagnosis.

Invasive hemodynamics can also be assessed during exercise. Exercise can be performed with the patient remaining flat with a supine bicycle or upright with a stationary bicycle. The patient may exercise against increasing resistance. During increasing effort, measurements of PCWP and cardiac output (via Thermodilution) are taken until the patient fatigues. A rise in PCWP with exercise to ≥25mm Hg is considered diagnostic of HFpEF. Alternatively, while it is common for LV filling pressures to increase with increasing cardiac output, an abnormal rate of increase may suggest HFpEF. In this case, a slope of ΔPCWP/ΔCO of >2 mm Hg/L/min over serial measurements during exercise is supportive of HFpEF diagnosis. This method has the benefit of being valid in the setting of submaximal testing.

C. **Magnetic resonance imaging (MRI).** In most patients with HFpEF, cardiac MRI is usually not required. It can be useful to measure ventricular function, mass, and volumes when echocardiography is not diagnostic. It is also helpful in establishing or excluding specific conditions, such as constrictive pericarditis, sarcoidosis, amyloidosis, or hemochromatosis.

D. **Endomyocardial biopsy.** Endomyocardial biopsy is used in selected circumstances, particularly when there is a high suspicion of a disorder whose diagnosis will profoundly impact management and prognosis. The most common indication in restrictive cardiomyopathy is to evaluate for cardiac amyloidosis. Biopsy in this setting can determine the presence of amyloid as well as differentiate between the different types of amyloid. The yield of endomyocardial biopsy for patchy diseases, such as sarcoidosis, is low.

VI. THERAPY. Numerous trials have evaluated the effects of medical therapy in HFpEF, including studies of angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and mineralocorticoid antagonists (MRAs) in patients with HFpEF. Unfortunately, none of these trials have shown a clear mortality benefit. There has been variable effect of these medications on morbidity end points, including HF hospitalizations, symptoms, and LVH regression. The relevance of some of these trials is in question, as their entry criteria included patients with LV dilatation and left ventricular ejection fraction (LVEF) <50%, a population that may be different from patients with HFpEF with LVEF >50%. Hypertension and congestion management remains the mainstay of therapy. Based on the results of the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme (CHARM-P) and Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trials, candesartan and spironolactone, respectively, have been shown to reduce hospitalization in HFpEF. The 2022 ACC/AHA Guideline for the Management of Heart Failure recommendations for the management of HFpEF are listed in **Table 8.3**.

TABLE 8.3 ACC/AHA Guideline Recommendations for Pharmacologic Therapy of HFpEF

Class I Recommendations	
Systolic and diastolic hypertension	Physicians should control hypertension in accordance with published guidelines (level of evidence: C-LD).
Diuretics	Physicians should use diuretics to control symptoms of volume overload (level of evidence: B-NR).
Class IIa Recommendations	
Atrial fibrillation	Management of AF according to guidelines reasonable to improve symptoms of HF (level of evidence: C-EO)
SGLT2i	SGLT2i therapy may be beneficial in decreasing heart failure hospitalizations and cardiovascular mortality (level of evidence: B-R).
Class IIb Recommendations	

ARB	ARB therapy can be considered to reduce hospitalizations (level of evidence: B-R).
ARNI	ARNI therapy can be considered to reduce hospitalizations (level of evidence: B-R).
MRA	MRA therapy can be considered to reduce hospitalizations (level of evidence: B-R).
Class III: No Benefit Recommendation	
Nitrates and PDE-5 inhibitors	Routine use of nitrates or phosphodiesterase-5 inhibitors is ineffective to improve QoL or activity in patients with HFpEF (level of evidence: B-R).

ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CAD, coronary artery disease; HFpEF, heart failure with preserved ejection fraction; MRA, mineralocorticoid antagonist; PDE-5, phosphodiesterase 5; QoL, quality of life; SGLT2i, sodium-glucose cotransporter-2 inhibitor.
Data from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1023.

A. Salt restriction. Sodium restriction is a reasonable dietary recommendation in patients with symptomatic HFpEF to reduce congestion.

B. Exercise training. Evidence from randomized controlled trials (RCTs) indicates that exercise training improves functional status, exercise performance, and quality of life (QoL) in patients with HFrEF and HFpEF.

C. Diuretics. Diuretics should be used for symptomatic treatment of edema and pulmonary congestion. Chronic use of loop diuretics may lead to diuretic resistance; in this scenario, a thiazide- or potassium-sparing diuretic may be used to augment diuresis. For this indication, hydrochlorothiazide (usually 25-50 mg, given once or intermittently) is effective within the first day. Patients may also present with significant bowel edema, rendering diuretics with poor oral absorption ineffective. In these patients, torsemide, which has a better oral absorption profile, is a reasonable option. Diuresis is often

limited by the occurrence of prerenal azotemia. This is particularly common in patients with HFpEF or restrictive cardiomyopathy with systemic disorders that have concomitant effects on the kidney, including hypertension, diabetes, or amyloidosis. In these cases, balancing congestive symptoms and azotemia can be challenging. On occasion, the patient may only achieve symptomatic relief after aggressive diuresis, even to the point where the blood urea nitrogen and/or creatinine are at levels higher than baseline values.

D. **Sodium-glucose cotransporter-2 (SGLT2) inhibitors.** Originally intended as a diabetes treatment, SGLT2 inhibitors (eg, dapagliflozin, empagliflozin) were shown to reduce HF events in patients with HFrEF. The results of EMPEROR-Preserved and DELIVER showed these favorable effects extended to patients with HFpEF as well. In the EMPEROR-Preserved trial, when compared to a placebo, empagliflozin was superior in reducing a composite of HF hospitalization or CV death (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.69-0.90). The primary end point occurred in 13.8% in the empagliflozin group compared to 17.1% in the placebo group. There was a significant benefit favoring empagliflozin compared to placebo in reducing time to HF hospitalization (HR 0.71, 95% CI 0.60-0.83), but this was not significant for CV death (HR 0.91, 95% CI 0.76-1.09). There was a significant improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary scores. The DELIVER trial similarly showed that dapagliflozin, when compared to placebo, reduced HF hospitalization, urgent HF visits, or cardiovascular disease (CVD) mortality (16.4% vs 19.5%; HR 0.82; 95% CI 0.73-0.92).

E. **ACE inhibitors.** The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized patients with LVEF ≥40% to perindopril versus placebo. The primary end point of all-cause mortality and unplanned HF hospitalization was not met, but after 1 year, there appeared to be a statistically significant decrease in HF hospitalizations in the active treatment arm.

F. **ARBs.** CHARM-P and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are two major trials that

evaluated the use of ARBs in the HFpEF population. CHARM-P, which randomized candesartan versus placebo, also failed to show a difference in its primary combined end point of cardiovascular (CV) death and HF hospitalization. Candesartan therapy did, however, reduce HF hospitalization in comparison to control. I-PRESERVE enrolled patients with LVEF ≥45% and randomized patients to irbesartan versus placebo. This trial showed no difference in the primary end point of mortality and HF hospitalizations between ARB therapy and placebo groups.

G. **Angiotensin receptor/neprilysin inhibitor (ARNI).** The ARNI sacubitril/valsartan has been shown to significantly reduce mortality in patients with HFrEF in the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial. The Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF) compared the effects of sacubitril/valsartan versus valsartan in patients with HF with EF ≥45%. The primary composite outcome of total hospitalizations for HF and death from CV causes did not differ significantly between the two groups (sacubitril-valsartan 894 events [12.8/patient-year] vs valsartan 1,009 [14.6/patient-year], rate ratio [RR] 0.87; 95% CI 0.75-1.01; $P = .06$). There was a signal of benefit for sacubitril-valsartan for HF hospitalizations (RR 0.85; 95% CI 0.72-1.00; $P = .056$) in a subanalysis.

H. **Beta-blockers.** While the benefit of beta-blockers therapy in HFrEF is well established, their use in HFpEF remains controversial due to mixed evidence. Beta-blocker medications have the possible benefit of improving heart rate and blood pressure control in patients with HFpEF, which may be of benefit in a patient population where the prevalence of concomitant hypertension, atrial fibrillation, or ischemic heart disease is high. However, there is concern that by prolonging diastolic filling times, beta-blockers may lead to an increase in ventricular wall stress by increasing ventricular load and pressure. Several studies have shown beta-blockers are associated increased natriuretic peptide levels and decreased exercise capacity.

As a counterpoint to lowering heart rate in HFpEF, the recently published myPACE trial assessed the effects of personalized accelerated pacing compared to the usual 60 bpm setting in patients with HFpEF and preexisting pacemakers. The study found that modestly increasing baseline pacing rates improved QoL, NT-proBNP levels, physical activity, and reduced atrial fibrillation over 1 year of follow-up. The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalization in Seniors with Heart Failure (SENIORS) trial randomized nebivolol versus placebo in patients aged 70 years or above with congestive HF. In the overall trial, the nebivolol group demonstrated a significant decrease in the primary end point of mortality and HF mortality, and in a subgroup analysis, the improvement appeared to hold in the 36% of patients with LVEF >35%, though there were too few patients and events to draw any conclusions in patients with preserved LVEF. A meta-analysis of the effect of beta-blockers using individual patient data from 11 randomized, placebo-controlled, double-blind clinical trials, which stratified the effect of beta-blockers by baseline, found no benefit to beta-blocker therapy in HFpEF.

I. **Digoxin.** The Digitalis Investigation Group (DIG) trial evaluated the use of digoxin in patients with HF. A subgroup of that trial examined patients with LVEF >5%. There was no significant difference in mortality in this subgroup. There was a nonsignificant trend toward decreased HF hospitalizations but an increased trend toward unstable angina hospitalizations in those treated with digoxin.

J. **Spironolactone.** The TOPCAT trial randomized patients with HF with EF ≥45% to receive spironolactone or placebo. The international trial, which enrolled patients from North and South America as well as Eastern Europe, showed that spironolactone reduced hospitalizations but had no effect on the primary outcome of CV death, aborted cardiac arrest, or HF hospitalization. Interestingly, subgroup analysis revealed a significant reduction in the primary outcome in patients enrolled in North and South America, but not those enrolled from Eastern Europe (who were younger and had less diabetes, chronic kidney disease, and atrial fibrillation than North and

South American patients). The Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF) trial randomized patients with HF with EF >50% to spironolactone versus placebo; at 12 months, there was no significant difference between the groups in the co-primary end points of changes in diastolic function by echocardiography (*E*/*é*) and maximal exercise capacity (peak VO_2) on cardiopulmonary exercise testing (CPET).

K. Sildenafil. The Phosphodiesterase-5 Inhibition to Improve Clinical Status and Exercise Capacity in Diastolic Heart Failure (RELAX) trial that randomized outpatients with HFpEF (EF ≥50%) to 24 weeks of sildenafil or placebo showed no significant improvement in VO_2max on CPET or 6-minute walk test.

L. Nitrates. The Nitrate's Effect on Activity Tolerance in Heart Failure with Preserved Ejection Fraction (NEAT) trial randomized patients with HFpEF (EF ≥50%) to isosorbide mononitrate or placebo for 6 weeks, with subsequent crossover to the other group for an additional 6 weeks. The trial revealed no significant change in daily activity level, 6-minute walk disease, QoL scores, or NT-proBNP levels with nitrate therapy compared to placebo.

VII. PRACTICAL APPROACH TO HEART FAILURE WITH PRESERVED EJECTION FRACTION

A. Diagnosis. In patients with dyspnea, HFpEF should be in the differential diagnosis, especially in the setting of appropriate risk profile (older, female, hypertension, chronic kidney disease, diabetes, and obese). BNP or NT-proBNP should be measured and resting echocardiogram should be performed, with particular attention paid toward the presence of resting diastolic dysfunction or any structural abnormality. In the absence of findings to support LV systolic dysfunction, valvular disease, or constrictive pericarditis, one should consider HFpEF if there is evidence of diastolic dysfunction and elevated LV filling pressures. If this is absent, one can consider exercise echocardiography to determine exercise-induced diastolic dysfunction or invasive cardiac catheterization with provocatory

testing. Risk scores such as the H2FPEF and HFA-PEFF can assist with the diagnosis.

Restrictive cardiomyopathy should be entertained when patients present with significant right-sided HF symptoms (ascites, hepatic congestion, and severe edema), have multiorgan presentations (amyloidosis—orthostasis and renal failure; Fabry—renal and skin involvement), or do not fit the typical risk profile for HFpEF (young and no hypertension). In these patients, additional, focused testing should be performed to establish the etiologic diagnosis. This may include cardiac MRI, nuclear imaging, and, in selected circumstances, endomyocardial biopsy.

B. Treatment. Because hypertension contributes to HFpEF pathophysiology in many patients, elevated blood pressure should be treated according to the established guidelines. Loop diuretics should be used for symptomatic benefit; they can be combined with thiazide diuretics to treat diuretic-resistant patients. In light of recent favorable evidence, SGLT2 inhibitors should be provided to all patients with HFpEF unless there is a contraindication. In addition, the use of ARBs or ARNIs and/or MRAs should be considered. Reductions in HF hospitalization have been seen with candesartan, sacubitril-valsartan, and spironolactone in clinical trials. The importance of concomitant obstructive CAD is unclear in asymptomatic patients. Revascularization should be reserved for patients in whom ischemia is thought to play a major, adverse role in cardiac function.

For patients with restrictive cardiomyopathy, treatment should be directed toward the specific etiology, where these therapies exist. The presence of congestive HF may portend a worse prognosis in patients with restrictive cardiomyopathy. Diuretics are used for symptomatic relief. Beta-blocker therapy must be used cautiously in these patients, as they may depend on their heart rate to maintain their cardiac output. In selected candidates, evaluation for cardiac transplantation can be pursued.

III. PROGNOSIS. The prognosis in symptomatic patients with HFpEF is not as well characterized as our understanding of the natural history of HFrEF.

Although population-level data suggest similar mortality risk in HFrEF and HFpEF, analyses from clinical trials and observational cohorts suggest lower mortality in HFpEF than in HFrEF. It is well known, however, that patients with HFpEF experience increased risk of death in comparison to those without HF. Furthermore, patients with a history of HFpEF and HF hospitalization experience even worse survival, with 20% to 30% of these patients dying within 1 year of discharge. Importantly, patients with HFpEF and HFrEF experience similar morbidity, with comparable rates of hospitalization and readmission, poor performance on objective measures of functional status such as 6-minute walk test, and reduced QoL questionnaire scores.

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CHAPTER 9

Amyloid Heart Disease

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I. INTRODUCTION

A. Amyloid heart disease, or cardiac amyloidosis (CA), is an **infiltrative, restrictive cardiomyopathy caused by the deposition of misfolded amyloid fibrils into the extracellular space of the myocardium**. Other infiltrative cardiomyopathies and restrictive physiology as a subset of heart failure (HF) with preserved ejection fraction (HFpEF) are discussed elsewhere.

B. CA can occur either in isolation or as one manifestation of a systemic disorder. Amyloid fibrils have a **pathognomonic appearance of "apple-green" birefringence** after staining with Congo red and visualization with polarized light. Although there are many different amyloid diseases, **two types account for over 95% of all CA: immunoglobulin (Ig) light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR)**. The clinical presentation of both can be similar, but treatments differ significantly, making accurate diagnosis critical. In addition, ATTR amyloidosis is either due to wild-type or variant disease.

C. CA was historically thought of as a progressive disease with irreversible morbidity, decline in quality of life, and mortality. However, in recent years, newer targeted therapies have been developed, dramatically altering the natural history of both transthyretin cardiomyopathy (ATTR-CM) and light chain cardiac amyloidosis (AL-CA), making early and accurate diagnosis paramount. Therapies are most beneficial in treating early disease; therefore, a high index of suspicion and low threshold for evaluation are needed to avoid late diagnosis.

II. EPIDEMIOLOGY AND NATURAL HISTORY OF THE MOST COMMON SUBTYPES.

The estimated prevalence of ATTR-CM is increasing with the expansion of accurate noninvasive diagnostic techniques. AL-CA, however, remains a rare disease with a yearly incidence of about 5,000 to 7,000 patients in the United States. The natural history of CA varies by subtype, but cardiac involvement is a major source of morbidity and mortality. Median survival is expected to shift significantly with emerging treatments for both ATTR-CM and AL-CA.

A. Transthyretin amyloidosis

1. **Transthyretin** (prealbumin) is a tetrameric protein made up of four identical monomers that functions for thyroxine and retinol transport and is produced by the liver, the choroid plexus for the cerebrospinal fluid, and the retina for the vitreous of the eye. Due to some predisposition (autosomal dominant gene variants or aging), the normally stable beta-sheet–rich tetramers dissociate into monomers that then misfold, aggregate, and deposit in tissue (myocardium, nerves, soft tissues) as amyloid fibrils. The two subtypes of ATTR amyloidosis are variant and wild type.
2. **Variant (ATTRv):** There are over 150 known variants, almost always caused by a single-nucleotide mutation and inherited in an autosomal dominant pattern. Epidemiology, phenotype, and clinical course vary widely with each specific variant, and the prevalence of specific variants has geographic variation. There are variants that present with predominant neuropathy, others with cardiomyopathy, and most with a mixed phenotype. Median survival is estimated to be 8 to 10 years in those with ATTRv neuropathy, versus 2.5 to 3.6 years in those with cardiac involvement. **Commonly used staging systems are in Table 9.1 and were developed in the pretreatment era of ATTR-CA.**

TABLE 9.1 Validated Prognostic Scoring Systems for ATTR Amyloid

Score System	Thresholds	Stage I: Both biomarkers within	Stage II: One of two biomarkers	Stage III: Both biomarkers abnormal

		normal range	above threshold	
NA' Score (ATTR-CM)	NT-proBNP >3,000 ng/L, eGFR >45 mL/min/1.73 m^2	Median survival: 69.2 mo	Median survival 46.7 mo	Median survival 24.1 mo. Stratified by ATTR subtype: ATTR wt 32.7 mo, ATTRv V122I 17.7 mo
Mayo Clinic ATTRwt-CM Staging System	Troponin T (>0.05 ng/mL), and NT-proBNP >3,000 pg/mL	4-y overall survival: 57%	4-y overall survival: 42%	4-y overall survival: 18%

eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

a. **Val122Ile (p.V142I)** is the most common TTR variant in the United States and in persons of West African and Afro-Caribbean ancestry (V122I or p.V1421).
   (1) Allele prevalence of 3% to 4% heterozygote carriers in the African American population
   (2) Time of diagnosis and clinical presentation are similar to ATTR wild type (ATTRwt), with an average age of diagnosis being reported as 69 years.
   (3) Mainly cardiomyopathy, but neuropathy can be present in some patients.
   (4) Median untreated survival is 2.5 years from the time of diagnosis for the V122I variant. This variant has shown reduced survival in some cohorts compared to patients with ATTRwt.

b. **Val30Met variant (p.V50M)** (Sweden and Southern Europe, Japan), predominately neuropathic phenotype

(1) Early onset (<50 years) endemic in areas in Portugal and Brazil with predominant neuropathy

(2) Late onset (>50 years) occurs more sporadically and is more likely to also have cardiac manifestations.

c. Thr60Ala (p.T80A) is seen in those with Irish ancestry.

(1) Presents with a mixed phenotype, mostly with cardiomyopathy

(2) Arteriovenous (AV) block is common.

(3) Median age at diagnosis in 50s and 60s.

d. **ATTRwt:** Previously known as "senile" CA. Occurs sporadically in **individuals typically over the age of 60**, **with a median age at diagnosis of 75 years**, affecting predominantly White males although with a recognition that females may be underdiagnosed. There is no mutation in the transthyretin gene; thus, the tetrameric protein is normal. Although not entirely clear, oxidative stress with aging can lead to tetrameric dissociation, misfolding, and aggregation of transthyretin amyloid in tissues. This is the most common type of ATTR cardiomyopathy.

(1) Has been reported in various studies in 5% to 17% of patients with HFpEF, and up to 16% of patients over 65 years old referred for transcatheter aortic valve replacement (TAVR) and 5% of people with presumed nonobstructive hypertrophic cardiomyopathy

(2) Most commonly a disease of the older but has been diagnosed, in rare occasions, in patients under 60

(3) Has 3.6 years median untreated survival from the time of diagnosis. In a UK cohort, median survival was 46.3 months for those diagnosed pre-2012 and 60.2 months for those diagnosed post-2012.

B. **Light chain amyloidosis:** This results from abnormal clonal proliferation of plasma cells, causing the production of kappa or lambda monoclonal light chains that then deposit into tissue (myocardium, kidneys, liver, gastrointestinal [GI] tract, nerves, soft

tissues). In untreated AL-CA presenting with HF, median survival is less than 1 year. Median overall survival from diagnosis is evolving, given effective chemotherapy and targeted use of stem cell transplantation. Of note, circulating free light chains (FLCs) and nonamyloid fibril protein aggregates can cause direct organ toxicity.

1. Typically presents in the fifth to seventh decades of life, though can present at any age above 30 years
2. Current prevalence in the United States is estimated to be 12,000 patients with a median age at diagnosis of 63, 55% are male, with about 5,000 new cases per year.
3. 15% of patients with newly diagnosed multiple myeloma are concurrently diagnosed with AL amyloidosis.
4. Validated Prognostic Scoring System "Mayo" Score: In a cohort of patients with AL amyloid, FLC-diff (difference between involved and uninvolved FLC), cardiac troponin, and N-terminal pro–B-type natriuretic peptide (NT-proBNP) were found to be independent prognostic markers for survival in AL amyloid and used to create a prognostic model. FLC-diff essentially represents plasma cell–clone burden (ongoing FLC production) and contribution to mortality. This score is intended for patients who have been diagnosed with AL amyloidosis and was **created prior to contemporary therapy** (**Table 9.2**).

TABLE 9.2 Validated Prognostic Scoring Systems for AL Amyloid

Score System	Thresholds	Stage I: All biomarkers within normal range	Stage II: One of three biomarkers above threshold	Stage III: Two of three biomarkers above threshold	Stage IV: All biomarkers abnormal
Mayo Score	FLC-diff >18 mg/dL, cardiac troponin ≥0.025 ng/mL, NT-	Median survival 55 mo	Median survival 19 mo	Median survival 12 mo	Median survival 5 mo

	proBNP ≥1,800 pg/mL

FLC, free light chain; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

III. CLINICAL PRESENTATION. This covers the common clinical presentation of the most common subtypes of systemic amyloidosis, but there is **significant overlap in presenting symptoms**. Symptoms are also dependent on variant phenotype.

A. Cardiac involvement: The initial presentation is often vague, including symptoms of dyspnea and fatigue.

1. HF with restrictive hemodynamics
2. "Cure" of hypertension with gradual need for less antihypertensive therapy
3. Inability to tolerate blood-lowering agents or nodal agents
4. Aortic stenosis (AS): There is a high prevalence of ATTR in patients with AS.
5. Patients with CA are at higher risk of intracardiac thrombus due to atrial myopathy, even in the absence of atrial arrhythmias. Embolic stroke can be the initial presentation.
6. Arrhythmias and conduction disease
   a. Atrial fibrillation: Has been reported to be present in 69% of patients with ATTR-CM, with 40% to 45% labeled as paroxysmal atrial fibrillation. In a limited cohort, maintenance of sinus rhythm was significantly associated with lower mortality. Less common in AL-CA.
   b. Antiarrhythmic medications, cardioversion, and ablation are more effective earlier in the disease course.
   c. Unexplained conduction disease

B. Extracardiac symptoms of ATTRv amyloidosis

1. Bilateral ascending sensorimotor polyneuropathy
2. Orthostatic hypotension and other manifestations of dysautonomia
3. GI involvement: Both diarrhea and constipation

4. Erectile dysfunction
5. Ophthalmologic involvement: Glaucoma, intravitreal amyloid deposition, scalloped pupils

C. Extracardiac symptoms of ATTRwt (can precede cardiac involvement by 5-7 years)

1. Bilateral carpal tunnel syndrome (deposits of amyloid in flexor retinaculum and tenosynovial tissue within the carpal tunnel)
2. Biceps tendon rupture
3. Lumbar spinal stenosis (thickening of ligamentum flavum)
4. Peripheral and autonomic neuropathy can be seen but are less common.

D. Extracardiac symptoms of AL amyloid

1. Weight loss
2. Nephrotic syndrome
3. Macroglossia
4. Hepatosplenomegaly
5. Skin bruising and periorbital purpura
6. Arthropathy
7. GI disturbance
8. Hoarseness
9. Jaw claudication

IV. DIAGNOSIS

A. Developing a diagnostic suspicion

1. Late and delayed diagnosis is common in CA as symptoms are often vague and get attributed to other causes of dyspnea or HF, including aging, hypertensive heart disease, and hypertrophic cardiomyopathy. Therefore, **when evaluating patients with HF and increased myocardial wall thickness, it is critical to maintain a high suspicion for CA**.
   a. Suspicion should be heightened based on clinical red flags that have been associated with CA **(Table 9.3)**.

TABLE 9.3 Clinical Suspicion for Cardiac Amyloid

Consider screening if left ventricular wall thickness >12 mm *plus* at least one red flag

- Heart failure age ≥65 y
- Aortic stenosis in ≥65 y
- Hypotensive or normotensive if previously hypertensive
- Peripheral polyneuropathy
- Autonomic neuropathy
- Macroglossia
- Proteinuria
- Periorbital purpura
- Bilateral carpal tunnel syndrome
- Ruptured biceps tendon
- Lumbar spinal stenosis
- Diffuse LGE or increased ECV
- Reduced longitudinal strain with apical sparing
- Decreased QRS voltage-to-mass ratio
- Unexplained conduction disease/arrhythmia
- Family history

ECV, extracellular volume; LGE, late gadolinium enhancement.

b. A detailed history and examination are necessary, including an orthopedic history, history of neuropathy (erectile dysfunction, orthostasis, diarrhea, neuropathic symptoms of extremities), and family history.

c. Clinical risk scores are being developed to aid in appropriate referral to more advanced imaging.

2. Red flag findings. Clinical suspicion based on the factors below should prompt further workup.

a. Clinical scenarios

(1) HF, with or without atrial fibrillation and/or conduction system disease

(2) History of **hypertension with de-escalation in medication doses**

(3) History of **orthopedic disease and surgeries** (carpal tunnel, lumbar spinal stenosis, trigger finger, biceps tendon

rupture, rotator cuff tear), with or without history of HF

(4) Cardiac disease in the presence of system conditions such as **plasma cell dyscrasia, nephrotic syndrome, and chronic systemic inflammatory conditions**

b. Echocardiogram: It is important to recognize that these findings should raise red flags in both patients with preserved and reduced ejection fraction.

(1) Wall thickness >12 mm, with or without the presence of hypertension and AS

(2) Low-flow, low-gradient AS

(3) Nondilated left ventricular (LV) cavity with grade 2 or 3 diastolic dysfunction

(4) Biatrial dilatation

(5) Mitral and tricuspid valve thickening

(6) Relative apical sparing of longitudinal strain

c. Electrocardiogram (ECG)

(1) Relative low voltage in the presence of LV wall thickness (although the absence of low voltage does not rule out cardiac amyloid)

(2) Atrial fibrillation

(3) Conduction disease (PR prolongation, increased QRS with intraventricular conduction delay [IVCD], left bundle branch block [LBBB], right bundle branch block [RBBB], prior pacemaker)

d. Biomarkers: Elevated in the setting of more advanced disease, limiting their utility as a screening tool for early disease

(1) Elevated troponin in the absence of acute coronary syndrome (troponin T)

(2) Elevated natriuretic peptide levels (NT-proBNP)

e. Cardiac magnetic resonance imaging (MRI)

(1) Late gadolinium enhancement (LGE) with a diffuse subendocardial or transmural rather than focal pattern

(2) Difficulty nulling myocardium with phase-sensitive inversion recovery (PSIR) LGE imaging

(3) Increased myocardial T1

(4) Increased extracellular volume (ECV) fraction (>0.4)

B. Multimodality and laboratory approach to diagnosis. The incorporation of cardiac biomarkers, clinical history, ECG, and multimodality cardiac imaging can aid in developing a suspicion for, and confirming the diagnosis of, ATTR-CM. Of note, a noninvasive diagnosis of ATTR amyloid is clinically acceptable; however, for accurate diagnosis, staging, and treatment strategy for AL amyloidosis, an invasive diagnosis is still required. **The noninvasive evaluation of ATTR must be done with the concomitant evaluation of light chain amyloidosis, particularly because cardiac scintigraphy can show myocardial uptake in both ATTR and AL amyloidosis.**

1. Lab work

a. Cardiac troponin elevation on multiple lab draws without other explanation for myocardial injury

b. NT-proBNP elevated out of proportion to HF severity (NT-proBNP preferred to BNP, given that the National Amyloidosis Centre [NAC] staging uses the former)

c. AL lab work: Taken in combination, standard lab work for AL amyloid is >99% sensitive.

(1) Serum FLC assay: **It is important to interpret these results in the context of chronic kidney disease (CKD) as the renal clearance of FLCs decreases with worsening CKD, which can impact the FLC ratio (typically associated with kappa predominance).**

(2) **Immunofixation** of the serum and urine

2. **ECG**

a. Relatively low voltage (ECG/left ventricular hypertrophy [LVH] discordance)

b. Pseudoinfarct pattern without prior myocardial infarction (MI)

c. Conduction disease

d. Atrial fibrillation

3. **Echocardiography:** This is often the first diagnostic clue due to wide availability. Echo findings do not confirm the diagnosis but can lead to the appropriate diagnostic workup. Classic changes such as ventricular wall thickening and thickening of the interatrial septum and valves resulting in biatrial enlargement, smaller LV cavity, and restrictive LV filling pattern appear in the later stage disease.

   a. **LVH: Wall thickness >12 mm**; can also see increased right ventricular (RV) free wall thickness

   b. Symmetric LV wall thickening is typical.

      (1) Not infrequently can have asymmetric septal hypertrophy, ATTR > AL.

      (2) A small subset can have dynamic LV outflow obstruction, mimicking hypertrophic obstructive cardiomyopathy (HOCM).

   c. Thickening of the AV valves

   d. Normal or small LV cavity, rarely mild-to-moderate dilation in AL > ATTR

   e. Atrial enlargement, interatrial septal thickening

   f. Restrictive diastolic filling pattern: $\acute{E}$ and $\acute{a}$ <5 cm/s.

   g. LV ejection fraction (LVEF) to global longitudinal strain (GLS) ratio >4.1, or reduced GLS (absolute value <−15%)

   h. Relative apical sparing of GLS (“cherry on top” pattern)

   i. Low QRS voltage-to-LV mass ratio

   j. Mitral annular tissue Doppler $\acute{S}$ <6 cm/s

   k. Apical/(average mid- and basal longitudinal strain) ratio >1 distinguished CA from LVH (93% sensitivity, 82% specificity).

   l. Pericardial effusion, idiopathic

   m. AS, typically low flow/low gradient in older males

   n. Although historically thought of as a disease of “HFpEF,” many patients present across the LVEF spectrum.

4. **Cardiac MRI (cMRI):** Benefits include excellent tissue characterization, anatomic detail, and functional assessment. A negative cMRI in a patient in whom clinical suspicion is high does not rule out CA.
    a. LGE: Global subendocardial LGE that progresses to transmural with advancing disease, and LGE in left atrial (LA) and RV. ATTR amyloid is more likely to be transmural and have RV involvement. PSIR sequence is required to minimize the effect of nulling.
        (1) Limited ability to quantify the degree of amyloid infiltration
    b. T1 mapping (native precontrast): Native myocardial T1 relaxation times are increased in ATTR and AL.
    c. ECV (T1 postcontrast): Reflective of amyloid deposition in the extracellular space. ECV $\geq$ 0.40% supports amyloid diagnosis and is prognostic.
    d. **T2 mapping: Quantifies myocardial edema and is an independent predictor of mortality**
    e. High-resolution imaging
        (1) Different patterns of LVH. May be asymmetric in both AL and ATTR; however, more common in ATTR
        (2) RV hypertrophy.
5. **Bone scintigraphy** (also labeled cardiac scintigraphy): This scan is based on the concept that technetium bone-avid compounds bind to something in the amyloid deposits (currently unknown) and allow for noninvasive diagnosis of ATTR amyloid.
    a. Multiple technetium-99m (^{99m}Tc) compounds are available. ^{99m}Technetium pyrophosphate (PYP scan) is used in the United States; ^{99m}Tc-DPD and ^{99m}Tc-HMDP are used predominantly in Europe.
    b. Results of planar imaging are reported using two main methods.
        (1) **Heart-to-contralateral lung ratio** (H/CL) >1.5 with 1-hour imaging and >1.3 with 3-hour imaging as diagnostic

of ATTR amyloid

(2) **Perugini grade**: (0 = absent cardiac uptake, 1 = uptake less than bone, 2 = uptake equal to bone, 3 = uptake greater than bone) with grades 2 to 3 uptake considered to be a positive scan for ATTR amyloid

c. H/CL ratio is not prognostic in contemporary data, and movement to remove this as a diagnostic criterion is ongoing, given the pitfalls of using this for diagnosis.

d. Acquiring single-photon emission computed tomography (SPECT) helps to confirm uptake is cardiac not in the blood pool (false positive) and is mandatory per the American Society of Nuclear Medicine guidelines.

e. Causes of a false-positive scan when using planar imaging alone:

(1) Blood pool

(a) If the blood pool is confused with the myocardium, a false positive is read if only planar imaging is done. Repeat scan with SPECT (if available SPECT/CT) to differentiate blood pool from true myocardial uptake.

(2) Rib fracture

f. Causes of true-positive scans other than ATTR-CM:

(1) AL amyloidosis: This leads to true myocardial uptake, about 20% of patients with AL-CM can have grade 2/3 uptake. **That is why AL-CM must be ruled out to confirm that the positive PYP is due to ATTR-CM.**

(2) ApoA1 CA

(3) Hydroxychloroquine toxicity

g. Causes of false-negative bone scintigraphy:

(1) Certain mutations, that is, Val30met, Phe64Leu

(2) Prior MI with scar

(3) Early disease

(4) Small radiotracer dose

(5) Breast implants

h. It is important to know the limitations of the test. If clinical suspicion is high, pursue endomyocardial biopsy.

i. Specificity for ATTR is very high if AL lab work is negative.

j. Nonbiopsy diagnosis:

(1) PYP scan (grade 2 or 3) is "positive" and confirmed by SPECT or SPECT/CT.

(2) Patient has clinical features of CA by echo/MRI finding.

(3) If AL lab workup (including serum FLCs and both serum and urine immunofixation) is negative, then a biopsy is not required for confirming the diagnosis of ATTR-CM.

6. Positron emission tomography (PET) scan with amyloid-specific tracers florbetaben or florbetapir: It is currently being studied for early diagnosis and disease progression.

7. Biopsy

a. **Endomyocardial biopsy remains the gold standard of diagnosis for CA** but is no longer required in ATTR amyloid (see Section IV.B.9). After a biopsy is obtained, it is first stained with Congo red (or thioflavin S). Green birefringence under polarized light confirms the presence of amyloid deposition. Then secondary testing is required to subtype the amyloid protein, including mass spectrometry, immunohistochemistry, or immunoelectron microscopy.

b. **A biopsy with histologic evidence of light chain amyloid deposition is necessary in AL amyloidosis to make the diagnosis and target treatment** (does not need to be endomyocardial biopsy). Bone marrow biopsy or fat pad biopsy is commonly performed in this scenario. Fat pad biopsy has variable yield in the literature but has less risk of serious complication than an endomyocardial biopsy. Endomyocardial biopsy is indicated if tissue from extracardiac sites is unable to give a histologic diagnosis. Risk of RV perforation causing cardiac tamponade is under 1% at experienced centers. Per clinician discretion, going directly to endomyocardial biopsy is appropriate.

c. **An endomyocardial biopsy is required to diagnose ATTR-CA if the diagnosis is uncertain**, that is, when both PYP scan and AL lab work are positive, and it is necessary to distinguish monoclonal gammopathy of undetermined significance (MGUS) or CKD with ATTR amyloid from true AL amyloidosis.

d. Less common forms of CA include ApoA1, lysozyme, and AA amyloidosis. Note, there is a form of cardiac amyloid limited to the atria, called atrial natriuretic factor (ANF), which can sometimes be found on LA appendage removal at the time of cardiac surgery. This is typically not clinically relevant and requires no treatment.

8. Role of genetic testing

a. **Genetic testing is recommended for all patients diagnosed with ATTR amyloidosis for distinguishing the wild-type and variant form, and testing of their immediate family members is recommended if diagnosis of ATTRv is confirmed**. Assessment of penetrance should begin 10 years before age of disease onset in the affected family member/proband, or when symptoms developed. The age threshold for testing children of probands is an individualized decision, referral to genetic counseling for this discussion is recommended.

b. Genetic testing in ATTR is appropriate, no matter the age of diagnosis.

c. The optimal method and interval of serial evaluation for identified TTR variant carriers is unknown but should prompt referral to an amyloidosis expert.

9. Diagnostic algorithms

a. AL amyloid: **International Myeloma Working Group criteria for diagnosis of AL amyloidosis**

(1) Clinical presentation compatible with AL pattern of injury

(2) Evidence of monoclonal or lymphoproliferative disorder based on bone marrow aspirate/biopsy and serologic

parameters

(3) Histopathologic identification of amyloidosis deposition in periumbilical fat or affected organ

(4) Amyloidosis typing for identification of Ig light chain precursor protein via mass spectroscopy or immunoelectron microscopy

b. ATTR amyloid: The **key to a noninvasive diagnosis of ATTR amyloidosis is to rule out AL amyloid using comprehensive blood work**. A comprehensive diagnostic algorithm is proposed in **Figure 9.1**.

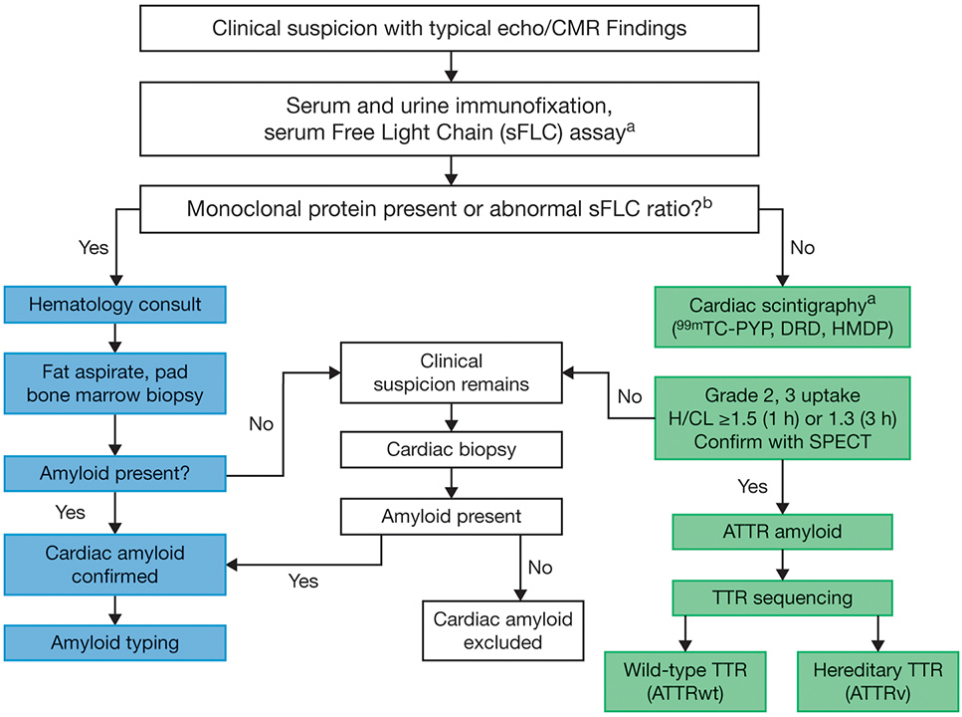

FIGURE 9.1 Diagnostic algorithm for cardiac amyloidosis. CMR, cardiac magnetic resonance; H/CL, heart-to-contralateral lung ratio; SPECT, single-photon emission computed tomography; v, variant, wt, wild type; ^{99m}TC-PYP, technetium-99m pyrophosphate.

[a]Serum and urine immunofixation and noninvasive imaging with cardiac scintigraphy can be pursued simultaneously for expedited evaluation.

[b]Serum free light chain (sFLC) by the binding site (Freelite) assay: *K*/*L* ratio 1.65 to 3.1 may be considered normal in patients with renal dysfunction; consultation with hematologist recommended.

C. At-risk populations: Several subpopulations of patients are known to be at higher risk for cardiac amyloid and thus warrant a higher diagnostic suspicion (**Figure 9.2**) and earlier screening.

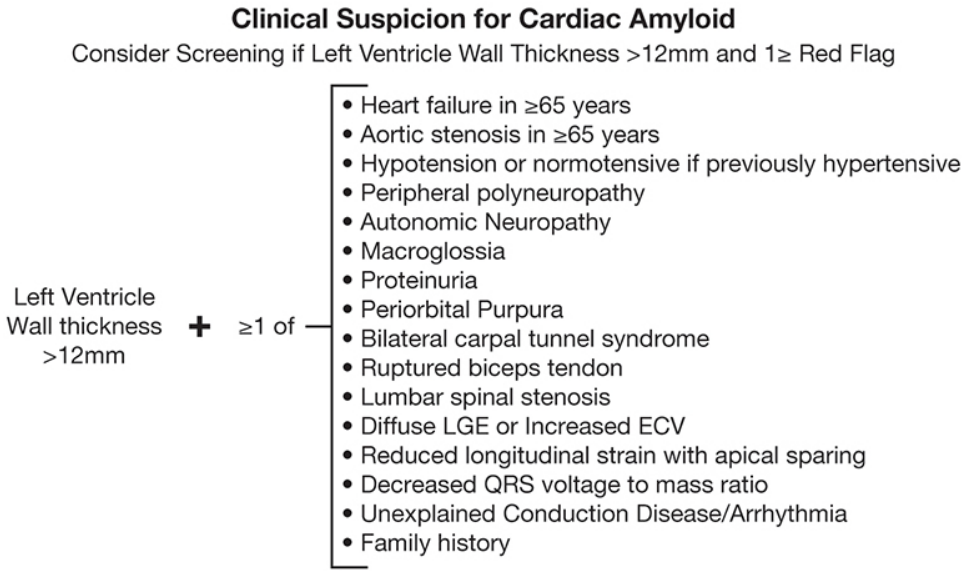

FIGURE 9.2 Developing clinical suspicion for cardiac amyloid.

1. **Patients with HFpEF**, both inpatient and outpatient, particularly with "red flags" associated with clinical HF
2. **Older patients with severe calcific AS** who are referred for TAVR with low-gradient AS
   a. Associated red flags include older age, elevated troponin T, conduction disease, and low-voltage ECG.
3. **Carpal tunnel and lumbar spinal stenosis**
   a. Tenosynovial biopsy samples from the time of carpal tunnel release have successfully diagnosed and subtyped amyloidosis.
   b. Few centers perform biopsy at the time of carpal tunnel release surgery in selected patients to screen for ATTR. Carpal tunnel diagnosis often precedes cardiac diagnosis by 5 to 7 years, and prospective pathologic evaluation of carpal tunnel tissue in patients has allowed for earlier identification of ATTR-CM.

V. MANAGEMENT. It is important to consider the management of CA in two broad categories: treatment of cardiomyopathy and cardiac sequelae, and targeted disease therapy to stop, slow, or, rarely, reverse amyloid deposition.

A. Treatment/prevention of complications

1. **HF:** CA is a restrictive cardiomyopathy, with reduced stroke volume and cardiac output. EF is generally preserved until later stages of disease. Fluid management is key; however, due to decreased LV and RV compliance, these patients are sensitive to changes in preload. Careful monitoring of renal function is required. Traditional invasive hemodynamic "tailoring" goals may lead to hypotension and acute kidney injury in patients with advanced CA that may require higher filling pressures to maintain perfusion.
   - **a.** Loop diuretics for volume management
   - **b.** Aldosterone antagonists in conjunction with loop diuretics if tolerated
   - **c.** Use digoxin with caution, given concern that there can be toxicity due to digoxin bindings to amyloid fibrils even at lower serum levels.
   - **d.** Avoid or dose reduce beta-blockers and nondihydropyridine calcium channel blockers, especially when there is known conduction disease. Also, suppressing heart rate can blunt the patient's ability to augment cardiac output, given fixed stroke volume.
   - **e.** Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and angiotensin receptor blocker-neprilysin inhibitors can be used with caution in patients with ATTR (much less likely to be tolerated with AL and should be avoided), given high prevalence of orthostasis and autonomic dysfunction. There is limited data to support guideline-directed medical therapy in CA, and a patient's individual physiology should be considered.

f. Mechanical support: LV assist device (LVAD) implantation may not be feasible difficult due to small LV cavity size and biventricular dysfunction, although in very highly selected patients may be feasible.

g. Cardiac transplant: Patient selection is discussed further under AL and ATTR treatment sections in more detail. Careful selection of patients with stage D HF for cardiac transplant has been done successfully in both ATTR-CM and AL-CA.

2. Arrhythmias and conduction disease

a. Atrial arrhythmias: CA is associated with atrial enlargement and dysfunction. When atrial fibrillation/flutter develops, anticoagulation is recommended, **regardless of CHAD-VASC score.**

(1) Amiodarone is often used for rhythm and rate control.

(2) Cardioversion is safe in these patients.

(3) Ablation for atrial fibrillation may be considered and has been shown to be more effective early in the disease course.

b. Ventricular arrhythmias

(1) Defibrillator implantation is recommended for secondary prevention after significant ventricular arrhythmias or aborted sudden cardiac death, with expected survival >1 year.

(2) There is no definitive evidence to support implantable cardioverter defibrillator (ICD) for primary prevention in CA. In select patients with AL-CA, ICD may be considered, although data are mixed.

c. Conduction system disease

(1) Implant pacemakers according to the most recent guidelines

(2) Consider cardiac resynchronization therapy (CRT) placement if pacemaker dependent as RV pacing may be tolerated, given reduced/fixed stroke volume.

3. **Autonomic dysfunction**
    a. Antidiarrheals and GI motility medication
    b. Midodrine and compression stocking can be used to help with orthostasis.
4. **Neuropathy:** Medications for neuropathic pain (gabapentin, pregabalin, duloxetine)
5. **Liver transplant**: Shown to be beneficial for those with Val30met mutations and is more beneficial in early-stage disease. Does not prevent ATTRwt from complexing with existing amyloid deposits; therefore, disease can still progress. Poorly tolerated without concurrent heart transplant in those with severe cardiac dysfunction.

B. Disease-modifying therapy in AL

1. The goal of treatment of amyloid light chain (AL) amyloidosis is to **eradicate the fibril precursor protein by targeting the underlying plasma cell dyscrasia**. Treatment requires a multidisciplinary team of hematology-oncology specialists and cardiology. Cardiac response is determined by hematologic response. The role of the cardiologist is in assessment of cardiac risk stratification for bone marrow transplant and other therapies, consideration of heart transplant evaluation, and ongoing cardiac monitoring during chemotherapy and longitudinally.
2. Treatment generally requires cytoreductive, clonal plasma cell–directed chemotherapy, and/or immune therapy. The goal of treatment is rapid and deep hematologic remission/reduction of FLC production to halt the progression of end-organ damage from amyloid deposition.
3. Cyclophosphamide, bortezomib, and dexamethasone with monoclonal antibody daratumumab hyaluronidase (Dara-CyBorD) is Food and Drug Administration (FDA) approved (Andromeda study). This regimen achieved very good partial response (VGPR) or better in 78.5% of trial participants.
4. Other agents used include other alkylating agents such as oral melphalan with dexamethasone (MalDex) and cyclophosphamide;

bendamustine; proteasome inhibitors (bortezomib and carfilzomib); immunomodulatory drugs like lenalidomide, thalidomide, and pomalidomide; and antiplasma cell monoclonal antibody drugs like daratumumab, isatuximab, and elotuzumab.

5. Autologous stem cell transplant (ASCT) historically gives sustained remission and best long-term survival and is used with high-dose melphalan but requires careful patient selection and a specialized treatment center for good outcomes.
6. Randomized clinical trials to determine the best combination and timing of chemo-immunotherapy and ASCT have not yet been done. The success of the therapy is variable according to specific translocation. t(11;14) predicts poor response to bortezomib and is an adverse prognostic factor. It is present in 40% to 60% of patients with AL amyloidosis. Venetoclax, a small-molecule B-cell lymphoma 2 (BCL-2) inhibitor, has shown to be an effective treatment for patients with AL-CM with t(11;14) translocation.
7. Agents targeting amyloid fibrils are currently under investigation with the goal of reversing amyloid fibril deposition in the heart and other affected organs.
    a. CAEL-101 (11-1F4) amyloid fibril–reactive monoclonal antibody that binds an epitope on misfolded human light chain amyloid fibrils enhances opsonization and proteolysis of misfolded fibrils. Remains under investigation.
    b. Birtamimab: This is also a monoclonal antibody targeting amyloid fibrils. Birtamimab in Mayo Stage IV Patients with AL Amyloidosis (AFFIRM-AL) will examine birtamimab + CyBorD/Dara compared to CyBorD/Dara alone.

C. Cardiac transplantation in AL

1. Consideration of cardiac transplantation is indicated when **three criteria** are met:
    a. Persistent significant cardiac limitations
    b. Successful hematologic response to AL therapy
    c. No significant extracardiac disease

2. Significant extracardiac organ involvement that generally contraindicates isolated heart transplantation includes renal dysfunction and nephrotic range proteinuria, GI involvement with malabsorption, pulmonary amyloidosis with recurrent pleural effusions, debilitating peripheral neuropathy, or autonomic dysfunction.

D. Disease-modifying therapy in ATTR: Many new therapies are available or currently being studied, and in general are more effective earlier in disease, with the goal being to prevent system manifestations of amyloid deposition, including neurologic and cardiac.

1. TTR tetramer stabilization

a. Tafamidis: This is a benzoxazole derivative that selectively binds to thyroxine-binding sites of transthyretin, inhibiting dissociation of tetramers into pathogenic monomers. **Only FDA-approved therapy for ATTR-CM.**

(1) Phase III trial results were published in *NEJM* in 2018 by Maurer et al (essential reading) and showed that patients with ATTRv and ATTRwt treated with tafamidis had reduced all-cause mortality in New York Heart Association (NYHA) class I and II patients, fewer cardiovascular (CV)-related hospitalizations in NYHA class I and II patients, and less decline in functional capacity and quality of life compared to those who received placebo.

(2) In NYHA III patients, there was a trend toward reduced mortality but greater CV hospitalization frequency.

(3) Currently the only approved treatment for CA in both ATTRv and ATTRwt

(4) Recommended to be initiated in ATTRv and ATTRwt CA with NYHA class I to III symptoms

(5) Patients with NYHA class IV symptoms and severe renal dysfunction (glomerular filtration rate [GFR] <25) were excluded from tafamidis trial; therefore, it is currently not recommended in this group.

(6) Affordability remains a major barrier to treatment with tafamidis.

b. **Diflunisal** (250 mg orally twice daily)

(1) Nonsteroidal anti-inflammatory drug (NSAID): Binds to thyroxine-binding sites, stabilizing TTR. Is not approved but has been given off-label for hereditary amyloidosis polyneuropathy

(2) Has shown decreased progression of neuropathy and improved quality of life compared to placebo. It has not been studied in patients with CA in a randomized trial.

(3) Shares general risks of NSAID therapy, contraindicated thrombocytopenia, patients with bleeding history, and renal failure. Use with caution in patients with HF.

(4) Consider initiating off-label for asymptomatic ATTR carriers, patients with ATTR-CM who are not eligible for other therapies

c. **Acoramidis**

(1) Selective molecule that binds to the TTR tetramer and stabilizes it, preventing the formation of amyloid fibrils and subsequent deposition

(2) Safe, well tolerated, and effective in stabilization in phase 2 study and open-label extension study

(3) ATTRibute-CM phase III is a large randomized trial in ATTR-CM that is currently ongoing.

2. **Gene-silencing therapies** for neuropathy with ongoing trials for cardiomyopathy

a. These agents are delivered to hepatocytes and are composed of complementary sequences to TTR messenger RNA (mRNA) and through Watson Crick binding set it up for cleavage. Thus, transcription is blocked, and the production of TTR is reduced, with much lower serum levels achieved.

b. **Patisiran** (Onpattro): An RNA interference (RNAi) therapeutic

(1) Currently FDA approved for the treatment of polyneuropathy in hereditary ATTR amyloidosis

(2) In the APOLLO trial (*NEJM*, 2018), it was shown to cause a significant improvement in the modified neuropathy impairment score and other clinical manifestations of ATTR amyloidosis.

(3) The Apollo-B trial for the use of patisiran in patients with cardiomyopathy met its primary end point at 12 months with respect to 6-minute walk test (6MWT). Subgroup analysis of APOLLO showed stabilizations of worsening LV GLS, LV wall thickness, and NT-proBNP levels in patients enrolled and assumed to have CA based on imaging findings.

c. Vutrisiran (Amvuttra): An investigational RNAi therapeutic

(1) Orphan drug approved in June 2022 for ATTRv polyneuropathy

(2) Vutrisiran is an RNAi therapeutic.

(3) HELIOS-A study showed that vutrisiran had a significant impact on measures of clinical manifestation of disease in patients with hereditary ATTR amyloid with polyneuropathy.

(4) HELIOS-B is an ongoing phase III randomized study in patients with ATTR-CA (over 600 patients).

d. Inotersen (Tegsedi)

(1) Inotersen is an antisense oligonucleotide.

(2) It is currently approved for the treatment of polyneuropathy in adults with ATTRv.

(3) It is a 2′-*O*-methoxyethyl-modified single-stranded antisense oligonucleotide inhibitor that binds TTR mRNA, leading to degradation, and, therefore, acts to lower hepatic production of transthyretin.

(4) The NEURO-TTR phase III trial (*NEJM*, 2018) results showed improvement in the modified neuropathy impairment score. Five deaths in the treatment score were

noted to be from glomerulonephritis and thrombocytopenia.

(5) CARDIO-TTRansform is a large phase III randomized for patients with CA is ongoing (1,400 patients).

E. Cardiac transplantation in ATTR. Indicated in patients who (1) have persistent symptoms despite initiation of tafamidis or optimization of volume status; and (2) have worsening objective markers, including NT-proBNP, echocardiogram, right heart catheterization (low cardiac output), functional status (VO_2 max), and/or HF hospitalizations. Severe peripheral and/or autonomic neuropathy, advanced age, or progressive renal dysfunction can be contraindications to heart transplantation alone. Combined heart-liver transplantation was considered the norm for hereditary ATTR-CM, given concern for ongoing amyloid fibril deposition post–heart transplant alone; however, heart transplant alone has proven safe and effective for V122I variant ATTR-CM. Tafamidis treatment protocols following heart transplant are an area of ongoing research.

F. Monitoring of response to treatment and optimal follow-up. The optimal follow-up strategy for patients with CA is unknown. The following recommendations are based on the European Society of Cardiology (ESC) 2021 Working Group on Myocardial and Pericardial Diseases position statement.

1. Light chain amyloidosis

a. Biomarkers, serum FLC, and basic labs are recommended monthly during initiation of hematologic treatment. Testing can be gradually spaced out as treatment concludes.

b. An ECG and cardiac lab work (cardiac troponin, NT-proBNP) may be obtained every 6 months, and an ECG may be obtained yearly, but testing can be performed at more or less frequent intervals at the discretion of the cardiologist.

2. Transthyretin amyloidosis

a. The ESC recommendation for patients with confirmed ATTR-CA is to obtain ECG, lab work, neurologic assessment (for ATTRv) about every 6 months (6MWT and Kansas City

Cardiomyopathy Questionnaire (KCCQ) can also be included) and cardiac imaging, 24-hour Holter ECG, and ophthalmologic evaluation (for ATTRv) yearly.

b. Asymptomatic carriers of ATTRv should be screened periodically with ECG, echocardiography, lab work, and neurologic and ophthalmologic evaluation.

c. cMRI and nuclear imaging may also be obtained.

VI. CONCLUSION. Knowledge of epidemiology, staging, imaging, diagnosis, and treatment of CA has grown greatly in the past decade. CA is a progressive disease with previously irreversible morbidity, decline in quality of life, and mortality. **With rising prevalence coinciding with improved treatment modalities, it is becoming increasingly important for the general cardiologist to develop a clinical concern for amyloidosis when red flag findings are present, to initiate workup, and to send appropriate referrals to experts in CA.**

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KEY REVIEWS

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CHAPTER 10

Hypertrophic Cardiomyopathy

Erika Hutt Centeno and Milind Desai

I. INTRODUCTION. Hypertrophic cardiomyopathy (HCM) is defined as the presence of left ventricular (LV) hypertrophy (LVH) in the absence of other cardiac, systemic, or metabolic diseases, which could explain the degree of LVH. There are many causes of LV wall thickening; however, these diseases can typically be identified by a history of significant hypertension, severe aortic stenosis, or due to multisystem organ involvement (ie, skeletal muscle weakness in Danon disease; **Table 10.1**).

TABLE 10.1 Differential Diagnosis of Left Ventricular Wall Thickening

Long-standing hypertension
Athlete's heart
Aortic stenosis
Amyloidosis
Mitochondrial disease
Fabry disease
Friedreich ataxia
Danon disease
Noonan syndrome
Pompe disease

Whereas there are many alternative names for HCM, including *idiopathic hypertrophic subaortic stenosis*, *hypertrophic obstructive cardiomyopathy*, and *muscular subaortic stenosis*, the term *hypertrophic cardiomyopathy* should be used because LV outflow tract (LVOT)

obstruction can be absent in one-third of patients with HCM. The distribution of hypertrophy is highly variable, with the basal anteroseptum and anterior wall being the most common phenotype. Other forms include apical hypertrophy and focal hypertrophy confined to one to two LV segments. Associated phenotypic findings includes systolic anterior motion (SAM) of the mitral valve, hypertrophied and apically displaced papillary muscles, anomalous insertion of the papillary muscle directly to the anterior mitral leaflet, elongated mitral leaflets, myocardial crypts, myocardial bridging, and right ventricular (RV) hypertrophy.

HCM is a heterogeneous disease that can present with or without symptoms of heart failure, angina, arrhythmias, and sudden cardiac death (SCD).

II. CLINICAL PRESENTATION

A. Natural history

1. The **histologic features** of HCM are disarray of cell-to-cell arrangement, disorganization of cellular architecture, and fibrosis. The most common sites of ventricular involvement are, in decreasing order, the septum, apex, and mid-ventricle. One-third of patients have wall thickening limited to one segment. Other morphologic abnormalities in HCM include hypertrophied and apically displaced papillary muscles, myocardial crypts, direct papillary muscle insertion to the anterior mitral valve leaflet, elongated mitral valve leaflets, myocardial bridging, and RV hypertrophy.
2. The **prevalence** of HCM ranges from 1:200 to 1:500 in the general population and is inherited in an autosomal dominant pattern with equal sex distribution and racial/ethnic differences in prevalence. It is a leading cause of sudden death among athletes aged <35 years.

B. Signs and symptoms

1. **Heart failure.** Symptoms include dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, and fatigue. These are largely a consequence of two processes: elevated LV diastolic pressure

caused by diastolic dysfunction and/or dynamic LV outflow obstruction.

a. Events that accelerate heart rate, decrease preload, shorten diastolic filling time, increase LV outflow obstruction (ie, exercise and tachyarrhythmias), or worsen compliance (ie, ischemia) exacerbate these symptoms.

b. Between 5% and 10% of patients with HCM progress to severe LV systolic dysfunction, characterized by progressive LV wall thinning and cavity enlargement.

2. **Myocardial ischemia.** Myocardial ischemia occurs in obstructive and nonobstructive HCM and is attributed to **mismatch** between myocardial oxygen supply and demand. Contributing factors include the following:

- Microvascular dysfunction with blunted coronary flow reserve
- Elevated myocardial wall tension as a consequence of delayed diastolic relaxation time and obstruction to LV outflow
- Decreased capillary-to-myocardial fiber ratio
- Decreased coronary perfusion pressure
- Myocardial bridging

a. The **clinical** presentation is similar to that of ischemic syndromes in persons without HCM. Patients with HCM may have abnormal electrocardiograms (ECGs) at baseline (eg, inferior q waves, T-wave inversions), with changes that can be seen in ischemic syndromes. Nuclear stress testing has shown that patients with HCM may have reversible or fixed perfusion defects in the absence of epicardial coronary artery disease. In addition, areas of infarction may be evident as delayed gadolinium enhancement on cardiac magnetic resonance.

b. The incidence of concomitant atherosclerotic coronary artery disease is estimated to be ~20% and is associated with poorer prognosis.

3. **Syncope and presyncope** are usually a consequence of diminished cerebral perfusion caused by inadequate cardiac

output. These episodes can occur secondary to LVOT obstruction or cardiac arrhythmia and are commonly associated with exertion.

4. **SCD.** Risk of SCD is low and <1% per year.
   a. HCM is the most common cause of SCD in children and young adults (age <30 years), with an estimated 5-year cumulative incidence of 8% to 10% in childhood. Although risk extends into mid-life, rates are lower even with significant risk factors (see Section VI.E.4.b). **Patients with SCD often have no or minimal symptoms prior**. Approximately 60% of deaths occur during periods of inactivity; the remaining deaths occur after vigorous physical exertion.
   b. SCD events are generally accepted to be due to sustained ventricular tachyarrhythmias. Proposed arrhythmogenic mechanisms include myocardial disarray and fibrosis, silent ischemia associated with microvascular coronary artery disease, and high sympathetic drive.

III. PHYSICAL EXAMINATION

A. Inspection of the jugular venous system may reveal a prominent *a* wave that indicates hypertrophy and lack of compliance of the RV. A precordial heave, representing RV strain, can be found in persons with concomitant pulmonary hypertension.

B. Palpation

1. The **apical precordial pulse is usually laterally displaced and diffuse**. LVH may cause a presystolic apical impulse or palpable fourth heart sound (S_4). A three-component apical impulse may occur, with the third impulse resulting from a late systolic bulge of the LV.
2. The carotid pulse has been classically described as bifid. This **rapid carotid upstroke followed by a second peak** is caused by a hyperdynamic LV.

C. Auscultation

1. S_1 (first heart sound) is usually normal and is preceded by S_4.

2. S_2 (second heart sound) can be normal or paradoxically split as a result of the prolonged ejection time of patients with severe outflow obstruction.
3. The **harsh, crescendo-decrescendo systolic murmur** associated with HCM is best heard at the left sternal border. It radiates to the lower sternal border, but not to the neck vessels or axilla.
   a. The intensity and duration of the murmur vary with maneuvers, which affect preload and afterload, which can be used to differentiate it from other systolic murmurs (**Table 10.2**). During periods of increased venous return, the murmur is of shorter duration and is less intense. In the underfilled ventricle and during periods of increased contractility, the murmur is harsh and of a longer duration.

TABLE 10.2 Effects of Maneuvers or Pharmacologic Intervention to Differentiate Murmur of Hypertrophic Cardiomyopathy from Aortic Stenosis

Maneuver	Physiologic Effect	HCM	AS	MR
Valsalva and standing	Decreases VR, SVR, and CO	↑	↓	↓
Squat and handgrip	Increases VR, SVR, and CO	↓	↑	↑
Amyl nitrite	Increases VR; Decreases SVR and LV volume	↑	↑	↓
Phenylephrine	Increases SVR and VR	↓	↑	↑
Extrasystole	Decreases LV volume	↑	↓	No change
Post-Valsalva release	Increases LV volume	↓	↑	No change

↓, decrease; ↑, increase; AS, aortic stenosis; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; SVR, systemic vascular resistance; VR, venous return.

(1) The **concomitant murmur of mitral insufficiency** can be differentiated because of its holosystolic, blowing quality

that radiates to the axilla.

(2) A soft, early, decrescendo, **diastolic murmur of aortic insufficiency** is found in ~10% of patients with HCM.

IV. GENETIC ASPECTS OF HCM. HCM is caused by genetic mutations of sarcomere genes **typically inherited in an autosomal dominant manner**. To date, HCM has been linked to over 1,400 different mutations in at least 11 genes (**Table 10.3**); however, not all mutations have the same evidence for pathogenicity, and a probable disease-causing mutation is identified in ~50% of cases currently. Of patients with positive genetic testing, mutations are most commonly found in the genes for **beta-myosin heavy chain (MYH7) and myosin-binding protein C (MBPC3)**.

TABLE 10.3 Strongly Linked Gene-Causing Mutations in Hypertrophic Cardiomyopathy

Gene	Protein	Frequency (%)
Thick Filament		
MYH7	Beta-myosin heavy chain	15-25
MYL2	Regulatory myosin light chain	<2
MYL3	Essential myosin light chain	<1
Thin Filament		
TNNT2	Cardiac troponin T	<5
TNNI3	Cardiac troponin I	<5
TPM1	Alpha-tropomyosin	<5
ACTC1	Alpha-cardiac actin	<1
Intermediate Filament		
MYBPC3	Myosin-binding protein C	15-25

HCM-positive genotype does not necessarily imply positive phenotype because variable penetrance exists, and environmental factors and modifier genes affect whether a particular subject will manifest HCM phenotypically. Current guidelines recommend three-generation

family history and genetic counseling for patients with known HCM as well as genetic testing to facilitate identification of family members at risk. Patients who are genotype positive, phenotype negative should undergo periodic screening based on age and clinical status (see Section VI.F).

It has been shown that certain pathogenic and likely pathogenic variants are associated with an increased risk for SCD and heart failure. Thus, identification of a genetic mutation may help risk stratify patients with HCM.

V. DIAGNOSTIC TESTING

A. ECG. Although most patients have ECG evidence of disease, there are no specific changes that are pathognomonic for HCM. Common ECG findings in HCM are listed in **Table 10.4**. These abnormalities do not correlate with disease severity.

TABLE 10.4 Electrocardiographic Findings in Hypertrophic Cardiomyopathy

Evidence of right and left atrial enlargement
Q waves in the inferolateral leads
Voltage criteria for LVH with repolarization abnormality
Large negative precordial T waves (associated with Yamaguchi or apical HCM)
Left-axis deviation
Short PR interval with slurred upstroke (preexcitation)

HCM, hypertrophic cardiomyopathy.

B. Echocardiography is the preferred diagnostic method because of its high sensitivity and low-risk profile. It allows characterization of the site and mechanism of obstruction. Careful assessment for conditions that cause increased wall thickness (aortic or subaortic stenosis, hypertension, infiltrative diseases, etc) should also be performed.

1. **M-mode and two-dimensional** echocardiographic findings in HCM are listed in **Table 10.5**. Close evaluation of the extent of

hypertrophy should be performed, given the role of septal thickness in risk stratification for SCD.

TABLE 10.5 Two-Dimensional, M-Mode, and Doppler Echocardiographic Findings in Hypertrophic Cardiomyopathy

Maximal left ventricular diastolic wall thickness >15 mm
Asymmetric left ventricular hypertrophy (septal > posterior wall thickness)
Systolic anterior motion of the mitral valve
Small left ventricular cavity
Resting gradient >30 mm Hg
Provocable gradient >50 mm Hg
Septal immobility
Normal or increased motion of the posterior wall
Premature closure of the aortic valve
Reduced rate of closure of the mitral valve in mid-diastole
Mitral valve prolapse with regurgitation

2. **Doppler echocardiography** enables recognition and quantification of dynamic LVOT obstruction as well as the response to various maneuvers.
   a. Approximately one-fourth of patients with HCM have a resting pressure gradient between the body and LVOT; approximately half of the patients with normal LVOT gradients at rest will have provocable gradients.
   b. The **diagnosis of HCM with obstruction** is based on resting peak instantaneous gradient >30 mm Hg. These gradients correlate directly with the time of onset and duration of contact between the mitral leaflet and the septum, as occurs during SAM of the mitral leaflet. The earlier and longer the contact, the higher the pressure gradient.
      (1) Inducing obstruction and, therefore, gradients, in patients believed to have latent obstruction, can be accomplished with substances (eg, amyl nitrite) or maneuvers (eg,

Valsalva maneuver and exercise) that decrease LV preload or increase contractility. The use of dobutamine is not recommended because it can provoke increased LVOT gradients in normal patients.

(2) Follow-up echocardiography is recommended every 1 to 2 years in patients with HCM without a change in clinical status.

c. Recognition of mitral regurgitation (MR)

(1) Approximately **60% of patients with HCM have structural abnormalities of the mitral valve**, including increased leaflet area, elongation of leaflets, and anomalous insertion of papillary muscles directly into the anterior mitral leaflet.

(2) When there is no leaflet abnormality, the degree of MR is directly related to the severity of obstruction and lack of leaflet coaptation.

C. Exercise stress testing. Exercise stress echocardiography testing provides significant information regarding functional capacity, exercise-induced symptoms, and prognosis.

D. Magnetic resonance imaging (MRI). Advantages of MRI in the evaluation of HCM include excellent spatial resolution, lack of radiation, inherent contrast, three-dimensional imaging, and tissue characterization. Disadvantages are cost, length of study, need for patient cooperation, and exclusion of patients with implantable cardioverter-defibrillators (ICDs) or pacemakers. MRI is indicated in suspected HCM when echocardiography is inconclusive, in patients with suspected infiltrative or storage disease, and for patients with HCM who are not otherwise identified as high-risk for SCD. MRI in these situations can help detect:

1. **LVH** missed by echocardiography, specifically in the anterolateral and basal LV free walls
2. **Myocardial scar**, on **delayed gadolinium** imaging, considered a predictor of SCD
3. MR, SAM, abnormal papillary muscles, and diastolic dysfunction

4. Alternative causes of increased LV wall thickness, such as Fabry disease and amyloidosis

E. Cardiac catheterization is most used for defining coronary anatomy before procedures for septal reduction or MR, or for the evaluation of ischemic symptoms. Invasive hemodynamic assessment may also be used to assess for provocable obstruction for symptomatic patients without obstruction on noninvasive imaging. The characteristic findings of HCM during hemodynamic assessment are listed in **Table 10.6** and illustrated in **Figure 10.1**.

TABLE 10.6 Hemodynamic Findings During Cardiac Catheterization

Subaortic or mid-ventricular outflow gradient on catheter pullback
Spike-and-dome pattern of aortic pressure tracing[a]
Elevated right and left ventricular end-diastolic pressures
Elevated pulmonary capillary wedge pressure
Increased V wave on wedge tracing[b]
Elevated pulmonary arterial pressure

[a]A consequence of outlet obstruction.
[b]May result from either mitral regurgitation or elevated left atrial pressure.

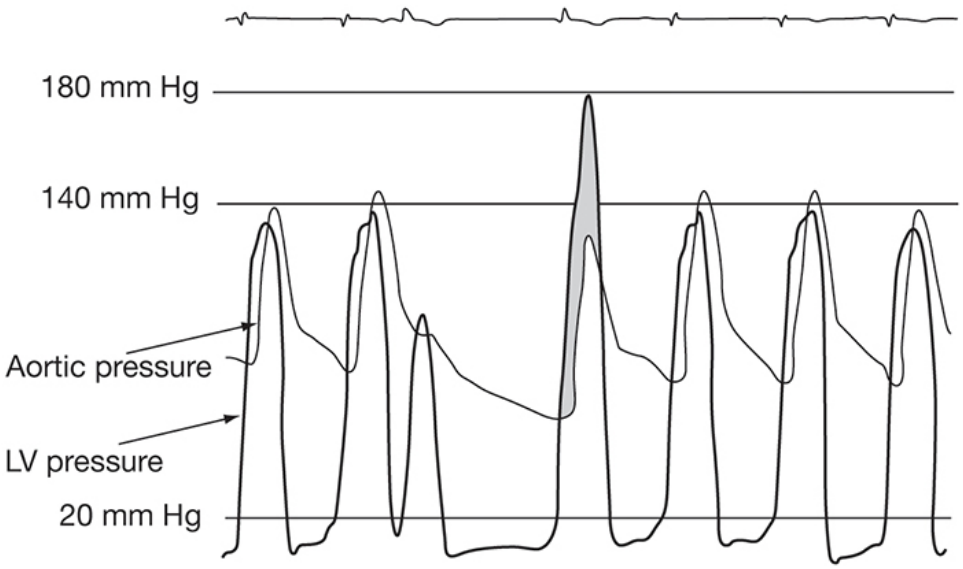

FIGURE 10.1 Severe increase in the left ventricular (LV) aortic gradient in the beat after a premature ventricular contraction (PVC) (Brockenbrough-Braunwald-Morrow sign) because of an increase in contractility and decrease in afterload during the post-PVC beat.

1. Patients with normal epicardial coronary arteries may have myocardial bridges, phasic narrowing during systole, reduced coronary flow reserve, or systolic reversal of flow in the epicardial vessels.
2. **Left ventriculography** usually reveals a hypertrophied ventricle, prominent septal bulge, near-complete obliteration of the ventricular cavity during systole, SAM, and MR. The **spade-like** appearance of the ventricular cavity is confined to ventricles with **apical involvement**.

VI. MANAGEMENT STRATEGIES

A. Goals of management. Management of patients with HCM is focused on three major goals: (1) treating symptoms, (2) preventing sudden death, and (3) familial screening. The etiologies of symptoms in HCM are multifactorial and include LVOT obstruction, diastolic dysfunction, ischemia, arrhythmias, and MR. Consequently, therapy varies among patients and is designed to target individual symptoms and mechanisms. See **Figure 10.2** for a simplified treatment algorithm.

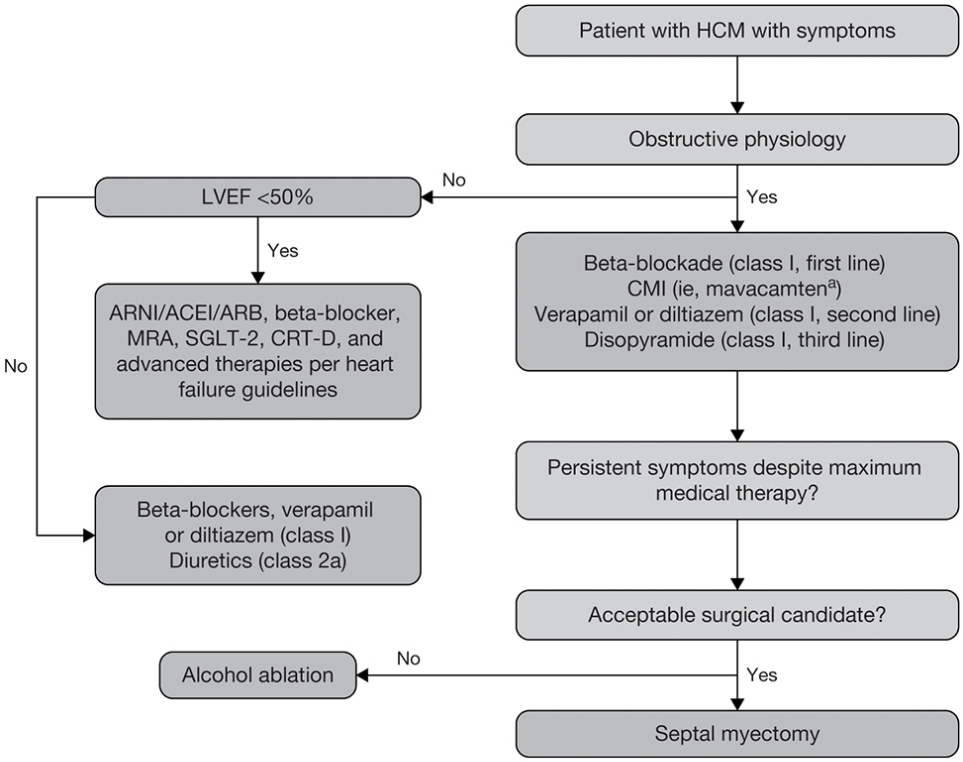

FIGURE 10.2 Management algorithm for hypertrophy cardiomyopathy DDD, dual pacing for both chambers, dual-chamber activity sensing, and dual response. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; CCB, calcium channel blocker; CMI, cardiac myosin inhibitor; CRT-D, cardiac resynchronization therapy with defibrillator; HCM, hypertrophic cardiomyopathy; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid antagonist; NYHA, New York Heart Association; SGLT-2, sodium-glucose cotransporter-2. (Adapted from Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2020;76(25):3022-3055. With permission from Elsevier.)

B. Medical therapy. General principles for medical therapy focus on medications that have negative inotropic and chronotropic properties and thus improve diastolic filling and decrease myocardial demand. Care should be taken to avoid medications that decrease preload because this can worsen LVOT obstruction.

1. **Beta-blockers** are considered first-line therapy for both obstructive and nonobstructive HCM. Even though they have not been shown to decrease mortality, recent randomized trials have shown that metoprolol improves symptoms, hemodynamics, and exercise tolerance. Beta-blockers with additional alpha-blocking properties, such as carvedilol and labetalol, should be avoided because of their additional vasodilatory properties.
    a. The mechanism of action of beta-blockers is inhibition of sympathetic stimulation brought about by the negative inotropic and chronotropic properties of the drugs. Beta-blockers diminish myocardial oxygen requirements and augment diastolic filling, which mitigate angina and the detrimental effects of LV outflow obstruction, respectively.
2. **Calcium channel blockers (CCBs)** are second-line agents that are also effective in reducing the common symptoms of HCM in patients who are unresponsive or intolerant to treatment with beta-blockers.
    a. **CCBs** have a negative inotropic effect and reduce the heart rate and blood pressure. They may also have beneficial effects on diastolic function by improving rapid diastolic filling, although possibly at the expense of higher LV end-diastolic pressures. The beneficial effects seem to be limited to the nondihydropyridines **verapamil** and **diltiazem**.
    b. Nondihydropyridines can have unpredictable vasodilatory effects and should be avoided in patients with considerable outlet obstruction and elevated pulmonary pressures.
3. **Disopyramide**, a class Ia antiarrhythmic agent, may be an effective alternative or adjunct to beta-blocker and CCB therapy. Its strong negative inotropic qualities coupled with its ability to suppress ventricular and supraventricular arrhythmias make it an effective treatment when marked outflow obstruction or arrhythmias are manifested. Potential disadvantages are anticholinergic properties, accumulation in patients with hepatic or renal dysfunction, the possibility of augmenting atrioventricular (AV) nodal conduction in the presence of atrial fibrillation (AF),

and waning hemodynamic effects with time. It is because of these significant side effects that disopyramide is not considered to be a long-term treatment for HCM but rather a bridge to septal reduction therapy (SRT).

4. **Mavacamten** is a first-in-class oral cardiac myosin inhibitor (CMI) that has been shown to be superior to placebo in improving exercise capacity, New York Heart Association (NYHA) functional class, quality of life, and LVOT obstruction in patients with obstructive HCM. Most recently, mavacamten was shown to decrease the need for SRT in patients with obstructive HCM when compared to placebo. This led to Food and Drug Administration (FDA) approval of the drug in April 2022 for patients with obstructive HCM and NYHA class II-III to improve functional capacity and symptoms. Studies evaluating the utility of mavacamten in nonobstructive HCM are under way. Mavacamten reduces LV systolic function and can cause heart failure, so monthly echocardiographic monitoring is recommended. It is contraindicated in systolic heart failure (LV ejection fraction [LVEF] ≤55%) and should be discontinued if LVEF drops to <50% after initiation. It should not be used in combination with disopyramide, or patients on dual therapy with beta-blocker and CCB. In addition, it is contraindicated in patients taking CYP2C19 inhibitors or CYP3A4 inducers.
5. **Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and digoxin** should be avoided in patients with obstructive HCM because these agents worsen LVOT obstruction, but it may be considered in nonobstructive HCM or patients with early HCM without significant obstruction. In the latter, a small randomized controlled trial (RCT) showed that valsartan was associated with decreased adverse LV remodeling in patients with early HCM.
6. **Diuretics** may be reasonable in obstructive or nonobstructive HCM when left-sided filling pressures are high despite guideline-directed management.

7. **Phenylephrine**, a pure alpha-agonist that causes vasoconstriction, can be considered in cases of refractory hypotension unresponsive to intravenous fluids. Pressors with positive inotropic effects, such as norepinephrine, dopamine, and dobutamine, can provoke LVOT obstruction and should be avoided.

C. **Nonpharmacologic treatment** includes lifestyle modifications and SRT.

1. **Lifestyle modifications** should be recommended to all patients with HCM. This includes avoidance of dehydration, moderate-intensity recreational exercise, and shared discussion regarding safety of pregnancy.
2. **SRT** is typically reserved for those patients with symptoms despite optimal medical therapy. Patients with symptomatic obstruction and resting or latent gradient of ≥50 mm Hg despite optimal medical treatment are candidates for septal myectomy or alcohol septal ablation. Younger patients with gradients >100 mm Hg and low surgical risk should be considered for septal myectomy, even in the absence of symptoms.
   a. **Septal myectomy**, when performed by an experienced surgeon, is considered the most definitive treatment for obstructive HCM and is associated with a mortality rate of <1% to 2%. It is effective in improving symptoms, resting LVOT gradients, MR, and filling pressures. After myectomy, survival is comparable to the general population when matched by age and gender. Concomitant surgery to address obstruction because of abnormal papillary muscle attachment, mitral valve regurgitation not improved following septal myectomy, or AF with a maze procedure may be performed, allowing for a more comprehensive approach compared with alcohol septal ablation. Apical myectomy by experienced surgeons may be reasonable to reduce symptoms in refractory nonobstructive HCM.
   b. **Alcohol septal ablation**—essentially a controlled infarction of the septum—is an alternative to septal myectomy and is reserved for **patients who are not candidates for surgical**

myectomy. There are no RCTs comparing myectomy and septal ablation.

(1) Technique. In the cardiac catheterization laboratory, a guidewire is advanced to probe the first or second septal perforator or both. An angioplasty catheter is placed in the proximal portion of the septal branch for vessel isolation. Ultrasonic contrast agents are infused in the cannulated perforator to define the area at risk for infarction. Infusion of 1 to 4 mL of absolute alcohol causes infarction in the zone of septal myocardium served by the cannulated septal branch. In most centers, a temporary ventricular pacing catheter is placed into the RV apex before performing the ablation to manage any transient conduction abnormalities.

(2) Results. In most patients, there is a marked immediate decrease in the LVOT gradient. This gradient response is thought to be triphasic: immediate reduction (because of stunning), early reappearance, and sustained fall by 3 months after the procedure (because of remodeling). Within this initial period, most patients attain satisfactory symptomatic relief. Risks of the procedure include high-grade AV block with subsequent pacemaker implantation, coronary dissection, large anterior wall myocardial infarction, pericarditis, and electrical instability of the scar that forms because of the infarction.

D. Special management considerations. AF occurs in up to one-third of patients with HCM and can worsen heart failure symptoms and increase risk of thromboembolic stroke. Loss of atrial systole and decreased diastolic filling times because of rapid ventricular rates can lead to acute hemodynamic decompensation and pulmonary edema because of LV diastolic dysfunction. Risk of stroke is ~0.8% per year, and all patients with HCM-associated AF should be on anticoagulation therapy, regardless of CHAD2S2VASc score and unless contraindicated. Given the poor tolerance of AF in HCM, a rhythm control strategy is preferred with prompt cardioversion, antiarrhythmics, or catheter ablation. The choice of antiarrhythmic

should be based on age, comorbidities, and symptom severity. Current guidelines recommend amiodarone, sotalol, or dofetilide, given modest effectiveness. Disopyramide is considered a reasonable agent, particularly in early-onset AF. If a rate control strategy is planned, beta-blockers, verapamil or diltiazem, are recommended agents.

1. **Ventricular arrhythmias**: In patients with HCM and symptomatic ventricular arrhythmias or recurrent ICD shocks despite beta-blockers, antiarrhythmic drug therapy is recommended, with the choice of agent guided by age, comorbidities, and preference. In cases of antiarrhythmic intolerance of ineffectiveness, catheter ablation may be reasonable to reduce arrhythmia burden.
2. **Advanced heart failure**: Patients with HCM who develop systolic dysfunction should be treated with guideline-directed medical therapy similarly to those without HCM. This includes discontinuation of negative inotropes such as CCB and disopyramide. Patients with nonobstructive HCM and advanced heart failure, despite therapy, should be evaluated for advanced therapies, including **cardiac resynchronization therapy**, **LV assist device, and cardiac transplantation**. It should be noted that LV assist device may not be an option in small LV cavities.

E. Risk stratification for sudden death and subsequent ICD implantation for primary prevention of SCD in high-risk patients continues to be one of the more challenging aspects for the management of patients with HCM. **Table 10.7** lists the established factors for risk stratification.

TABLE 10.7 Risk Factors for Sudden Cardiac Death

Established Risk Markers for Secondary Prevention
Previous cardiac arrest
Sustained ventricular tachycardia
Established Risk Markers for Primary Prevention
Family history of SCD in ≥1 first-degree relative

Massive LVH (left ventricular wall thickness ≥30 mm) Syncope without other attributable cause HCM with LV systolic dysfunction (LVEF <50%) Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor LV apical aneurysm Extensive delayed gadolinium enhancement on MRI (≥15% of LV mass)
Established Risk Markers for Secondary Prevention
Previous cardiac arrest Sustained ventricular tachycardia
Established Risk Markers for Primary Prevention
Family history of SCD in ≥1 first-degree relative Massive LVH (left ventricular wall thickness ≥30 mm) Syncope without other attributable cause HCM with LV systolic dysfunction (LVEF <50%) Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor LV apical aneurysm Extensive delayed gadolinium enhancement on MRI (≥15% of LV mass)

LV, left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; SCD, sudden cardiac death.

1. The decision to implant an ICD should be individualized by taking into consideration patient risk factors as well as age. The frequency of annual ICD-related complications in patients with HCM is 4%. Patients who are younger at the time of implantation are at higher lifetime risk for complications (eg, infection, inappropriate ICD discharge) because of the longer length of device implantation. Current guidelines state that it is reasonable to consider ICD implantation in patients with a family history of SCD or multiple risk factors. The HCM Risk-SCD calculator was developed to estimate risk for SCD.
2. Patients with a history of cardiac arrest and sustained ventricular arrhythmias should be strongly considered for an ICD. In this group, the annual rate of appropriate ICD discharge is ~10%.

F. Screening of family members

1. In first-degree relatives of patients with HCM, both clinical screening with 12-lead ECG and transthoracic echocardiogram and genetic testing (when a pathogenic or likely pathogenic variant has been identified in the proband) should be offered.
2. In genotype positive, phenotype negative, serial clinical assessment with ECG and echocardiogram should be offered every 1 to 2 years in children and adolescents and every 3 to 5 years in adults.
3. First-degree relatives that are genotype negative do not require further screening.

VIII. SPECIAL CONSIDERATIONS

A. Athlete's heart

1. **Differentiating HCM from hypertrophy of athletes.** Failure to diagnose HCM places an athlete at undue risk for sudden death, whereas incorrect labeling of HCM often leads to irrational treatments, unnecessary fears, and inappropriate recommendations concerning exercise. Diagnostic uncertainty is greatest when maximal diastolic LV wall thickness exceeds the upper limit of normal (12 mm) but is less than the defined lower limit of expected hypertrophy (15 mm) in HCM, and in the absence of SAM and LV outflow obstruction.
   a. Characteristics that **substantiate the diagnosis of HCM** include unusual patterns of hypertrophy, an LV end-diastolic diameter of <45 mm, septal thickening >15 mm, left atrial enlargement, abnormal diastolic function, family history of HCM, and abnormal LV filling.
   b. Findings more consistent with physiologic LVH in **an athlete** are LV end-diastolic diameter >45 mm, septal thickening <15 mm, left atrial size <4 cm, and a decrease in LV thickness with deconditioning.
   c. Cardiometabolic stress testing can be useful to distinguish between patients with physiologic LVH and HCM. A peak $\dot{V}O_2$

>50 mL/kg/min or >120% predicted maximum $\dot{V}O_2$ differentiates athlete's heart from HCM.

d. Should differentiation still not be possible, the patient should stop training and over several months ventricular hypertrophy will typically regress if physiologic but persist in HCM.

B. Participation in sports. HCM is the most common cause of sudden death in young athletes. Current guidelines recommend mild- to moderate-intensity recreational exercise in patient with HCM for its overall health benefit. Participation in high-intensity competitive sports may be considered after a shared discussion, which should be repeated annually and cover the risk of SCD and ICD shocks. However, ICD placement for the purpose of participation in competitive sports is discouraged.

C. Infective endocarditis (IE)

1. Prophylaxis. Since 2007, guidelines on the prevention of IE recommend against antibiotic prophylaxis in HCM, except in the setting of prior endocarditis. Given the catastrophic consequences of endocarditis in patients with HCM, routine antimicrobial prophylaxis for IE should be weighed on an individual basis.

D. Yamaguchi or apical HCM

1. Clinical presentation. Patients experience chest pain, dyspnea, fatigue, and, in rare instances, sudden death.

2. Prevalence. Within Japan, apical HCM constitutes 25% of all cases of HCM. Outside Japan, only 1% to 2% of cases are associated with isolated apical hypertrophy.

3. Diagnostic testing

a. An **ECG** reveals giant negative T waves in the precordial leads and LVH (**Figure 10.3**).

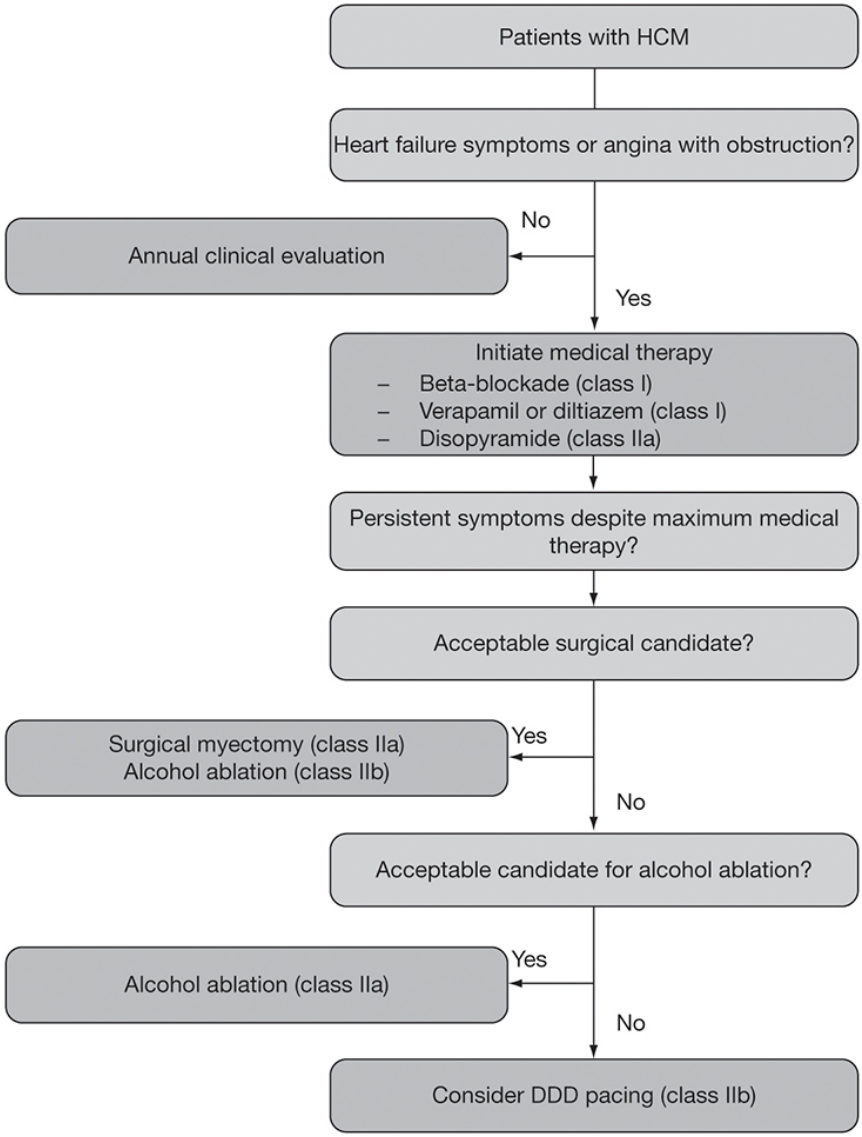

FIGURE 10.3 Electrocardiogram (ECG) in an apical hypertrophic cardiomyopathy (HCM, Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions. HCM, hypertrophic cardiomyopathy.

b. Echocardiographic findings include the following:

(1) Localized hypertrophy in the distal LV beyond the origin of the chordae tendineae

(2) Wall thickness in the apical region of at least 15 mm or a ratio of maximal apical to posterobasal thickness >1.5

(3) Exclusion of hypertrophy in other parts of the ventricular wall

(4) No LVOT obstruction or gradient

c. **MRI** demonstrates localized hypertrophy to the cardiac apex. MRI is useful in the care of patients with poor echocardiographic windows.

d. **Cardiac catheterization** reveals a spade-like configuration of the LV cavity at end-diastole and apical end-systolic LV cavity obliteration.

4. **Prognosis** of SCD is favorable, but symptoms may be more limiting compared with other forms of HCM.

5. **Management.** Therapeutic efforts are limited to management of diastolic dysfunction with beta-blockers and calcium channel antagonists, apical myectomy may be considered at experienced centers, and cardiac transplantation should be considered in refractory cases. Prevention of SCD with ICD should be considered in patients with apical aneurysm.

E. HCM among the older patients

1. **Clinical presentation.** In addition to the signs and symptoms of other forms of HCM, hypertension is more common with HCM in the older population.

2. **Incidence.** Although the incidence is unknown, HCM among the older patients is probably more common than expected.

3. **Genetic aspects.** Reports have suggested that the delayed expression of mutations in the gene for cardiac MBPC may play an important role in HCM in the older patients.

4. **Echocardiographic findings** for older patients (65 years or above) are compared to findings for young patients (40 years or below) as follows:

a. **Common findings**

(1) LVOT gradient, both provocable and at rest

(2) Asymmetric hypertrophy

(3) SAM of the mitral valve

b. **Differences pertaining to the elderly**

(1) Less hypertrophy

(2) Less RV involvement
(3) Ovoid versus crescentic LV
(4) Prominent septal bulge (ie, sigmoid septum)
(5) More acute angle between the aorta and the septum as the aorta uncoils with age

5. **Prognosis.** Favorable compared with patients who present at a younger age
6. **Management.** Like that of patients with other HCM

ACKNOWLEDGMENTS The authors acknowledge the contributions of Drs Albree Tower-Rader, Eiran Gordeski, Mark Robbins, A. Thomas McRae III, and Anthony Hart to prior editions of this chapter.

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CHAPTER 11

Myocarditis, Inflammatory Cardiomyopathy, and Other Nonischemic Cardiomyopathies

Tahir S. Kafil and W. H. Wilson Tang

I. OVERVIEW OF MYOCARDITIS. **Myocarditis** is an inflammatory disease of the myocardial muscle due to various etiologies. When myocarditis is accompanied by cardiac dysfunction, it is called **inflammatory cardiomyopathy** according to the 1995 World Health Organization Task Force on Cardiomyopathies. Although diagnostic criteria for myocarditis vary, myocarditis is generally diagnosed based on either histologic, immunologic, immunohistochemical, or clinical criteria. Clinical criteria utilize a combination of symptoms, physical examination, cardiac enzymes, inflammatory markers, and cardiac imaging. The incidence of myocarditis has increased over the past few decades due to increased use of cardiac magnetic resonance (CMR) imaging. The highest risk for myocarditis historically has been among younger men aged 20 to 40 years. Myocarditis is a common cause of cardiogenic shock and sudden cardiac death in young people.

A. Classification systems for myocarditis

1. Clinicopathologic classification of myocarditis (1991). This older classification divides myocarditis into acute forms with symptoms <3 months (fulminant and acute) and chronic forms with symptoms >3 months (chronic active and chronic persistent):

a. Fulminant myocarditis usually has a distinct onset. It can result in either spontaneous resolution or rapid deterioration and death due to severe cardiac compromise. Usually, there are multiple active foci of inflammatory infiltrate on histology with complete resolution.

b. Acute myocarditis has an indistinct onset, with moderate cardiovascular compromise and incomplete recovery, often resulting in cardiac dysfunction or subsequent death. Histologically, there are active or borderline inflammatory infiltrates that resolve completely over time.

c. Chronic active myocarditis has a presentation similar to that of acute myocarditis, but the chronic form usually progresses to only mild or moderate cardiac dysfunction, occasionally with restrictive physiology. Histologic examination often shows ongoing fibrosis, suggesting chronic inflammatory changes.

d. Chronic persistent myocarditis has an indistinct onset, with nonresolving active or borderline inflammatory infiltrates seen on histologic examination. Usually, there is no cardiovascular compromise.

2. Levels of certainty for myocarditis. There has been a shift toward less invasive methods to diagnose myocarditis and a decreased reliance on endomyocardial biopsy (EMBx) to classify myocarditis. In this context, newer classification systems rely on levels of certainty using the amount of objective evidence for myocarditis. These include electrocardiographic (ECG) features, echocardiography, CMR (revised Lake Louise criteria [LLC]), cardiac enzymes, and inflammatory markers. The highest levels of certainty are with either EMBx confirmation or the combination of abnormal CMR imaging with elevated troponin.

a. Centers for Disease Control and Prevention (CDC) case definitions for myocarditis (2003). These were first used in the context of smallpox vaccination-associated myocarditis. CDC criteria have three levels: *suspected, probable, or confirmed myocarditis.*

b. Brighton Collaboration Criteria case definitions for myocarditis (2021). These were developed by international experts for myocarditis/pericarditis associated with messenger RNA (mRNA) vaccination. The Brighton criteria have five levels: *level 1 (definitive), level 2 (probable), level 3 (possible), level 4 (insufficient evidence), and level 5 (not myocarditis)* (**Table 11.1**).

TABLE 11.1 Brighton Collaboration Criteria for Myocarditis

Level of Certainty	Symptoms	Objective Finding
Level 1: Definitive (highest specificity)	Cardiac symptoms (one), nonspecific symptoms (two), OR Infants/children specific symptoms (two)	Autopsy or endomyocardial biopsy showing myocardial inflammation OR Elevated troponin **AND** Abnormal cardiac imaging (CMR or echo) **AND** No alternative diagnosis for symptoms
Level 2: Probable	Same as level 1	Abnormal cardiac imaging (CMR or echo) OR Abnormal troponin or CK-MB OR Abnormal ECG (level 2 features) **AND** No alternative diagnosis for symptoms
Level 3: Possible (highest sensitivity)	Same as level 1	Abnormal inflammatory marker (CRP/hs-CRP, ESR, D-dimer) OR Abnormal ECG (level 3 features) **AND** No alternative diagnosis for symptoms

CK-MB, creatine kinase-MB; CRP, C-reactive protein; ECG, electrocardiogram; ESR, erythrocyte sedimentation rate; hs, high sensitivity.
Adapted from Sexson Tejtel SK, Munoz FM, Al-Ammouri I, et al. Myocarditis and pericarditis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2022;40(10):1499-1511.

c. American Heart Association/American College of Cardiology (AHA/ACC) Criteria for COVID-19 Myocarditis (2022). This was developed to characterize COVID-19 infection–related myocarditis. These criteria use three levels: *possible, probable, and definite myocarditis* (**Table 11.2**).

TABLE 11.2 AHA/ACC 2022 Criteria for COVID-19 Myocarditis

Level of Certainty	Case Definition
Definite	All features of possible myocarditis (cardiac symptoms, elevated troponin, abnormal ECG and/or echo) **AND** CMR *or* biopsy at time of COVID-19 infection has findings consistent with active myocarditis.
Probable	All features of possible myocarditis (cardiac symptoms, elevated troponin, abnormal ECG and/or echo) **BUT** CMR and/or biopsy within 6 mo of COVID-19 infection demonstrates abnormalities consistent with "previous myocarditis"
Possible	Cardiac symptoms, elevated troponin, abnormal ECG **and/or** echo **BUT** *Negative* endomyocardial biopsy *or* CMR, *or* Circumstances where *neither* biopsy nor CMR were performed. **NB:** Ideally, flow limiting coronary artery disease is excluded in men >50 y and women >55 y.

ACC, American College of Cardiology; AHA, American Heart Association; CMR, cardiac magnetic resonance; ECG, electrocardiogram.
Adapted from Writing Committee, Gluckman TJ, Bhave NM, et al. 2022 ACC expert consensus decision pathway on cardiovascular sequelae of COVID-19 in adults: myocarditis and other myocardial involvement, post-acute sequelae of SARS-CoV-2 infection, and return to play: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2022;79(17):1717-1756.

3. Expert Consensus Statement Glossary (2020). Experts have attempted to provide guidance on myocarditis terminology in the context of evolving diagnostic criteria.

a. Acute myocarditis: Symptom onset within 1 month (rather than 3 months in older classifications). Associated with elevated troponin and edema on CMR if within 4 weeks. Alternatively, abnormal

^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Histologically, it is characterized by active myocardial inflammation.

b. Complicated versus uncomplicated acute myocarditis: Complicated is used to describe higher risk patients with one or more of the following: left ventricular (LV) dysfunction (LV ejection fraction [LVEF] <50% on first echocardiogram), sustained ventricular arrhythmias, advanced heart block, heart failure (HF), or cardiogenic shock. Uncomplicated myocarditis is without these features.

c. Chronic myocarditis: Ongoing inflammatory process with fibrosis, but no cardiomyopathy, myocyte necrosis, or myocyte abnormalities

d. Chronic inflammatory cardiomyopathy: Persistent myocardial inflammation (symptom onset >1 month) with evidence of cardiomyopathy. Histologically characterized by myocyte abnormalities, focal or diffuse fibrosis with inflammatory infiltrates

II. CLINICAL PRESENTATION

A. Signs and symptoms. Myocarditis can be asymptomatic, or present with a broad range of symptoms, including nonspecific symptoms (**Table 11.3**). About 60% of patients may have antecedent myalgias, arthralgias, abdominal discomfort, malaise, fever, sweats, or chills consistent with preceding infection or systemic illness (eg, pharyngitis, tonsillitis, upper respiratory tract infection, or gastroenteritis) in the 1 to 4 weeks before onset. There are certain scenarios highly suggestive of acute myocarditis (**Table 11.4**) or fulminant myocarditis (**Table 11.5**). Cardiac manifestations can include:

TABLE 11.3 Symptoms in the Brighton Collaboration Criteria for Myocarditis

Description	Symptoms
Cardiac symptoms (at least one finding)	Acute chest pain or pressure Palpitations Dyspnea after exercise, at rest, or lying down Diaphoresis Sudden death
Nonspecific symptoms (at least two findings)	Fatigue Abdominal pain Dizziness or syncope Edema Cough
Infants and young children (at least two findings)	Irritability Vomiting Poor feeding Tachypnea Lethargy

Adapted from Sexson Tejtel SK, Munoz FM, Al-Ammouri I, et al. Myocarditis and pericarditis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine*. 2022;40(10):1499-1511.

TABLE 11.4 Specific Scenarios in Which to Consider Myocarditis (ESC 2013)

Scenarios for Acute Myocarditis
1. "Acute coronary syndrome like," but in the absence of angiographic evidence of obstructive CAD. Often within 1-4 wk of respiratory or gastrointestinal illness.
2. New onset or worsening heart failure in the absence of CAD and known causes of heart failure. Can be new or progressive in last 2 wk to 3 mo.
3. Chronic heart failure in the absence of CAD and known causes of heart failure. This can be >3 mo in duration.
4. "Life-threatening cardiac condition" in the absence of CAD and known causes of heart failure. These include ventricular arrhythmia, heart block, sudden death, cardiogenic shock, and severe cardiac dysfunction.

ESC, European Society of Cardiology; CAD, coronary artery disease.
Adapted from Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and

Pericardial Diseases. *Eur Heart J*. 2013;34(33):2636-2648, 2648a-2648d.

TABLE 11.5 Specific Scenarios in Which to Consider Fulminant Myocarditis (AHA 2020)

Scenarios for Fulminant Myocarditis
1. Young patient presenting with a cardiovascular condition typically seen in older patients such as acute coronary syndrome or new decompensated heart failure
2. Young patients without typical cardiovascular risk factors and WITH recent viral upper respiratory infection or enteroviral infection presenting with cardiovascular symptoms
3. Any patient with combination of cardiogenic shock AND electric instability, or rapidly evolving conduction abnormalities
4. Signs and symptoms of right heart failure such as RUQ pain, LFT abnormalities, jaundice, elevated neck veins, peripheral edema, and hepatomegaly with liver pulsatility

AHA, American Heart Association; LFT, liver function test; RUQ, right upper quadrant.

[a]Need to distinguish right heart failure from a primary liver pathology such as cholecystitis quickly before the progression to cardiogenic shock.

Reprinted with permission Kociol RD, Cooper LT, Fang JC, et al. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation*. 2020;141:e69-e92. Copyright © 2020 American Heart Association.

1. **Chest pain**. The chest pain can range from mild persistent chest pain of acute myopericarditis (35% of cases) to severe symptoms that mimic acute myocardial infarction. Chest pain may be typical for pericarditis, suggesting pericardial involvement and myopericarditis. Chest pain associated with coronary artery vasospasm may rarely occur in patients with myocarditis.
2. **Cardiomyopathy, HF, cardiogenic shock.** Some patients may develop asymptomatic cardiomyopathy (AHA stage B). However, many patients will present with features of decompensated HF, including dyspnea, orthopnea, fatigue, pedal edema, abdominal distention, or rapid weight gain. In patients who develop HF, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis can rapidly progress to cardiogenic shock.
3. **Arrhythmias or heart block.** Patients may present with presyncope, syncope, palpitations, Stokes-Adams attack, chest pain, dyspnea, or even sudden cardiac death. Life-threatening ventricular arrhythmias are a common feature of acute myocarditis. Alternating heart block and ventricular arrhythmia should raise suspicion for myocarditis. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias. Palpitations secondary to frequent premature atrial or ventricular extrasystoles are common.
4. **Cardiac arrest or sudden cardiac death.** Myocarditis is a common etiology of cardiac arrest or sudden death in patients <40 years of age.

B. Physical findings. There are no pathognomonic examination findings for myocarditis. Patients often present with signs of **acute decompensated HF**, including an S_3 (third heart sound) gallop, central and peripheral edema, jugular venous distention, and tachycardia (see Chapter 7). Clinical features of pericardial effusion such as an audible pericardial friction rub, pulsus paradoxus, and cardiac tamponade may accompany concomitant myopericarditis. Findings in specific diagnoses of myocarditis may include:

1. **Sarcoid myocarditis:** Lymphadenopathy and pulmonary findings of interstitial lung disease if there is sarcoid involvement in other organs (up to 70%)
2. **Acute rheumatic fever**: Associated signs such as erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules **(ie, Jones criteria)**
3. **Hypersensitivity or eosinophilic myocarditis (EM):** Pruritic maculopapular rash and history of onset temporally related to initiation of potential culprit medications
4. **Lyme carditis**: Bull's-eye rash and recent history of tick bite
5. **Giant cell myocarditis (GCM):** Sustained ventricular tachycardia and rapidly progressive HF

III. LABORATORY EVALUATION

A. **Cardiac enzymes.** Elevated creatine kinase-MB (CK-MB) and troponin are markers of myonecrosis. Creatinine kinase (myoglobin subfraction) is elevated in only 7.5% of patients with biopsy-proven myocarditis, whereas the cardiac **troponin I or T is elevated in at least 50% of patients** with biopsy-proven myocarditis (89%-94% specificity and 34%-53% sensitivity).

B. **B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP).** Sensitive initial tests for HF associated with myocarditis. This can rise with the degree of inflammation. Very high or persistent levels are associated with poor prognosis. Very high levels can be suggestive of acute myocarditis over takotsubo cardiomyopathy. Conversely, disproportionately high troponin, but relatively low NT-proBNP may portend poorer prognosis in acute myocarditis.

C. **Inflammatory markers.** Elevated erythrocyte sedimentation rate (ESR) or high sensitivity C-reactive protein (hs-CRP) can be seen in myocarditis. These are nonspecific acute phase reactants and may not correlate with true disease severity. However, if they are elevated, they can be good monitors of clinical progression or response to therapy.

D. **Complete blood count with differential.** Eosinophilia can be seen in EM; however, up to 25% of patients with EM do not have elevated peripheral eosinophils. Leukocytosis is common (often lymphocytic) in myocarditis but is nonspecific.

E. **Rheumatologic screening.** Screening for disease-specific antibodies is indicated if the following conditions are suspected:

1. **Systemic lupus erythematosus:** Antinuclear antibody (ANA) and anti–double-strand DNA (anti-dsDNA). C3 and C4 to assess disease activity
2. **Mixed connective tissue disease:** Extractable nuclear antigen panel (anti-ribonucleoprotein [anti-RNP])
3. **Vasculitis** (granulomatosis with polyangiitis [GPA] or eosinophilic granulomatosis with polyangiitis [EGPA]): Cytoplasmic antineutrophil cytoplasmic antibody (C-ANCA) (PR3+) and perinuclear antineutrophil cytoplasmic antibody (P-ANCA) (anti-MPO). Can have ANCA-negative vasculitis. ESR and CRP may help assess disease activity.
4. **Rheumatoid arthritis:** Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). ESR and CRP may help assess disease activity.
5. **Dermatomyositis and polymyositis:** ANA, extractable nuclear antigen panel (anti–Jo-1 and others). CK, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH) for myositis assessment
6. **Scleroderma (systemic sclerosis):** ANA, extractable nuclear antigen panel (anti–Scl-70, anticentromere antibody, anti-RNA polymerase III antibody, anti-Th/To antibody)

F. **Infectious screening**

1. **Serum viral antibody titers.** Measurement of viral antibody titers is rarely indicated and low yield. In specific circumstances, checking for parvovirus B_{19} and Epstein-Barr virus (EBV) can be considered. Myocarditis/pericarditis panels (such as FMYPP at Mayo Clinic) include coxsackievirus, echovirus, influenza types A and B, and *Chlamydia pneumoniae*.
2. **Severe acute respiratory syndrome** coronavirus 2 **(SARS-CoV-2) testing.** This may be positive if COVID-19 myocarditis occurs within 2 weeks of infection. However, COVID-19 myocarditis associated with multisystem inflammatory syndrome in adults (MIS-A) may occur >4 weeks after infection, and polymerase chain reaction (PCR) may be negative by then.
3. **Lyme serology (Borrelia).** This can be sent depending on endemic area, seasonality, and presence of associated rash.
4. **Antistreptolysin O (ASO) titer.** This is nonspecific and can be elevated in patients with acute or relatively remote history of group A *Streptococcus*.

G. **Biomarkers (research and experimental). Serum-soluble ST2.** This has been found to be elevated in males with myocarditis and associated with worse HF in men ≤50 years of age. This may be useful to predict HF in men <50 years of age, but not in women.

IV. DIAGNOSTIC TESTING AND ADVANCED CARDIAC IMAGING

A. ECG. A broad range of rhythm and conduction system disturbances can be seen on ECG, Holter monitor, or telemetry monitoring. Sinus tachycardia is common. The presence of nonspecific ST-segment and T-wave abnormalities may represent focal or global ischemia. Occasionally, the changes in ECG are suggestive of an acute myocardial infarction and may include ST-segment elevation. Pericarditis can accompany myocarditis and is often manifested in pericarditis like changes seen on ECG. The sensitivity of the ECG for myocarditis is low (47%). In some cases, fascicular block or atrioventricular (AV) conduction disturbances and ventricular tachyarrhythmia may be hemodynamically significant.

B. Echocardiogram. A range of abnormalities can be seen in myocarditis. Potential abnormalities include LV or right ventricular dysfunction, systolic or diastolic dysfunction, global or regional wall motion abnormalities, or decreased global longitudinal strain (GLS). The sensitivity of echocardiogram is low for myocarditis and can be normal even in patients with myocarditis with significant CMR findings of active myocarditis. If there is pericardial involvement (myopericarditis), then a significant pericardial effusion, pericardial thickening, or echocardiographic features of cardiac tamponade may be present. Echo can also help exclude alternative causes of HF such as valvular disease, assess for mechanical complications of myocarditis, assess for intracardiac thrombi such as LV or right ventricular thrombus, and quantify the degree of LV dysfunction to monitor response to therapy.

C. CMR imaging. CMR is an important noninvasive method to assess for myocarditis. The LLC were developed in 2009 to identify myocarditis on CMR. These incorporated T2-weighted imaging (for edema), early gadolinium enhancement (for hyperemia, capillary leak), and late gadolinium enhancement (LGE; for scar, fibrosis, necrosis). This had a sensitivity of 72.5% and a specificity of 96.2%. The LLC were updated in 2018 to include other T1-based criteria, including extracellular volume (ECV) (for extracellular edema, capillary leak, necrosis, fibrosis), and novel CMR mapping techniques with T1 and T2 relaxation times and mapping. This increased sensitivity to 87.5% and had similar high specificity. Of note, LGE patterns in myocarditis can vary but are usually in a non–coronary artery distribution. Specific LGE patterns such as septal LGE have been associated with increased ventricular arrhythmia. A limitation of CMR is that it cannot distinguish between different etiologies of myocarditis.

D. FDG-PET. This is a nuclear scan that can assess metabolic information (radiolabeled glucose uptake) in the myocardium. Increased FDG uptake in the myocardium can be seen in acute myocarditis. FDG-PET imaging is primarily used not only when cardiac sarcoidosis (CS)-related myocarditis is suspected but also in situations where CMR may not be ideal (eg, the presence of implantable cardioverter-defibrillator [ICD] or tachycardia/irregular heart rhythm). Similar to CMR, while FDG-PET can detect inflammation and identify patterns suggestive of CS, it cannot definitively identify the etiology of inflammation.

E. Coronary angiography and computed tomography coronary angiogram (CCTA). Obstructive coronary artery disease needs to be ruled out as the cause of ECG changes, troponin rise, or abnormal cardiac imaging findings. This is especially important in older patients and those with coronary artery disease risk factors. In older age and patients with tachycardia or hemodynamic instability, a coronary angiogram may be preferred. In younger patients who are stable and without tachycardia, CCTA may be preferred. This may also better assess for anomalous coronary arteries.

F. EMBx. This is the gold standard to diagnose myocarditis, but it is reserved for specific scenarios (**Tables 11.4** and **11.5**). Biopsy results are interpreted using histologic criteria (Dallas criteria from 1986) as well as immunohistochemical criteria. EMBx has a high false-negative rate even in patients with active myocarditis based on clinical, imaging, and biomarker criteria. This is due to multiple factors including sampling error that can miss areas of active inflammation. Further, biopsy is commonly performed only in the right ventricle, even in patients with left-sided cardiac inflammation. Eosinophilic infiltrate, giant cells, or noncaseating granulomas would support disease-specific steroid treatment. In refractory myocarditis, a repeat EMBx may be needed for searching giant cells, suggestive of GCM. CD68 macrophage staining may be helpful in GCM.

G. Genetic testing. An overlap between myocarditis and arrhythmogenic cardiomyopathies has been identified, with myocarditis being considered an "active phase" of gene mutations. Those with desmosomal gene mutations are more likely to have a recurrence of myocarditis and ventricular

arrhythmias. Genetic testing should be sent if a family history of myocarditis or sudden death is present, and if there is an inflammatory skin condition.

V. ETIOLOGIES OF MYOCARDITIS. Numerous etiologies of myocarditis have been reported (**Table 11.6**). Despite appropriate investigations for etiology, up to 50% of all cases may not have a clear underlying cause (ie, idiopathic). Select etiologies are discussed here.

TABLE 11.6 Examples of Etiologies of Myocarditis

Cause	Examples
Infectious Causes	
Viruses	COVID-19 (SARS-CoV-2), enteroviruses, coxsackievirus A and B, echovirus, influenza virus, poliovirus, herpesviruses, adenovirus, mumps, rubella, rubeola, hepatitis B or C virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B_{19}
Rickettsia	Rocky Mountain spotted fever
Fungi	Cryptococcosis, aspergillosis, coccidioidomycosis, and histoplasmosis
Protozoa	*Trypanosoma cruzi* (Chagas disease) and *Toxoplasmosis gondii*
Helminths	Trichinosis and schistosomiasis
Bacteria	*Legionella*, *Clostridium*, streptococci, staphylococci, *Salmonella*, and *Shigella*
Spirochetes	*Borrelia burgdorferi* (Lyme disease)
Noninfectious Causes	
Hypersensitivity reaction	Eosinophilic myocarditis
Cardiotoxic drugs	Immune checkpoint inhibitors (ICI), catecholamines, amphetamines, cocaine, chemotherapeutic drugs (eg, anthracyclines, fluorouracil, streptomycin, cyclophosphamide, interleukin-2, trastuzumab [Herceptin])
Systemic inflammatory diseases	Sarcoidosis, giant cell myocarditis, Kawasaki disease, large-vessel vasculitis (eg, polyarteritis nodosa and Takayasu arteritis), inflammatory bowel diseases (eg, ulcerative colitis and Crohn disease), systemic lupus erythematosus (ie, lupus carditis), Wegener granulomatosis or Churg-Strauss syndrome, dermatomyositis or polymyositis, scleroderma, mixed connective tissue disease
Malignancy	Metastatic lung cancer, breast cancer, melanoma, hypereosinophilic syndrome
Bites and stings	Venoms of scorpions, snakes, wasps, and black widow spiders
Chemicals	Hydrocarbons, carbon monoxide, thallium, lead, arsenic, and cobalt
Physical injury	Radiation to chest trauma to chest
Alloantigen	Heart transplant rejection
Vaccines	Small pox vaccine, mRNA COVID-19 vaccine, influenza vaccine, tetanus vaccine, diphtheria-tetanus-acellular pertussis vaccine

mRNA, messenger RNA; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

A. Infectious etiologies

1. **Viral myocarditis.** Cardiotropic viruses such as enteroviruses (specifically, the coxsackie group B and echoviruses) and angiotensin-converting enzyme 2 (ACE2)-tropic viruses such as SARS-CoV-2 (COVID-19) may cause direct cardiotoxic injuries, cytokine activation, cytoskeletal damage, and autoimmune responses. Viral myocarditis is often considered when accompanied by a clinical picture of recent febrile illness, often with prominent myalgias, followed by rapid onset of cardiac symptoms. However, direct proof is lacking (and often unnecessary), and many cases of idiopathic dilated cardiomyopathies have been attributed to antecedent viral myocarditis. Antiviral therapies have not proved to be useful.
2. **Lyme carditis.** This is caused by a tick-borne disease *Borrelia.* It is a multisystem disease, and cardiac involvement occurs in the early phase. However, cardiac symptoms can occur anywhere between ~1

and 28 weeks after infection, and it can be the only feature of infection (eg, Lyme carditis without any bull's-eye rash). Patients may be asymptomatic or severe symptoms with sudden cardiac death. AV block is common, especially if PR >300 ms. Diagnosis is established in the setting of myocarditis features together with positive Lyme serologic testing (ELISA and Western blot analysis). Treatment is initially with intravenous (IV) antibiotics, and prognosis is favorable if treated. AV block can be resolved with treatment. Admission and telemetry monitoring are recommended if symptomatic, heart block, PR >300 ms, or other arrhythmias noted.

3. **Chagas myocarditis and cardiomyopathy.** This is caused by the parasite *Trypanosoma cruzi*. It is estimated that 6 million persons have Chagas disease as of 2010. Although the majority are in Mexico, South and Central America, migration has led to large numbers of Chagas disease in previously unaffected areas, including Europe and the United States. Cardiac involvement occurs in the chronic phase, which may be 10 to 30 years after acute infection. See Section IX for further details.
4. **Human immunodeficiency virus (HIV)-related myocarditis and cardiomyopathy.** HIV disease has been recognized as an important cause of dilated cardiomyopathy, with an estimated incidence of 1.6%. HIV type 1 (HIV-1) virions appear to infect myocardial cells in patchy distributions, leading to cytokine activation and progressive tissue damage. Cardiac autoimmunity, nutritional deficiencies, and drug toxicities (ie, mitochondrial damage from zidovudine and vasculitis or coronary artery disease associated with highly active antiretroviral therapy regimens) are possible contributing causes. In addition, other known viral pathogens, including cytomegalovirus, EBV, and coxsackievirus B, have been isolated from EMBx specimens of HIV-positive patients with myocarditis in conjunction with HIV nucleic acid sequences, suggesting that opportunistic viral infections may play an important role in the pathogenesis of this type of cardiomyopathy.
5. **COVID-19 (SARS-CoV-2) myocarditis and MIS-A myocarditis.** Myocarditis is a rare complication of COVID-19 infection. The risk of COVID-19 myocarditis is higher than mRNA vaccine myocarditis. Patients can present with or without MIS-A (MIS-A+ or MIS-A−). MIS-A+ myocarditis likely represents a postinfectious complication and is characterized by greater delay from initial COVID-19 symptoms (after 4 weeks) than MIS-A− myocarditis. COVID-19 PCR can be negative by then. MIS-A− myocarditis occurs soon after COVID-19 infection (within 2 weeks) and is associated with positive COVID-19 PCR, profound cardiogenic shock, and higher mortality. Hemodynamic support for cardiogenic shock and transfer to a tertiary care center may be needed for COVID-19 myocarditis. If there is myocarditis and concurrent COVID-19 pneumonia, lung injury, or MIS-A, then corticosteroids are recommended. Unlike other etiologies of myocarditis, EMBx rarely shows infiltrates. Further research is needed for this condition.

B. Immune-mediated etiologies

1. **GCM.** Other names include pernicious myocarditis, Fiedler myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis. This is a rare disorder with an unclear origin. The hallmark feature is the presence of fused, multinucleated (>20 nuclei) epithelioid **giant cells** of histiocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes.
   a. GCM often presents with an **aggressive clinical course**, with progression over days to weeks. Rapidly progressive HF is the presentation in 75% of affected patients. Sustained ventricular tachyarrhythmia occurs in 29% of patients with GCM, and AV block occurs in 50%.
   b. The prognosis is **dismal without therapy**, but the disease is often refractory to standard medical therapy, with a 1-year mortality rate of up to 80% (median survival of 3-5 months from symptom onset).
   c. Small observational series have suggested potential benefits of immunosuppressive therapy, and a randomized, prospective multicenter study is ongoing. Consideration for **early cardiac transplantation** is appropriate (71% 5-year survival after successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. A 20% to 25% rate of histologic recurrence in surveillance EMBx has been observed after transplantation.
2. **EM.** Eosinophilic endomyocardial disease (ie, Loeffler endomyocardial fibrosis; see Chapter 8) occurs as a result of direct toxic damage caused by eosinophil granule proteins within the heart. The two most

frequently associated conditions are hypersensitivity and EGPA (Churg-Strauss syndrome). This is a challenging diagnosis, given only EMBx is diagnostic with the hallmark feature being eosinophil-rich infiltrate. The mechanism of thrombosis associated with EM is thought to be related to the prothrombotic properties of the major basic protein, which is within eosinophilic granules. Drug-induced EM is independent of cumulative dose and duration of therapy. The absence of peripheral eosinophilia does not rule out EM. Eosinophil count may be normal in up to 25% of cases of EM. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent when known.

a. Medications that may cause EM include the following:

(1) Antibiotics (eg, ampicillin, chloramphenicol, tetracycline)

(2) Diuretics (eg, hydrochlorothiazide and spironolactone)

(3) Anticonvulsants (eg, phenytoin and carbamazepine)

(4) Other drugs (eg, lithium, clozapine, and indomethacin)

b. Collagen vascular diseases such as Wegener granulomatosis or Churg-Strauss syndrome (ie, allergic granulomatosis and vasculitis) may also lead to EM.

c. Other causes include parasitic infection, drug hypersensitivity, and cellular rejection after cardiac transplantation.

3. Systemic autoimmune disorders with myocarditis (vasculitis and inflammatory bowel disease). Although the histologic appearance of myocarditis occurring as part of sarcoidosis, systemic lupus erythematosus, or polymyositis is similar to that seen in isolated myocarditis, the natural history is different. **Systemic causes of myocarditis often respond poorly to medical therapy and cardiac transplantation**, and their prognoses are often unfavorable. However, small retrospective surveys and case series have identified a significant decrease in mortality and improved clinical course among patients with cardiac sarcoid treated with corticosteroids and other immunosuppression strategies. See Section IX for further details on CS.

C. Select other etiologies

1. Immune checkpoint inhibitor (ICI) myocarditis. ICI therapy has improved treatment for patients with cancer, but there is a risk of myocarditis as a serious cardiovascular toxicity. This can develop in the absence of cardiac risk factors, and time to onset is variable. The risk may be higher with combination immunotherapy compared to monotherapy. It can be fatal if not recognized early and treated aggressively. Initial treatment includes holding the ICI and high-dose pulse steroids. Symptoms may progress despite treatment (see **Table 11.7**). Urgent transfer to a cardiac care unit must be considered if there is troponin rise, arrhythmias, or conduction abnormalities. Evaluation includes detailed cardiac assessment, CMR, and/or EMBx. A multidisciplinary approach is recommended, especially given these patients may already be quite sick with advanced malignancy.

TABLE 11.7 Immunosuppression for Specific Etiologies, Fulminant Myocarditis, or Acute Myocarditis Complicated by Severe Heart Failure

	Lymphocytic Fulminant Myocarditis	ICI-Associated Myocarditis	Eosinophilic Myocarditis	Giant Cell Myocarditis	Cardiac Sarcoidosis
First line	Methylprednisolone IV, 7-14 mg/kg (pulsed once daily for 3 d), then 1 mg/kg/d PO/IV and taper				
Alternative/addition	Alternative: IVIG or plasmapheresis	Hold ICI. If grade ≥2, initiation within 24 h of high-dose corticosteroids (prednisone 1-2 mg/kg/d PO/IV)	Hypersensitivity: Withdraw allergen. EGPA: Cyclophosphamide HES, myeloproliferative variant: Imatinib Helminthic infection: Albendazole	ATG or alemtuzumab, combined with cyclosporine OR Mycophenolate or azathioprine combined with	[a]The CHASM-CS-RCT is evaluating early addition of methotrexate to prednisone.

	Lymphocytic Fulminant Myocarditis	ICI-Associated Myocarditis	Eosinophilic Myocarditis	Giant Cell Myocarditis	Cardiac Sarcoidosis
				cyclosporine or tacrolimus	
Second line	Treat any associated systemic autoimmune disorders aggressively.	If no immediate response to high-dose steroids, start methylprednisolone 1 g every day, and addition of mycophenolate, infliximab or ATG. **NB:** Infliximab is contraindicated at high doses if mod-severe heart failure. Consider additional alemtuzumab or abatacept in life-threatening cases.	HES, myeloproliferative variant: Alemtuzumab	Rituximab	Methotrexate, mycophenolate mofetil, infliximab, or adalimumab. **NB:** Further research is needed in all of these.

ATG, antithymocyte globulin; CHASM-CS-RCT, Cardiac Sarcoidosis multi-center randomized controlled trial; EGPA, eosinophilic granulomatosis with polyangiitis; ICI, IV, intravenous; IVIG, intravenous immunoglobulin; HES, hypereosinophilic syndrome; PO, oral.
Data from Ammirati E, Frigerio M, Adler ED, et al. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail*. 2020;13(11):e007405; Bang V, Ganatra S, Shah SP, et al. Management of patients with giant cell myocarditis. *J Am Coll Cardiol*. 2021;77(8):1122-1134; Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. 2021;39(36):4073-4126; and Birnie D, Beanlands RSB, Nery P, et al. Cardiac sarcoidosis multi-center randomized controlled trial (CHASM CS- RCT). *Am Heart J*. 2020;220:246-252. PMID: 31911261.

2. **COVID-19 mRNA vaccine–associated myocarditis.** This is a rare adverse event after vaccination. Symptoms typically begin within 2 weeks after vaccination but may occur up to 6 weeks (42 days) postvaccine. The risk of vaccine myocarditis in young males after the second dose of vaccine is lower than the risk of COVID-19 infection–related myocarditis. Risk factors for vaccine myocarditis include younger age, male sex, Moderna (mRNA-1273) more than Pfizer (BNT162b2) vaccine, second dose of vaccine, and shorter time interval between doses. This condition is usually mild and self-limited. Persistent LGE may be seen on serial CMR imaging, although overall LGE burden decreases. Long-term outcomes are unknown. Further research is needed in this condition.

VI. PROGNOSIS. Adults with myocarditis may present with few symptoms or with an acute state of cardiogenic shock, frank HF, or sudden death. However, patients may also present with HF years after the initial index event of myocarditis (up to 12.8% of patients with idiopathic dilated cardiomyopathy had presumed prior myocarditis in one case series).

A. Natural history and sequelae of myocarditis. The outlook is poor in the acute phase, regardless of clinicopathologic classification, but those surviving the acute phase have a more favorable prognosis (except for those with chronic active myocarditis).

1. Many patients may have **full spontaneous clinical recovery**, even after weeks of mechanical support (eg, intra-aortic balloon counterpulsation and mechanical assist devices).
2. In the Myocarditis Treatment Trial, the 1-year mortality rate was 20%, and the 4-year mortality rate was 56%.
3. In-hospital case series point to an 11-year survival rate of 93% for patients with fulminant myocarditis and 45% for nonfulminant myocarditis.
4. Evolution to dilated cardiomyopathy
   a. Up to one-half of patients with myocarditis develop subsequent cardiomyopathy over a range of 3 months to 13 years.

b. Histologic evidence of myocarditis is seen in 4% to 10% of EMBx of patients with idiopathic dilated cardiomyopathy.

5. Severe heart block requiring permanent pacemaker placement occurs in 1% of patients.

B. Predictors for morbidity and mortality

1. Systematic reviews have shown that the presence of LGE on CMR, extensive LGE, and anteroseptal location of LGE are associated with worse cardiac outcomes in acute myocarditis. Further, the presence of LGE without edema at 6-month follow-up is associated with a worse prognosis, likely due to fibrosis.
2. Unfavorable factors for survival include extremes of **age** (ie, very old or very young), **ECG abnormalities** (eg, QRS alterations, atrial fibrillation, and low voltages), **syncope**, and **specific diagnoses** (eg, peripartum cardiomyopathy and GCM).
3. Favorable factors for survival include normal ventricular function, shorter clinical history, and fulminant presentation at onset.

/II. TREATMENT

A. HF medical therapy

1. Patients who present with inflammatory cardiomyopathy should be treated with optimal HF goal-directed medical therapy (HF GDMT) according to most recent Heart Failure guidelines. HF GDMT in 2022 consists of diuretics, ACE inhibitors or angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 (SGLT2) inhibitor. The TRED-HF study assessed the withdrawal of HF GDMT in recovered dilated cardiomyopathy. They found many patients had recurrence of HF months after GDMT treatment withdrawal. Treatment should continue indefinitely until further research is available.
2. Because of its proarrhythmic properties in animal models, digoxin should be avoided.
3. Inotropic therapy is reserved for severe hemodynamic compromise, particularly in fulminant myocarditis.
4. Aggressive support with mechanical and surgical intervention is often indicated (see Chapters 12 and 13).
   a. Intra-aortic balloon counterpulsation for hemodynamic support and afterload reduction
   b. Mechanical assistive devices (LV assist device)
   c. Extracorporeal membrane oxygenation
5. Early consideration for cardiac transplantation should be given, especially for patients with progressive, biopsy-proven GCM or peripartum cardiomyopathy. However, patients with myocarditis have increased rates of rejection and reduced survival after heart transplantation compared with those without myocarditis, and recurrent disease may affect the allograft.

B. Anticoagulation in specific scenarios

1. Anticoagulation is recommended if LV thrombus or atrial fibrillation/flutter is present.
2. Prophylactic anticoagulation to prevent thromboembolic events might be considered in Chagas cardiomyopathy with risk factors that increase risk of LV thrombus formation (ie, apical aneurysm) and EM with risk factors that increase risk of LV thrombus formation (ie, prior embolic episode).

C. Arrhythmia management

1. Antiarrhythmics provide first-line treatment using standard therapy, such as beta-blockers and amiodarone.
2. ICDs are used for patients stabilized in the chronic phase with persistently low ejection fraction (EF) and for those with malignant arrhythmias that are refractory to medical therapy. A wearable defibrillator is often recommended while recovering.
3. Permanent pacemakers are used for heart block or bradyarrhythmia, but ICD is preferred in specific cardiomyopathies such as CS due to the risk of future ventricular arrhythmia.

D. Immunosuppressive therapy. This is reserved for disease-specific treatment, fulminant myocarditis, or acute myocarditis complicated by severe HF. First-line therapy is generally pulse with IV methylprednisolone (see **Table 11.7**). However, there is limited supportive evidence from clinical trials for these. No benefits have been established for antiviral regimens, and there is no evidence supporting nonsteroidal anti-inflammatory drug (NSAID) use. More work is needed to identify patient cohorts who will benefit from tailored antiviral and immunosuppressive therapy.

E. Exercise restriction

1. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death, as shown in animal models.
2. Strenuous physical activity should be avoided for 3 to 6 months or longer after the onset of symptoms. The length of activity restriction is reassessed based on recovery of LV function, inflammatory markers, and repeat CMR to assess for residual inflammation.

F. Follow-up

1. Close clinical follow-up is recommended because persistent chronic inflammation may lead to dilated cardiomyopathy. Initially, 1- to 3-month intervals are used for drug and physical activity titration.
2. Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment after myocarditis.

III. CONTROVERSIES AND KNOWLEDGE GAPS

A. Endomyocardial biopsy

1. Routine EMBx confirmation of myocarditis is unnecessary

a. EMBx can be considered in those patients with a **rapid deterioration in cardiac function** of unknown etiology who do not respond to standard medical therapy.

b. Incidence of biopsy-proven myocarditis in recent-onset, unexplained HF can be as low as 8% to 10%. Concerns have emerged that this is caused by low sensitivity of the Dallas criteria, and several recent trials of immunosuppressive therapy have utilized supplemental pathologic criteria to assess myocarditis, including upregulation of human leukocyte antigen, presence of virus, and anticardiac antibodies.

c. **False-negative rates are high** (50% even in four or five biopsies) because of the small number of lymphocytes and difficulties in distinguishing cell types, with wide interobserver variability.

2. However, EMBx may be considered in patients with the following conditions in which a diagnostic biopsy may provide information on prognosis and/or therapeutic possibilities (**Table 11.8**):

TABLE 11.8 AHA/ACC/HFSA (2022) Heart Failure Guidelines on Endomyocardial Biopsy

Scenario	Class of Recommendation
In patients with HF, endomyocardial biopsy may be useful when a specific diagnosis is suspected that would influence therapy.	IIa
For patients undergoing routine evaluation of HF, endomyocardial biopsy should not be performed because of the risk of complications.	III: Harm

ACC, American College of Cardiology; AHA, American Heart Association; HF, heart failure; HFSA, Heart Failure Society of America.

Reprinted with permission Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032. Copyright © 2020 American Heart Association.

a. Rapidly progressive HF symptoms despite conventional therapy or new-onset frequent ventricular tachyarrhythmia or conduction disturbances

b. Suspected specific causes of myocarditis (eg, GCM, EM, CS, and vaccinia myocarditis)

3. Although specificity is high (98%), sensitivity has been found in some series to be as low as 10% to 22%. It increases with multiple biopsies, but postmortem examinations have found that more than 17 specimens were needed to make the diagnosis with 80% sensitivity in proven myocarditis cases.
4. **Biopsy** for staging of myocarditis
   a. Cell types include lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed.
   b. Amount of cells: None (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3)
   c. Distribution: Focal (ie, outside vessel lumen), confluent, diffuse, and reparative (ie, in fibrotic areas)
5. Other tests
   a. Immunohistochemical staining to examine upregulation of major histocompatibility complex antigens and quantify inflammation, although rates of correlation with biopsy-proven myocarditis have not been consistent between studies
   b. Approximately 12% to 50% of patients with acute or chronic myocarditis have persistent viral mRNA detected in biopsy samples.

B. Immunosuppressive therapy in acute myocarditis

1. Routine immunosuppressive therapy is not recommended because of the neutral findings from multiple trials, including the Myocarditis Treatment Trial and the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study. There is no Food and Drug Administration–approved regimen for the treatment of acute or chronic myocarditis.
2. Considerations are reserved for patients with new-onset, rapidly deteriorating, advanced HF with suspicion of the following conditions:
   a. GCM is treated with combination therapy (**Table 11.9**).

TABLE 11.9 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) Study[a]
Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV × 2 d
Giant Cell Myocarditis Study[b]
Cyclosporine: 25 mg PO bid, increase by 25 mg increments to target level
Monoclonal whole-blood immunoassay: 200-300 ng/mL
High-performance liquid chromatography assay: 150-250 ng/mL
Fluorescence polarization immunoassay serum-based polyclonal assay: 100-150 ng/mL
Dose reduction if renal dysfunction develops
Corticosteroid: methylprednisolone, 10 mg/kg IV qd × 3 d, followed by prednisone, 1-1.25 mg/kg with extended taper
Azathioprine: 200 mg PO qd
Myocarditis Treatment Trial[c]
Corticosteroid/cyclosporine vs corticosteroid/azathioprine versus placebo (biopsy-proven myocarditis, LVEF <45%, NYHA ≥class II)
Oral prednisone: 1.25 mg/kg/d in divided doses × 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is 0.33 mg/kg/d at week 12; maintain oral dose until week 20, and then reduce dose by 0.08 mg/kg/wk until week 24; then off
Oral cyclosporine: 5 mg/kg bid to achieve level of 200-300 ng/mL × 1 wk; adjust oral dose to achieve level of 100-200 ng/mL from weeks 2 to 4; adjust oral dose to achieve level of 60-150 ng/mL from weeks 4 to 24
Immunosuppressive Therapy for Active Lymphocytic Myocarditis[d]
Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

bid, twice daily; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PO, oral.

[a]McNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;103:2254-2259.

[b]Rosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. *Semin Arthritis Rheum*. 2000;30:1-16.

[c]Mason JW, O'Connell JB, Herskowitz A, et al; Myocarditis Treatment Trial Investigators. A clinical trial of immunosuppressive therapy for myocarditis. *N Engl J Med*. 1995;333:269-275.

[d]Frustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation*. 2003;107:857-863.

b. EM or sarcoid myocarditis is treated with high-dose steroids.

c. Specific therapy is used for underlying collagen vascular diseases, if present.

3. Studies are ongoing to identify markers to predict favorable response to immunosuppressive regimens. A study of 112 patients with histopathologic acute lymphocytic myocarditis who failed to improve with conventional therapy and subsequently received prednisone and azathioprine found that one-half of the treated group improved, with EF rising from 26% to 47% and improvement in biopsy findings. Of those who failed conventional therapy, those patients who responded to immunosuppression were significantly more likely to have positive cardiac antibodies (90% vs 0%) and less likely to have viral persistence when compared with nonresponders (14% vs 85%).

IX. OTHER NONISCHEMIC CARDIOMYOPATHIES. See **Table 11.10** for discussion of arrhythmogenic right ventricular cardiomyopathy (ARVC), arrhythmogenic cardiomyopathy (includes ARVC), CS and sarcoid cardiomyopathy, Chagas myocarditis and chronic Chagas cardiomyopathy, dilated cardiomyopathy, alcohol-induced cardiomyopathy, arrhythmia- or tachycardia-induced cardiomyopathy, LV noncompaction, Fabry disease, Gaucher disease, hemochromatosis, and carcinoid heart disease.

TABLE 11.10 Other Nonischemic Cardiomyopathies

Cardiomyopathy	Precipitant or Underlying Mechanism	Specific Characteristics	Diagnostic Criteria or Specific Tests	Specific Treatment Considerations
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	Fibrous or fibrofatty replacement of myocardium	Ventricular arrhythmia and HF. Specific ventricular pathology of fibrofatty infiltration of the myocardium. This can result in RV failure, dilation, and WMA. LV involvement can also occur.	2010 revised Task Force criteria for ARVC include echo, CMR, ECG, Signal-averaged electrocardiogram (SAECG), arrhythmias, and family history.	1. Activity restriction 2. Beta-blockers 3. HF GDMT 4. Consideration of ICD 5. Antiarrhythmic therapy 6. Cardiac transplant workup
Arrhythmogenic cardiomyopathy (AC) (includes ARVC)	Genetic susceptibility and "second hit" contribute to cardiomyopathy. Pathogenic variants in genes encoding desmosomal components, including plakophilin 2 and desmoplakin, PKP2, and DSP.	Ventricular arrhythmia and HF. More likely to have a family history of myocarditis and sudden death. Increased risk of recurrence of myocarditis and ventricular arrhythmias. Associated skin diseases such as epidermis bullosa and eczema.	Genetic testing; echo; CMR	1. HF GDMT 2. Antiarrhythmic therapy 3. Consideration of ICD 4. Cardiac transplant workup 5. Genetic counseling and family screening
Cardiac sarcoidosis (CS) and sarcoid cardiomyopathy	Noncaseating granulomas deposit in myocardium	Diagnosed in two common pathways: 1. known diagnosis of extracardiac Sarcoidosis presenting with cardiac symptoms or abnormal cardiac investigations, or in de novo patient presenting with ventricular arrhythmia, heart block, cardiomyopathy, or SCD (especially if age <60). Hilar and	HRS 2014 criteria; JCS 2017 criteria; CMR and FDG-PET; lymph node/pulmonary nodule biopsy or cardiac biopsy	1. ICD for heart block or ventricular arrhythmia 2. Antiarrhythmic therapy 3. HF GDMT 4. Immunosuppression if cardiac symptoms with active inflammation (see **Table 11.7**)

Cardiomyopathy	Precipitant or Underlying Mechanism	Specific Characteristics	Diagnostic Criteria or Specific Tests	Specific Treatment Considerations
		mediastinal lymphadenopathy often present, but 25% can be isolated CS.		
Chagas myocarditis and chronic Chagas cardiomyopathy (CCC)	*Trypanosoma cruzi* parasite infection	Acute phase (4-8 wk) of localized entry site and flulike symptoms. Chronic phase (10-30 y after acute infection): 1. Rhythm abnormalities and highly arrhythmogenic (SND, AV block, BBB, ventricular arrhythmias, AF) 2. HF with global or segmental WMA, dilated cardiomyopathy, functional MR and TR 3. Aneurysms (LV apical, inferior, and inferolateral walls) 4. Thromboembolism (cerebral or PE) 5. Concomitant megaesophagus or megacolon may develop.	1. Serologic test results should be positive for at least two types of tests (ie, indirect immunofluorescence, indirect hemagglutination, complement fixation, immunoenzymatic, and radioimmune assays). 2. Cardiac lesions diagnosed by in situ polymerase chain reaction methods of analyzing biopsies	1. HF GDMT 2. Antiarrhythmic therapy 3. Antimicrobial therapy for stage A or B HF to reduce parasitemia and prevent complications (benznidazole or nifurtimox). This is avoided in advanced HF as the benefit is negligible and there is risk of treatment-related adverse effects. 4. ICD for VT or SCD 5. Anticoagulation for LV thrombus or PE
Dilated cardiomyopathy	Myocyte hypertrophy and scatter fibrosis; reduced contractility	LV or biventricular dilation and dysfunction. Usually idiopathic, other causes can include prior stress-induced CDM, infection, toxin, genetic, peripartum, or prior myocarditis, among others.	Echo; CMR; etiology is a diagnosis of exclusion.	1. HF GDMT 2. ICD consideration 3. Cardiac transplant workup if needed
Alcohol-induced cardiomyopathy	EtOH intake >80 g/d over ≥5 y	Features of dilated CDM, no other etiology identified. Concomitant liver disease, nutritional deficiencies, and social stressors may exist.	Echo; CMR; etiology is a diagnosis of exclusion.	1. Complete and perpetual abstinence from alcohol consumption. 2. HF GDMT 3. ICD consideration 4. Addictions counseling/referral 5. Cardiac transplant workup if needed
Arrhythmia- or tachycardia-induced cardiomyopathy	Prolonged periods of rapid heart rates (generally >120 bpm) or PVC burden >10% on Holter	Cardiomyopathy improves/resolves following rate/rhythm control and has good prognosis.	Echo; CMR; ECG; Holter; may need to rule out obstructive CAD	1. HF GDMT 2. Antiarrhythmic therapy 3. Anticoagulation if AFib/flutter 4. PVC ablation
Left ventricular noncompaction (LVNC)	Prominent trabeculations	Asymptomatic or HF features. Echo features include (1) ratio >2:1 at end systole in parasternal short axis of thin compacted epicardial layer and thickened endocardial	Echo with Jenni criteria; CMR	1. Monitoring if asymptomatic 2. HF GDMT 3. Antiarrhythmic therapy 4. Anticoagulation if EG <40% or AFib 5. ICD consideration

Cardiomyopathy	Precipitant or Underlying Mechanism	Specific Characteristics	Diagnostic Criteria or Specific Tests	Specific Treatment Considerations
		layer with trabeculations and deep recesses; (2) color Doppler flow within deep recesses; (3) prominent trabeculae meshwork in LV and RV; compacted wall thickness <8.1 mm		6. Genetic testing 7. Screening for coexistent neuromuscular disorders
Fabry disease	X-linked inborn error of metabolism with deficiency/defect in lysosomal hydrolase alpha-Gal-A. Results in Gb3 accumulation in lysosomes	Significant LV or RV hypertrophy, ischemia, or cardiomyopathy. Systemic illness with typical presentation in males including neurologic symptoms in the second decade of life, dermatologic symptoms in the third decade, and cardiac/renal symptoms in the fifth decade.	Leukocyte alpha-Gal-A activity is decreased <35% or undetectable; genetic testing; EMBx if diagnosis unclear	1. Enzyme replacement therapy (ERT) with alpha-Gal-A enzyme or chaperone therapy (migalastat) to bind/stabilize alpha-Gal-A to increase the enzyme's activity 2. HF GDMT 3. Antiarrhythmic therapy 4. Heart transplant workup if needed 5. Genetic testing and counseling/family screening
Gaucher disease	Autosomal-recessive disorder; lysosomal storage disease with deficiency of acid beta-glucosidase, GCase. Results in accumulation of glycolipids in lysosomes	Clinical spectrum varies. Cardiac involvement uncommon but can have mitral and aortic valve calcification leading to valvular insufficiency and stenosis. Recurrent pericarditis resulting in constriction and DCM can occur. Systemic features include splenomegaly, hepatomegaly, cytopenia, and pulmonary disease.	GCase levels and genetic testing for GBA1	1. Enzyme replacement therapy. This can stabilize or reverse the disease process.
Hemochromatosis	Iron deposition in heart	Arrhythmias and conduction system disease accompany progressive myocardial dysfunction. Can have DCM, diastolic dysfunction, and HFpEF can occur. Conduction disturbances and arrhythmias can occur. Significant liver iron deposition also occurs.	CMR T2* imaging <20 ms (normal: >20 ms); iron studies (ferritin >200 ng/mL, TSAST >45%; HFE gene mutation; EMBx)	1. Phlebotomy (cardiac function may improve as iron is depleted) 2. Iron chelator 3. Genetic testing and counseling/family screening
Carcinoid heart disease	Neuroendocrine malignancy (carcinoid) secreting vasoactive substances (including serotonin [5-hydroxytryptamine or 5-HT] and others), which cause progressive fibrotic endocardial plaque deposits as well as valve thickening and	Plaque-like deposits of fibrous tissue on right-sided heart valves causing severe TR, and pulmonic stenosis or regurgitation. Left-sided disease can occur when atrial right-to-left shunting (ASD or PFO) or if very high levels of vasoactive substances.	24-H urinary excretion of 5-hydroxyindoleacetic acid (5-HIAA) and CT of the abdomen to localize tumor; echo; NT-proBNP	1. Diuretics 2. Valve replacement

Cardiomyopathy	Precipitant or Underlying Mechanism	Specific Characteristics	Diagnostic Criteria or Specific Tests	Specific Treatment Considerations
	retraction from myofibroblast proliferation and deposition of collagen/smooth muscle			

AF, atrial flutter; AFib, atrial fibrillation; ASD, atrial septal defect; AV, atrioventricular; BBB, blood-brain barrier; CAD, coronary artery disease; CDM, cardiomyopathy; CMR, cardiac magnetic resonance; CT, computed tomography; DCM, dilated cardiomyopathy; EMBx, endomyocardial biopsy; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; HF, heart failure; HF GDMT, heart failure goal-directed medical therapy; HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter-defibrillator; PE, pulmonary embolism; PFO, patent foramen ovale; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PVC, premature ventricular contraction; SCD, sudden cardiac death; SND, sinus node dysfunction; TR, tricuspid regurgitation; VT, ventricular tachycardia; WMA, wall motion abnormality.

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CHAPTER 12

Nontransplantation Surgical Interventions for Chronic Heart Failure

Samuel Kelly, Ryan R. Keane, Edward Soltesz, W. H. Wilson Tang, and Andrew Higgins

I. INTRODUCTION

A. This chapter reviews the mainstays of nontransplantation surgical strategies for treating advanced heart failure (HF), particularly surgical revascularization via coronary artery bypass grafting (CABG) and durable mechanical circulatory support (MCS) using left ventricular assist devices (LVADs) in addition to a brief review of alternative and experimental surgical interventions for HF. Valvular surgery, percutaneous interventions, and temporary MCS (tMCS) are discussed elsewhere.

II. SURGICAL REVASCULARIZATION FOR ISCHEMIC CARDIOMYOPATHY

A. Pathophysiology. Ischemic cardiomyopathy describes myocardial dysfunction caused by coronary artery disease (CAD). Three major pathophysiologic mechanisms contribute to the pathophysiology of ischemic cardiomyopathy, including:

1. **Myocardial hibernation.** Myocardial hibernation is defined as persistent contractile dysfunction at rest caused by chronically reduced coronary blood flow that can be partially or completely restored to normal by coronary revascularization. Hibernating myocardium may represent a compensatory shift in metabolic activity to match the reduction in coronary blood flow.
2. **Myocardial stunning.** Viable myocardium may demonstrate transient, reversible, postischemic contractile dysfunction after

revascularization. This is believed to be caused by the generation of reactive oxygen species and loss of myocardial filament calcium sensitivity.

3. **Myocyte loss.** The most severe manifestation of ischemic cardiomyopathy is the irreversible loss of cardiac myocytes and progression to fibrosis. Negative remodeling of the left ventricle (LV) then leads to progressive ventricular dilation, increased wall tension, and subsequent impairment of systolic and diastolic function.

B. Clinical significance and recommendations

1. While coronary revascularization has robust indications in the setting of acute coronary syndrome or refractory angina, the role for revascularization to treat HF without these comorbidities remains controversial.
2. The 2012 Surgical Treatment of Ischemic Heart Failure (STICH) trial provided the first randomized clinical trial data regarding the impact of revascularization in patients with ischemic cardiomyopathy; prior trials comparing CABG to medical management had excluded patients with LV dysfunction or HF. In the STICH trial, 1,212 patients with ischemic cardiomyopathy, LV ejection fraction (LVEF) ≤35%, and coronary anatomy suitable for CABG were randomized to medical therapy or medical therapy and CABG. Those with acute coronary syndrome or critical left main stenosis were excluded. Initial results at 5-year follow-up showed a 16% relative risk reduction in the composite end point of death or HF hospitalization but did not demonstrate statistically significant differences in the primary end point of all-cause mortality. However, follow-up data published in the 2016 STICH Extension Study (STICHES) did demonstrate a significant reduction in all-cause mortality at 10 years. Taken together, these data suggest that CABG for appropriately selected patients with ischemic cardiomyopathy offers a long-term mortality benefit that is counterbalanced in the short term by the risks associated with undergoing cardiac surgery.
3. Patient selection for surgical revascularization includes evaluation of the presence of angina, LV dimension and ejection fraction,

hemodynamic compromise, and suitability of targets for revascularization. Tools such as the Society of Thoracic Surgeons (STS) risk score are available online and can be utilized to estimate the short-term risk of undergoing surgical revascularization.

4. The 2021 guidelines from the American College of Cardiology, American Heart Association, and Society for Cardiovascular Angiography and Interventions (ACC/AHA/SCAI) give a class I recommendation for coronary artery revascularization via CABG with LVEF ≤35% and multivessel CAD anatomically amenable to revascularization and for all patients with significant left main stenosis, regardless of LVEF. The recommendation for CABG is reduced to class IIa for those with amenable multivessel CAD and LVEF 35% to 50%.
5. In the STICH trial, myocardial viability was tested in a subset of patients. However, the role of viability testing prior to surgical revascularization remains controversial and of uncertain value. Lack of viable myocardium on imaging studies should not exclude otherwise eligible patients from being considered for surgical revascularization.

III. MECHANICAL CIRCULATORY SUPPORT

A. Introduction. Despite remarkable advances in the treatment of systolic HF, the prognosis of patients with New York Heart Association (NYHA) IIIB or IV symptoms and stage D HF remains poor. Those who have progressed to dependence on intravenous (IV) inotropes have an average life expectancy of less than 6 months.

1. Cardiac transplantation is the only definitive treatment for end-stage HF, with average post-transplant survival now >12 years. Unfortunately, there remains a wide discrepancy between the limited availability of donor organs and the ever-increasing number of patients with HF. Organ availability aside, many patients are not eligible for transplantation due to advanced age, comorbid conditions, or psychosocial limitations.
2. MCS includes a range of devices designed to offload the heart and improve cardiac output. MCS can be classified based on the site of support (either LV, right ventricular [RV], or biventricular), duration

of support (temporary or durable), pulsatility (continuous or pulsatile flow), device design (axial or centrifugal flow), or indication for use (bridge or destination therapy [DT]). We focus primarily on continuous flow LVADs as these have become the standard of care for durable MCS, comprising >95% of devices implanted since 2010.

3. LVADs have proved an increasingly beneficial tool in the treatment of advanced HF. By mechanically unloading the LV and increasing cardiac output, LVADs can significantly improve both survival and quality of life in appropriately selected patients with advanced HF. For several decades following their conception in the 1960s, LVADs remained a rarely used, last-ditch effort to temporarily support patients awaiting transplantation. Over the past 20 years, however, due to improvements in both device design and patient selection, LVADs have become the mainstay of durable MCS and a pillar of the advanced therapy armamentarium. Devices for temporary percutaneous MCS are covered elsewhere in this manual.

B. Early LVAD experience

1. The **landmark 2001 Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial** was the first to demonstrate an improvement in survival with LVAD use among patients ineligible for transplantation. Previously, LVADs were used exclusively in those awaiting transplantation. In REMATCH, patients randomized to LVAD were found to have 1-year survival of 52% versus 25% with optimal medical therapy, in addition to improved quality of life. The device implanted at that time was the HeartMate (HM) XVE LVAD (Thoratec), a pulsatile pump that, for many years, was among the most commonly used LVADs worldwide (**Figure 12.1**).

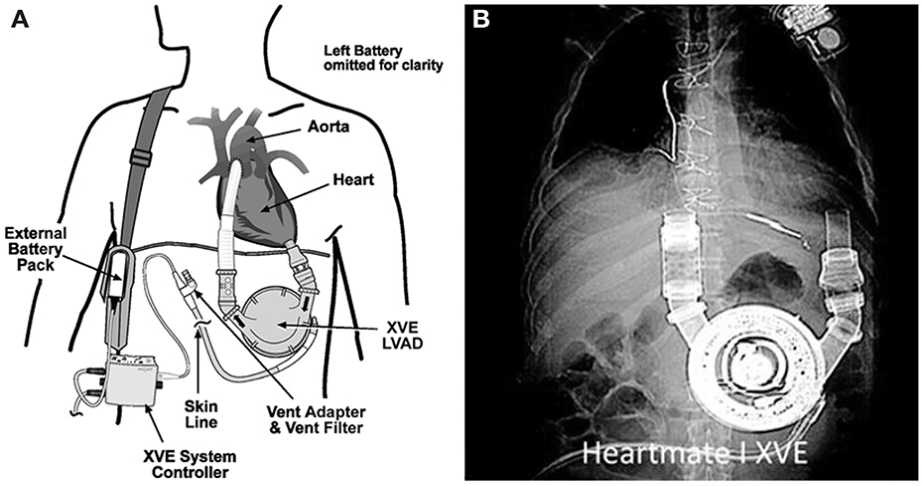

FIGURE 12.1 **A.** Schematic of the pulsatile HeartMate XVE and (**B**) chest radiograph demonstrating an implanted HeartMate XVE. LVAD, left ventricular assist device. (HeartMate 2, HeartMate 3, and HeartMate XVE are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, Copyright © 2024. All rights reserved.)

2. Despite the benefits demonstrated by the REMATCH trial, these early LVADs had significant limitations. They were usable only in larger patients, specifically those patients with a body surface area (BSA) of 1.5 m^2 or greater. Device durability was also a critical limitation, with high rates of valve and motor failure after 12 months of use. Even with revisions to the design, the durability at 2 years was only 5%.
3. **Development of continuous flow LVADs.** The limitations of these first-generation, pulsatile pumps led to the development of the now widely used continuous flow LVADs. These LVADs are smaller, more durable, and allow for long-term MCS in a wider patient population. Such improvements have led to expanded LVAD use for several different indications, also referred to as implantation strategies.

C. Implantation strategies for LVADs

1. Although the Centers for Medicare & Medicaid Services (CMS) have removed terminology surrounding “bridge-to-transplant” (BTT) and DT from their LVAD approval, these distinctions remain useful parlance for both medical teams and patients to understand

the intent with which these devices are placed; with that said, these delineations are increasingly fluid as LVAD technology advances.

2. **BTT** was the original indication for LVAD implantation and remains an important use. Multiple prospective studies and extensive retrospective registry data have shown that LVAD implantation can improve both survival and quality of life in appropriately selected patients awaiting cardiac transplantation.
3. **Bridge-to-decision** (BTD), also known as bridge-to-candidacy, describes the use of MCS in patients who are not currently transplant candidates but may be in the future. Patients eligible for BTD LVAD implantation have comorbidities that are potentially reversible or of unclear prognosis. Permanent LVAD implantation as BTD tends to have worse outcomes compared with BTT implantation. When there is uncertainty about future transplant candidacy, temporary circulatory support devices such as extracorporeal membrane oxygenation or percutaneous LVAD support are typically preferable. Ideal devices for this group of patients should be easily implanted, easily explanted, and cost-efficient.
4. **DT** describes the use of durable MCS in patients with end-stage HF who are not eligible for cardiac transplantation. During early experience with BTT LVAD use, recognition of improved outcomes among patients who did not end up receiving a heart transplant prompted the investigation of LVAD use as DT. First approved in the wake of the landmark REMATCH trial, DT has expanded to become the most common indication for LVAD implantation. DT use is expected to continue expanding in years to come as devices improve and the prevalence of HF increases. Currently, the CMS mandates the following criteria for LVAD implantation:
   a. NYHA class IV HF
   b. LVEF ≤25%
   c. Inotrope dependence OR an index of <2.2 L/min/m^2 despite receiving optimal medical management for 45 out of the last 60 days OR advanced HF for at least 14 days with dependence on an intra-aortic balloon-pump or other tMCS for at least 7 days

5. **Bridge-to-recovery**, though not an indication for implantation, describes the circumstance of durable LVAD implantation for one of the above indications and subsequent explantation following recovery of native cardiac function.

D. Patient evaluation and selection for LVAD

1. Successful use of durable MCS **critically hinges on appropriate patient selection**. A multidisciplinary team is needed for appropriate consideration of the numerous facets that influence LVAD candidacy.
2. Initial indications for LVAD therapy were derived from the inclusion criteria of clinical trials: symptomatic advanced HF refractory to conventional therapy, LVEF <25%, and peak oxygen consumption <14 mL/kg/min or <50% predicted.
3. While work on MCS for HF with preserved EF (HFpEF) is ongoing, attempts at LVAD use in this population have thus far been limited by both anatomic and physiologic challenges, particularly chamber collapse following ventricular offloading in restrictive or hypertrophic phenotypes. At this time there is no Food and Drug Administration (FDA)-approved durable MCS for HFpEF.
4. The **Interagency for Mechanical Circulatory Support (INTERMACS) profiles capture disease severity** by categorizing patients with advanced HF potentially eligible for MCS. These profiles divide patients into seven categories ranging from profile 1 (critical cardiogenic shock) to profile 7 (ambulatory NYHA class III) (**Table 12.1**).

TABLE 12.1 INTERMACS Profiles

Adult Profiles	IV Inotropes	Official Parlance
INTERMACS Level 1	Yes	"Crash and burn"
INTERMACS Level 2	Yes	"Sliding fast" on inotropes
INTERMACS Level 3	Yes	"Stable" on inotropes

Adult Profiles	IV Inotropes	Official Parlance
INTERMACS Level 4	No	Resting symptoms on oral therapy at home
INTERMACS Level 5	No	"Housebound," comfortable at rest, symptoms with minimal activity or ADLs
INTERMACS Level 6	No	"Walking wounded," ADLs possible but meaningful activity limited
INTERMACS Level 7	No	Advanced class III

ADLs, activities of daily living.

5. The latest INTERMACS registry data demonstrated that around two-thirds of LVAD recipients are INTERMACS profile 2 or 3 at the time of implantation. A further 18% were INTERMACS profile 1, though an initial temporary/bridging MCS strategy, is often preferred in this population as they have poorer outcomes following LVAD implantation. The remaining roughly 15% of implantations were predominantly INTERMACS profile 4; very few INTERMACS profile 5 to 7 patients are sufficiently ill to meet the criteria for durable MCS.
6. The optimal timing of LVAD implantation remains a subject of ongoing debate, as centers attempt to balance the need to allow adequate time for effective attempts at institution of guideline-directed medical therapy (GDMT) while also minimizing the "failure-to-rescue" phenomenon of allowing a patient with HF to progress to late-stage end-organ dysfunction or death.
7. Several specific characteristics important to patient with LVAD selection include RV function, renal function, nutritional status, and psychosocial factors.
8. **RV function**
    a. RV function is a critical factor for effective LVAD therapy. Because LVADs support only the LV, the development of right-sided HF (RHF) after LVAD implantation is strongly associated with multisystem organ failure, prolonged hospitalizations, and mortality. Although pulmonary hypertension is not a

contraindication to LVAD implantation (and in fact may improve with chronic unloading), RV function must be rigorously evaluated and considered during patient selection.

b. Unfortunately, prediction of post-LVAD RV failure (RVF) has proven challenging. Many pertinent risk factors, patient characteristics, and hemodynamic parameters have been identified as potential predictors of RVF (**Table 12.2**).

TABLE 12.2 Echo, Hemodynamic, and Patient Factors Associated With Risk of Post-LVAD RV Failure

Echocardiographic Parameters
RV diastolic dysfunction • Tricuspid *E*/*é* >10 • Decreased RA peak strain
RV systolic dysfunction • TAPSE <8 mm
RV to PA uncoupling • Load adaptation index <14
Hemodynamic Parameters
Increased afterload • DTPG >7 mm Hg
Systolic and diastolic dysfunction • PAPi <1.85 • Steep Y descent • RVSWI <350 mm Hg/mL/m^2
Increased preload • CVP >10 mm Hg • CVP/PCWP >0.63 • MAP/CVP <7.5
Poor RV reserve • No normalization of CVP after optimization • PAPi <3.3 after optimization
No change in indexed stroke volume with vasodilators
Patient Factors
Demographics: • Female sex • BMI >30

End-organ dysfunction:

- eGFR <30 mL/min, proteinuria
- MELD-XI >12, high Fibroscan score, high INR
- DLCO <80%, VE/VCO_2 slope >36

Labs

- Elevated BNP
- Low prealbumin
- Elevated WBC or neutrophil/lymphocyte ratio

Device Support

- ECMO, RRT, or IMV at the time of implant
- Prolonged inotropic support (>30 d)
- INTERMACS 1/2

BMI, body mass index; BNP, brain natriuretic peptide; CVP, central venous pressure; DLCO, diffusing capacity of the lungs for carbon monoxide; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; IMV, invasive mechanical ventilation; INR, international normalized ratio; LVAD, left ventricular assist device; MAP, mean arterial pressure; MELD-XI, Model for End-stage Liver Disease eXcluding INR; PA, pulmonary artery; PAPi, pulmonary artery pulsatility index; PCWP, pulmonary capillary wedge pressure; RA, right artery; RRT, renal replacement therapy; RV, right ventricle; WBC, white blood cell.
Data from Rodenas-Alesina E, Brahmbhatt DH, Rao V, et al. Prediction, prevention, and management of right ventricular failure after left ventricular assist device implantation: a comprehensive review. *Front Cardiovasc Med*. 2022;9:1040251.

c. An independent hemodynamic parameter that has recently been validated for predicting RVF post-LVAD is the pulmonary artery pulsatility index (PAPi), which is calculated as the pulmonary artery pulse pressure divided by the right atrial pressure. A lower PAPi is associated with increased rates of RVF and mortality following LVAD implantation.

d. Another hemodynamic parameter used for predicting post-LVAD RVF is the central venous pressure to pulmonary capillary wedge pressure (CVP/PCWP) ratio. A higher CVP/PCWP ratio (generally >0.63) is associated with increased risk of RVF.

e. Among these, the PAPi (both the initial PAPi and the optimal PAPi achieved with aggressive presurgical therapy) currently has the most robust evidence supporting its use as an independent predictor of RVF following LVAD implantation. Still, PAPi is

itself an imperfect predictor and requires invasive hemodynamic measurements to be calculated. Efforts are ongoing to establish more reliable means of predicting RVF in this setting.

9. **End-organ function**
    a. **Renal dysfunction.** Many patients with end-stage HF have abnormal renal function. Although if acute cardiorenal syndrome is the primary cause of renal insufficiency renal function will typically improve after LVAD implantation, intrinsic renal dysfunction or end-stage impairment requiring renal replacement therapy has been associated with poorer postimplantation survival. Although not an absolute contraindication for LVAD implantation, significant renal dysfunction must be considered a complicating factor.
    b. **Hepatic dysfunction.** Underlying liver dysfunction and cirrhosis confer higher perioperative and long-term mortality and are considered a significant barrier to LVAD support.
    c. **Pulmonary dysfunction.** Underlying significant pulmonary comorbidity (eg, chronic obstructive pulmonary disease [COPD], interstitial lung disease [ILD]), particularly with associated long-term oxygen dependence, poses significant risk perioperatively due to issues with prolonged ventilatory dependence, as well as conferring significantly higher risk for long-term RV dysfunction after LVAD implantation.
10. **Nutrition/frailty.** Malnutrition and sarcopenia represent risk factors for both infection and mortality after LVAD implantation. Therefore, nutritional status must be considered during evaluation and should be optimized prior to LVAD implantation.
11. **Psychosocial factors.** Psychosocial factors play a pivotal role in LVAD outcomes because the care and maintenance of the LVAD requires strict patient adherence and extensive caregiver support. Nonadherence to obligate anticoagulation or device maintenance will likely prove fatal in LVAD recipients. It is, therefore, critical for patients to undergo neuropsychiatric evaluation for assessment of adherence, substance use, social support, and health literacy.

E. LVAD surgical approaches

1. The inflow cannula, outflow graft, and driveline exit must each be considered when deciding on a surgical approach to LVAD implantation.
2. Open sternotomy allows for all three components to be placed via a single access site. It is almost always performed with an on-pump, beating heart technique.
3. Lateral thoracotomy can be used for placement of the inflow cannula and drive line exit, though an additional access is needed for the outflow graft. The lateral approach can be performed off-pump.
4. The need for adjunctive valve intervention, particularly for correction of concurrent aortic insufficiency that may complicate LVAD use, may influence the choice of approach.

F. LVADs currently in use

1. Background

a. Early LVADs were designed to mimic the pulsatility of the native ventricle. Second- and third-generation devices transitioned to a continuous flow design, marking a significant milestone in the evolution of MCS. Continuous flow LVADs draw blood from the LV apex into the pump and return the blood to the circulation via an outflow graft attached to the ascending aorta.

b. These pumps are connected to an external controller and power source via a driveline that runs subcutaneously before exiting the body. They can be powered using AC power or an external battery system. Maintenance of charged backup batteries is a critical facet of LVAD care.

c. The rotor in these devices rotates at a set constant speed, the ranges of which vary from device to device

d. Given that there is continuous flow, the main contribution of pulsatility is from the native LV. Most patients with LVAD do not have palpable or audible pulses. Modern devices including the HM III and HeartWare Ventricular Assist Device (HVAD) also include algorithmic speed decreases to minimize stasis; although not palpable as a pulse, these may show a rhythm variation in systemic pressure when measured invasively.

e. A major advantage of the continuous flow LVADs is their smaller size and increased durability, which has allowed for wider application. The only device currently approved for BTT and DT is the HM III (Abbott), which is a centrifugal flow continuous LVAD. Prior to the HM III, the two approved continuous flow LVADs were the HM II (Abbott), an axial flow continuous LVAD, and the HVAD (HeartWare, Medtronic).

2. HeartMate II

a. The HM II is an axial continuous flow LVAD (**Figure 12.2**). It has an electromagnetically powered impeller that spins on a blood-lubricated ruby bearing. The pump itself weighs about 10 oz, has an implant volume of 63 mL, and generates up to 10 L of flow per minute. The inflow cannula is implanted in the LV apex, with the pump placed in the preperitoneal space. The HM II is one-seventh the size and one-fourth the weight of the previous HM XVE.

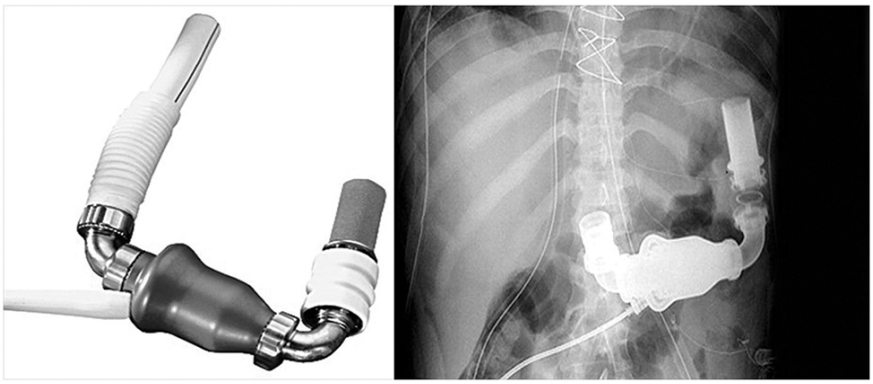

FIGURE 12.2 HeartMate II left ventricular assist device (LVAD) and radiograph demonstrating an implanted HeartMate II LVAD. (HeartMate 2, HeartMate 3, and HeartMate XVE are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, Copyright © 2024. All rights reserved.)

b. The axial flow design and the absence of blood sac eliminate the need for venting, which was required for the first generation of implantable pumps, thus reducing the size of the percutaneous

driveline and also eliminating the need for internal one-way valves.

c. The FDA approved the HM II LVAD for BTT in 2008 and subsequently for DT in 2010 on the basis of the HM II trial, which demonstrated a 58% 2-year survival compared to 11% in the pulsatile LVAD group. In 2011, in a postapproval analysis, 1-year survival for the HM II was 85%.

d. Though no longer being implanted, a number of HM II LVADs are still in use by prior recipients.

3. HeartWare

a. The HeartWare HVAD is a miniaturized centrifugal pump without bearings (**Figure 12.3**).

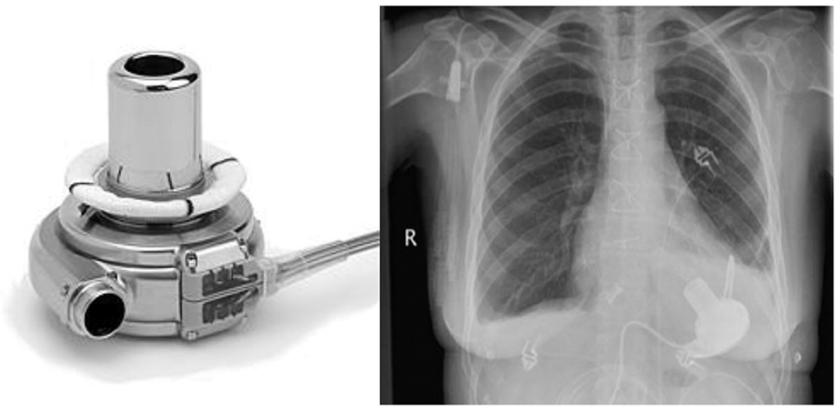

FIGURE 12.3 HeartWare left ventricular assist device (LVAD) and chest radiograph demonstrating the intrapericardial implantation. (Image courtesy of HeartWare.)

b. The pump weighs only 5 oz (half the weight of HM II) and has a volume of 45 mL and yet still supports flows up to 10 L/min.

c. The small size allows for implantation within the pericardial space, obviating the need for the creation of a peritoneal pocket.

d. It has a wide-blade impeller design, which is suspended via a passive magnetic and hydrodynamic bearing system.

e. The HVAD was evaluated for BTT in the ADVANCE trial, a multicenter noninferiority study. Participants were compared to a

comparable, contemporary group of patients receiving continuous flow LVADs who were entered into the INTERMACS registry. Based on the demonstration of noninferiority in survival to either transplantation or explantation, the HVAD was approved by the FDA in 2012 for BTT.

f. The HVAD was then evaluated for DT in the ENDURANCE trial, a multicenter noninferiority trial comparing it to the HM II. The results showed no difference in survival but a higher rate of stroke in the HVAD arm, which prompted the ENDURANCE supplemental trial that mandated blood pressure (BP) control aimed at a mean arterial pressure (MAP) of <85 mm Hg. This subsequent trial showed no statistically significant difference in survival or stroke, leading to the HVAD's FDA approval for DT in 2017.

g. In 2021, Medtronic issued a recall of the HVAD due to a high rate of hemolysis and subsequent pump thrombosis, as well as the aforementioned increased risk of stroke. The approximately 4,000 to 5,000 patients with existing HVADs were advised to continue using the device as before, though further implantation of HVADs was halted.

4. HeartMate III

a. The HM III is currently the only FDA-approved LVAD. It is a continuous flow LVAD with a centrifugal, magnetically levitated, bearing-less design. It is a small device that can be implanted in the pericardial space, similar to the HVAD (**Figure 12.4**).

FIGURE 12.4 HeartMate III left ventricular assist device. (HeartMate 2, HeartMate 3, and HeartMate XVE are trademarks of Abbott or its related companies. Reproduced with permission of Abbott, Copyright © 2024. All rights reserved.)

b. The MOMENTUM 3 trial compared the HM II and HM III, with the newer HM III demonstrating improved 2-year survival free of disabling stroke or device malfunction requiring replacement (77% vs 65%).

c. In a small secondary analysis combining DT patients from ENDURANCE and MOMENTUM 3, the HVAD was found to have a higher risk of pump thrombosis, arrhythmia, and infection compared to the HM III.

G. LVAD hemodynamics and parameters

1. There are two forms of continuous flow: axial (HM II) and centrifugal flow (HM III and HVAD). Centrifugal flow allows for a smaller pump profile and allows blood to be moved at slower speed, thus leading to less hemolysis, stroke, and pump malfunction/thrombus. However, this makes centrifugal flow pumps more sensitive to increases in afterload.

2. There are four key parameters to monitor in modern continuous flow LVADs:

a. Speed

b. Flow

c. Power

d. Pulsatility index (HM devices) or pulsatility (HVAD)

3. Typical parameters for these devices are listed in **Table 12.3**.

TABLE 12.3 Typical Continuous LVAD Parameters

	HM III	HM II	HVAD
Type of Flow	**Centrifugal**	**Axial**	**Centrifugal**
Pump speed (rpm)	5,000-6000	8,000-10,000	2,400-3,200
Pump flow (L/min)	4-6	4-6	4-7
Pump power (W)	4.5-6.5	3-7	5-8
PI/flow pulsatility	3.5-5.5	2-4	5-8

HM, HeartMate; HVAD, HeartWare Ventricular Assist Device; LVAD, left ventricular assist device; PI, pulsatility index.
Derived from Dalia AA, Cronin B, Stone ME, et al. Anesthetic management of patients with continuous-flow left ventricular assist devices undergoing noncardiac surgery: an update for anesthesiologists. *J Cardiothorac Vasc Anesth*. 2018;32(2):1001-1012.

4. Speed is the only parameter that is adjustable. Normal speed parameters by device are as follows:
   a. HM III: 5,000 to 6,000 rpm
   b. HVAD: 2,400 to 3,200 rpm
   c. HM II: 8,000 to 10,000 rpm
5. Flow is calculated based on power, speed, and blood viscosity (as estimated based on hematocrit). A normal flow range is 4 to 6 L/min. Importantly, **LVAD flow is a calculated estimate and not directly equivalent to cardiac output**; it is calculated based on other parameters and does not account for residual native LV output. Flow is indirectly proportional to afterload and systolic BP.
6. Power is the work, measured in watts, needed to spin the rotor. It is directly proportional to speed and flow, such that faster rotational speed requires an increase in power.

7. Pulsatility is a reflection of the flow and power variability over a 15-second period of time (in the HM III). Factors that affect pulsatility are volume status, native contractility, rotational speed, and the LV-aortic pressure gradient. A normal pulsatility index is typically between 3 and 5.
8. **Pulsatility events** describe a sudden change in the pulsatility index. These events can be caused by suction events (associated with insufficient preload), changing afterload, arrhythmia, sudden changes in power or pump speed, or changes in intrathoracic pressure, such as coughing or sneezing.
   a. If a pulsatility index event is detected, the HM III will lower the speed to the lower limit and then ramp back up to the previously set speed.
9. Pulsatility, flow, and power should be directly related to each other; low pulsatility and power suggest hypovolemia, RVF, or inflow/outflow graft obstruction. High pulsatility and flow/power are seen with changing physiologic conditions, such as exercise or improvement in native cardiac function (**Table 12.4**).

TABLE 12.4 Interpretation of Power and Pulsatility on Different LVAD Conditions

Pulsatility	Power/Flow	Etiologies
Increased	Decreased	• Increased afterload (hypertension) • Decreased pump speed • Outflow/inflow thrombus/kink
Increased	Increased	• Normal • Exercise • LVEF recovery
Decreased	Decreased	• Hypovolemia • RV failure • Tamponade • Outflow/inflow thrombus/kink
Increased	Decreased	• Hypotension/vasodilation • Increased pump speed

Pulsatility	Power/Flow	Etiologies
		• Thrombus on rotor bearings

LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; RV, right ventricle.
Derived from Lim HS, Howell N, Ranasinghe A. The physiology of continuous-flow left ventricular assist devices. *J Card Fail*. 2017;23(2):169-180.

a. Low pulsatility but high-flow readings (estimated) and power (measured) suggest hypotension from decreased systemic vascular resistance, pump thrombosis, or excessive pump speed.

b. High pulsatility but low flow and power suggests low pump speed or increased afterload.

c. Echocardiographic evaluation is invaluable in assessing LVAD loading conditions and for troubleshooting. Common echo findings for different loading conditions are listed in **Table 12.5**.

TABLE 12.5 Interpretation of LVAD Conditions by Bedside Echo

Condition	LV Diameter	AV Opening	MR	IVC Diameter	Septal Position
Low speed	Increased	Increased or Unaffected	Increased	Increased or Unaffected	Rightward
Pump thrombosis	Increased	Increased	Increased	Increased or Unaffected	Rightward
Pump stoppage	Increased	Increased	Increased	Increased	Rightward
Aortic insufficiency	Increased	Decreased	Increased	Increased or Unaffected	Rightward
RV failure	Decreased	Decreased	Decreased	Increased	Leftward
Hypovolemia	Decreased	Decreased	Decreased	Decreased	Leftward

AV, atrioventricular; IVC, inferior vena cava; LV, left ventricle; LVAD, left ventricular assist device; MR, mitral regurgitation; RV, right ventricle.
Derived from Stainback RF, Estep JD, Agler DA, et al.; American Society of Echocardiography. Echocardiography in the management of patients with left ventricular assist devices: recommendations from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2015;28(8):853-909. PMID: 26239899.

10. **Measurement of BP** in patients with LVAD is vital but often challenging. As most patients lack a palpable or audible pulse, automatic BP cuffs often fail to provide accurate measurements. Instead, BP is measured using a manual cuff and Doppler probe. First, a distally Dopplerable pulse is identified. A manual cuff is inflated proximally until obliteration of that pulse, then slowly deflated. The pressure at which the Doppler signal reappears represents the MAP. The goal MAP for patients with LVAD is generally considered to be 60 to 85 mm Hg.
11. **Neurohormonal blockade** post-LVAD (with beta-blocker, mineralocorticoid receptor antagonist [MRA], and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/angiotensin receptor-neprilysin inhibitor [ACEI/ARB/ARNI]) has been shown to have a survival benefit in a retrospective review of the INTERMACS registry. Usage of sodium-glucose cotransporter 2 inhibitor (SGLT2i) in this population is not contraindicated and has a reasonable safety profile, although similar data demonstrating survival benefit are currently lacking.
12. Finally, **patients with LVAD must be continuously maintained on systemic anticoagulation** to prevent embolic stroke and pump thrombosis. This is accomplished with either a vitamin K antagonist (warfarin) or IV heparin and is supplemented with antiplatelet therapy in the form of low-dose aspirin.
    a. Direct oral anticoagulants (DOACs) such as apixaban and dabigatran have been associated with an increased risk of both thromboembolic *and* bleeding events in LVAD users.
    b. The 2013 RE-ALIGN trial compared dabigatran to warfarin in patients with mechanical valves; results have been extrapolated to other intracardiac devices, such as LVADs. It was terminated early due to an increased risk of thromboembolism and bleeding in the DOAC arm. Second, a small 2017 trial comparing a nonwarfarin vitamin K antagonist with dabigatran in the HVAD was also terminated early due to increased thromboembolic events in the DOAC group.

c. Recently, a small nonrandomized trial compared apixaban and warfarin in a group of HM III patients and found no difference in thromboembolic or bleeding events. While similar work is ongoing, the current standard of care for patients with LVAD remains anticoagulation with vitamin K antagonists.

H. LVAD complications

1. Ongoing improvements in patient selection and device design have dramatically reduced the incidence of LVAD complications. Nevertheless, major complications still occur, including pump thrombosis, bleeding, infection, stroke, and RVF. Complication rates for the HM III as described below and listed in **Table 12.6**.

TABLE 12.6 Complication Rates With HM III

Adverse Event	Complication Rate (%)
Pump thrombosis	1.4
Stroke	9.9
Right heart failure	34.2
Bleeding	43.7
Infection	58.3
Renal dysfunction	14.2
Hepatic dysfunction	4.9

HM, HeartMate.
Data from Mehra MR, Uriel N, Naka Y, et al. A fully magnetically levitated left ventricular assist device—final report. *N Engl J Med*. 2019;380:1618-1627.

2. Pump thrombosis

a. As with most implanted devices, LVADs activate the coagulation system. Untreated, this leads to pump thrombosis and device failure. Thus, LVAD use obligates the continuous use of both warfarin anticoagulation (international normalized ratio [INR] goal 2-3) and an antiplatelet agent, typically aspirin. Holding anticoagulation should be avoided if at all possible, and heparin bridging should be used whenever INR is below therapeutic range.

b. Pump thrombosis is preceded by hemolysis, which can be clinically evaluated by following serum lactate dehydrogenase, haptoglobin, and plasma-free hemoglobin levels, as well as urinalysis.

c. Clinical signs of pump thrombosis include hemoglobinuria, power spikes, and worsening HF symptoms. Patients with suspected pump thrombosis need to be evaluated immediately as they may require intensified anticoagulation, thrombolytics, or pump exchange. Of note, LVAD flow is calculated based on power requirements, so estimated flow tends to paradoxically increase in the event of pump thrombosis.

d. Evaluation with a ramp study (an echo done with serial increases in pump speed) will show a fixed LV size and an aortic valve that does not continuously close.

e. The risk of pump thrombosis is substantially lower with centrifugal flow LVADs compared to axial flow LVADs and is lower with the HM III than with the HVAD.

f. In MOMENTUM 3, there were 10-fold fewer instances of pump thrombosis in the HM III group compared to the HM II.

3. Bleeding

a. The necessity of antithrombotic therapy inevitably puts LVAD recipients at increased risk of bleeding.

b. Furthermore, shear stress from LVAD use has been shown to cause an acquired von Willebrand syndrome, which further increases bleeding risk. Similar to Heyde syndrome seen in critical aortic stenosis, high shear stress induces a structural change in the von Willebrand molecule. This leads to lysis of the high-molecular-weight multimers and impairment of platelet-mediated hemostasis.

c. As a result of these factors, significant bleeding (typically gastrointestinal) is a common complication of LVAD use, occurring at a rate of approximately 50% per year of use.

d. In the event of severe bleeding, anticoagulation and antiplatelet agents can be temporarily held. These should be restarted as soon

as possible, making source control with the assistance of gastroenterology or other pertinent specialists a high priority.

4. Infection

a. Along with bleeding, infection is the other major complication commonly seen in LVAD recipients.

b. The most common are driveline infections, occurring at the exit site connecting the LVAD to the outside world. Local inflammatory changes and purulent drainage are often seen when infection is present. Bloodstream or pump pocket infections also occur though less frequently.

c. *Staphylococcus aureus* and coagulase-negative staphylococci account for more than 50% of cases of LVAD-related infections. Enterococci, *Enterobacter* spp., and *Pseudomonas aeruginosa* are other commonly isolated bacterial pathogens in LVAD-related infections.

d. Preoperative factors such as obesity and malnutrition have been identified as risk factors for LVAD-related infections. Unlike most complications, which tend to peak shortly after implantation, the risk of infection seems to increase slightly over time.

e. Strategies to treat LVAD-related infections include long-term suppressive antibiotics, localized debridement, and device exchange or removal. Preventive measures such as perioperative antibiotics, absorbable local antibiotic-eluting beads (eg, vancomycin), and meticulous driveline care are important in reducing the risk of infection.

5. Stroke

a. Ischemic and hemorrhagic stroke are both known complications of LVAD therapy and occur with similar frequencies.

b. The most recent data from the INTERMACS registry report stroke rates of around 13% within the first year following implantation.

c. Adequate anticoagulation to prevent pump thrombus and strict **BP management (target MAP <85 mm Hg)** are the main

strategies to reduce the rate of ischemic and hemorrhagic stroke, respectively.

6. **RV failure**
   a. RVF is a leading cause of mortality after LVAD implantation and a major contributing factor to other serious adverse events, such as bleeding, renal failure, liver failure, and prolonged hospitalization.
   b. Studies to date have found a wide range of reported RVF rates requiring the addition of right-sided MCS. In MOMENTUM 3, both the HM II and HM III had a ~1/3 incidence of RVF.
   c. These observations underscore the need for careful patient selection, identification of those at high risk for RVF, and consideration of providing preoperative right ventricular assist device (RVAD) support. There are numerous risk calculators to evaluate a patient's risk of RVF prior to LVAD implantation.
   d. There is no universal definition of RVF post-LVAD; common definitions include typical symptoms and findings of RHF (peripheral edema, ascites, jugular vein distention [JVD]), hemodynamic parameters (elevated CVP and decreased cardiac index [CI]), echocardiographic parameters (dilated inferior vena cava [IVC]), and requirement of RVAD and/or inotropic support.
   e. RVF post-LVAD most commonly occurs in the first several weeks postimplantation, referred to as "early-onset RVF." However, a subset of patients will develop late-onset RVF after the immediate postoperative period. This definition is variable in regard to time frame, but is generally defined as >30 days after implantation. Late-onset RVF is associated with worse outcomes, including survival, HF hospitalization, and quality of life.
   f. Treatment of late RVF post-LVAD requires optimization of RV hemodynamics. Based on observational data and expert opinion, current guidelines recommend the use of pulmonary vasodilators such as inhaled nitric oxide (iNO), iloprost, epoprostenol, and phosphodiesterase-5 (PDE5) inhibitors to optimize RV hemodynamics in the setting of post-LVAD RVF. However, there

is no definitive evidence that these therapies improve survival in post-LVAD RVF.

7. Low-flow alarms

a. Causes of low flow include bleeding, arrhythmia, RVF, arrhythmia, reduced preload, pump suction, inflow or outflow obstruction, cardiac tamponade, and increased afterload.

b. Treatment for these conditions should be tailored to the specific precipitating etiology.

c. Failure to treat low-flow states promptly, depending on etiology, may lead to either inadequate LV unloading with ensuant HF and potentially cardiogenic shock or conversely to hypovolemic shock.

d. An algorithmic approach to LVAD hypotension (MAP <60) is provided in **Figure 12.5**.

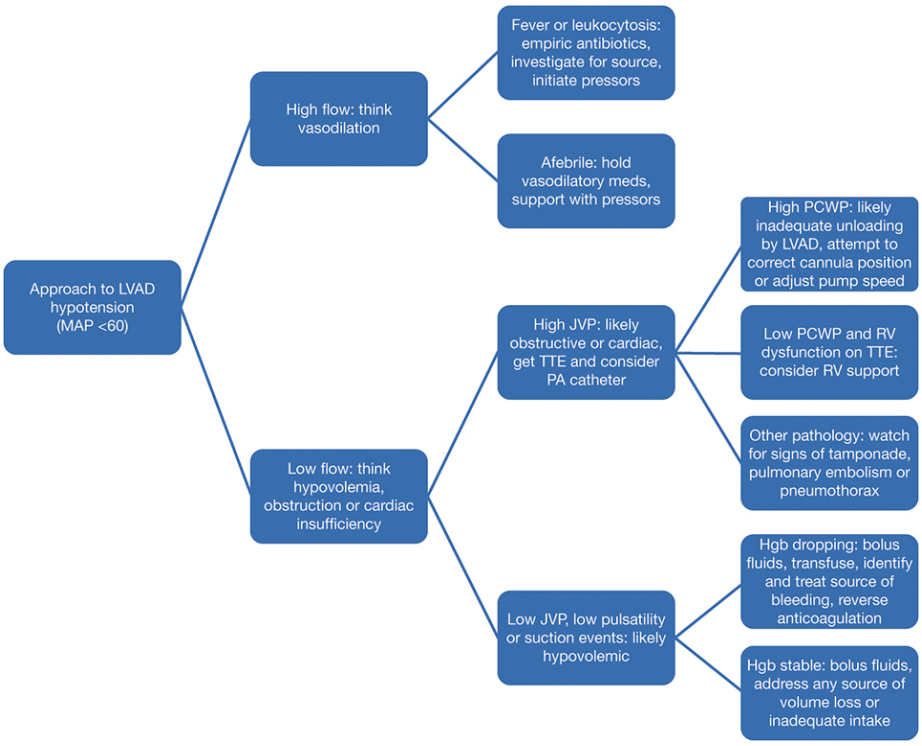

FIGURE 12.5 Schematic approach to left ventricular assist device hypotension.

8. Worsening HF

a. Inadequate LV unloading can lead to acute decompensated HF; this can be caused by inadequate pump speed (see low-flow alarms discussed earlier), RVF, arrhythmia, severe aortic insufficiency, pump thrombosis, inflow/outflow cannula obstruction, circulatory volume overload, or excess afterload.

b. Conventional HF therapy including, but not limited to, diuretic management, afterload reduction, and rhythm control should be employed in conjunction with troubleshooting of LVAD function (eg, evaluating for and treating pump thrombosis, modulating speed).

9. Ventricular arrhythmias and cardiac arrest

a. Reversible causes of ventricular tachycardia (VT) in LVADs are similar to those in patients without LVADs and include electrolyte abnormalities and acute coronary syndromes. Additional considerations in LVADs include suction events and RVF.

b. Patients with LVADs may hemodynamically tolerate VT comparatively well due to the presence of their continuous flow pump; however, VT and VF should still be treated promptly as prolonged ventricular arrhythmia may compromise RV function and lead to inadequate LVAD preload over time.

c. Implantable cardioverter-defibrillator (ICD) therapy in the setting of LVAD use remains controversial. While there is no randomized clinical trial data to suggest benefit or harm, multiple retrospective observational studies have demonstrated no survival benefit with ICD implantation.

d. The risk of an ICD-related infection and inappropriate shocks are nontrivial and must be weighed carefully.

e. In patients with LVAD with cardiac arrest or who are unresponsive, external chest compressions should only be performed if the patient has an MAP <50 mm Hg or an end-tidal (ET) CO_2 of <20 mm Hg (if endotracheal). Routine ACLS protocol should be otherwise followed.

I. Biventricular assist devices and total artificial hearts

1. While LVADs are effective for LV systolic failure, they are of limited utility in cases of biventricular HF or conditions such as infiltrative cardiomyopathies, which tend to have small ventricular cavity sizes.
2. Currently, there is no durable RVAD approved. Temporary RVADs include the surgically implanted Centrimag (Levitronix LLC) and newer percutaneous RVADs, such as the Impella-RP and RP Flex (Abiomed) and the Protek Duo RVAD (Protek). These devices can be utilized during LVAD implantation for temporary RV support in select patients to mitigate post-LVAD RVF.
3. The so-called "HeartMate 6" (two HM III in a biventricular arrangement) has been implemented in a small, carefully selected group of patients in an off-label use for durable biventricular support in a BTT strategy.
4. **Total artificial hearts**
    a. A strategy for durable treatment of biventricular HF can include the total artificial heart (TAH) as a BTT (**Figure 12.6**). Currently, the SynCardia TAH (SynCardia Systems) is approved for BTT use up to a maximum of 1 year.

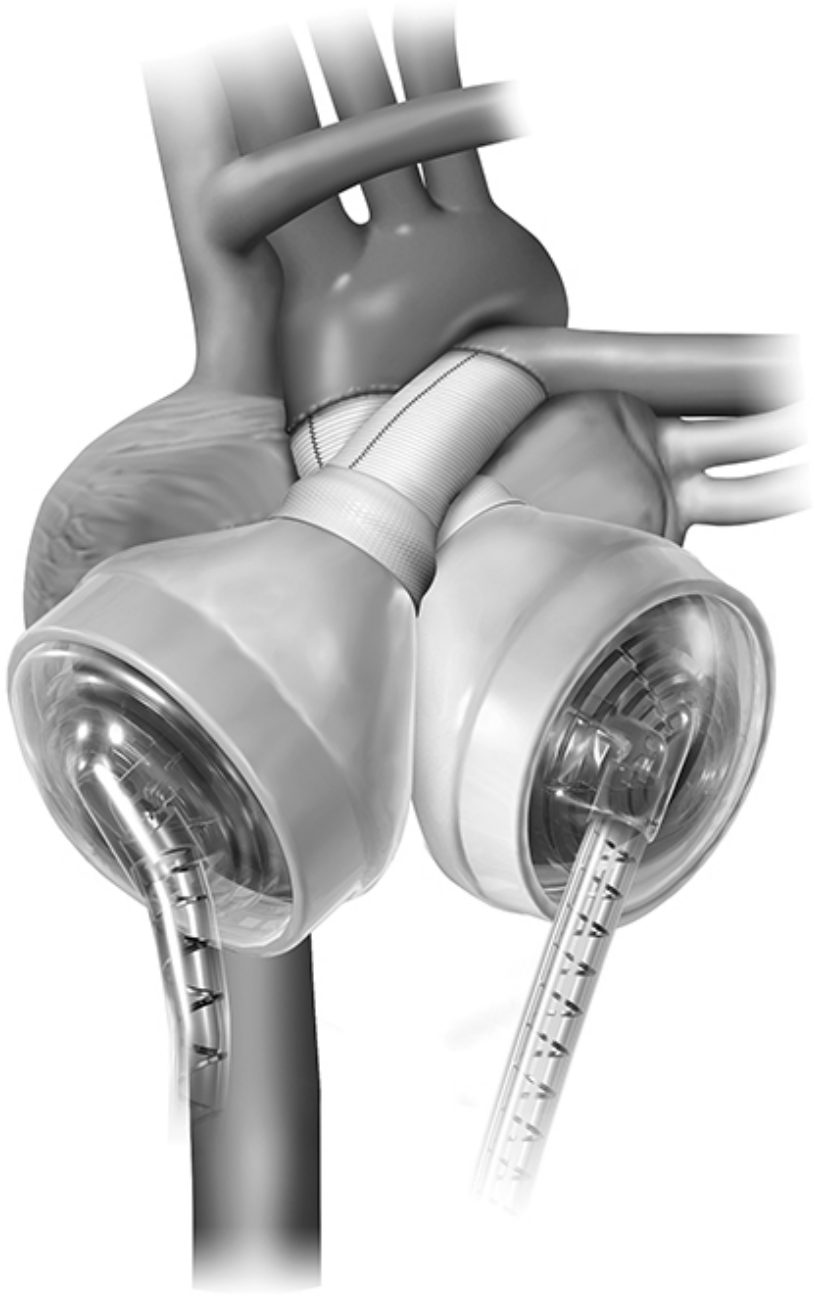

FIGURE 12.6 SynCardia total artificial heart device. (Courtesy of syncardia.com.)

b. The SynCardia TAH has two artificial ventricles made from a semirigid polyurethane with flexible diaphragms with mechanical valves in the inflow and outflow ports of each ventricle.

c. During implantation of the TAH, the native ventricles are resected and the TAH is attached to the atrial cuffs and great vessels. Pneumatic drivelines are tunneled outside the body.

d. The SynCardia TAH is available in a 50- and 70-mL ventricle to allow for implantation in different body sizes.

e. The SynCardia TAH also has a smaller, portable version that was approved in 2014 and potentially allows patients to be discharged from the hospital while awaiting transplantation.

f. More recently, the Aeson TAH (Carmat) was approved for early feasibility trials by the FDA in 2021.

IV. VALVULAR AND VENTRICULAR SURGERY IN HEART FAILURE

A. Functional mitral regurgitation (MR). Overall management of valvulopathy is reviewed elsewhere and generally unchanged in the presence of comorbid HF. However, certain circumstances may favor surgical intervention on functional MR secondary to systolic HF and LV dilation.

1. Pathophysiology

a. In the setting of systolic HF, changes in LV geometry and dilation cause apical and posterolateral tethering of the papillary muscles. The resulting tethering of one or both mitral leaflets prevents them from meeting at the original coaptation line, classically causing posteriorly directed eccentric or central regurgitation. Other contributing mechanisms may include LV dyssynchrony, papillary muscle ischemia/infarction, and, least commonly, annular dilation of the mitral valve (MV).

b. The functional MR caused by systolic HF results in an increased hemodynamic load on the LV, which, in turn, causes further dilatation and hypertrophy. Uninterrupted, this can progress to a downward spiral of reciprocally worsening MR and HF.

2. Management

a. GDMT optimization remains the mainstay treatment for functional MR. Neurohormonal therapy may improve the severity via favorable reverse remodeling. In selected patients, cardiac resynchronization therapy (CRT) may also provide a

hemodynamic benefit and reduction of regurgitation grade by improving the synchrony of LV and MV motion. Current guidelines give a class 1 recommendation that GDMT be optimized and the severity of functional MR be reassessed prior to considering valvular intervention. This step is vital to ensure that surgical and transcatheter interventions enjoy the best possible outcomes by being targeted to those patients most likely to benefit.

b. Surgical intervention may be reasonable in select patients with severe secondary MR. For patients already undergoing CABG (or other open heart surgery), guidelines give a class 2a recommendation to consider treating functional MR with concurrent surgical repair or chordal-sparing replacement. If not already undergoing open heart surgery, this recommendation is downgraded to class 2b and applied only to those with severe stage D MR, severe symptoms despite optimal GDMT, and mitral anatomy not amenable to transcatheter repair.

c. Transcatheter therapies to address MR are reviewed elsewhere.

B. LV reconstruction

1. Pathophysiology of adverse LV remodeling

a. LV reconstruction surgeries were initially developed as an alternative to cardiac transplantation. The goal was to restore normal LV geometry, reducing wall stress and increasing cardiac efficiency.

b. Unfortunately, most of these procedures have proven ineffective or harmful. Current guidelines mostly recommend against their use. The only two clinically available procedures include the Dor procedure and LV constraint devices (currently under investigation).

2. Endoventricular circular patch plasty (EVCPP)

a. Classically named the “Dor” procedure, EVCPP is the one ventricular reconstruction surgery still recommended in the appropriate setting. Specifically, EVCPP may be considered in patients with anteroapical LV aneurysm after anterior myocardial

infarction, particularly if already undergoing open heart surgery such as CABG.

b. A ventriculotomy is created in the true aneurysm, then closed with a Dacron or pericardial patch. This restores normal long-axis LV chamber geometry.

c. EVCPP is typically done concomitantly with CABG (90%) and additional valvular surgeries, including MV surgery (50%).

d. The STICH trial evaluated surgical LV reconstruction. Despite a reduction in LV volume, there was no difference in symptoms, exercise tolerance, hospitalization, or mortality in patients who had CABG and surgical anterior ventricular restoration procedure (a modified EVCPP) in comparison with those who underwent CABG alone.

e. Ventricular reconstruction does not have a demonstrated significant survival benefit in HF. It has a class IIB guideline indication in carefully selected patients with intractable HF and arrhythmias.

3. LV constraint devices

a. While surgical cardiomyoplasty has been abandoned, the concept of ventricular restraint has led to ongoing experimental work using synthetic materials to physically constrain a dilated LV.

b. The Acorn CorCap, Paracor HeartNet, Myocor Myosplint, and CardioClasp are examples of LV constraint devices that were attempted and ultimately abandoned.

c. In 2019, the FDA granted breakthrough device designation to the Bioventrix Revivent TC System, a transcatheter ventricular constraint device currently under investigation.

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CHAPTER 13

Cardiac Transplantation

Jeremy A. Brooksbank and Randall C. Starling

I. INTRODUCTION. In 1967, Christian Barnard performed the historic, first human-human heart transplantation in Cape Town, South Africa. Since then, cardiac transplantation has evolved into a well-established therapeutic intervention for a select group of patients living with end-stage heart disease. It offers these patients a chance for improved survival and quality of life. However, cardiac transplantation should not be perceived as a curative procedure. Following transplant, a new set of long-term complications may arise primarily owing to the limitations of transplantation, underlying patient comorbidities, and secondary effects of chronic immunosuppression.

Approximately 140,000 adult heart transplants have been reported at 390 centers according to the International Society for Heart and Lung Transplantation (ISHLT) registry. The majority of these transplants come from reporting centers within North America (~55%) and Europe (~35%). Within the United States, the number of heart transplants performed each year has been steadily increasing recently. In 2021, the United Network of Organ Sharing (UNOS) reported a record 3,817 total heart transplants in the United States, including 3,304 adult and 513 pediatric patients. Yet, the number of candidates awaiting heart transplant has risen 34% from 2009 to 2020 according to the Scientific Registry of Transplant Recipients (SRTR). Currently, there are ~140 active cardiac transplant centers in the United States.

The increase in cardiac transplantation is multifactorial and has been attributed to an expansion of the donor pool (hepatitis C, donation after circulatory death [DCD], etc) and suitable donors related to drug overdoses and the opioid crisis. Furthermore, there have been numerous regulatory and listing/procurement changes over the past few years. UNOS implemented changes in the allocation of donor hearts in October 2018 to update the prior allocation system (status 1A, 1B, and 2) to **six categories based on diagnosis, severity of illness, and risk factors associated with mortality while on the waitlist**. The urgency status in the heart allocation criteria ranges from tier 1 (requiring venoarterial extracorporeal membrane oxygenation [VA-ECMO] or nondischargeable biventricular assist device [BiVAD] support) to tier 6 (stable outpatients not meeting higher tier criteria). The majority of cardiac transplants go to patients in tiers 1 to 4. Furthermore, in June 2019, the Organ Procurement and Transplantation Network (OPTN) approved changes in the organ allocation system to eliminate donation service areas in favor of a fixed distance of 250 nautical miles from each transplant system in order to improve organ availability and equitable distribution.

Although the long-term ramifications of these changes have yet to be determined, these initiatives were designed to reduce wait times and minimize mortality while on the waitlist. Early data suggest a shift from durable left ventricular assist device (LVAD) support to more temporary support devices, including intra-aortic balloon pumps (IABPs), percutaneous VAD, and ECMO. According to the most recent SRTR report, LVAD at the time of transplant declined from 47.8% to 33.4%, while the proportion of patients on temporary mechanical support with IABP (8%->26%) and ECMO (1.2%->5.4%) at the time of transplant increased. Whereas mechanical circulatory support (MCS) remains on the rise, the role of inotropes as a bridge to transplant (BTT) has declined.

Global and national characteristics of transplant patients have evolved over the past decade, demonstrating a growing nonischemic cardiomyopathy cohort and decreasing proportion of patients listed for coronary artery disease. Transplantation candidates due to other etiologies such as congenital heart disease, retransplant, and valvular disease remain similar. According to the annual SRTR report from 2021, 73.4% of heart transplant recipients were male, with close to half (48%) being between 50 and 64 years of age and living in metropolitan areas (83.9%). There has been an increase in candidates over the age of 65 (11.9% in 2009 vs 15.9% in 2020) and Black candidates (19.5% in 2009 vs 27.3% in 2020) compared to the prior decade. Also, the prevalence of obesity among orthotopic heart transplant (OHT) candidates has increased, with ~42% having a body mass index (BMI) >30 kg/m^2. Blood types O and A remain the most common blood type to receive heart transplantation (39% each).

Despite the growing use of guideline-directed medical therapy, permanent and temporary MCS devices, and increased use of implantable cardioverter-defibrillator/cardiac resynchronization therapy (ICD/CRT), mortality remains high in patients with stage D heart failure. However, survival rates post–cardiac transplantation have improved over the years, with the advancements in medical care, surgical techniques, and immunosuppression. According to the SRTR registry, the 1-year survival after OHT in the United States was 90.6% in the United States in 2019. Outcomes are influenced by multiple factors, including etiology, age, and comorbidities. The risk of death remains highest in the first 6 months post-transplantation predominately secondary to infection and graft failure. Examples of pretransplant multivariable factors associated with the higher risk of mortality in the first post-transplant year include requiring temporary MCS (ECMO, etc) and congenital heart disease. Additional variables that may impact 1-year mortality include history of renal replacement therapy, mechanical ventilation, prior blood transfusion, and infection as well as recipient age, weight, height, donor gender mismatch, pretransplant bilirubin, creatinine, allograft ischemic time, and transplant center volume.

The issue of supply and demand remains problematic and demonstrates why it is imperative for transplant programs to adequately screen and responsibly select potential transplant recipients anticipated to experience long-term survival. Equally important and related to survival is donor selection and pairing an acceptable donor with an appropriate recipient.

II. INDICATIONS FOR CARDIAC TRANSPLANTATION

A. Symptoms progressing despite optimal medical and device therapy for congestive heart failure, as recommended by the American College of Cardiology/American Heart Association guidelines, including, but not limited to, a beta-blocker (specifically metoprolol succinate, carvedilol, and bisoprolol), angiotensin receptor-neprilysin inhibitor/angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ARNI/ACEi/ARB), mineralocorticoid receptor antagonist, and sodium-glucose cotransporter 2 inhibitor (SGLT2i). When indicated, select patients should have received CRT or ICD.

B. Medically reversible causes of decompensated congestive heart failure should be excluded, including thyroid disease, tachycardia-mediated cardiomyopathy, alcohol abuse, obstructive sleep apnea, hypertension, and medical nonadherence.

C. Surgically reversible causes of decompensated congestive heart failure should be excluded, including valvular heart disease, un-revascularized symptomatic coronary artery disease, hypertrophic obstructive cardiomyopathy, and LV aneurysm for which resection or other LV remodeling would improve quality of life and survival.

D. If the previous criteria are met, indications for a cardiac transplant evaluation are as follows:

1. **Progressively worsening or refractory congestive heart failure symptoms**, New York Heart Association class IIIb or IV
2. Cardiogenic shock requiring **continuous intravenous (IV) inotropic therapy** for hemodynamic stabilization
3. Cardiogenic shock requiring **MCS** (ie, either temporary or durable)
4. **Recurrent life-threatening ventricular arrhythmias** despite an ICD, antiarrhythmic medications, and/or when appropriate an attempt at catheter-based ablation
5. **Refractory angina** without therapeutic options
6. **Adult congenital heart disease** without pulmonary hypertension (PH) and advanced heart failure

III. COMPONENTS OF A CARDIAC TRANSPLANT EVALUATION AND CONTRAINDICATIONS

(**Figure 13.1**). The purpose of a cardiac transplant evaluation is to quantify the severity of a patient's cardiac impairment, evaluate for additional potentially beneficial therapies, and exclude patients with high-risk medical and psychosocial impairments for which risks outweigh benefits of transplantation. Recommended investigations prior to a transplantation are summarized in **Table 13.1**, and exclusion criteria for cardiac transplantation are summarized in **Table 13.2**.

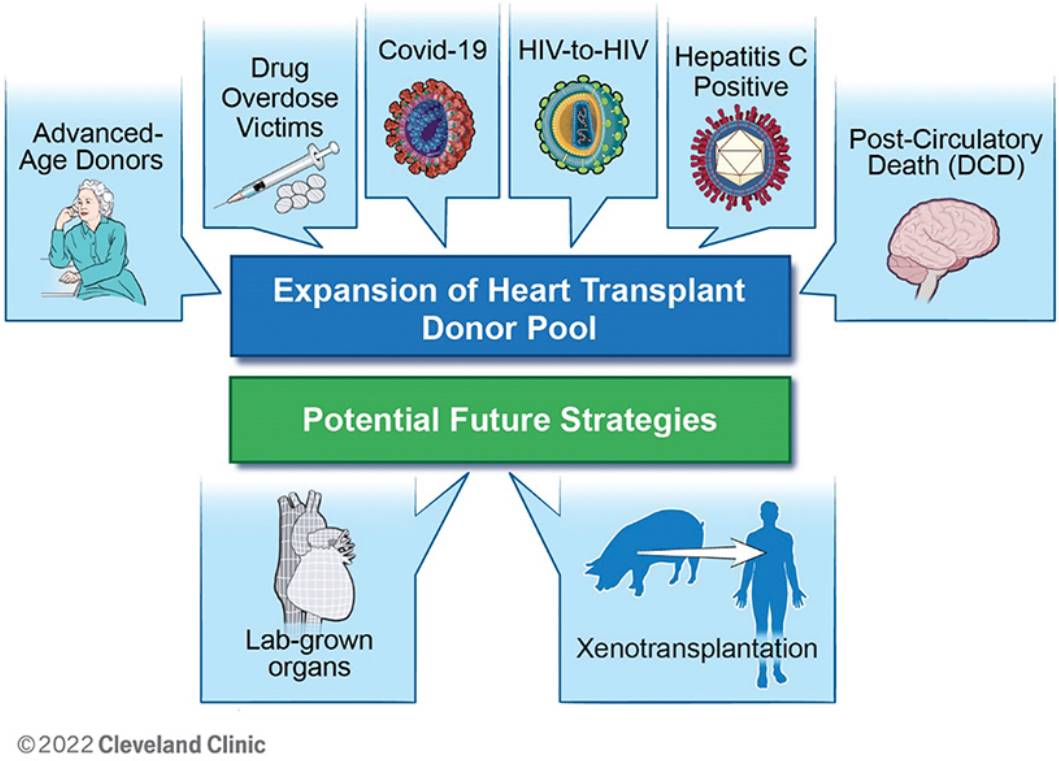

FIGURE 13.1 Evaluation for cardiac transplantation. (Reprinted with permission, Cleveland Clinic Foundation, Copyright © 2024. All Rights Reserved.)

TABLE 13.1 Recommended Evaluation Prior to Transplantation

Complete history and physical examination
Laboratory investigations
• Complete blood count with differential and complete metabolic panel • Thyroid function studies (thyroid-stimulating hormone) • Liver function panel, creatinine, glomerular filtration rate • Lipid profile, hemoglobin A1c, and urinalysis
Immunologic data
• Blood type and antibody screen • Human leukocyte antigen typing • Panel reactive antibodies' screen
Serology for infectious diseases
• Hepatitis (HBsAg, HBsAb, HBcAb, and HepCAb) • Herpes group virus • Human immunodeficiency virus • Cytomegalovirus IgG antibody

Complete history and physical examination
• Toxoplasmosis
• Varicella and rubella titers
• Epstein-Barr virus IgG and IgM antibodies
• Syphilis studies
• COVID-19
Cardiovascular investigations
• Electrocardiogram, chest x-ray, and echocardiogram
• Exercise test with oxygen consumption
• Right and left heart catheterization
• Endomyocardial biopsy (if indicated)
Vascular assessment
• Carotid Doppler
• Peripheral vascular assessment (ankle-brachial index and/or duplex ultrasound)
• Abdominal ultrasound
• Ophthalmology examination (if indicated, eg, to rule out diabetic retinopathy)
Cancer screening
• Prostate-specific antigen (in men, if indicated)
• Papanicolaou smear and mammography (in women, if indicated)
• Colonoscopy (if indicated)
• Lung cancer screening (if indicated)
Psychosocial evaluation
• Support system
• Substance abuse history (alcohol, tobacco, and drug use)
• Psychiatric history
Baseline investigations
• Dental examination
• Bone density scan
• Pulmonary function tests
• Frailty assessment
• Neurocognitive testing (if indicated)

HBsAg, hepatitis B surface antigen; HBsAb, hepatitis B surface antibody; HBcAb, hepatitis B core antibody; HepCAb, hepatitis C core antibody; IgG, immunoglobulin G; IgM, immunoglobulin M.

TABLE 13.2 Contraindications for Cardiac Transplantation

Irreversible pulmonary parenchymal disease
Renal dysfunction with Cr >2.0-2.5 or CrCl <30-50 mL/min (unless for combined heart-kidney transplant)
Irreversible hepatic dysfunction

Severe peripheral and cerebrovascular disease
Insulin-dependent diabetes with suboptimal glycemic control and end-organ damage
Acute pulmonary embolism
Irreversible pulmonary hypertension (PVR >3 Wood Units after vasodilators)
Psychosocial instability or substance abuse
History of active malignancy or recent with probability of recurrence
Active infection
Severe osteoporosis

Cr, creatinine; CrCl, creatinine clearance; PVR, pulmonary vascular resistance. Reprinted with permission, Cleveland Clinic Foundation, Copyright © 2024. All Rights Reserved.

A. Blood work. A standard blood workup includes a complete blood cell count with differential, complete metabolic panel, thyroid function tests, and blood type. Human leukocyte antigen (HLA) typing, panel reactive antibody (PRA), and antibody screening are also collected. A serologic assessment should also be performed to determine the recipient's exposure to cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus, toxoplasmosis, syphilis, hepatitis B and C (HCV) viruses, tuberculosis, and human immunodeficiency virus (HIV). In addition, immunization status should be verified to vaccine-treatable infections, such as hepatitis A, hepatitis B, *Streptococcus* pneumonia, tetanus, mumps, measles, rubella, varicella, and COVID-19.

1. Patients who are **anemic** should have a thorough evaluation, including iron studies and colonoscopy. When indicated, an esophagogastroduodenoscopy and/or a hematologic evaluation, including a bone marrow biopsy, should be considered. Some patients may benefit from erythropoietin treatment to increase red blood cell counts without the need for transfusions that may expose the patient to further antigens.
2. Patients found to have an **elevated serum creatinine** level should undergo further evaluation to determine its relationship with low renal perfusion. This should include an assessment of cardiac hemodynamics and a renal ultrasound to assess renal parenchymal size and the presence of two kidneys without evidence of obstruction. A normal urinalysis result suggests the absence of intrinsic renal parenchymal disease. Consultation with a transplant nephrologist and consideration of combined heart and renal transplantation should be considered with estimated glomerular filtration rate (eGFR) <30.
3. Patients found to have **elevated hepatic enzymes** should undergo further evaluation with hepatic ultrasound, right heart catheterization, serologic evaluation, and, possibly, liver biopsy to further delineate potential etiologies of hepatic insult. Hepatology consultation is indicated when there is suspicion for underlying cirrhosis or recurrent ascites requiring paracentesis.
4. The patient's serum should be **screened for antibodies** against HLA, both class I (all nucleated cells) and class II (antigen-presenting cells: B cells, dendritic cells, and macrophages). These antibodies are collectively referred to as panel reactive antibodies (PRAs) and are often elevated in multiparous women and patients with multiple blood transfusions (often perioperatively in the past).

   Elevated PRA levels may increase the likelihood of a positive crossmatch, making it more difficult to find an ideal allograft match. In addition, sensitized patients have associated increased post-transplant morbidity: rejection and cardiac allograft vasculopathy (CAV). Although controversial, some centers have highly sensitized patients (PRA >80%) undergo desensitization protocols as an attempt to facilitate a negative crossmatch. The following agents have been tried: IV immunoglobulin, plasmapheresis, rituximab, bortezomib, and combination therapies.

   Traditionally, each potential recipient undergoes **a thorough HLA tissue typing analysis**, via a complement-dependent cytotoxicity assay or molecular typing for assistance in finding an ideal donor. Once a possible donor is identified, random donor lymphocytes are incubated with recipient sera and evaluated by flow cytometry to determine the presence of potential donor-specific antibodies, also known as the crossmatch. Currently, most programs use solid-phase assay, such as flow cytometry, to assess for preformed antibodies. This allows for the detection of weaker interactions and provides a more efficient and sensitive screening process. Rather than always requiring a prospective crossmatch to accept a donor

organ, most centers now perform "virtual crossmatches" based upon HLA data with good clinical outcomes that are predictive of final crossmatches. In the past, the distance and time to perform a crossmatch limited organ allocation.

B. Imaging

1. All patients should undergo anatomic assessment for coronary artery disease with **coronary angiography** or computed tomography angiography (CTA). In addition, a functional assessment for ischemia and myocardial viability may be performed. If ischemia or viability can be demonstrated, consideration should be given to percutaneous or surgical revascularization.
2. Vascular studies may be obtained to exclude patients with significant peripheral arterial disease or cerebrovascular disease.
3. An abdominal aortic ultrasound, chest CT, and/or CTA with runoff are obtained. Proximity of the aorta, bypass grafts, and the right ventricle (RV) is important for the surgeon when planning entry or reentry of the chest.

C. Functional assessment

1. **Metabolic stress testing** is performed to assess the severity of cardiac functional impairment. Patients with compensated congestive heart failure and a peak oxygen consumption **(V_{O_2})** of <14 mL/kg/min in patients intolerant to beta-blocker or <12 mL/kg/min in the presence of a beta-blocker, or <50% predicted are considered sufficiently impaired for transplantation. Adequate patient effort during the stress test can be assessed by the respiratory exchange ratio (RER). An RER >1.05 denotes adequate aerobic achievement; RER <1.05 denotes a suboptimal test. The minute ventilation-carbon dioxide production relationship **(V_E/V_{CO_2} slope)** serves as an additional marker, with >35 portending a worse prognosis.
2. A **right heart catheterization** is performed to assess cardiac hemodynamics and to optimize a patient's medical therapy prior to listing for transplant and routinely at intervals determined by the transplant team once listed for continued assessment. An attempt should be made to medically decrease the PH with inotropic agents, nitrates, or nitroprusside. Sometimes, a temporary support (balloon pump or percutaneous temporary LVAD) or LVAD is required to sufficiently decompress the LV to reverse the PH. Endomyocardial biopsy (EMB) is rarely performed, except when an infiltrative cardiomyopathy or giant cell myocarditis is suspected. **Irreversible, severe PH, defined as a pulmonary vascular resistance (PVR) >3 Wood Units may be a contraindication to cardiac transplantation.** In this setting, the donor RV will likely quickly fail after implantation because it is not accustomed to high pulmonary pressures. Similarly, the pulmonary artery pulsatility index (PAPi), which is calculated as the PA pulse pressure ($PA_s - PA_d$) divided by the right atrial pressure, is used to assess for RV function. PAPi value >2 is considered normal and value <1.0 often indicates significant RV dysfunction and may be a marker for worse outcomes post-OHT.
3. Pulmonary function tests are performed to exclude patients with significant chronic obstructive or restrictive pulmonary disease. The goal is to avoid prolonged mechanical ventilation and trach after heart transplantation.

D. Comorbidities and implications of heart transplant listing. Advanced age, cancer, and obesity are three common comorbidities with institution-specific thresholds for listing a patient for heart transplantation.

1. Age criteria for eligibility were initially quite rigorous; however, it has become apparent that **chronologic and physiologic age are often discrepant.** Most centers do not have a fixed upper age limit, but generally, patients >70 years of age are very carefully screened to rule out comorbidities. ISHLT recommends considering patients for cardiac transplantation if they are ≤70 years of age. Patients >70 years of age may be considered for cardiac transplantation at the discretion of the transplant program and should theoretically be in excellent health, except for heart disease. An alternate type of program has been proposed for these patients, whereby older donor hearts would be utilized in this population. The advantage is that donor hearts that would be discarded due to age might be acceptable in an individual with advanced age. The prevalence of coronary allograft vasculopathy increases with age of the donor over time; hence, the reluctance to accept an older donor in a recipient under 50 years of age.
2. Active **malignancy** other than skin cancer or other systemic illness with a life expectancy <2 years despite heart transplant is an absolute contraindication because of limited survival rates. Chronic

immunosuppression is associated with a higher than average incidence of malignancy and with increased recurrence of prior malignancy. Patients with cancers who have been in remission for ≥5 years and patients with low-grade or curable malignancies such as some skin cancers, resected renal cell carcinoma with clear margins, some thyroid cancers, or low-grade prostate cancers are generally accepted for transplant evaluation. Preexisting malignancies are heterogeneous in nature, and some are readily treatable with chemotherapy. Thus, an individualized approach to these patients is required, and consultation with an oncologist regarding prognosis is often very helpful. Traditionally, centers have been cautious when considering patients who are **obese** for transplantation. Most currently available data indicate that patients with a pretransplant BMI >35 kg/m^2 have poor outcomes following cardiac transplantation. Current ISHLT recommendations are that patients achieve a BMI <35 kg/m^2 prior to being listed for cardiac transplantation. This cutoff will vary from center to center, but generally, a BMI >35 kg/m^2 will preclude listing for cardiac transplantation.

3. Clinically severe symptomatic cerebrovascular disease and cognitive deficits can lead to poorer outcomes post-OHT. Dedicated neurocognitive testing may be pursued in the correct clinical setting for an objective assessment.
4. Active substance (drug or alcohol) abuse is considered a contraindication for heart transplantation. Patients with heart failure at high risk for decompensation should be advised to abstain from the use of these substances and may benefit from group support and counseling. The legalization of marijuana in some states has led to increased controversy regarding listing status in this population. There are concerns related to drug metabolism in individuals with active use of recreational or medical marijuana.
5. **Assessment of frailty** should be considered during the evaluation process, including >10 lb. of unintentional weight loss over a 1-year period, muscle loss, fatigue, slow gait speed, and change in activity level. Patients with pronounced sarcopenia or diminished hand-grip strength are markers for frailty and may predict worse outcomes in patients undergoing evaluation for advanced therapies, such as VAD or OHT.

E. Consultations

1. A psychosocial assessment is a crucial component of every cardiac transplant evaluation. Accepted psychosocial contraindications for cardiac transplantations include active smoking, active substance abuse (including alcohol and illicit substances), continued medication nonadherence, and significant untreated psychological or psychiatric diagnoses. Relative psychosocial contraindications to cardiac transplantation include post-traumatic stress disorder and lack of an adequate support structure. The Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) score serves as a useful means to standardize psychosocial assessment and identify patients at elevated risk for poor outcomes with transplantation. Formal neuropsychiatric testing may be pursued in select patients with cognitive impairment.
2. For patients with diabetes, an ophthalmology consultation is obtained for an assessment of retinal end-organ damage related to diabetes. Prior to listing for transplant, patients with suboptimal glycemic control (HbA_{1c} >7.5%) without end-organ dysfunction should work with an endocrinologist and nutritionist to improve glucose control and ensure medication adherence.

IV. ALLOCATION CRITERIA. After a patient is accepted as a potential cardiac transplant recipient by a UNOS-certified transplant program, the patient's name is entered on a national list compiled by UNOS. A new allocation system was implemented in October 2018 as an update to the prior system. The current system categorizes transplant candidates into six categories (status 1-6) designated by diagnosis, severity of illness, and risk factors associated with increased waitlist mortality (**Table 13.3**).

TABLE 13.3 UNOS Adult Heart Transplantation Allocation Criteria

Status	Criteria
1	VA-ECMO (up to 7 d) Nondischargeable BiVAD MCS with life-threatening ventricular arrhythmia
2	IABP (up to 14 d) Acute percutaneous endovascular circulatory support (eg, Impella; up to 14 d) MCS with device malfunction/failure

Status	Criteria
	TAH Dischargeable BiVAD or RVAD VT/VF
3	LVAD (up to 30 d) Multiple inotropes or single high-dose inotrope with continuous hemodynamic monitoring LVAD-related complications such as thromboembolism, infection
4	Stable LVAD (after 30 d) Congenital heart disease with 1 or 2 ventricle repairs, unrepaired/incompletely repaired abnormalities; often with cyanosis Ischemic heart disease with intractable angina Inotrope dependent without invasive hemodynamic monitoring Hypertrophic cardiomyopathy Restrictive cardiomyopathy (amyloidosis, etc) Retransplant
5	Approved combined organ transplantation (heart-lung, heart-kidney, or heart-liver)
6	All remaining active candidates not meeting above criteria
7	Inactive on list because of improved clinical status or short-term contraindications to cardiac transplantation (eg, active infection)

BiVAD, biventricular assist device; VA-ECMO, venoarterial extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

The goals of the new allocation system are to equitably decrease waiting times and waitlist mortality without impacting clinical outcomes. Since the updated allocation system has been in place, a higher proportion of patients are receiving temporary MCS and durable BTT LVAD patients are receiving cardiac transplantation with longer waiting times. Longitudinal studies are underway to evaluate the effects of the new allocation system and ensure safety and equivalent (if not improved) outcomes, particularly in the setting of higher short-term risks with temporary MCS devices.

V. WORKUP OF A POTENTIAL CARDIAC DONOR. Potential cardiac donors are patients who are declared brain dead but otherwise have viable internal organs. Generally, these are patients with lethal head injuries or catastrophic central nervous system events (ie, intracranial hemorrhage, stroke, or cerebral anoxia).

A. Potential donor screening. After a patient is declared brain dead, local organ procurement under the auspices of UNOS performs the initial evaluation of a potential donor. This evaluation includes a thorough patient and family history, focusing specifically on cardiac risk factors and potentially transmittable diseases (ie, malignancy and infection). Preliminary blood tests are done, including comprehensive metabolic panel, complete blood count, cardiac enzymes, hepatitis B and C serology, HIV, toxoplasmosis, CMV, and EBV. In addition, ABO blood group typing and HLA typing are performed. An echocardiogram is routinely obtained to assess cardiac function and rule out congenital anomalies, valvular disease, and other anomalies. At the request of the potential recipient's transplant center, a coronary angiogram may be acquired if the donor has significant cardiac risk factors and elevated cardiac enzymes or is beyond 40 years of age. For example, a potential donor who is a 40-year-old male with active tobacco use would usually result in a request for coronary angiography.

Potential recipients undergo both a virtual and a prospective crossmatch, in which the recipient's serum is incubated with donor lymphocytes to identify potential donor-recipient HLA incompatibility. If the HLA tissue typing of the potential donor does not include the antigens against which the recipient is sensitized, it is assumed that the actual crossmatch will be negative (ie, a "virtual" negative crossmatch). If a prospective crossmatch is not performed, a retrospective crossmatch (typically by flow cytometry) is performed using donor lymphocytes obtained from donor aortic lymph nodes retrieved at the time of harvest. Generally, most transplant centers in the United States are comfortable with a "virtual" crossmatch to accept a donor but will also subsequently perform a final crossmatch.

B. Donor-recipient matching. UNOS maintains a computerized list of all patients listed and waiting for cardiac transplantation. A list of potential recipients with compatible blood types is generated for each potential donor organ and is made available to transplant centers. Allocation guidelines can be found within the OPTN policy manual; see the UNOS website for current guidelines.

Transplant physicians of the potential recipient may also reject a potential organ because of a positive prospective crossmatch, donor-recipient size mismatch, or a prolonged projected ischemic time (usually related to long-distance travel). Matching donor and recipient size is important, because an oversized donor organ may not allow closure of the chest without compression of the organ and an undersized donor organ may not be able to pump a sufficient quantity of blood to meet the recipient's needs. Recommendations suggest a donor weight should ideally be within approximately 30% of a potential recipient (20% if female donor to male recipient) to avoid size mismatch.

VI. SURGICAL ISSUES RELATED TO CARDIAC TRANSPLANTATION. Most surgical issues related to cardiac transplantation are beyond the scope of this chapter and are mainly of interest to the cardiac surgeon. The main surgical issue of interest to the transplant cardiologist is related to the anastomosis of the right atrium. The surgeon may suture the donor atrium to the recipient atrium (ie, **biatrial anastomosis**) or suture the donor superior vena cava to the recipient superior vena cava and the donor inferior vena cava to the recipient inferior vena cava (ie, **bicaval anastomosis**). The bicaval anastomosis approach is more time-consuming but reduces the incidence of atrial arrhythmias (including sinus node dysfunction), reduces the incidence of post-transplant tricuspid regurgitation, and improves right atrial hemodynamics. Currently, most centers employ the bicaval anastomosis approach, although no survival advantage has been conclusively demonstrated with this approach.

VII. EXPANSION OF THE DONOR POOL (**Figure 13.2**). Over the past decade, numerous strategies have been employed to expand the donor pool for cardiac transplantation. Innovations in the management of acquired infectious diseases such as HIV and hepatitis C and increasing definitions of suitable heart donors and organ transportation improvements are expanding the donor pool to improve outcomes and further reduce waiting times and waitlist mortality. The COVID-19 pandemic further complicated the donor pool; however, many centers have now begun utilizing donor hearts from patients with COVID-19 as well.

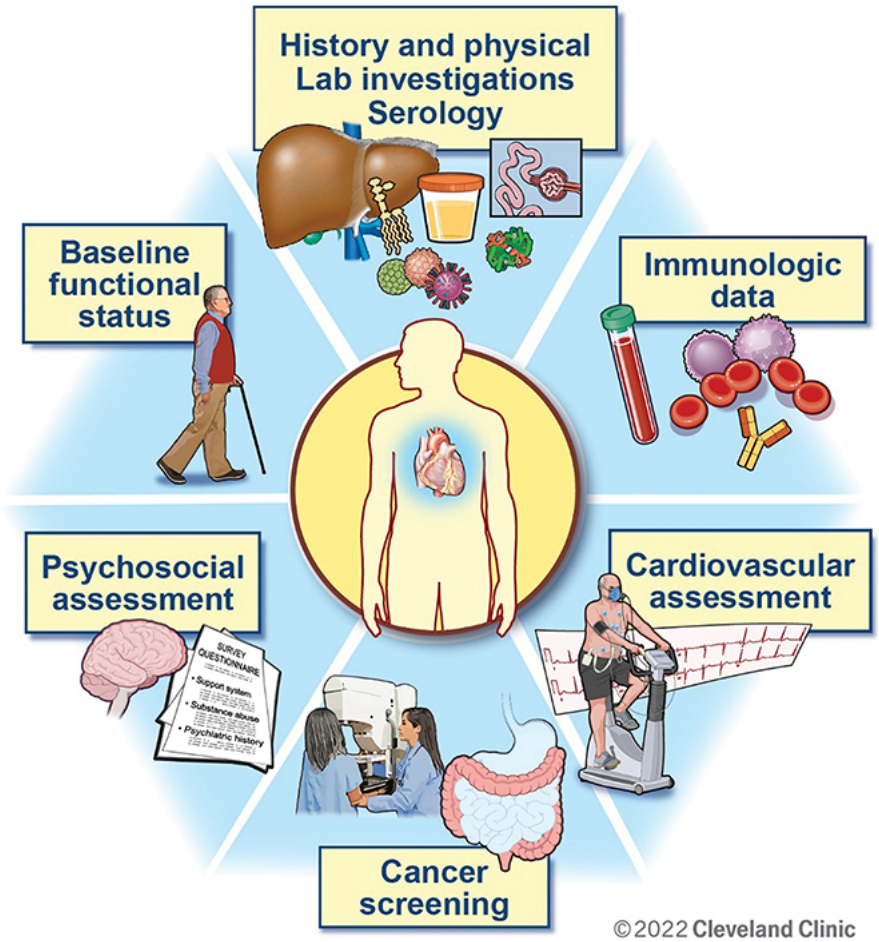

FIGURE 13.2 Current and potential future mechanisms for expansion of the heart transplant donor pool. DCD, donation after circulatory death. (Reprinted with permission, Cleveland Clinic Foundation, Copyright © 2024. All Rights Reserved.)

A. Hepatitis C. With the development of effective antiviral regimens, hepatitis C has essentially become a curable disorder. Patients at a growing number of institutions are receiving organs from HCV-positive donors. These patients are then able to be treated if seroconversion occurs post-transplant. The percentage of U.S. transplant centers performing heart transplants using HCV-positive donors has increased from 8.5% in 2016 to 29.4% in 2018. Since then, the number of transplant centers utilizing HCV-positive donors has continued to rise.

The advent of HCV-positive heart transplantation coincides with the opioid epidemic and increases in **overdose-related deaths**. Historically, these patients were often excluded from consideration for organ donation due to concerns for concurrent viral infections, which may pose a risk to the transplant recipient. However, registry data demonstrate that outcomes with overdose-death donors are equivalent to non–overdose-related donors.

B. HIV. HIV is often considered a contraindication for cardiac transplantation. However, 10-year survival with HIV seroconversion far exceeds 90% with new antiretroviral regimens. With adequate therapy and follow-up, many patients with HIV can now anticipate a normal lifespan. As HIV becomes more of a chronic disorder, there is renewed interest in HIV-positive to HIV-positive heart transplantation. The HIV Organ Policy Equity (HOPE) Act, signed into law in November 2013, initially authorized kidney and liver transplantations between donor-recipients with HIV infection. This was later expanded to include heart transplantation in November 2020. The first successful HIV-positive to HIV-positive heart transplantation occurred in July 2022.

C. DCD. As compared to traditional heart donation from brain-dead patients, DCD cardiac transplantation has garnered interest to help expand the donation pool. DCD transplantation involves donors with devastating brain injury on life support who do not meet the legal criteria for brain death. These patients have cardiac arrest and subsequent organ harvest after withdrawal of life support.

This strategy has been used successfully in the United Kingdom and Australia over the past decade and is experiencing expansion at centers in the United States. If successful and scalable, DCD cardiac transplantation may increase the rate of heart transplantation in the United States by up to 30%. Furthermore, innovations in ex vivo heart perfusion are serving to reduce ischemic time and improve transportability of harvested organs for transplantation.

D. Xenotransplantation. Xenotransplantation involves the transplantation of tissue or organs from one species to another. Cross-species transplantation is an attractive goal as this would sharply increase organ availability, particularly to high-risk patients. The first xeno-heart transplantation was performed by Dr Hardy in 1964, but the patient died within 2 hours after transplant. Recent advancements in genetic engineering, epigenetic alterations, and cloning technology are reinvigorating interest in xenotransplantation as a complementary method to allotransplant. In January 2022, Dr Bartley Griffith performed the first genetically modified porcine-to-human cardiac xenotransplantation in a 57-year-old man with nonischemic cardiomyopathy and biventricular heart failure who was turned down for allotransplantation. The patient lived 60 days following xenotransplantation but eventually succumbed to infection and irreversible atypical antibody-medicated rejection. It remains unclear whether xenotransplantation will ever become a feasible complement to human-to-human heart transplantation.

III. POSTOPERATIVE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

A. Surgical complications. The most common surgical complication is the development of a pericardial effusion with or without tamponade. Pericardial effusions are very common because of the large potential space left behind as the dilated and dysfunctional recipient LV is replaced with a more appropriately sized donor LV. Rarely, pericardial tamponade develops, necessitating percutaneous or surgical evacuation of the pericardium. Other surgical complications are much less common but can be catastrophic and usually result from a problem either at a site of anastomosis or at a site of cannulation (**Figure 13.3**).

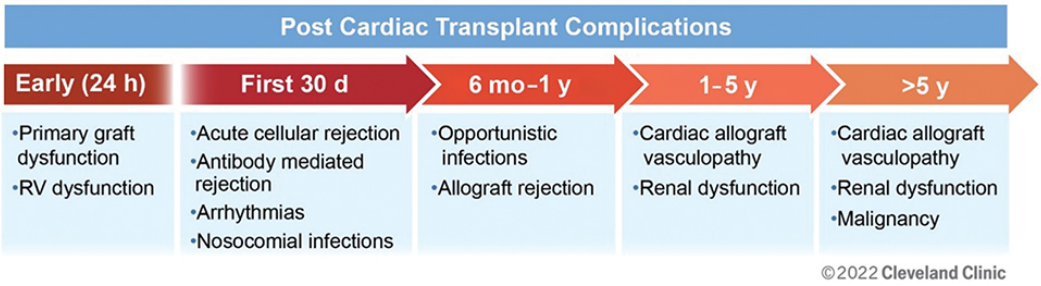

FIGURE 13.3 Complications following cardiac transplantation. RV, right ventricle. (Copyright © 2022 Cleveland Clinic.)

B. Early graft dysfunction

1. **LV systolic dysfunction.** It is common for transplant recipients to require inotropic support as they come off cardiopulmonary bypass. The most commonly used inotropic agents in this setting are dobutamine, milrinone, and isoproterenol, used either alone or in combination. It is also common for transplant recipients to require vasoactive medications such as epinephrine, norepinephrine, vasopressin, and dopamine in the early postoperative period. Most patients can be weaned off inotropic therapy and peripheral vasoconstrictors within the first few days after OHT.
2. **LV diastolic dysfunction** is very common soon after cardiac transplantation. It usually results from reversible ischemia or reperfusion injury to the donor organ and normally resolves over a period of days to weeks. If the ischemia or reperfusion injury is sufficiently severe to induce significant contraction band necrosis or myocardial fibrosis, as seen on EMB, chronic diastolic dysfunction can ensue. Another

potential cause of diastolic dysfunction is donor-recipient mismatch, particularly with a small donor organ or acute rejection.

3. **RV dysfunction** is much more common than LV dysfunction after cardiac transplantation, especially in patients with preexisting PH. The RV is subjected to similar ischemic or reperfusion injury risks as the LV. RV dysfunction is usually accompanied by RV dilation and the failure of coaptation of the tricuspid valve leaflets, leading to severe tricuspid regurgitation. The treatment for perioperative RV dysfunction is usually IV milrinone, dobutamine, or pressors with or without atrioventricular (AV)-synchronized temporary pacing for those who are persistently hypotensive. In patients with RV dysfunction confounded by persistent, predominantly precapillary PH, dedicated PH medications such as prostanoids or inhaled nitric oxide may be considered.

C. Cardiac arrhythmias. Most transplant recipients require perioperative temporary AV pacing. Sinus node dysfunction is very common, probably because of a combination of surgical trauma, ischemia, reperfusion injury, and denervation. The incidence of sinus node dysfunction is believed to be reduced with bicaval anastomosis. With time, the sinus node typically recovers and a permanent pacemaker is not necessary. Preoperative use of amiodarone increases the likelihood of bradycardia post-transplantation. Other cardiac arrhythmias are rare in the immediate post-transplant period and may signify rejection. A permanent pacemaker is infrequently needed. For persistent bradycardia requiring pacing, terbutaline or theophylline may be considered for short duration.

D. Renal dysfunction. Preoperatively, many transplant recipients have some degree of impaired renal function. There is a risk of worsening renal function perioperatively. This risk is compounded by the fact that the major immunosuppressive agents (ie, calcineurin inhibitors [CNIs]) are nephrotoxic. Induction therapy should be considered for patients who are at increased risk for perioperative renal dysfunction as a means to delay calcineurin therapy. Interleukin-2 receptor (IL-2R) blocker (ie, basiliximab or Simulect) or, less commonly, thymoglobulin (rabbit—antithymocyte globulin) remains the mainstay for induction therapy.

IX. SYSTEMIC IMMUNOSUPPRESSION. Much of the success in cardiac transplantation today is attributed to advances in immunosuppression. However, balancing the risk of allograft rejection against the inherent risk of immunosuppression (ie, infection, malignancy) remains a challenge. Immunosuppressant protocols during and after cardiac transplantation vary greatly from program to program and even from patient to patient within a specific center. Triple therapy, which constitutes the cornerstone of modern immunosuppressive regimens in cardiac transplantation, includes a CNI (such as cyclosporine or tacrolimus), a cell cycle–modulating or antiproliferative agent (such as mycophenolate mofetil [MMF] or azathioprine), and a corticosteroid. Controversy remains about the advisability of using induction therapy in the nonsensitized recipient without renal failure, with institution-specific variation in practice patterns (**Table 13.4**).

TABLE 13.4 Common Immunosuppressants

	Steroids	Calcineurin Inhibitors	MMF	AZA	TOR Inhibitors	Polyclonal Antilymphocyte Antibodies
Drugs	Prednisone (P) (po)	Neoral (N)	–	–	Rapamycin (R)	Atgam (A)
	Solu-Medrol (S) (IV)	Tacrolimus (T)	–	–	Everolimus (E)	Thymoglobulin (T
Indication	Chronic IM, acute rejection	Chronic IM	Chronic IM, skin cancer with AZA	Chronic IM	Chronic IM, vasculopathy	Induction, acute rejection
Dosing						
Initial	IV 125-150 mg q8h	N: 100 mg bid T: 2 mg bid	1.5 g bid	1-2 mg/kg/d	R: 2-5 mg qd E: 1.5-3 mg qd	–
Induction	–C	–	–	–	–	A: 15 mg/kg/d T: 1.5 mg/kg/d × 15 d
Maintenance	Weaned off	Adjusted to levels	1.5 g bid	1-2 mg/kg/d	Adjusted to levels	–

	Steroids	Calcineurin Inhibitors	MMF	AZA	TOR Inhibitors	Polyclonal Antilymphocyte Antibodies
Acute rejection	P: 100 mg qd × 3 S: 1 g IV qd × 3	Consider change from CsA to tacrolimus	–	–	–	As above
Target levels	–	–	2-4 ng/mL, 12-h trough, WBC >4.0	WBC >3.0	R: 4-12 ng/mL, 18-h trough	CD3 count <20 cells/mL
Common side effects	Diabetes, osteoporosis, weight gain, hypertension, and adrenal insufficiency	Nephrotoxicity, hypertension, tremors, and gingival hyperplasia	Diarrhea, nausea, and myelosuppression	Myelosuppression, skin cancer	Hypertriglyceridemia and thrombocytopenia	Thrombocytopen fevers, chills, PTLD, and CM superinfection
Common drug interactions	–	Erythromycin, diltiazem, verapamil, rapamycin, anticonvulsants, rifampin, and statins	Cholestyramine and probenecid	Allopurinol	Cyclosporine	–

AZA, azathioprine; CMV, cytomegalovirus; CsA, cyclosporine A; IL, interleukin; IM, immunosuppression; MMF, mycophenolate mofetil; PTLD, post-transplant lymphoproliferative disorder; TOR, target of rapamycin; WBC, white blood cell count.

A. Steroids. The mechanism by which steroids serve as immunosuppressants is complex and not completely understood. Steroids bind to nuclear receptors, thereby preventing gene expression of various cytokines important for B- and T-cell activation and proliferation, the most important of which is IL-2. Steroids also have important anti-inflammatory properties and suppress macrophage activity. Important side effects of steroids include **diabetes**, hypertension, weight gain, **osteoporosis**, and avascular necrosis of the femoral head.

Steroid-dosing protocols also vary from one institution to another. A dose of 500 to 1,000 mg of IV methylprednisolone is usually given to the patient intra-op and then 125 to 150 mg is usually repeated every 8 hours for a total of three additional doses. Some centers then start a dose of 1 mg/kg/d prednisone and wean by 5 mg daily, whereas others start 20 mg oral daily or the equivalent of 16 mg IV methylprednisolone until the patient can tolerate an oral regimen. The dose of steroid is typically slowly tapered, provided the patient remains free of rejection. The trend in clinical practice is to wean most patients completely off steroids by the end of the first year, if not sooner. Some centers continue to advocate the indefinite use of low-dose prednisone (2.5-5 mg daily). If a decision is made to withdraw steroids completely, it should be done approximately 1 month before the next scheduled biopsy to ensure continued lack of rejection. If a patient has acute rejection associated without hemodynamic compromise, they may be admitted for 1 g of IV methylprednisolone daily for 3 days and may be given cytolytic therapy, plasmapheresis, or both if hemodynamic compromise and/or antibody-mediated rejection (AMR). If no hemodynamic compromise is associated with the episode of rejection, a daily dose of 100 mg oral prednisone for 3 days, followed by repeat biopsy at most 2 weeks later to ensure resolution—again this is center specific and highly variable.

B. CNIs. Calcineurin is a phosphatase enzyme that triggers transcription of new messenger RNA after activation of the T-cell receptor by an appropriate antigen, leading to increased gene expression of IL-2 and other important cytokines. Calcineurin antagonists inhibit this phosphatase activity, thereby preventing the synthesis of these cytokines, which prevent B- and T-cell proliferation.

1. **Tacrolimus** (Prograf), previously known as FK506, serves as the predominant CNI in many transplant centers. Tacrolimus-based regimens have demonstrated lower rates of acute rejection compared with cyclosporine-based therapy. The major side effects of tacrolimus are **nephrotoxicity and neurotoxicity** (most commonly tremor). Tacrolimus may be administered orally, sublingual, or IV. Tacrolimus when given sublingually using an oral-to-sublingual dose ratio of 1:1 with dose adjustment based on serum drug levels (**Table 13.5**). Usually, 12-hour trough target levels early after transplant are 10 to 15 ng/mL with gradual reduction in the target levels over the initial 12 months after transplant.

TABLE 13.5 Target Serum Cyclosporine A Levels

Time (months)	Target Level (12-h Trough) (ng/mL)
0-3	250-350
3-12	200-250
>12	150-175

2. **Cyclosporine** (Neoral, Gengraf, and Sandimmune) is a calcineurin antagonist with a highly variable pattern of bioavailability, depending on the oral formulation taken. Bioavailability of the original soft gelatin capsule (Sandimmune) was low and depended on emulsification by bile salts. The microemulsion formulation (Neoral) does not depend on bile salts for emulsification and has a more consistent bioavailability. Nevertheless, there remain tremendous interpatient differences in bioavailability, and dosing of Neoral is primarily based on serum drug trough levels. Because of the narrow therapeutic range of cyclosporine, drug trough levels are monitored to prevent toxicity. **Nephrotoxicity** is the most important side effect of cyclosporine therapy and is related to renal afferent arteriolar vasoconstriction and the resultant reduced renal perfusion. Other side effects include systemic hypertension, gingival hyperplasia, and tremors. Calcium channel blockers (CCBs), particularly diltiazem, reduce hepatic metabolism of cyclosporine, thereby increasing serum drug levels. This drug interaction is frequently used clinically to reduce the oral dose of cyclosporine required to achieve a given serum drug concentration, thereby minimizing the cost of immunosuppression.

   Postoperatively, once the patient is hemodynamically stable with good urine output, cyclosporine is initiated via continuous infusion at 1 mg/h. When the patient is able to take oral medicines, Neoral is begun at a dose of 100 mg twice daily, with adjustments in the dose based on serum trough levels (**Table 13.6**). The dose of Neoral is gradually reduced over a period of 1 year if the patient has a clean biopsy record. Cyclosporine is used infrequently, and tacrolimus is preferred by most heart transplant programs.

TABLE 13.6 Target Serum Tacrolimus (FK506 or Prograf) Levels

Time	Target Level (12-h Trough) (ng/mL)
0-30 d	12-20
1-6 mo	8-15
6-18 mo	5-15
>18 mo	5-10

C. MMF (CellCept). MMF inhibits DNA synthesis by inhibiting de novo purine synthesis. Because human lymphocytes depend on the de novo synthesis of purines for DNA replication, MMF has the unique ability to inhibit B- and T-lymphocyte proliferation without affecting DNA synthesis in other cell lines, which can obtain purines through the parallel and unaffected purine salvage pathway. MMF has become the preferred immunosuppressant to azathioprine at most transplant centers because of a reduced mortality rate at 1 year (6.2% vs 11.4%; $P = .03$). The main disadvantage of MMF over azathioprine is the potential **increased risk of opportunistic viral infections.** Toxicities of MMF include **gastrointestinal symptoms** (nausea, vomiting, and diarrhea) and **myelosuppression**. Some patients on MMF develop clinically significant leukopenia, necessitating dose reduction or discontinuation of the drug. Most symptoms will resolve with the reduction of dose.

MMF is given IV or orally. Because of the high bioavailability (>90%), the initial dose of MMF is 1 g taken twice daily, regardless of the route of administration. The initial dose is given within the first 12 hours after transplantation. Routine monitoring of mycophenolic acid (MPA), the active metabolite of MMF, is not recommended; however, an MPA level <1.5 mg/L is considered subtherapeutic. Serum levels of MPA are higher when MMF is administered with tacrolimus compared with cyclosporine; therefore, it may be advisable to empirically reduce the dosage of MMF when switching from cyclosporine to tacrolimus.

D. Azathioprine (Imuran) is a purine analog that impairs DNA synthesis, thereby preventing B- and T-lymphocyte proliferation in response to antigen stimulation. Azathioprine has largely been replaced by MMF as the antiproliferative agent of choice in modern immunosuppressant regimens. Because there is no drug-

level assay available, azathioprine dosing is usually fixed between 1 and 2 mg/kg/d. The major side effect of azathioprine is **myelosuppression**, and the dose of azathioprine is usually adjusted to maintain a white blood cell count of >3,000/mL. Azathioprine is metabolized by xanthine oxidase, and xanthine oxidase inhibitors, such as allopurinol, can lead to toxic levels of azathioprine and profound, prolonged myelosuppression.

E. Inhibitors of the target of rapamycin (TOR) enzyme: sirolimus (Rapamune) and everolimus (Certican). TOR is activated after IL-2 stimulation of the T-cell IL-2R and is critical for lymphocyte growth and proliferation. In contrast to CNIs, TOR inhibitors do not block cytokine production (eg, IL-2) but rather block the cellular response to these cytokines. TOR inhibitors also inhibit vascular smooth muscle cell growth and proliferation in response to various growth factors. It is hoped that this property of TOR inhibitors will help reduce the rate of progression of CAV. When used in combination with cyclosporine, TOR inhibitors appear to act synergistically with regard to immunosuppression. However, worsening of renal function is common but can be prevented by lowering the CNI dose. The main side effects of this class of compounds are significant **hypertriglyceridemia, thrombocytopenia, and poor wound healing**.

Sirolimus and everolimus are both mTOR inhibitors. They are structurally similar, but everolimus has a much higher bioavailability than sirolimus. The appropriate dosing of these agents is arbitrary, but for sirolimus, it is typically 1 to 5 mg/d, and for everolimus, it is 1.5 to 3 mg/d. Sirolimus appears to lower the incidence of acute cellular rejection (ACR) in humans and may slow the progression of transplant coronary vasculopathy. Preliminary human studies using intravascular coronary ultrasonography (IVUS) have also shown a reduction in neointimal proliferation with both sirolimus and everolimus. One-year post-transplant IVUS data demonstrated significantly lower increase in maximal intimal thickness in patients receiving everolimus compared with MMF. It remains unclear where TOR inhibitors will fit in with current immunosuppressive protocols.

F. Induction therapy and therapy for steroid-resistant acute rejection. The purpose of induction therapy is to deplete T lymphocytes or to prevent lymphocyte proliferation during the most immunoreactive phase, which occurs immediately after transplantation. Induction therapy remains controversial, and practice patterns across centers continue to vary. According to the SRTR data, approximately 50% of centers utilize induction therapy at the time of transplant. A retrospective review of over 17,000 patients from the UNOS registry demonstrated that the use of induction therapy did not impact overall survival. Three indications to use induction therapy are as follows: in patients with renal dysfunction, which would preclude the early introduction of CNIs; in the highly sensitized patient at the time of transplant; and in patients with compromised graft function secondary to rejection.

1. **Polyclonal antilymphocyte antibodies** are produced by injecting animals with human lymphocytes or thymocytes and then collecting the animal's serum. Two commercially available formulations are antithymocyte globulin (Atgam), which is horse based, and thymoglobulin, which is rabbit based. The antibodies produced in this manner are directed against a variety of targets on the surface of B and T cells and induce complement-mediated lymphocytolysis. The recommended doses of Atgam and thymoglobulin are 15 and 1.5 mg/kg/d, respectively; the total dose depends on the course of action: induction versus rejection. Adequate lymphocyte depletion can be ensured, and dose adjustments made by quantifying the CD3 or CD2 counts. Immunity may develop to the animal component of these antibodies, rendering them ineffective if further courses of therapy are necessary. An increased incidence of post-transplant lymphoproliferative disorder (PTLD), lymphoma, and opportunistic viral infections has also been observed. Patients receiving either formulation are often prophylactically treated with ganciclovir or valganciclovir to prevent CMV infection.
2. **IL-2R blockers: basiliximab (Simulect) and daclizumab (Zenapax)**. IL-2R antagonists target the IL-2R-alpha chain (CD25) on activated T lymphocytes and inhibit IL-2–mediated activation of subsequent lymphocytes. Prior daclizumab studies demonstrated a reduced risk of rejection; however, one large, multicenter randomized control trial demonstrated excess risk of death. Subsequently, daclizumab was removed from the market in 2009.Basiliximab is predominately used for induction therapy, and use is center dependent.

X. REJECTION. According to the ISHLT registry, rates of rejection within the first year of transplant continue to decline and were 24% in 2015 compared to 25% in 2010 and 32% in 2004. Females and young patients were at higher risk than males and older patients, respectively. Allograft rejection involves both the cellular and

humoral arms of the adaptive response. An ideal immune monitoring strategy has been described as the one that would be noninvasive, would reliably distinguish between the presence and absence of rejection, and would detect overimmunosuppression. Such an ideal strategy does not exist; however, surrogate markers are available through gene expression profiling (GEP) tests and immune function assays. The immunologic status of a transplant recipient is currently monitored by immunosuppressant drug levels, echocardiographic assessment of allograft function, and EMB. Noninvasive monitoring therapies have been tested in the hope of overcoming these limitations. The GEP test, also known as AlloMap, may serve as an alternative to help rule out significant ACR in the appropriate clinical setting. Information from AlloMap can be combined with AlloSure, which evaluates donor-derived cell-free DNA (dd-cfDNA) and can provide information regarding the likelihood of both ACR and AMR. These noninvasive tests continue to be studied and are becoming more commonly used in clinical practice, particularly in lower risk patients with no prior history of rejection.

A. EMB. The current gold standard of rejection surveillance after cardiac transplantation is EMB. Rejection of the cardiac allograft is usually clinically silent unless it is accompanied by significant hemodynamic compromise (ie, congestive heart failure). As a result, EMBs are routinely performed for rejection surveillance. However, EMB is invasive, inconvenient, expensive, and subject to sampling and interpretation error. To mitigate interobserver variability, the ISHLT revised and simplified the grading criteria for ACR and AMR (**Table 13.7**). Because the likelihood of acute rejection is highest early post-transplant, the frequency of biopsies remains high during this period and then gradually tapers off, depending on the results (**Table 13.8**).

TABLE 13.7 Rejection Grading Scale for Endomyocardial Biopsies

Grade	Severity of Cellular Rejection	Histologic Findings
1R	Mild	Interstitial and/or perivascular infiltrate with up to one focus of necrosis
2R	Moderate	≥2 foci of infiltrate with associated necrosis
3R	Severe	Diffuse infiltrate with multifocal necrosis ± edema ± hemorrhage ± vasculitis
pAMR 0		Negative for pathologic AMR. Both histologic and immunopathologic studies are negative
pAMR 1 (H+)		Histopathologic AMR alone. Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)		Immunopathologic AMR alone. Histologic findings are negative and immunopathologic findings are positive.
pAMR 2		Pathologic AMR. Both histologic and immunopathologic findings are present.
pAMR 3		Severe pathologic AMR

AMR, antibody-mediated rejection.

TABLE 13.8 Example of Endomyocardial Biopsy Schedule—Center Dependent

Weeks After Transplantation	Biopsy Frequency
1-4	Weekly
5-12	Every 2 wk
13-24	Monthly
25-52	Every 2 mo
Year 2	Every 3-4 mo
Years 3-4	Every 6 mo
>4 y	Only if clinically indicated
After biopsy with acute rejection	2 wk after initial biopsy

B. Surrogate markers of rejection

1. **Peripheral biomarkers.** Although high levels of circulating pretransplant, **donor-specific antibodies to HLAs have been demonstrated to predict greater risk of severe rejection**, no peripheral markers have been shown to reliably correlate with allograft rejection post-transplantation among those evaluated, including cytokine levels, markers of myocardial necrosis (creatine kinase-muscle/brain and troponin), complement fragments, prothrombin, P-selectin fragments, CD69 membrane protein, soluble CD30, endothelin, serum nitrate, thromboxane A_2, matrix metalloproteinase-1 in brain, vascular endothelial growth factor, natriuretic peptide, and C-reactive protein.
2. **Echocardiography.** Echocardiography is ubiquitous in cardiac transplant centers, drawing investigative attention to it as a noninvasive surveillance alternative to EMB for cardiac allograft rejection. For it to be a useful screening tool, however, echocardiography must identify graft rejection before global LV systolic dysfunction ensues. The challenge has been to identify such sentinel markers. Myocardial performance index, pressure halftime, intraventricular relaxation time, and acoustic quantification of cardiac filling volumes have not shown consistency. Changes >10% in serial measurements of pulsed-wave tissue Doppler measurements of early diastolic basal posterior wall motion velocity were able to exclude clinically relevant rejection with positive predictive value and negative predictive value of 92% and 95%, respectively. Myocardial strain indices, particularly global longitudinal strain (GLS), may help identify post-transplant patients with early allograft dysfunction before the onset of systolic dysfunction. Investigative work in this space is ongoing. Technical limitations with this technique in the cardiac transplant population together with inconsistent observer interpretation have meant that echocardiography is neither sufficiently sensitive nor specific to supplant routine EMB.
3. **GEP.** GEP is a newer modality for surveillance of cardiac allograft rejection. **This test uses microarray and quantitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells to measure the expression of 20 genes** (11 informative and 9 control and normalization). A score ranging from 0 to 40 is generated by a multigene algorithm. It has been shown to correlate strongly with histologically diagnosed ACR. In the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study**, a score of <34 was associated with a negative predictive value of >99% for grade ≥3A/2R rejection**. Several factors influence AlloMap score, including time post-transplantation, peripheral alloimmune activity, corticosteroid dose, and CMV. Transplant vasculopathy has been shown to be associated with increased AlloMap GEP score. GEP testing can be used in clinically stable cardiac transplant recipients who are >15 years of age and 6 months or more post-transplantation. It is used to identify patients at low risk for moderate/severe (≥3A original ISHLT grade or ≥2R revised ISHLT grade) cellular rejection. In the Invasive Monitoring Attenuation through Gene Expression (**IMAGE**) trial, 602 patients who had undergone cardiac transplantation at least 6 months previously were randomly assigned to the AlloMap test or EMB. The composite primary outcome of the study was allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with GEP and 15.3% with EMB. The AlloMap test was thus not inferior to EMB in detecting allograft cellular rejection. However, the wholesale embrace of the IMAGE trial is tempered by the limitations of the trial, including the enrollment of only 20% of potentially eligible patients and of patients at lower risk for rejection. The noninferiority margin chosen was wide and included events that would not be associated with rejection because not all cases of graft dysfunction, death, or retransplantation are due to rejection. The frequency of rejection surveillance using the GEP or AlloMap testing should be individualized to the patient's rejection history, immunosuppression regimen, time post-transplantation, and transplant center protocol. GEP is a cost-effective and less expensive alternative to EMB for monitoring allograft cellular rejection in cardiac transplant patients.
4. **cfDNA.** This is an emerging area and will require additional clinical trials to fully define its application and usefulness. cfDNA is elevated in the setting of myocyte necrosis, which could be related to cellular rejection or AMR or coronary disease.
5. **Cardiac positron emission tomography (PET) with coronary flow reserve (CFR).** Cardiac PET is an additional testing modality that has clinical utility in surveillance after OHT. Cardiac PET has promise in detection of CAV or microvascular ischemia post-OHT, and abnormalities portend a worse prognosis. It was previously shown to be more predictive in detecting myocardial ischemia than serial dobutamine stress echo (DSE). When combined with software enabling calculation of myocardial blood flow (MBF) and CFR, additional prognostic information regarding epicardial stenosis, CAV, and microvascular

disease can be obtained. Another recent trial showed that an MBF <2.0 post-OHT was associated with significantly increased risk of death or retransplantation

C. Types of rejection

1. **Hyperacute rejection** is usually fatal and is the result of allograft rejection by preformed antibodies. It can occur immediately on surgical reperfusion. The incidence of hyperacute rejection is rare in the era of PRAs and virtual and prospective crossmatch.
2. **Cell-mediated rejection (ACR) is characterized by infiltration of mononuclear inflammatory cells that are predominantly T cells directed against the allograft.** Variability in the interpretation of histologic grading of cellular rejection of EMB by pathologists led to the revision of the grading system in 2004. Biopsy grades of ≥2R warrant accentuation of immunosuppression. If there is no hemodynamic compromise, then patients are routinely treated as outpatients with 100 mg of prednisone taken orally for 3 days; again, this varies from center to center. If there is hemodynamic compromise or persistent or recurrent severe rejection (at least grade 2R), then many therapeutic options are available: methylprednisolone, cytolytic therapy with Atgam or thymoglobulin, plasmapheresis, photopheresis, and, in severe cases, total lymphoid irradiation combined with optimization of maintenance immunosuppression.
3. **AMR** occurs because of preformed or de novo alloantibodies (immunoglobulin G or M) against donor antigens. Such antibodies and complements are deposited in the donor coronary microvasculature and are demonstrable by immunofluorescence or by immunohistochemistry staining against CD68, C4d, or C3d complement fragments that mediate vascular injury and, ultimately, allograft failure. The ISHLT proposed a framework for reporting pathologic AMR, which includes any combination of histopathologic and immunopathologic findings. Treatment regimens for patients with AMR include IV or oral steroids, plasmapheresis, or immunoadsorption and are determined by the degree of rejection defined by the presence of graft dysfunction, pathologic, and serologic assessment.

XI. INFECTIOUS DISEASE AFTER TRANSPLANTATION. The risk of infection is highest in the first year after cardiac transplantation, accounting for 29% of deaths within the first year. Thereafter, the risk falls but remains >10%. In the first month post-transplantation, nosocomial infections predominate. The therapeutic immunosuppression consequent upon transplantation leaves cardiac allograft recipients vulnerable to **opportunistic infections** or **reactivation of latent infection**, particularly between 1 and 6 months. Infections after 6 months are usually **community acquired**. An infectious disease specialist with an interest in transplantation is an invaluable resource to any transplant program. The two pathogens of particular interest in the transplant patient are CMV and *Pneumocystis jirovecii* pneumonia (PJP). However, several potential pathogens including *Mycobacterium*, *Nocardia*, *Listeria*, *Candida*, *Aspergillus*, *Strongyloides*, and several viruses are known to contribute to morbidity and mortality in patients after cardiac transplantation.

A. CMV. Primary CMV infection occurs when a CMV-negative recipient receives a CMV-positive donor organ (ie, CMV mismatch) or the recipient is infected de novo from another source. **Secondary CMV** infection occurs when a CMV-positive recipient has reactivation of quiescent CMV infection with viremia after immunosuppression, particularly with induction therapy or bolus immunosuppression prescribed for a rejection episode. Active CMV disease may manifest as fevers, myalgias, gastritis, colitis, pneumonitis, retinitis, or leukopenia and thrombocytopenia. **The most sensitive and specific test for diagnosing CMV is quantitative PCR**. PCR detects CMV DNA in plasma and quantifies the CMV viral load. Although CMV DNA replication may be detected by PCR, most patients do not have the clinical syndrome of CMV disease. The issues of whether a detectable CMV viral load will progress to the clinical syndrome and whether to treat patients with CMV detection in the absence of symptoms remain controversial.

Prophylaxis against CMV disease with ganciclovir or acyclovir is considered to be the standard of care for CMV-positive recipients (regardless of the CMV status of the donor) and CMV-negative patients with a CMV-positive donor. There is no consensus on the duration of antiviral therapy in these patients. Most patients are initially treated with IV ganciclovir, followed by a variable course of oral valganciclovir or acyclovir. Periodic monitoring of the CMV viral load may assist in guiding the duration of therapy in these patients.

Passive immunization with CMV immunoglobulin (CytoGam) may be considered in patients deemed at risk for CMV disease, particularly if they have low levels of serum immunoglobulins (<500 mg/dL). Patients

undergoing induction therapy, polyclonal or monoclonal antibody therapy for steroid-resistant rejection, or increased immunosuppressive therapy for acute rejection should be deemed at risk for reactivation of CMV disease.

The duration of therapy with valganciclovir for active CMV disease is usually 3 to 6 weeks. An undetectable CMV viral load should be demonstrated in such patients before consideration is given for antiviral therapy discontinuation.

B. PJP. Transplant recipients are at increased risk for the development of PJP because of their immunocompromised state. **PJP is rare if appropriate prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is provided.** Patients intolerant to TMP-SMX may be treated with inhaled pentamidine or dapsone. PJP is rarely seen at maintenance immunosuppressant doses in transplant patients. TMP-SMX may be discontinued 6 to 12 months after transplantation in most patients.

XII. CARDIAC ALLOGRAFT VASCULOPATHY

A. CAV is a progressive, neointimal proliferative process in the epicardial coronary arteries and microcirculation. It is common, with an incidence of 30% and >50% at 5 and 10 years, respectively. CAV is a significant cause of mortality beyond the first year after transplantation, accounting approximately 15% after 5 years post-transplant. The pathophysiology of CAV is not completely understood. **Initially, CAV was thought to be an accelerated form of atherosclerosis; however, it is now clear that both immunologic and nonimmunologic factors are involved in the process.** Chronic, subclinical, and immune-mediated injury at the level of the donor coronary endothelium creates a chronic inflammatory milieu. The exact mediator of the endothelial injury remains controversial, but it is probably multifactorial, including chronic humoral and cellular rejection, ischemic and reperfusion injury at the time of transplantation, and chronic CMV infection of endothelial cells. **Table 13.9** lists risk factors for the development of CAV, of which older donor age and hyperlipidemia are well-established risk factors, whereas the others are potential risk factors.

TABLE 13.9 Risk Factors for the Development of Cardiac Allograft Vasculopathy

Advanced donor age
Hyperlipidemia
Donor brain death secondary to spontaneous intracranial hemorrhage
Cytomegalovirus infection
Increased C-reactive protein levels
Recurrent cellular rejection
Humoral (vascular) rejection
HLA mismatch
Donor hepatitis B and C
Female donor
Prolonged ischemic time
Pretransplant coronary atherosclerotic disease
Conventional atherosclerosis risk factors (diabetes, hypertension, and smoking)

HLA, human leukocyte antigen.

B. Monitoring. Because donor hearts are denervated at explanation, **the transplant recipient typically will not experience cardiac angina from advanced CAV.** The clinical presentation of CAV previously unrecognized in a patient may include symptomatic or asymptomatic LV dysfunction, myocardial infarction, or cardiac arrhythmia, including ventricular arrhythmias, heart block, syncope, or sudden cardiac death. Owing to the usually asymptomatic nature of CAV, **transplant recipients require frequent surveillance studies to detect significant vasculopathy**, including coronary angiography with or without IVUS, stress echocardiography, cardiac perfusion magnetic resonance imaging, and PET. The frequency and method of surveillance remain site specific. Although coronary angiography is useful for the diagnosis of nontransplant coronary artery disease, its sensitivity is considerably less in CAV because of the diffuse nature of this

disease. Coronary IVUS and optical coherence tomography (OCT) imaging provide useful tomographic perspective to study the development and progression of CAV and are now considered by many to be the gold standard modality for diagnosing CAV. However, not all centers have access to routine intravascular imaging, and thus, its use will vary greatly from center to center.

C. The recommended nomenclature for CAV is as follows:

1. **CAV 0 (not significant).** No detectable angiographic lesion
2. **ISHLT CAV 1 (mild).** Angiographic left main (LM) <50%, primary vessel with maximum lesion of <70%, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
3. **ISHLT CAV 2 (moderate).** Angiographic LM <50%, a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of two systems, without allograft dysfunction
4. **ISHLT CAV 3 (severe).** Angiographic LM ≥50%, two or more primary vessels ≥70% stenosis, or isolated branch stenosis ≥70% in all three systems; or ISHLT CAV 1 or CAV 2 with allograft dysfunction (defined as LV ejection fraction [LVEF] ≤45% usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific)

D. The **detection of significant CAV** should prompt aggressive percutaneous or (rarely) surgical revascularization. Because of its relationship with chronic rejection, advancement of the immunosuppressant regimen has also been advocated. **Statins have been shown prospectively to decrease the incidence of transplant vasculopathy and improve survival**, regardless of the patient's lipid profile. Furthermore, studies investigating the antiproliferative effects of TOR inhibitors suggest a significant reduction in coronary neointimal proliferation and, therefore, transplant coronary vasculopathy with larger, prospective clinical trials ongoing. In severe, advanced CAV, frequently the only viable option is retransplant. Despite improved recognition and diagnostic/therapeutic tools, the management of advanced CAV remains challenging.

III. MALIGNANCY

A. Malignancy is a common and devastating complication of cardiac transplantation. In immunocompetent people, the cellular arm of the immune system actively defends against a variety of neoplastic processes. With the initiation of immunosuppression after transplantation, this defense mechanism is reduced, and previously undeclared neoplastic foci may proliferate. Common malignancies include cancer of the skin, lung, colon, breast, and lymphomas. Post-transplant malignancies are particularly common in patients who have received cytolytic or induction therapy with OKT3 (no longer used), Atgam, or thymoglobulin, and the risk correlates with cumulative dosing of immunosuppression. The risk of developing a malignancy as a result of immunosuppression is enhanced by the inability to adequately assess for overimmunosuppression. Under-immunosuppression is readily detected because of the development of acute rejection, whereas there is no clinical finding to suggest overimmunosuppression.

B. PTLD is an EBV-related clonal expansion of B lymphocytes. PTLD may develop in any location but most commonly affects the gastrointestinal tract, lungs, and central nervous system. The primary treatment for PTLD is a reduction in immunosuppression (by about 50%), which can frequently be curative. Surgical debulking, systemic chemotherapy, and antiviral therapy may also be indicated in selected patients. Routine screening for donor and recipient EBV titers is recommended; mismatch patients are at increased risk for PTLD, and reduction in immunotherapy when possible is the only effective strategy.

IV. HYPERTENSION.

Arterial hypertension commonly develops after cardiac transplantation secondary to the untoward effects of immunosuppression. **Hypertension developing after cardiac transplantation occurs in most cyclosporine- and tacrolimus-treated patients.** Three mechanisms proposed are as follows: direct sympathetic activation, increased responsiveness to direct circulating neurohormones, and direct vascular effects. A common end point of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention and an elevated plasma volume. Corticosteroids may also play a role in the pathogenesis of cardiac transplant hypertension and are described as a salt-sensitive subgroup. Abnormal cardiorenal reflexes secondary to cardiac denervation may also contribute to salt-sensitive hypertension and fluid retention.

Patients with blood pressure consistently >130/80 mm Hg should be treated like the general population. Titrated monotherapy is with ACE/ARB, CCB, or diuretics, with combination of multiple agents being common. The use of diltiazem, verapamil, or amlodipine necessitates the use of lower doses of the CNI and

initially more frequent trough level monitoring because these drugs are competitive antagonists of CNI at the cytochrome P450 level. In refractory cases, an alpha-blocker such as clonidine or a vasodilator like hydralazine may be used. SGLT2i may be an emerging consideration for their diuretic effects, but potential benefits for this indication remain unproven.

XV. OUTCOMES AFTER CARDIAC TRANSPLANTATION. Survival outcomes after cardiac transplantation continue to improve on a yearly basis despite what is generally accepted as a population of transplant recipients at greater risk, primarily because of advancing recipient age and increasing severity of heart failure. The 1-year survival rate after cardiac transplantation is 91% nationwide. The mortality in the first year after transplantation primarily results from postoperative complications, including multiorgan failure, primary graft failure, and systemic infection (**Table 13.10**). Those surviving the first year after transplantation have a median survival of 13 years. Later mortality after cardiac transplantation primarily results from progressive CAV, malignancy, or renal failure. It is hoped that a major impact can be made on long-term survival with newer immunosuppressive drug regimens that may be less nephrotoxic and more effective at preventing transplant coronary vasculopathy.

TABLE 13.10 Complications After Cardiac Transplantation

Early (24 h)
Primary graft dysfunction
Right ventricular dysfunction
First 30 d
Acute cellular rejection
Antibody-mediated rejection
Arrhythmia
Nosocomial infection
6 mo to 1 y
Opportunistic infection
Allograft rejection
1-5 y
Cardiac allograft vasculopathy
Renal dysfunction
>5 y
Cardiac allograft vasculopathy
Renal dysfunction
Malignancy

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RELEVANT WEB SITES

International Society for Heart and Lung Transplantation. www.ishlt.org

Scientific Registry of Transplant Recipients. http://www.srtr.org

United Network for Organ Sharing. https://www.unos.org

CHAPTER 14

Pulmonary Hypertension

Phoo Pwint Nandar, W. H. Wilson Tang, and Miriam Jacob

I. INTRODUCTION. Pulmonary hypertension (PH) is a routinely made diagnosis in contemporary cardiology and pulmonary clinics. Substantial advances are being made in the management of pulmonary arterial hypertension (PAH), which is more rapidly available at centers specializing in PH management.

A. Terminology/definitions. PH is defined as mean pulmonary artery pressure (mPAP) >20 mm Hg. PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The terms *pulmonary hypertension*, which is a hemodynamic condition, and *pulmonary arterial hypertension*, which is a clinical condition, are different terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly employed in PH include the following:

1. **Transpulmonary gradient (TPG)** is defined as the pressure difference between mean left atrial pressure (LAP) (more commonly, pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP [TPG = mPAP − PCWP].
2. **Pulmonary vascular resistance (PVR)** is defined as TPG divided by the cardiac output (CO) [PVR in Wood units (WU) = TPG/CO].
3. **Precapillary PH** is characterized by mPAP ≥20 mm Hg, PCWP <15 mm Hg, and PVR ≥3 WU.
4. **Postcapillary PH** is characterized by mPAP ≥20 mm Hg, PCWP ≥15 mm Hg, and PVR <3 WU.

5. **Combined pre- and postcapillary PH** is characterized by mPAP ≥20 mm Hg, PCWP ≥15 mm Hg, and PVR ≥3 WU.
6. **PAH** is hemodynamically defined as precapillary PH, and it is a clinical condition due to pathologic changes in the pulmonary microcirculation.
7. **Exercise PH** is characterized by mPAP/CO slope between rest and exercise >3 mm Hg/L/min.

B. Classification. The World Health Organization (WHO) has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics. This classification is listed in **Table 14.1**.

TABLE 14.1 Dana Point Classification of Pulmonary Hypertension (Simplified)

	Type	Subtype
1	Pulmonary arterial hypertension	Idiopathic Heritable Drugs and toxins induced Associated with CTD, HIV, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia Persistent PH of newborn
1'	Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	
2	PH because of left heart disease	Systolic Diastolic Valvular
3	PH because of lung disease and/or hypoxia	COPD ILD Mixed obstructive and restrictive lung disease Sleep-disordered breathing Alveolar hypoventilation syndromes, etc
4	Chronic thromboembolic PH	
5	PH with unclear and/or	Hematologic

Type	Subtype
multifactorial mechanisms	Systemic such as sarcoid and vasculitis

COPD, chronic obstructive pulmonary disease; CTD, connective tissue disease; HIV, human immunodeficiency virus; ILD, interstitial lung disease; PH, pulmonary hypertension.

C. Epidemiology. The prevalence of PH is ~1% of the global population. Left heart disease (LHD) followed by lung diseases causing hypoxia are leading causes of PH. Only <10% of PH are PAH. Data from registries estimate the prevalence of PAH at around 48 to 55 cases per million adults and its incidence at around 6 cases per million adults per year. Idiopathic PAH (IPAH) is the most common subtype (50%-60% of PAH), followed by PAH associated with connective tissue disease (CTD), congenital heart disease (CHD), and porto-pulmonary hypertension (PoPH). Overall, 25% to 30% of patients with IPAH have an underlying genetic cause. Mutations in the *bone morphogenetic protein receptor-II* (*BMPR2*) gene have been identified in about 75% of patients with familial PAH and 25% of patients with sporadic IPAH. Other genes such as *EIF2K4*, *TBX4*, *ATP13A3*, *GDF2*, *SOX17*, *AQP1*, *ACVRL1*, *SMAD9*, *ENG*, *KCNK3*, and *CAV1* have also been identified in patients with PAH. Genetic testing and annual screening echocardiograms may be considered for first-degree relatives.

A certain number of PAH cases have been associated with environmental factors such as the use of drugs and exposure to toxins. Anorexigens (appetite suppressant drugs that increase serotonin release and block serotonin reuptake), aminorex, (dex)fenfluramine, methamphetamines, rapeseed oil, and dasatinib have been associated with PAH.

Select patient populations are at an increased risk of developing PAH:

1. **Patients with CTDs**, especially the **limited cutaneous form of systemic sclerosis**. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 5% to 19%, with an annual incidence of developing PAH of 0.7% to 1.5%.

2. **Human immunodeficiency virus (HIV) infection** is associated with approximately 0.5% incidence of PAH.
3. Estimated 1% to 2% of patients with **cirrhosis and portal hypertension** are at an increased incidence of PoPH.
4. **CHD** may lead to PAH when the underlying systemic-to-pulmonary shunt is not corrected. Most commonly, it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (eg, ventricular septal defect and patent ductus arteriosus). However, high blood flow alone, as in atrial septal defect, may be sufficient. Once PVR approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to desaturation and cyanosis (Eisenmenger syndrome).

II. SIGNS AND SYMPTOMS

A. Symptoms. The symptoms of PH can be gradual in onset; therefore, there is a lag time from the symptom onset to diagnosis. In the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) registry, 21.1% of patients experienced symptoms for more than 2 years prior to PAH was diagnosed. These symptoms may include dyspnea on exertion, fatigue, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Symptoms at rest occur only at late stages of the disease and portend poor prognosis.

Some patient populations are at an increased risk for developing PH and should be carefully screened by clinicians by careful history-taking, examination, and laboratory tests. These populations include patients with known, or relatives of those with BMPR2 mutation carriers, systemic sclerosis or limited cutaneous sclerosis, portal hypertension, prior appetite suppressant use, CHD with shunt, recent acute pulmonary embolism, LHD, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea.

It is advisable to perform annual screening with echocardiography in select high-risk groups, such as BMPR2 mutation carriers, patients with systemic sclerosis (strong recommendation), and those with sickle cell disease.

B. Physical examination. Physical examination may provide clues as to the cause of PH. Physical findings specific to systemic sclerosis, interstitial lung disease, or stigmata of liver disease can be helpful. Cardiovascular examination of patients with PH may reveal a left parasternal lift, a loud P_2, a holosystolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a right ventricular (RV) S_3 (in 23%). Lung sounds are usually normal (except for those with class 3 PH). Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are ominous signs suggestive of advanced stages of right-sided heart failure.

III. INVESTIGATION (Figure 14.1)

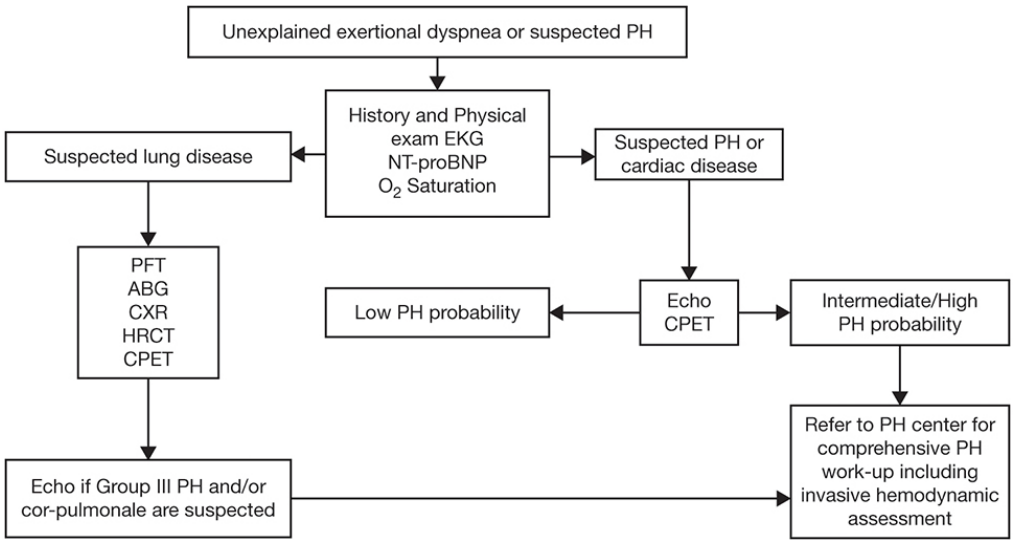

FIGURE 14.1 Investigation algorithm of a patient with unexplained exertional dyspnea and/or suspected pulmonary hypertension. ABG, arterial blood gas; CPET, cardiopulmonary exercise testing; CXR, chest x-ray; ECG, electrocardiogram; HRCT, high-resolution computed tomography; NT-proBNP, N-terminal prohormone B type natriuretic peptide; PFT, pulmonary function test. (Adapted from Humbert M, Kovacs G, Hoeper M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.)

A. Blood work

1. Routine biochemistry including liver function test and hematology tests should be done.
2. **Serologic testing** is important to detect the underlying CTDs (antinuclear antibodies, anticentromere antibodies, and anti-Ro), HIV, hypercoagulable workup including biomarker for antiphospholipid syndrome (in chronic thromboembolic pulmonary hypertension [CTEPH]), and hepatitis (in patients with suspected liver disease).
3. **Biomarkers.** Several circulating biomarkers have prognostic implications in patients with PAH. Uric acid levels are shown to be increased in patients with IPAH. Elevated plasma troponin T levels (>150 pg/mg) have been associated with worse outcomes in patients with CTEPH and PAH. Brain natriuretic peptide (BNP) or N-terminal-proBNP (NT-proBNP) plasma levels should be checked for the initial risk stratification and monitoring of the effects of treatment, in view of their prognostic implications. Low and stable or decreasing BNP/NT-proBNP suggests successful disease control in PAH.

B. The electrocardiogram (ECG). In typical cases of PH, the ECG shows right atrial (RA) enlargement, RV hypertrophy with strain, and a right-axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occurs. However, a normal ECG does not exclude the presence of PH.

C. Chest radiograph (CXR). Initial CXRs are abnormal in the majority of patients with PH; however, a normal CXR does not exclude PH. Abnormal radiographic finding includes central pulmonary arterial (PA) dilation with "pruning" (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. The CXR may also point to lung abnormalities in WHO group III PH and show features suggestive of LHD in WHO group II PH.

D. Echocardiography. If PH is suspected, an echocardiogram is the next appropriate study. The measured peak velocity of the tricuspid regurgitation jet (TRv) can be used to estimate pulmonary artery systolic pressure (PASP) by using the simplified Bernoulli equation ($\Delta P = 4v^2$). In the absence of pulmonary stenosis, PASP = RVSP = (4

× TRv^2) + RAP (where RVSP is right ventricular systolic pressure and RAP is right atrial pressure). Other echocardiographic characteristics may raise the suspicion of PH, such as RA or RV dilation, flattening of the interventricular septum with D-shaped left ventricle (LV), increased RV wall thickness, dilation of the PA, and presence of pericardial effusion. These features tend to occur later in the course of the disease. Echocardiogram also provides data on RV function by measuring parameters like tricuspid annular plane systolic excursion (TAPSE), right ventricular index myocardial performance (RIMP), fractional area change (FAC), and RV strain. TAPSE <1.7 cm, RIMP >0.43 by pulsed-wave Doppler or >0.54 by tissue Doppler, RV FAC <35%, or abnormal RV strain indicates RV dysfunction. Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with wide-open tricuspid regurgitation or RV failure and overestimate PASP in patients with non-PH. Ultimate confirmation requires the performance of an RHC.

E. **Cardiac magnetic resonance (CMR) imaging.** CMR is a reasonable test if there is high suspicion of CHD such as intracardiac shunt in the setting of poor echocardiographic images. CMR also provides accurate RV function and anatomy.

F. **Abdominal ultrasound (US)** should be part of the initial investigation for newly diagnosed PH if liver disease is suspected.

G. **Pulmonary testing and arterial blood gas (ABG).** Pulmonary function tests and ABGs are used to identify underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (DLCO), typically in the range of 40% to 80% predicted and mild-to-moderate reduction in lung volumes. Arterial oxygen partial pressure (PaO_2) is normal or only slightly lower than normal at rest, and arterial carbon dioxide partial pressure ($PaCO_2$) is decreased because of alveolar hyperventilation. Sleep study should be performed if there is any suspicion of sleep apnea with hypoventilation as the underlying etiology.

H. **Chest computed tomography CT and ventilation/perfusion lung scan (V̇/Q̇ scan):** Chest CT and V̇/Q̇ scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding CTEPH, V̇/Q̇ scan is the preferred screening test. A normal or low-probability V̇/Q̇ scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%, whereas a high-probability scan warrants further evaluation with a pulmonary angiogram.

I. **RHC.** RHC is required to **confirm the diagnosis of PH, to assess the etiology and severity, and to test for vasoreactivity of the pulmonary circulation**. Consecutively, RAP, RV pressure, PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter (**Table 14.2**). CO can be determined using the thermodilution method and/or the Fick method (measurement of mixed venous saturation; Svo_2 is needed). In the absence of mitral stenosis, PCWP is taken as a surrogate measure of LAP and LV end-diastolic pressure. This measurement is very important because it helps differentiate precapillary PH from postcapillary PH and combined pre- and postcapillary PH.

TABLE 14.2 Normal Values of Pressures and Measurements Derived From a Right Heart Catheterization

Measured Characteristic	Normal Value
Right atrial pressure	Mean 2-6 mm Hg
RVSP/RVDP	15-30/1-10 mm Hg
PASP/PADP	15-30/4-12 mm Hg
Pulmonary capillary wedge pressure	Mean 5-12 mm Hg (≤15 mm Hg)
Left ventricular end-diastolic pressure	5-12 mm Hg
Cardiac output	4-8 L/min
Cardiac index	2.5-4.0 L/min/m^2
Pulmonary vascular resistance	0.3-2 Wood Units
Transpulmonary gradient	4-6 mm Hg

PASP/PADP, pulmonary artery systolic and diastolic pressures; RVSP/RVDP, right ventricular systolic and diastolic pressures.

1. **Temporal evolution of the hemodynamic variables with progression of PAH** is depicted in **Figure 14.2**. As the disease progresses, the RV starts to fail, leading to reduction in CO. As a result, PAP may decrease again. This decrease may give a false impression of hemodynamic improvement or suggest that there is mild-to-moderate disease. Therefore, it is imperative to measure PVR, which will be high in this situation, and calculate pulmonary artery pulsatility index (PAPi) to assess RV function. Usually, the RAP and PCWP also increase, implying RV failure and LV diastolic dysfunction, respectively. The latter is the consequence of ventricular interdependence and abnormal compliance of the LV produced by an enlarged RV.

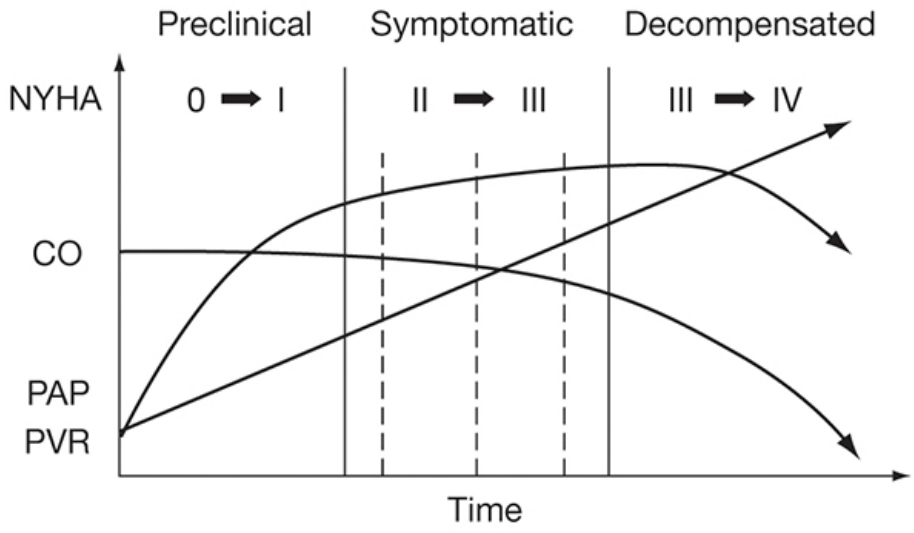

FIGURE 14.2 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (From Galie N, Manes A, Palazzi M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J*. 2007;9(suppl H):H68-H74. Reproduced by permission of The European Society of Cardiology.)

2. **Vasoreactivity testing in PAH**
   a. In patients with **idiopathic, hereditary, or drug-induced** PAH and PCWP <15 mm Hg and PA mean ≥40 mm Hg, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with high-dose calcium channel blockers (CCBs). The agent most often used to test vasoreactivity is inhaled nitric oxide (iNO for 5-10 minutes, of note many different doses have been studied from 10 to 80 ppm), inhaled iloprost (5-10 mcg for 10-15 min), or intravenous (IV) epoprostenol (2-12 ng/kg/min for 10 min).
   b. A positive acute response is defined as a >10 mm Hg decrease in mPAP to reach an absolute value of mPAP <40 mm Hg with an increased or unchanged CO and without significant drop in systemic blood pressure. In postcapillary PH or combined pre- and postcapillary PH, it can even provoke pulmonary edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.
   c. It is important to understand the difference between PAH vasoreactivity testing and the assessment of PH reversibility in left-sided heart failure. In PAH, vasodilator response testing is performed to select patients who may respond favorably to CCBs as the first agent versus those who will likely not. In left-sided heart failure and PH, vasodilatory drugs that affect the LV afterload, such as sodium nitroprusside, are given with an intention to reduce LV filling pressure and evaluate for reversible PH. Those who have persistent elevation in TPG (>15 mm Hg) and PVR (>4 WU) despite the reduction of PCWP to <15 mm Hg are at high risk for post-transplant RV failure, as the transplanted heart may not withstand persistently elevated PAPs, which results in right heart failure.
3. **Exercise RHC:** RHC hemodynamics should be obtained during exercise to define exercise PH in patients with unexplained dyspnea and normal resting RHC hemodynamics. At each exercise level, mPAP, PCWP, CO by thermodilution, systemic blood

pressure, and heart rate should be measured and PVR should be calculated. RAP, SvO_2, and SaO_2 should also be measured at rest and peak exercise. In patients with exercise PH, PVR may be normal or mildly elevated at rest. However, during exercise, there may be a steep increase in mPAP with mPAP/CO slope >3 mm Hg/L/min, while PCWP/CO slope remains <2 mm Hg/L/min. In those with LHD, there will be a steep increase in both mPAP and PCWP with mPAP/CO and PCWP/CO slope during exercise.

J. **Six-minute walk distance (6MWD).** The 6-minute walk test (6MWT) is the most employed measure of exercise capacity in patients with PH, both in clinical assessment and in research settings. In addition to the distance walked, the degree of dyspnea (Borg score) and oxygen saturation are also measured. **A 6MWD of <332 m and a drop in oxygen saturation by >10% are suggestive of poor prognosis**. It is also measured on routine follow-ups and can be indicative of clinical deterioration. It may also be used to assess the response to therapy during follow-up visits.

K. **Cardiopulmonary exercise testing (CPET):** CPET can be performed to assess the underlying mechanism leading to exercise intolerance in patients with suspected PH. In those with risks of PAH such as scleroderma, a normal peak oxygen uptake (VO_2) seems to exclude the diagnosis of PAH.

L. **Genetic counseling and testing:** Genetic testing can be done in patients with confirmed PAH diagnosis. Genetic counseling should be performed prior to genetic testing to address the complex questions related to penetrance, genetically at-risk family members, reproduction, and psychosocial issue.

M. **Risk stratification:** Once PAH is confirmed, risk assessment should be done every visit by using WHO functional classification (WHO-FC) (**Table 14.3**), functional assessment, for example, with 6MWT and BNP or NT-proBNP. Using this information, one can determine risk with various scoring systems (eg, REVEAL 2.0 risk scoring system at https://pahriskcalculatorre.com and French criteria for low-risk goal at https://pahriskcalculatorfr.com). The WHO-FC is one of the strongest predictors of survival.

TABLE 14.3 World Health Organization Classification of Functional Status of Patients With Pulmonary Hypertension

Class	Description[a]
WHO-FC I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
WHO-FC II	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
WHO-FC III	Patients with PH resulting in mark limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
WHO-FC IV	Patients with PH with an inability to carry out any physical activity without symptoms. These patients manifest signs of right HF. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

HF, heart failure; PH, pulmonary hypertension; WHO-FC, World Health Organization functional class.

[a]From FC of PH modified after the New York Heart Association functional classification according to the WHO 1998.

IV. PATHOGENESIS

A. Hemodynamically, PH is a disease state with increased pulmonary pressures. Elevation in mPAP may be a consequence of *elevation in PCWP, increase in flow, or increase in PVR*. However, pulmonary vessels are highly compliant and capable of recruitment with progressive reduction in PVR for the increment in flow. These low-pressure, low-resistance, and high-compliance characteristics of the pulmonary vascular bed are regulated by a balance between vasodilators and vasoconstrictors and between cell proliferation and apoptosis. Genetic and environmental factors may disturb this balance, resulting in excessive vasoconstriction, vascular remodeling, and microthrombosis, which leads to pulmonary (arterial) hypertension. This leads to elevated PVR and an increase in RV afterload, ultimately resulting in RV dilation and hypertrophy.

B. Histologically, PAH is a pan-vasculopathy predominantly affecting the small PAs. The initial lesions seem to be intimal hyperplasia and medial hypertrophy, followed by more irreversible lesions such as intimal fibrosis, thrombosis in situ, inflammation, and plexiform arteriopathy. These lesions may be present in various distributions, local or diffuse, in a patient.

C. Molecular and endothelial abnormalities. Various vasoactive molecules play an important role in the pathologic evolution of PAH. Our understanding of these factors and various pathologic forces is limited, but some pathways have been elucidated, mainly because of their therapeutic potential (**Figure 14.3**).

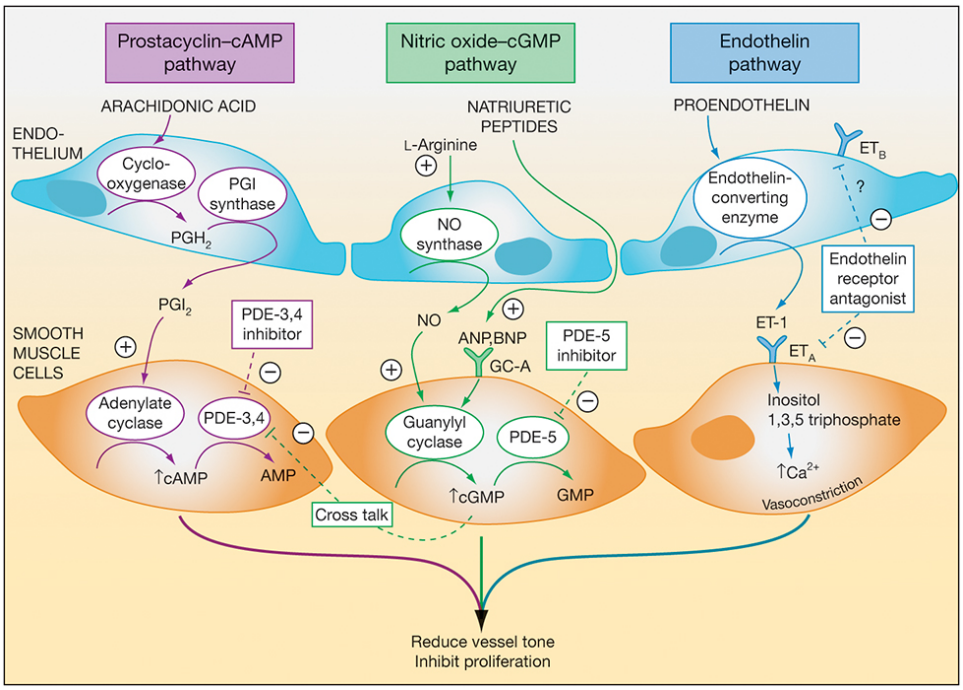

FIGURE 14.3 Therapeutic targets in pulmonary hypertension. ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; cAMP, cyclin adenosine monophosphate; cGMP, cyclin guanosine monophosphate; ET, endothelin; GC, guanylate cyclase; NO, nitric oxide; PDE, phosphodiesterase; PGI_2, prostacyclin; PGH_2, prostaglandin H_2. (Reprinted from Benza RL, Park MH, Keogh A, et al. Management of pulmonary arterial hypertension with a focus on combination therapies. *J Heart Lung Transplant*. 2007;26(5):437-446. Copyright © 2007 International Society for Heart and Lung Transplantation. With permission.)

1. **Prostacyclin/thromboxane A2.** Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin has potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 has the opposite effect. In PAH, the balance is shifted toward thromboxane A_2 in small- and medium-sized PAs.
2. **Endothelin-1 (ET-1).** ET-1 is produced by endothelial cells and exerts its effect on the smooth muscle cells through two receptors: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of ET_B on the endothelial cells causes vasodilation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are increased, and ET_A receptors are abundant.
3. **Nitric oxide.** NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of NO synthases (NOSs). It is a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle cell proliferation. Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in patients with PAH.

V. TREATMENT. The treatment of group 1 PH (or PAH) is primarily in the form of pulmonary-specific vasodilator therapy, whereas treatment in groups 2, 3, and 5 PH is mainly oriented toward treating the underlying condition as first line. Treatment of group 4 PH includes surgical interventions, catheter-based interventions, and pulmonary vasodilator therapy.

A. General measures. A few general measures apply to all the PH groups:

1. Mild physical activity, possibly via exercise rehabilitation, is beneficial.
2. Routine influenza, pneumococcal, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccinations are recommended.
3. Effective contraception should be discussed with females of childbearing age and pregnancy should be avoided in patients with PAH, as pregnancy carries a 30% to 50% maternal mortality risk and around 13% neonatal mortality risk.
4. Oxygen supplementation as indicated
5. Exposure to high altitude >1,500 m without supplemental oxygen should be avoided. If flying, supplemental oxygen should be used if the patient's preflight saturation is less than 92% or Pao_2 <60 mm Hg.
6. Diuretic therapy is indicated to manage RV failure with volume overload.
7. Digoxin may be considered for rate control in the case of atrial tachyarrhythmia, which fails to convert to sinus rhythm by chemical or electrical cardioversion. Amiodarone is the safest antiarrhythmic in patients with PH.
8. Lifelong therapeutic dose of anticoagulation is recommended in all patients with CTEPH.

B. Pulmonary vasodilators (**Table 14.4**). The initial treatment choice in PAH is guided by vasoreactivity testing. For the responders, CCBs are the first line of treatment. Verapamil should be avoided due to the negative inotropic effect on RV. Close reassessment in 3 to 4 months including RHC for safety and efficacy is mandatory, because only half of these patients will prove to be long-term responders, and many will need additional vasodilators. The current treatment algorithm for PAH adapted from the 2022 European Society of Cardiology and the European Respiratory Society is shown in **Figure 14.4**.

TABLE 14.4 Pulmonary Vasodilators

	Starting Dose	Target Dose
Calcium channel blockers		
Amlodipine	5 mg once daily	15-30 mg once daily
Diltiazem	60 mg twice daily	120-360 mg twice daily
Felodipine	5 mg once daily	15-30 mg once daily
Nifedipine	10 mg 3 times daily	20-60 mg 2-3 times daily
Endothelin receptor antagonists (oral)		
Ambrisentan	5 mg once daily	10 mg once daily
Bosentan	62.5 mg twice daily	125 mg twice daily
Macitentan	10 mg once daily	10 mg once daily
Phosphodiesterase 5 inhibitors (oral)		
Sildenafil[a]	20 mg 3 times daily	20 mg 3 times daily
Tadalafil	20-40 mg once daily	40 mg once daily
Soluble guanylate cyclase stimulator (oral)		
Riociguat[b]	0.5 mg 3 times daily	2.5 mg 3 times daily
Prostacyclin analogs (oral)		
Treprostinil	0.125 mg 3 times daily	Maximum tolerated dose
Prostacyclin analogs (Inhaled)		
Iloprost[c]	2.5 mcg 6-9 times/d	5 mcg 6-9 times/d
Treprostinil[c]	18 mcg (3 breaths) 4 times/d	72 mcg (12 breaths) 4 times/d
Prostacyclin analog (IV or SC)		
Epoprostenol IV	2 ng/kg/min	Maximum tolerated dose
Treprostinil SC or IV	1.25 ng/kg/min	Maximum tolerated
Prostacyclin receptor agonist (oral)		
Selexipag	200 mcg twice daily	Maximum tolerated dose up to 1,600 mcg twice daily

IV, intravenous; SC, subcutaneous.

[a]Sildenafil is approved at a dose of 20 mg 3 times daily, but doses used in practice vary widely and are sometimes higher.

[b]In patient at risk of systemic hypotension, riociguat may be started at 0.5 mg 3 times daily.

[c]Doses provided are for nebulizers and may differ with the use of other formulations and other inhalation devices.
Adapted from Humbert M, Kovacs G, Hoeper M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38): 3618-3731.

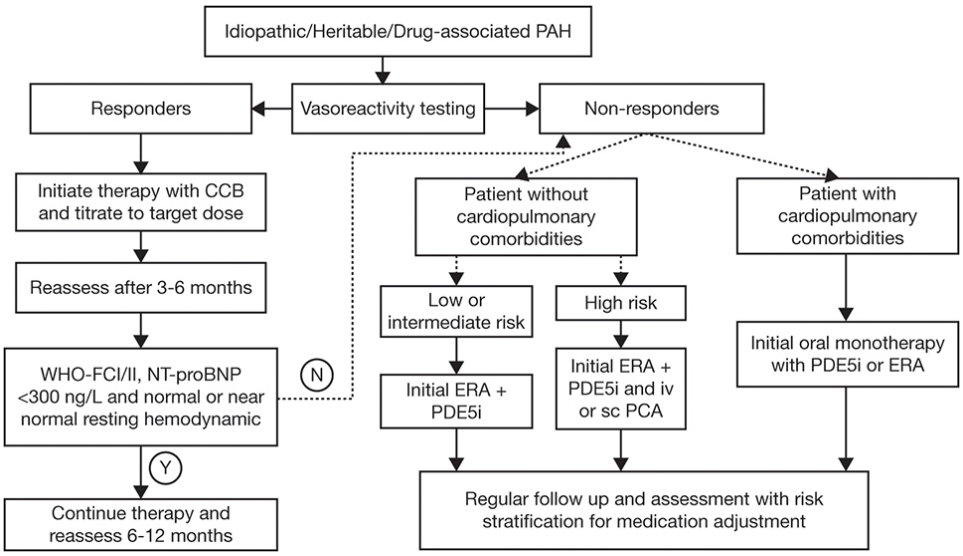

FIGURE 14.4 Pulmonary arterial hypertension treatment algorithm. (Adapted from Humbert M, Kovacs G, Hoeper M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731.)

1. Prostacyclin receptor agonists and prostacyclin analogs.

Prostacyclin is a potent endogenous vasodilator and an inhibitor of platelet aggregation and also appears to have both cytoprotective and antiproliferative activity. This may explain why *epoprostenol* (Flolan, Veletri) and *iloprost* can be used to acutely lower PAPs (as used in vasoreactivity testing) as well as to achieve long-term hemodynamic improvement in patients with PH who are nonresponders. The most common side effects with these compounds are related to systemic vasodilation such as headache,

flushing, jaw pain, and diarrhea. In randomized controlled trials (RCTs), epoprostenol has been shown to improve the functional class, exercise tolerance, hemodynamics, and survival in patients with IPAH. Epoprostenol has to be administered in a continuous IV infusion. *Treprostinil* (Remodulin) is another prostacyclin analog that can be administered by continuous inhalation (Tyvaso), via continuous subcutaneous pump (Remodulin), IV infusion (Remodulin), or oral administration (Orenitram). It has been shown to improve the exercise capacity, hemodynamics, and symptoms. Infusion site pain is the most common side effect. Selexipag is a prostacyclin receptor agonist and can be administered orally or IV. In RCTs, it was shown to reduce PVR and mortality and morbidity events. *Iloprost* (Ventavis) is available as an aerosol administration and has proven beneficial effects (such as an increase in exercise capacity, improvement of symptom, PVR, and clinical event) in patients with PAH and CTEPH.

2. **Endothelin receptor antagonists (ERAs).** Selective blocking of ET_A receptors alone or nonselective blocking of both ET_A and ET_b receptors has shown similar effectiveness in PAH. ERAs have teratogenic effects and should be avoided during pregnancy. *Bosentan* (Tracleer) is an orally active dual ET_A/ET_B receptor antagonist that has been shown to improve the exercise capacity, functional class, hemodynamics, and cardiac performance as measured by echocardiography and clinical outcomes. Liver injury is a major concern and requires monthly monitoring. Moreover, pharmacokinetic interactions are observed between bosentan with sildenafil, hormonal contraceptives, and vitamin K antagonists. *Ambrisentan* (Letairis) is an oral and more selective ET_A receptor antagonist, and *Macitentan* (Opsumit) is an oral dual ET_A/ET_B receptor antagonist with similar benefits as bosentan. However, there was no increased incidence of abnormal liver function.
3. **PDE-5 inhibitors (PDE-5i).** Orally active PDE-5i prevent the degradation of cGMP, causing vasorelaxation. Headache, flushing, dyspepsia, and epistaxis are the usual side effects. *Sildenafil*

(Revatio) has favorable effects on exercise capacity, symptoms, and hemodynamics. Tadalafil (Adcirca) has the same effects, although it also delays the time to clinical worsening.

4. **Soluble guanylate cyclase (sGC) stimulators.** The sGC stimulators enhance cGMP production both in the presence and absence of endogenous NO. This, in turn, causes vasodilation and inhibits smooth muscle proliferation. Riociguat (Adempas) is given orally and is approved for the treatment of both primary PH and CTEPH on the basis of improvements in 6MWD, which were comparable to other oral agents. The side-effect profile is similar to that of PDE-5i. Therefore, PDE-5i and sGC stimulators must not be given together and combined with other nitrates as this can result in significant systemic hypotension.
5. **Proliferative ligands binder:** Sotatercept, a ligand trap linked to the extracellular domain of human ActRIIA, targets select TGF-β superfamily members to rebalance pulmonary vascular homeostasis toward anti-proliferative and pro-apoptotic signaling. In animal models of pulmonary hypertension, it inhibited vascular cell proliferation, promoted apoptosis, and reduced inflammation, facilitating reverse vascular remodeling. In STELLAR trial, sotatercept improved exercise capacity (6-minute walk test at 24 weeks) compared to placebo, but was associated with higher incidences of adverse events such as epistaxis, dizziness, telangiectasia, thrombocytopenia, increased hemoglobin levels, and elevated blood pressure.

Initial combination therapy with ERA and PDE-5i is recommended for patients presenting at low or intermediate risk. Adding selexipag should be considered in the low-intermediate risk group if there is a risk of clinical worsening. In patients who are at high risk while receiving oral therapies, the addition of IV epoprostenol or IV treprostinil should be considered, and switching from PDE-5i to riociguat may be considered.

C. **Treatment of non–group 1 PAH.** Many pulmonary vasodilators have been evaluated for various non-PAH groups, such as left-sided

heart disease and lung disease. The following recommendations are based on current evidence:

1. **Group 2 PH (left-sided heart disease).** Prostanoids and ERAs are associated with an increased event rate in patients with LV dysfunction and are contraindicated. ERA therapy is associated with an increased risk of fluid retention in patients with LHD. There is some evidence of improvement in the quality of life, exercise performance, and hemodynamics with sildenafil in patients with LHD and in patients bridged to transplantation with an LV assist device.
2. **Group 3 PH (lung disease of hypoxia).** There is new evidence that inhaled treprostinil (Tyvaso) may be used in patients with Interstitial Lung Disease due to improvement in exercise capacity. A study of Inhaled treprostinil in COPD is ongoing.
3. **Group 4 PH (CTEPH).** The current data on therapy with riociguat have shown to improve 6MWD and reduce PVR in the microvascular component of CTEPH and in patients with inoperable CTEPH or those with persistent/recurrent PH after PE. There is also evidence for the use of sildenafil, tadalafil, and macitentan in patients with CTEPH.

D. **Interventional and surgical therapies.** In CTEPH, pulmonary thromboendarterectomy (PTE) is potentially curative and treatment of choice in patients with accessible disease. Balloon pulmonary angioplasty has become an available treatment option for patients with inoperable CTEPH or persistent/recurrent PH with PVR >4 WU after PTE. It is recommended that surgical evaluation and balloon angioplasty be performed at high-volume centers. Balloon atrial septostomy and Potts shunts are rarely performed for palliation in patients with advanced PAH with recurrent syncope and/or right heart failure who have failed all available medical treatments. RV assist devices and venoarterial extracorporeal membrane oxygenation have become established therapies in postoperative RV failure in the presence of PH and bridging tools to transplantation in patients with irreversible right heart failure. Lung transplantation should be considered in eligible patients who remain in New York Heart

Association functional class III or IV or high risk (based on clinical risk scores) despite optimal vasodilator therapy, progressive disease despite therapy, signs of end-organ dysfunction (including liver and renal dysfunction), and those with high-risk PH etiologies, including pulmonary veno-occlusive disease.

VI. PROGNOSIS, FOLLOW-UP, AND PERIOPERATIVE MANAGEMENT

A. Prognosis. Survival in patients with PH differs between PH groups and also within each group depending on the etiology. Best data regarding prognosis are available for the IPAH subset population. The natural history of this group shows survival rates of 68%, 48%, and 34% after 1, 3, and 5 years, respectively. There is registry-level evidence that prognosis has improved with pulmonary vasodilator therapies. **Table 14.5** outlines clinical, echocardiographic, and hemodynamic features that may predict the prognosis in patients with PAH. Again, these data are mainly derived from the IPAH population, and it is unknown whether these data are transferable to other PH populations.

TABLE 14.5 Prognostic Variables in Pulmonary Hypertension

Determinant of Risk	Lower Risk	Higher Risk
Clinical evidence of RV failure	No	Yes
Progression	Gradual	Rapid
WHO class	II, III	IV
6-Min walk distance	Longer (>400 m)	Shorter (<300 m)
BNP	Minimally elevated	Very elevated
Echocardiographic findings	Minimal RV dysfunction	Pericardial effusion Significant RV dysfunction
Hemodynamics	Normal/near-normal RAP and CI	High RAP, low CI

BNP, brain natriuretic peptide; CI, cardiac index; PH, pulmonary hypertension; RAP, right atrial pressure; RV, right ventricular; WHO, World Health Organization.

Adapted from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest*. 2004;126:78S-92S.

B. Follow-up: **Routine evaluation.** Assessment at each visit should include physical examination, assessment of functional class, 6MWT at each visit, and echocardiogram at 6 to 12 months. Blood work including biomarkers (NT-proBNP) is usually performed at each visit or with a change in clinical status or therapy; RHC is performed every 6 to 12 months in unstable patients, whereas in stable patients, it is performed when there is a clinical deterioration or change in therapy.

C. Perioperative management of PH. Surgical procedures, which include sedations in patients with PH, are associated with increased mortality, accounting 2% in elective and 15% in emergent noncardiac, nonobstetric surgeries. The mortality risk is directly proportionate to the severity of PH. Local/regional or monitored anesthetic care is preferred due to hemodynamic risks related to general anesthesia (GA), intubation, and mechanical ventilation. If GA is inevitable, etomidate is a favorable induction agent. Propofol should be avoided. Perioperative monitoring with a PA catheter and arterial line is recommended. Supplemental oxygen should be used for all procedures to ensure maintenance of adequate alveolar and systemic oxygenation. If significant postoperative pain is anticipated, it is advisable to use regional analgesia with paravertebral block or epidural analgesia to mitigate the deleterious effect of high-dose opioid use. It is crucial to avoid abruptly stopping all pulmonary vasodilators perioperatively. Vasopressors should be readily available to prevent systemic hypotension. Norepinephrine and vasopressin are preferred vasopressors in patients with PH. In those who require mechanical ventilation, tidal volume and positive end-expiratory pressure (PEEP) should be adjusted to maintain the plateau pressure below 27 and 30 cm H_2O and driving pressure below 14 cm H_2O. Inhaled pulmonary vasodilators (iNO, epoprostenol, iloprost), IV prostanoids (epoprostenol, treprostinil), oral PDE-5i, and IV milrinone can be used in patients with severe PH with postoperative

RV failure. Sildenafil has also been used to help facilitate weaning of iNO without rebound PH.

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SECTION III

Valvular Heart Disease

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Wang

CHAPTER 15

Native Aortic Valve Disease

Nabil Sabbak and Brian P. Griffin

AORTIC STENOSIS

I. INTRODUCTION. Aortic stenosis (AS) causes progressive obstruction of the left ventricular outflow tract (LVOT), resulting in pressure hypertrophy of the left ventricle (LV) and the classic symptoms of heart failure, syncope, and angina pectoris. Stenosis most commonly occurs at the level of the valve; however, subaortic stenosis and supravalvular stenosis are also well-defined entities. Untreated AS is associated with significant morbidity and mortality. The prevalence of all AS among patients >75 years of age is estimated to be approximately 12.4%, with the prevalence of severe AS at roughly 3.4%. As prompt recognition and treatment are associated with improved life expectancy in those patients with symptomatic severe AS, careful evaluation and management can have a significant impact on survival.

II. ETIOLOGY

A. Valvular AS has several causes, including congenital, rheumatic, bicuspid, and most commonly degenerative with resultant calcification.

1. The most common cause of AS in the United States is calcific degeneration. Although initially thought to be the result of normal "wear and tear" of the valve leaflets, there is now ample evidence that suggests that the progression of stenosis is related to an **active** process of inflammation involving the renin-angiotensin system, lipid accumulation, and resultant calcification. Several inflammatory pathways are implicated, including those that utilize osteopontin, bone morphogenetic proteins, and receptor activator

of nuclear factor kappa B ligand. Recent studies suggest that those with excess lipoprotein (a) are at greater risk of aortic valve calcification and progression to stenosis.

   a. Aortic sclerosis is caused by calcification and thickening of the aortic valve without the increased gradients seen in AS. Both aortic sclerosis and calcific AS have been associated with traditional risk factors for atherosclerosis, such as smoking, hypertension, and hyperlipidemia. Aortic sclerosis is associated with increased risk of cardiovascular death and myocardial infarction and can progress to AS. Other conditions associated with calcific AS include Paget disease and end-stage renal disease.

2. **Bicuspid aortic valve (BAV)** is the most common congenital heart defect with a prevalence estimated between 0.5% and 2%, with a 3:1 male predominance. It is present in ∼10% of first-degree relatives; thus, all first-degree relative of patients with BAV should undergo echocardiographic screening for BAV. The most common abnormality seen in bicuspid valves is fusion of the right and left coronary cusps (79.3%), whereas right and noncoronary cusps (19.4%) are less common, and least common is left and noncoronary cusp fusion (0.5%; **Figure 15.1**). Concurrent dilation of the thoracic aorta occurs in as many as 50% of patients, while coarctation, aortic dissection, and coronary anomalies are seen in a minority of patients. BAV may be associated with Shone syndrome (in which multiple left-sided lesions of inflow/outflow obstruction occur), Williams syndrome with supravalvular stenosis, and Turner syndrome with coarctation. Severe AS usually develops by the fifth or sixth decade; however, earlier and later presentations are common.

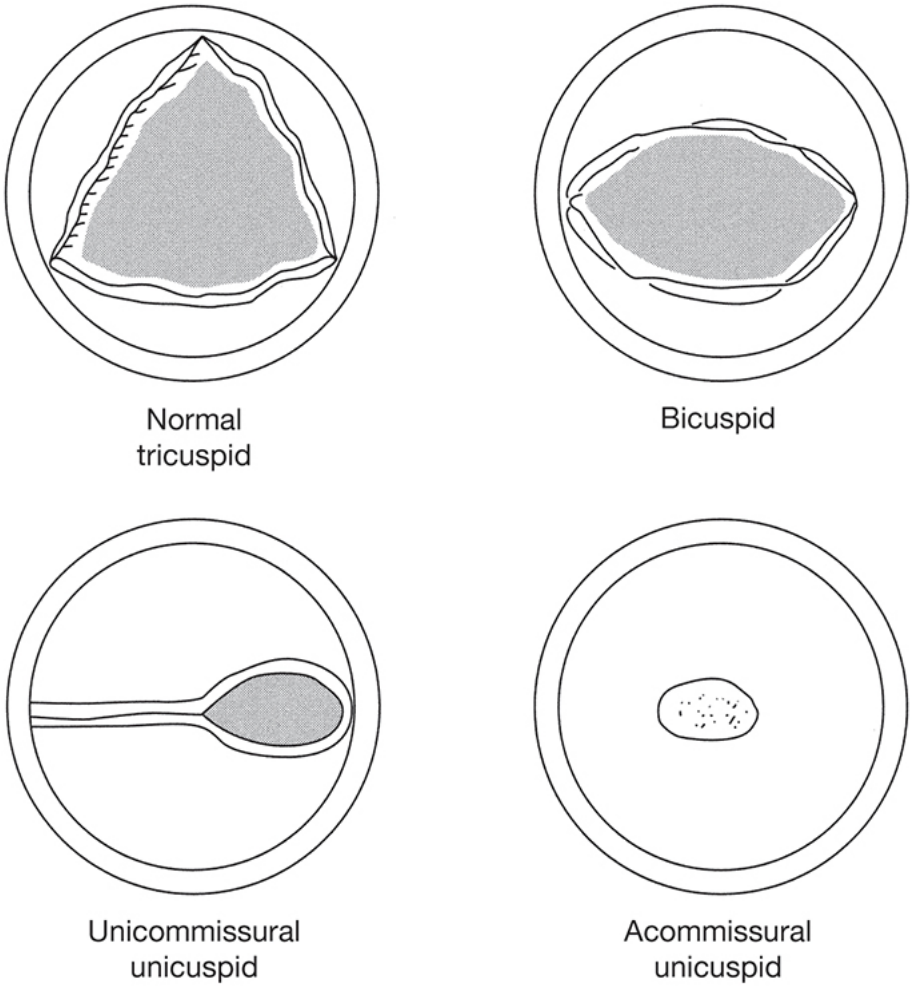

FIGURE 15.1 Schematic representation of parasternal short axis of a congenitally abnormal aortic valve.

a. Diagnosis. The mainstay of diagnosis is echocardiography (transthoracic or transesophageal if transthoracic imaging is suboptimal; 92% sensitivity and 96% specificity if adequate images are obtained). The diagnosis is made during systole in the short-axis view and classically the valve opens as an oval rather than as a triangle in normal people. In situations when echocardiography is nondiagnostic, cardiac magnetic resonance imaging (MRI) and computed tomography (CT) can be used to improve the diagnostic accuracy (American College of Cardiology [ACC]/American Heart Association [AHA] class I indication). In particular, elevated valve calcium score can

elucidate the severity of AS when other tests are equivocal (>2,000 AU in men, >1,300 AU in women). Gated four-dimensional (4D) CT may also provide additional information regarding valve anatomy, area, and degree of leaflet restriction.

b. Complications

(1) Infective endocarditis. The lifetime risk of infective endocarditis (IE) in the current era is 3%. On the basis of these data, prophylactic antibiotic therapy for dental procedures in isolated BAV is no longer recommended, except in patients with prior IE. Unfortunately, when IE does occur in BAVs, it is associated with a higher incidence of perivalvular abscess and worse outcomes compared with tricuspid aortic valves.

(2) Aortopathy is present in ~50% of individuals with BAV and typically involves the aortic annulus, sinus, and proximal ascending aorta. In patients undergoing aortic valve replacement (AVR), 30% will require concomitant aortic root surgery. Per the 2020 ACC/AHA valve guidelines, aortic surgery is indicated when the aorta is ≥5.5 cm (class I) and there is no indication for valve surgery. However, if the patient is undergoing concurrent AVR and the aorta is ≥4.5 cm, concomitant aortic replacement is a class IIa indication. When the aorta is ≥5.0 cm and the rate of increase in diameter is ≥0.5 cm/y, this is considered a class IIa indication for aortic replacement. In addition, if the surgery is to be performed by an experienced aortic surgical team and the patient has a low surgical risk, it is reasonable to perform aortic surgery once the aorta is ≥5.0 cm. Increasingly, the relationship of patient size to aorta size is being appreciated and therefore when the maximal ascending/aortic root area in square centimeters divided by the patient's height in meters exceeds 10, this is considered an indication for surgical intervention by some authorities. In addition, serial evaluation of the aortic sinuses and

ascending aorta by echocardiography, cardiac MRI, or CT angiography is recommended in all patients with BAV and should be performed annually in patients with aortic diameter >4.0 cm (ACC/AHA class I).

3. **Unicuspid aortic valve (UAV)** is a rare valvular anomaly and is described as being either pinhole-shaped acommissural UAV (typically presents at birth) or slit-shaped unicommissural UAV (**Figure 15.1**). Patients typically present for cardiac surgery in their 30s and UAV shares many of the features of BAV including risk of aortopathy, aortic dissection, IE, coronary artery anomalies, patent ductus arteriosus (PDA), and coarctation.
4. **Rheumatic AS** often coexists with aortic regurgitation (AR) and mitral valve lesions, especially mitral stenosis. It is a rare cause of isolated severe AS in the industrialized world. Fusion of the commissures occurs, leaving a small central orifice.

B. **Subvalvular AS** is a congenital condition, although it may not be apparent at birth. Typically, a circumferential **fibromuscular membrane involving the anterior mitral valve leaflet is present in the LVOT below the aortic valve**. In more extreme cases, a tunnel-like obstruction may be present, rather than a discrete membrane. The pathogenesis of this condition is not perfectly understood but is thought to represent a maladaptive response to abnormal flow dynamics in the LVOT. It may exist with other left-sided obstructive lesions, such as coarctation or as part of Shone syndrome. The condition may recur even after successful membrane resection. Subvalvular AS may be difficult to distinguish from hypertrophic obstructive cardiomyopathy (HOCM), especially when secondary left ventricular hypertrophy (LVH) is pronounced. The echocardiographic Doppler profile across the LVOT may distinguish between a fixed versus dynamic LVOT obstruction in such cases. Characteristically, a "dagger-shaped" profile is associated with the dynamic obstruction from systolic anterior motion (SAM) of the anterior mitral valve leaflet in HOCM.

C. **Supravalvular AS** is uncommon and may occur as part of a congenital syndrome such as Williams syndrome in which a mutation

in the elastin gene occurs. Characteristic features of Williams syndrome include hypercalcemia, elfin facies, developmental delay, small stature, and multiple stenoses in the aortic and peripheral arteries. Lipid deposits in severe forms of familial hypercholesterolemia may also cause obstruction above the valve in the ascending aorta.

III. PATHOPHYSIOLOGY

A. Pressure overload. All forms of AS are characterized by progressive narrowing of the effective valve orifice area. To maintain cardiac output in the face of increased afterload, the LV must generate higher systolic pressures, which increases LV wall stress. In response to the pressure overload and increased wall stress, the LV undergoes compensatory concentric hypertrophy. The increase in LV wall thickness allows the wall stress to normalize according to Laplace's law: wall stress = (pressure × radius)/(2 × thickness). Eventually, the LV is unable to adequately compensate for the pressure overload and LV dilation and systolic dysfunction ensue (**Figure 15.2**).

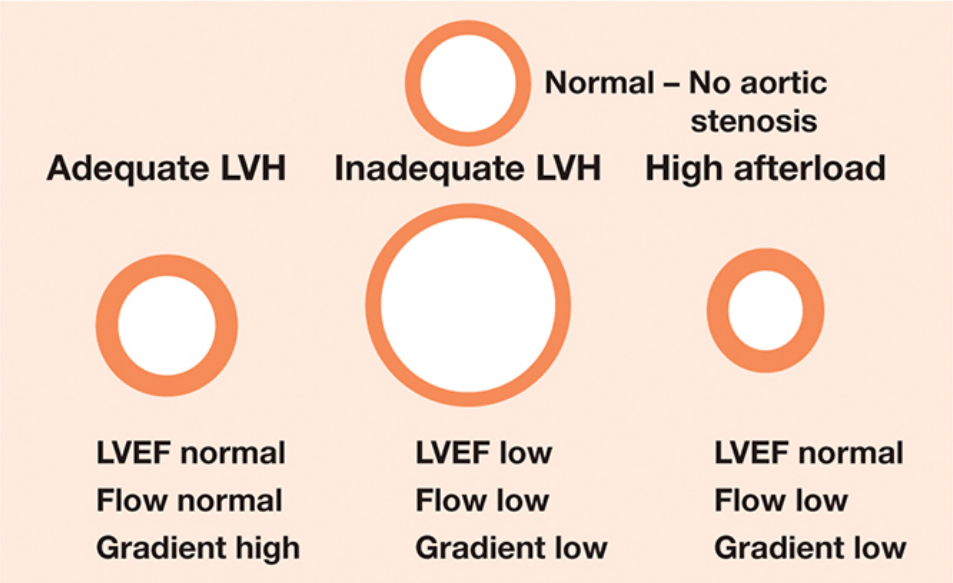

FIGURE 15.2 Aortic stenosis: left ventricular compensatory response. LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy.

B. Diastolic dysfunction. LV diastolic function is determined by LV relaxation properties and LV compliance (ie, change in volume with change in pressure [d*V*/d*P*]). Increased afterload and LVH lead to a reduction in LV compliance. Furthermore, there are changes in strain and torsion characteristics of the LV in AS. Passive early diastolic filling is reduced, and maintenance of an adequate LV preload becomes more dependent on active left atrial contraction.

C. Supply-demand mismatch. Myocardial oxygen is determined by heart rate, contractility, and myocardial wall stress imposed on the LV by progressive pressure overload. As the AS becomes more severe, wall stress and myocardial oxygen demand increase in parallel. Concurrently, AS is associated with a decrease in myocardial oxygen supply. Progressive LVH and diastolic dysfunction lead to an elevation in left ventricular end-diastolic pressure (LVEDP). Elevated LVEDP leads to decreased perfusion pressure across the coronary bed and causes endocardial compression of small intramyocardial arteries, impairing coronary flow reserve. The imbalance between myocardial oxygen supply and demand can precipitate ischemia during exertion, even in the absence of significant obstructive coronary disease.

IV. NATURAL HISTORY. The classic survival curve for patients with untreated AS, as described by Ross and Braunwald, is shown in **Figure 15.3**.

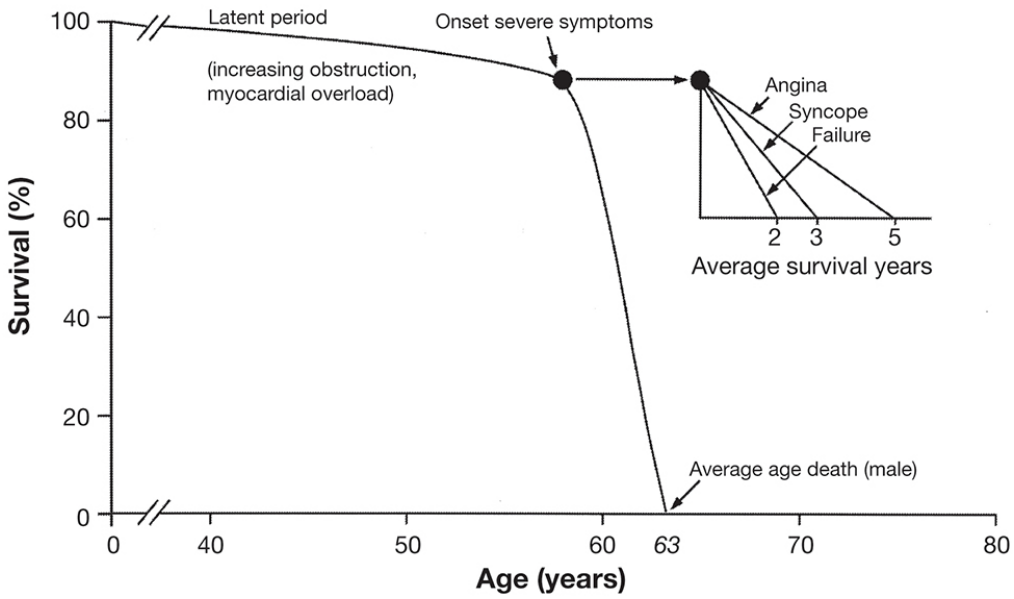

FIGURE 15.3 Patient survival in aortic stenosis.

A. Asymptomatic patients

1. The disease process of AS is characterized by a long latent phase, during which the patient has no symptoms. This period is associated with near-normal survival. The risk of sudden cardiac death in asymptomatic patients with critical AS is <2% per year.
2. Although the underlying cause helps predict the age of symptom onset, there is marked individual variability in the length of the latent period and the subsequent rate of progression of disease. In general, among patients with asymptomatic valvular AS, the mean aortic valve gradient rises by 7 mm Hg/y, peak transvalvular velocity increases by 0.1 to 0.3 m/s/y, and aortic valve area (AVA) decreases by 0.1 cm^2/y.
3. Because of the variable rate of disease progression, all patients with AS should be advised to report the onset of any symptoms to their physician and should be followed clinically and with Doppler echocardiography with increasing frequency as the lesion progresses.

a. 2020 ACC/AHA guidelines for frequency of echocardiogram monitoring

(1) Mild—Every 3 to 5 years

(2) Moderate—Every 1 to 2 years

(3) Severe—Every 6 to 12 months

4. Once the **valve becomes severely stenotic, as evidenced by a peak Doppler velocity of 4 m/s, the likelihood of development of symptoms or requiring surgical intervention over the following 2 years is very high**. This likelihood is increased if the valve is heavily calcified.

B. Symptomatic patients. When symptoms of AS develop, the survival rate decreases markedly, unless AVR is performed.

1. In historical studies, patients with **angina** have a 50% 5-year survival rate without surgical intervention. Those with **syncope** have a 50% 3-year survival rate without surgical intervention. Patients with **heart failure** have a mean survival time of <2 years if treated medically.
2. In patients with severe, symptomatic AS, sudden cardiac death can occur in the setting of hypotension or arrhythmia due to ischemia, LVH, or impaired LV function. Resuscitation in this situation is difficult because of the difficulty of obtaining adequate transmural LV perfusion and cardiac output.
3. Signs and symptoms of severe AS may be subtle in some patients. Since AS is a slowly progressive disease, patients may subconsciously adapt their activities and thus remain "asymptomatic." Information concerning activity levels from family members may be useful in this situation, as may a symptom-limited stress echocardiogram to quantify the patient's functional capacity. Those with impaired functional capacity have been shown to have worse outcomes in the absence of valve replacement. **Exercise stress testing is absolutely contraindicated in the setting of definite symptoms (class III)**.

V. CLINICAL MANIFESTATIONS

A. Signs and symptoms. The onset of symptoms usually indicates progression to severe AS and heralds the need for surgical evaluation.

1. **Angina.** Patients with severe AS can experience ischemia from myocardial supply-demand mismatch due to high LV diastolic pressures, decreased myocardial perfusion, and increased wall stress. Angina can also result from underlying coronary artery disease (CAD). CAD is common among patients with severe AS and occurs in 40% to 80% of patients with angina and 25% of patients without angina.
2. **Syncope.** Because of a fixed LVOT obstruction, patients with severe AS are unable to augment their cardiac output under conditions of low systemic vascular resistance (SVR) (ie, induced by certain medications or vasovagal reactions). The ensuing hypotension can cause presyncope, syncope, or even cardiovascular collapse and death. Syncope can also result from atrial or ventricular arrhythmias, abnormal baroreceptor function, or abnormal vasodepressor responses induced by LV pressure overload.
3. **Heart failure** symptoms, such as exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and fatigue, may result from LV systolic or diastolic dysfunction.

B. Physical findings

1. **Arterial examination.** A hallmark finding in AS is a diminished and delayed carotid upstroke, pulsus parvus et tardus. However, older patients with noncompliant vessels or patients with concomitant AR may often maintain a normal carotid pulsation, despite severe AS. These findings are rare with obstruction above or below the valve. It is classically thought that severe AS is not associated with hypertension, as the narrowed valve limits the flow into the arterial system and thus gives rise to a narrowed pulse pressure and relative hypotension. In fact, in the older patients, hypertension and severe AS may often coexist, likely as a result of impaired elasticity of the aortic walls, and the finding of arterial hypertension does not preclude significant associated AS.
2. **Palpation.** With LVH and normal LV cavity dimensions, the apical impulse is usually nondisplaced, diffuse, and sustained. However, the apical impulse may later be displaced when there is

LV systolic dysfunction. A double apical impulse represents a palpable *a* wave or S_4, caused by a noncompliant LV. A systolic thrill may be palpable in the second right intercostal space.

3. **Auscultation.** The main auscultatory findings are shown in **Figure 15.4**.

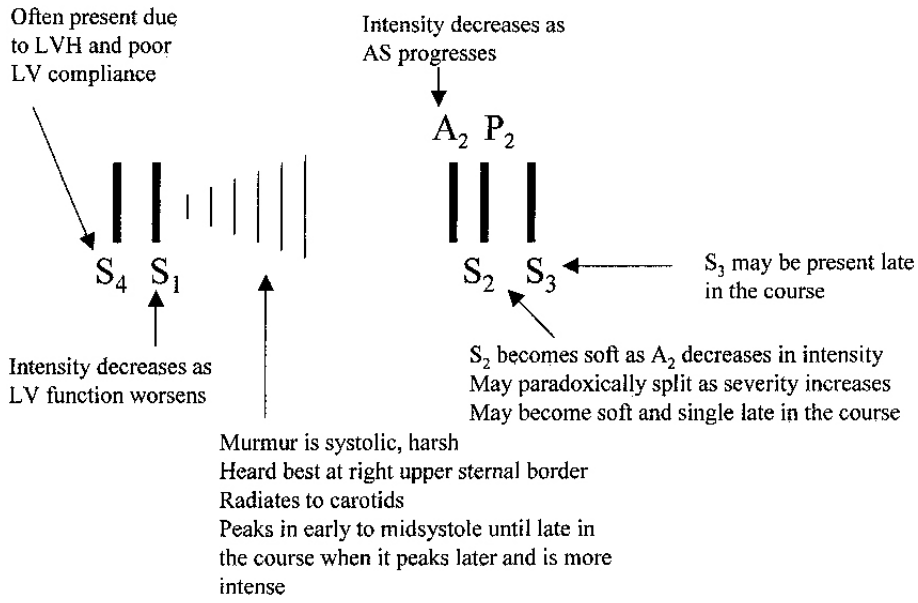

FIGURE 15.4 Auscultatory findings in aortic stenosis. AS, aortic stenosis; LV, left ventricle; LVH, left ventricular hypertrophy.

a. The typical murmur of AS is a systolic ejection murmur heard at the right upper sternal border that radiates to the neck. With a mobile bicuspid valve, an aortic opening sound or **click** may precede the murmur. As the severity of the stenosis increases, the murmur becomes longer and peaks later in systole. The intensity of the murmur does not necessarily correspond to the severity of AS. S_1 is usually normal in AS. As the AS becomes more severe, the aortic component of S_2 diminishes and eventually disappears, resulting in a soft, single S_2. Often, with severe AS, S_2 is paradoxically split because of the prolonged ejection duration through the severely narrowed valve. The

presence of an S_3 is indicative of poor LV systolic function. An S_4 is appreciated because of reduced LV compliance.

b. Careful examination for other murmurs should be performed. AS is often accompanied by AR. Maneuvers performed during the physical examination can help differentiate different types of LV outflow obstruction, whether this is at, below, or above the valve. These are summarized in **Table 15.1**.

TABLE 15.1 Physical Findings and Maneuvers Useful in Distinguishing Various Forms of Left Ventricle Outflow Tract Obstruction

Maneuver/Finding	Valvular	Supravalvular	Subvalvular	Hypertrophic Cardiomyopathy
Pulse volume after PVC	Increases	Increases	Increases	Decreases
Valsalva effect on systolic murmur	Decreases	Decreases	Decreases	Increases
Aortic regurgitation	Common	Rare	Common	Rare
S_4	Common	Uncommon	Uncommon	Common
Carotid pulse	Normal to anacrotic (parvus et tardus)	Unequal	Normal to anacrotic	Rapid jerky upstroke

PVC, premature ventricular contraction.

C. Diagnostic testing

1. The typical **electrocardiogram (ECG)** of a patient with isolated severe AS usually demonstrates left atrial abnormality (80% of cases) and LVH (85% of cases), but a normal ECG does not exclude severe AS. **Chest radiography** can be entirely normal, even in patients with critical LVH. The cardiac silhouette may become boot-shaped because of the concentric LVH. Cardiomegaly may be identified if there is LV dysfunction or coexisting AR. Aortic valve and root calcification can be seen in

adults with severe calcific, degenerative AS. Poststenotic dilation of the ascending aorta may also be evident.

2. **Natriuretic peptides** are released in response to pressure overload of the LV. There is increasing evidence that supranormal levels of these peptides may indicate early decompensation of the LV even in the presence of normal left ventricular ejection fraction (LVEF).
3. **Anemia** commonly coexists with AS in the older patients who appear to be at increased risk of dysplastic vascular lesions in the bowel, which may bleed. Increased risk of bleeding may also occur because of disruption of Von Willebrand molecules with turbulent flow at the stenotic aortic valve (Heyde disease). Rarely, AS is so severe and turbulent to lead to intravascular hemolysis in a native valve.

D. Severity of AS. The severity of AS as defined by the 2020 ACC/AHA valve guidelines is summarized in **Table 15.2**. A normal aortic valve opens 3 to 4 cm^2.

TABLE 15.2 Aortic Stenosis Severity Parameters

Valve Severity	AVA (cm^2)	Mean Gradient (mm Hg)	Jet Velocity (V_{max}) (m/s)	Miscellaneous
Mild	>1.5	<20	2.0-2.9	
Moderate	1.0-1.5	20-30	3.0-3.9	
Severe	0.6-1.0	≥40	≥4.0	
Very severe	<0.6	≥60	≥5	
LFLG severe	<1.0	<40	<4	LVEF <50%; DSE shows AVA[a] <1.0 cm^2 with V_{max} ≥4 m/s at any flow rate.
Pseudosevere	<1.0	<40	<4	LVEF <50%; DSE increases AVA[a] by >0.3 cm^2.

Valve Severity	AVA (cm^2)	Mean Gradient (mm Hg)	Jet Velocity (V_{max}) (m/s)	Miscellaneous
Paradoxical LFLG	<1.0	<40	<4	LVEF ≥50%; stroke volume index <35 mL/m^2

AVA, aortic valve area; DSE, dobutamine stress echocardiography; LFLG, low-flow/low-gradient; LVEF, left ventricular ejection fraction; V_{max}, aortic valve maximum velocity.

[a]Dependent on the presence of contractile reserve (20% increase in stroke volume with DSE).

E. Echocardiography

1. **Transthoracic Doppler echocardiography** is the test of choice to establish the diagnosis of AS, to determine the cause and location, and to assess its severity. It should be performed when the diagnosis of AS is first suspected and information such as LV wall thickness, size, and function should also be obtained. After the diagnosis is established, patients should have frequent regular clinical follow-up examinations to look for the development of symptoms. Development of new symptoms and signs should quickly prompt a repeat evaluation.

   a. The parasternal long-axis views, 2D and M-mode, provide valuable information for determining the mechanism and severity of AS. In this view, the coaptation line of the aortic valve is normally centered within the LVOT in a trileaflet valve. The leaflets of a bicuspid valve often have an eccentric closure line, typically posterior to the midline. Systolic leaflet doming can be seen in congenital AS and rheumatic AS. The degree of LVH, chamber enlargement, or left atrial enlargement can be quantitated using 2D and M-mode imaging. The LVOT diameter used in the continuity equation is measured in the 2D, parasternal long-axis view. Subaortic stenosis and supravalvular AS may also be detected in this view. **Subaortic stenosis** may be evident as a membrane below the aortic valve with normal opening of the valve. Pulsed Doppler may indicate that the obstruction is occurring below the valve, and 2D

echocardiogram often shows AR because of the turbulent jet hitting the aortic valve leaflets and causing leaflet scarring and impaired coaptation. In **supravalvular AS**, narrowing above the valve is evident on imaging.

b. The parasternal short-axis view is the most useful view for establishing the cause of congenital AS. The number of commissures and the shape of the valve orifice should be assessed (**Figure 15.1**). In diastole, the valve appears as three commissures and three cusps of equal size creating an inverted Y configuration or "Mercedes-Benz sign." However, this view alone should not be used to determine the anatomic morphology of the valve because in "functionally" bicuspid valves from commissural fusion, a raphe is present creating the appearance of a trileaflet valve. Thus a systolic image should be used to evaluate whether there is a triangular opening (trileaflet) or ellipsoid appearance (bicuspid valve). In UAV, the opening is elliptical but occurs across a radius rather than the diameter of the valve.

c. The apical five-chamber and three-chamber views are well aligned with flow through the aortic valve. Continuous wave Doppler recordings across the aortic valve and pulsed wave Doppler flow in the LVOT proximal to the aortic valve are recorded in these views for the continuity equation.

d. Continuous wave Doppler should be performed at multiple sites, including the suprasternal notch and the right sternal border, to ensure that the maximal velocity across the aortic valve is recorded. **Failure to obtain the maximum velocities will result in underestimation of the severity of AS**. The dimensions of the ascending aorta should be sought, especially in those with BAV.

e. Newer technologies such as strain imaging are increasingly being employed in the assessment of ventricular function especially in those with normal LVEF. There is an increasing body of evidence that global myocardial strain is abnormal

before the onset of reduced LVEF and may of itself be an indicator of higher long-term risk.

2. **Transesophageal echocardiography (TEE).** Planimetry of the aortic valve orifice is often possible with TEE and relates well to that measured by cardiac catheterization. Although 2D planimetry correlates reasonably with valve area measured by other techniques, where possible 3D TEE assessment of valve area should be performed to optimize the detection of the smallest valve area. Planimetry is difficult when the valve is extremely calcified. In a bicuspid valve, the smallest area should be sought carefully, as the valve opening is not planar but rather forms a cone because of the doming of the valve as it opens. TEE is particularly useful for determining the morphologic features of the valve in congenital AS. TEE is often necessary to confirm the diagnosis of subaortic membrane and to differentiate it from hypertrophic cardiomyopathy or valvular AS.
3. **Dobutamine stress echocardiography (DSE) and exercise stress echocardiography (ESE).** When discrepancy exists regarding the severity of valve disease and symptoms, exercise stress testing can be helpful in objectively quantifying their functional capacity and appropriate classification of their valve disease. In patients with asymptomatic severe AS, two-thirds of ESEs are abnormal, including one-third being attributed to the development of symptoms alone. In addition, a normal test provides reassurance with an excellent 1-year prognosis with continued medical management and monitoring for the development of symptoms.

   Low-dose DSE is used in appropriately classifying patients with low-flow, low-gradient AS into true severe AS, pseudosevere AS, or paradoxical severe AS.
4. **Other imaging modalities.** CT scanning is increasingly used in the assessment of patients with AS, particularly those in whom transcatheter aortic valve replacement (TAVR) is a consideration to determine appropriate valve annulus and peripheral vessel sizing and to avoid complications such as coronary impingement,

aortic size and calcification, and other comorbidities. When there is doubt about the severity of AS, the degree of calcification of the aortic valve by CT imaging as well as direct valve area planimetry may provide useful information. An aortic valve calcium score on noncontrast CT of >2,000 AU in men and >1,200 AU in women is highly correlated with severe AS. MRI is helpful in patients with congenital forms of AS associated with other anomalies. MRI may also be helpful in quantifying regurgitant volume, LV chamber quantification, and aortic size in cases of concomitant aortic insufficiency. In patients with renal dysfunction, which may preclude contrast CT study, MRI may be an option. A CT without contrast may still provide adequate information to assess vascular calcification and AS severity as mentioned earlier.

F. Hemodynamic calculations

1. **Doppler echocardiography** is the standard modality used for the assessment of transvalvular pressure gradients and AVA.
   a. **Simplified Bernoulli equation ($\Delta P = 4v^2$)**, in which P is the pressure and v is peak velocity of flow across the aortic valve, is used to estimate the peak instantaneous gradient. The mean gradient across the valve can be determined by measuring the area under the Doppler envelope. The peak velocity of flow across the aortic valve should be measured in three areas: the LV apex, the right sternal border, and the suprasternal notch. The highest measured velocity is used to calculate the peak transvalvular gradient. When stenosis is present at two levels (ie, in LVOT and at the valve), the gradient across the LVOT reflects the integrated effects of the obstruction at both levels. It is usually impossible with Doppler to precisely differentiate the contribution of each level of obstruction to the total. This may be inferred by analysis of the images, by TEE, or by direct measurement by cardiac catheterization.
   b. Calculation of AVA based on the **continuity principle**, which states that flow of an incompressible fluid in a closed system must remain constant. Flow in a vessel is the product of the cross-sectional area (A) of the vessel and the velocity (V). Area

is calculated as πR^2 or $\pi D^2/4 = 0.785D^2$, where R is the radius of the vessel and D is the diameter. A schematic representation of the variables for calculating AVA is shown in **Figure 15.5**. The continuity equation for the aortic valve is as follows:

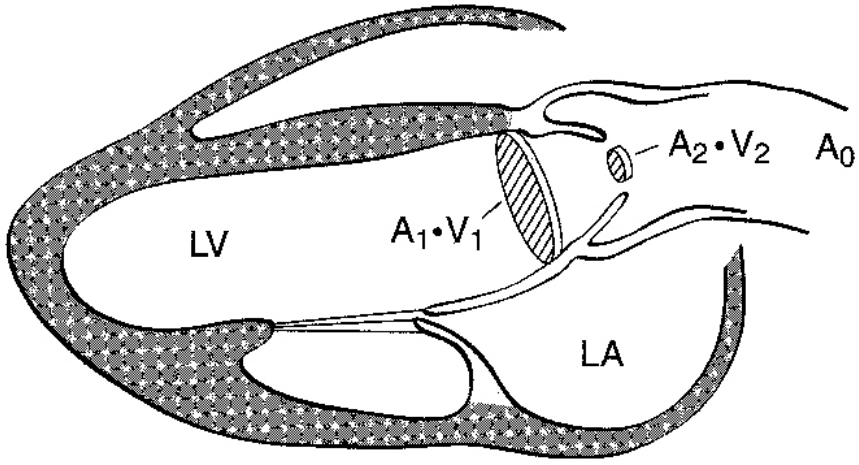

FIGURE 15.5 A schematic representation of parasternal long-axis view and the continuity principle. LA, left atrium; LV, left ventricle.

$$\text{Area}_{\text{aortic valve}} = \text{diameter}_{\text{LVOT2}} \times 0.785 \times \text{VTI}_{\text{LVOT}}/\text{VTI}_{\text{aortic valve}}$$

In the above equation, VTI is the time-velocity integral. The continuity equation is valid only for valvular AS. It cannot be used to assess valve area when there are stenoses in series such as valvular and subvalvular narrowing occurring simultaneously. Accurate measurement of the LVOT is imperative for an accurate calculation, and this value is squared, and a misrepresentation may drastically miscalculate the valve area.

c. Care should be taken to avoid measuring post-extrasystolic beats. If the patient is in atrial fibrillation, ideally 10 consecutive beats should be measured and averaged for both velocity measurements.

d. During evaluation of an aortic valve prosthesis, the standard continuity equation cannot be used. Instead, the velocity ratio or dimensionless index is used to estimate the severity of prosthetic stenosis. It is calculated by dividing the peak velocity in the LVOT by the peak velocity through the aortic valve. **A dimensionless index of <0.25 is generally accepted to represent severe stenosis**. This is also useful if the LVOT diameter is difficult to ascertain.

2. **Cardiac catheterization** was once considered the gold standard for the quantification of AS but is now only indicated in symptomatic patients when there is discrepancy between physical examination and noninvasive testing or when noninvasive tests are inconclusive in regard to the severity of the valve lesion (ACC/AHA class I indication).

   a. Preoperative left heart catheterization is indicated before valve intervention in patients with symptoms of angina, objective evidence of ischemia, decreased LV systolic function, history of CAD, or coronary risk factors (including men aged >40 years and postmenopausal women) (ACC/AHA class I indication).

   b. Catheter-derived hemodynamics often differ from those of echocardiography and thus it is important to understand the differences in what is being measured. The mean gradients obtained during catheterization should be equivalent to the mean gradients obtained by echocardiography. These correlate well when performed expertly and simultaneously. The peak gradient measured during catheterization is the peak-to-peak gradient, which is lower than the peak instantaneous gradient obtained with echocardiography (**Figure 15.6**). **In the setting of reduced cardiac output of any cause, the aortic gradient may be lower and may be <20 mm Hg in severe LV dysfunction despite critical AS**.

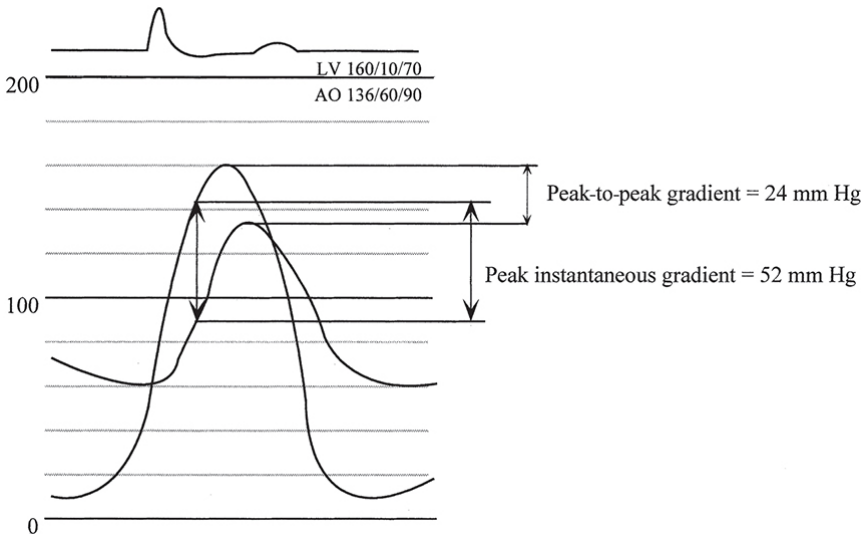

FIGURE 15.6 Simultaneous recording of LV and aortic pressures. AO, aorta; LV, left ventricle.

c. The most precise measurement of transaortic valvular gradient is made with two different catheters (one in the LV cavity and the other in the ascending aorta or with a double lumen pigtail catheter). A less optimal method is measuring the peak-to-peak gradient by catheter pullback from the LV to the ascending aorta. A typical pressure tracing of simultaneous LV and aortic pressures is shown in **Figure 15.6**.

d. Catheterization of the patient with severe AS should be performed with low-osmolar, nonionic contrast agents. These cause less hypotension because of peripheral arterial vasodilation, less bradycardia, less transient myocardial dysfunction, and less osmotic diuresis after the procedure. Left ventriculography should be avoided.

e. The **Gorlin formula** is used to estimate the AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/(44.3 \times \text{heart rate} \times \text{SEP} \times \sqrt{\text{MVG}})$$

In this equation, SEP is the systolic ejection period, defined as the time from aortic valve opening to closing (in seconds), and MVG is the mean valvular gradient (mm Hg). The **Gorlin formula** measures the **true anatomic area** of the aortic valve,

as it has a correction factor (the discharge coefficient) to account for the difference of flow across the true anatomic valve versus the flow at the level of the vena contracta. The continuity equation measures the physiologic area (vena contracta) and as such is smaller than that measured by Gorlin.

f. An alternative measurement can be made by the **Hakki equation**, which is a simplification of the Gorlin formula, where the observation of heart rate × SEP approximates 1,000. This then simplifies the estimation of AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output}/\sqrt{\text{MVG}}$$

VI. THERAPY

A. Medical therapy. The mainstay of therapy for AS is replacement of the aortic valve. Onset of symptoms in patients with severe AS is associated with a marked reduction in lifespan when treated medically, rather than replacement. Medical therapy alone is ineffective for severe symptomatic valvular AS.

1. **Antibiotic prophylaxis.** The 2020 ACC/AHA Guidelines for the Prevention of Infective Endocarditis do not recommend antibiotic prophylaxis before dental procedures with valvular pathology including BAVs unless the patient has a valve prosthesis or prior history of IE.
2. **Medical therapy in patients at risk for developing AS and asymptomatic AS.** Therapy should be directed at primary prevention of CAD, maintenance of sinus rhythm, and blood pressure control. Patients with hypertension should be treated according to guideline-directed medical therapy (GDMT) and started at a low dose, and slowly titrated upward as needed with appropriate clinical monitoring (ACC/AHA class I). Angiotensin-converting enzyme inhibitors (ACEIs) are no longer contraindicated and are potentially advantageous through a reduction in LV fibrosis. Alternatively, diuretics should be avoided solely for use as an antihypertensive if the LV size is small as this can result in a decrease in cardiac output.

3. **Medical therapy in symptomatic patients.** Medical therapies may be necessary in patients with symptomatic severe AS who are awaiting surgery or who are considered inoperable and require palliation. Therapy for heart failure is directed at relief of pulmonary congestion. This is usually achieved with cautious use of diuretics. Overly aggressive diuresis may cause hypotension if hypovolemia significantly impairs cardiac output by diminishing preload. Nitrates may also cause hypotension and syncope by reducing preload and should be avoided or used with extreme caution. Thus, the management of symptomatic patients with AS and CAD is difficult, and urgent valve replacement and revascularization is the optimal treatment where feasible. Digoxin is used for symptom relief in the setting of impaired LV systolic function and volume overload, particularly if atrial fibrillation develops.
4. **Vasodilator therapy** has been formerly relatively contraindicated in patients with AS because of the concern about lowering SVR in the setting of a fixed cardiac output causing syncope, especially in the ambulatory setting. However, patients with severe heart failure and LV dysfunction with severe AS may benefit from the careful titration of intravenous nitroprusside in the intensive care unit with concomitant invasive arterial and pulmonary artery catheter monitoring (ACC/AHA class IIb). One study suggests an improvement in hemodynamic indices with this approach. Intra-aortic balloon counterpulsation is another strategy that can be used while patients with LV dysfunction and severe AS in cardiogenic shock are worked up toward urgent valve replacement. Asymptomatic patients who have been successfully treated with vasodilator therapy for hypertension over a period of years do not necessarily need to have this adjusted on diagnosis of AS unless there is evidence of significant hypotension.
5. **Treatment of hyperlipidemia.** The association between AS and risk factors for atherosclerosis has prompted trials with statins to retard the progression of AS. Several studies suggested that when statin therapy is indicated on the basis of current guidelines for

hyperlipidemia, it is associated with a modest effect in slowing the rate of progression of AS. However, in more recent randomized controlled trials of patients with calcific AS, where statin therapy was not otherwise mandated, statins had little effect on AS progression or need for AVR. As such, statin therapy is not indicated for the prevention of progression of calcific AS in patients with mild-to-moderate disease (ACC/AHA class III). However, aggressive low-density lipoprotein (LDL) lowering with statins appears warranted in patients who have an indication for statin therapy. In patients with supravalvular AS due to severe familial hyperlipidemia, improvement in the obstruction may occur after LDL apheresis or aggressive lipid lowering by other means. The impact of lowering lipoprotein (a) levels on AS progression is currently under investigation in clinical trials.

B. Percutaneous aortic balloon valvuloplasty (PABV) is a procedure involving inflation of a balloon across a stenotic aortic valve resulting in an increase in the AVA and cardiac output. Because of the risk of worsening AR, this procedure is contraindicated in patients with concomitant moderate or severe AR. With the advancement in percutaneous AVR, the usage of PABV has increased significantly as a bridge to valve replacement.

1. In pediatric congenital, noncalcific AS, PABV is a safe and effective therapy comparable to surgical repair or replacement. The goal of PABV in congenital AS is to achieve a 60% to 70% reduction in measured peak-to-peak transvalvular gradient. Redilation or AVR becomes necessary within 10 years of the initial PABV in >50% of children. AR is well recognized as a potential early or late complication of PABV, although moderate-to-severe AR only occurs in a minority of cases.
2. In adults, PABV has limited utility and long-term effectiveness while also being associated with substantial risks. On average, the effective orifice area is increased by 0.44 cm^2 with a decrease in mean aortic gradient of 24 mm Hg. However, the effects are short lived with an ~50% restenosis rate at 5 months and 80% at 15 months. **No survival benefit with PABV has been reported even**

in those with the largest increment in valve area. Complication rates are diminishing with improvements in technology and techniques, but there are still considerable risks of vascular complications (6.8%), respiratory failure (6.5%), and strokes (2.9%).

The general indications for PABV are (1) as a bridge to definite replacement with either TAVR or surgical AVR in critically ill patients (SAVR; ACC/AHA class IIb); (2) to assess degree to symptomatology due to AS when the patient has other comorbidities (ie, severe COPD), which may mimic the symptoms of AS; and (3) as a means of palliation for patients who are not candidates for TAVR/SVR. PABV is generally not recommended before moderate-risk elective noncardiac surgery in patients with asymptomatic severe AS. Such patients are better served with appropriate intraoperative and postoperative hemodynamic monitoring to avoid significant periprocedural hypotension (ACC/AHA class IIa).

C. TAVR. Since it was first performed by Alain Cribier in 2002, TAVR has evolved as an established method to treat severe AS. TAVR involves the placement of a stented bioprosthetic valve over the native aortic valve, or within a prior implanted bioprosthetic valve (valve-in-valve). This is typically performed percutaneously via the transfemoral arterial approach. Occasionally, when there are access site limitations, this may be performed via subclavian, axillary, or carotid approach. Rarely, transaortic or transapical approach via mini-sternotomy or thoracotomy is employed.

1. **Indications.** Patients with severe AS should be evaluated by a multidisciplinary group including healthcare professionals in valvular heart disease, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery (ACC/AHA class I). The indications for AVR, whether surgical or transcatheter, are summarized in **Table 15.3**. In patients for whom a bioprosthetic AVR is appropriate, the decision to pursue TAVR versus SAVR is based on surgical risk, age, life expectancy, and anatomy (**Table 15.4**). Generally, in patients who are at high or prohibitive

surgical risk with a life expectancy >1 year, TAVR is recommended (ACC/AHA class I). In patients who are at low or intermediate risk between the ages of 65 and 80, TAVR or SAVR may be considered based on patient-specific characteristics and preferences (ACC/AHA class I). In patients aged 65 years or below, SAVR is the preferred approach. Procedure- and patient-specific factors that may influence the decision to pursue TAVR versus SAVR are summarized in **Table 15.5**. In patients aged 80 years or above, TAVR is preferred (ACC/AHA class I) and SAVR may be considered (ACC/AHA class IIa).

TABLE 15.3 Recommendations for Aortic Valve Replacement in Patients With Aortic Stenosis

Class I
• Symptomatic severe high gradient AS • Asymptomatic patients with severe AS and LVEF <50% • Asymptomatic patients with severe AS undergoing cardiac surgery for another reason • Symptomatic patients with low-flow, low-gradient severe AS with reduced LVEF • Symptomatic patients with low-flow, low-gradient severe AS with normal LVEF
Class IIa
• Apparently asymptomatic patients with severe AS and low surgical risk when exercise test demonstrates decreased functional capacity or a fall in systolic blood pressures ≥10 mm Hg • Asymptomatic patients with very severe AS (defined as aortic velocity ≥5 m/s) and low surgical risk • Apparently asymptomatic patients with severe AS and low surgical risk when the serum BNP level is >3 times normal • Asymptomatic patients with severe AS and low surgical risk when serial testing shows an increase in aortic velocity ≥0.3 m/s/y
Class IIb
• Asymptomatic patients with severe AS and progressive decrease in LVEF on at least three serial imaging studies to <60%

- Patients with moderate AS who are undergoing cardiac surgery for another indication

AS, aortic stenosis; BNP, B-type natriuretic peptide; LVEF, left ventricular ejection fraction.
Adapted with permission from Otto CM, Nishimura RA, Bonow RO, et al; Writing Committee Members. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021;77(4):e25-e197. Copyright © 2020 by the American Heart Association, Inc, and the American College of Cardiology Foundation.

TABLE 15.4 Recommendations for Choice of TAVR Versus SAVR When Bioprosthetic AVR Is Indicated

Class I

SAVR is recommended for patients with any indication for AVR who are <65 y of age or have a life expectancy >20 y.
For patients between 65 and 80 y of age without anatomic contraindication to transfemoral TAVR, either SAVR or TAVR is recommended after shared decision-making incorporating the balance of valve durability and life expectancy.
TAVR is preferred over SAVR in patients >80 y of age or for younger patients with a life expectancy <10 y.
TAVR is recommended for patients of any age with symptomatic AS and high or prohibitive surgical risk if predicted survival is >12 mo.
Palliative care is recommended for patients with symptomatic severe AS and predicted survival <12 mo or for whom minimal improvement in quality of life is expected.

Class IIb

1. Percutaneous aortic balloon valvuloplasty may be considered in critically ill patients with severe AS as a bridge to TAVR or SAVR.

AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical AVR; TAVR, transcatheter AVR.
Adapted with permission from Otto CM, Nishimura RA, Bonow RO, et al; Writing Committee Members. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021;77(4):e25-e197. Copyright © 2020 American Heart Association, Inc, and the American College of Cardiology Foundation. With permission.

TABLE 15.5 Patient-Specific and Anatomic Risk Considerations for TAVR Versus SAVR

TAVR	SAVR
Technical or Anatomic	
• Preclusive aortoiliac disease • Low coronary height • Extensive LVOT calcification • Bicuspid or unicuspid valve	• Porcelain aorta • Prior mediastinal radiation • Redo sternotomy
Comorbidities	
• The comorbidities listed for SAVR place patients in the intermediate- or high-risk group and would encourage to proceed with the transcatheter option.	• Severe pulmonary disease • Pulmonary hypertension • Severe RV dysfunction • Hepatic dysfunction • Frailty • High STS score

LVOT, left ventricular outflow tract; RV, right ventricular; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

Adapted with permission from Otto CM, Nishimura RA, Bonow RO, et al; Writing Committee Members. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2021;77(4):e25-e197. Copyright © 2020 American Heart Association, Inc, and the American College of Cardiology Foundation. With permission.

2. **Valve types.** Several percutaneous transcatheter aortic valves have received U.S. Food and Drug Administration (FDA) approval in the United States: Edwards SAPIEN XT, SAPIEN 3, SAPIEN 3 Ultra, SAPIEN 3 RESILIA valves; Medtronic CoreValve, CoreValve Evolut R, CoreValve Evolut PRO and PRO+, and Evolut FX; and Abbott Navitor Valve (previously Portico). The ACURATE neo2 (Boston Scientific) is currently undergoing

clinical trials for FDA approval in low-, intermediate-, and high-risk patients. Specifics of these valves are displayed in **Table 15.6**.

TABLE 15.6 Current Available Transcatheter Aortic Valve Replacement Valves

	Company	Deployment	FDA Approval in the United States for Severe AS	Sizes (mm)
Lotus	Boston Scientific	Controlled mechanical expanding	Discontinued production November 2020	23, 25, 27
ACURATE neo2	Boston Scientific	Self-expanding	Under clinical investigation	23, 25, 27
SAPIEN	Edwards Lifesciences	Balloon expandable	Yes, but no longer available	23, 26
SAPIEN XT	Edwards Lifesciences	Balloon expandable	Inoperable, intermediate and high risk; valve-in-valve for AS/AR	20, 23, 26, 29
SAPIEN 3 (S3)	Edwards Lifesciences	Balloon expandable	Low-, intermediate-, high-, or extreme-risk patients; valve-in-valve for AS/AR	20, 23, 26, 29
SAPIEN 3 Ultra	Edwards Lifesciences	Balloon expandable	Low-, intermediate-, high-, or extreme-risk patients	20, 23, 26, 29
SAPIEN 3 Ultra RESILIA	Edwards Lifesciences	Balloon expandable	Low-, intermediate-, high-, or extreme-risk patients	20, 23, 26, 29
CoreValve	Medtronic	Self-expanding	Intermediate-, high-, or extreme-risk patients[a]; valve-in-valve for AS/AR	23, 26, 29, 31
CoreValve Evolut R	Medtronic	Self-expanding	Intermediate-, high-, or extreme-risk patients[a]	23, 26, 29

	Company	Deployment	FDA Approval in the United States for Severe AS	Sizes (mm)
CoreValve Evolut PRO	Medtronic	Self-expanding	Intermediate-, high-, or extreme-risk patients[a]	23, 26, 29
Portico	Abbott	Self-expanding	High- or extreme-risk patients	23, 25, 27, 29
Navitor	Abbott	Self-expanding	High- or extreme-risk patents	23, 25, 27, 29

AR, aortic regurgitation; AS, aortic stenosis; FDA, U.S. Food and Drug Administration.

[a]FDA approval for use in intermediate-risk patients is currently under review.

a. Edwards SAPIEN

(1) **SAPIEN** valve was a **balloon-expandable** bovine pericardial valve attached to a stainless steel stent with a polyethylene terephthalate fabric cuff. This valve is no longer available.

(2) **XT** is a **balloon-expandable** bovine pericardial valve attached to a stainless steel mesh frame with a polyester wrap.

(3) **S_3** is a **balloon-expandable** bovine pericardial valve with polyethylene terephthalate outer skirt to minimize the potential for paravalvular leak.

(4) **S_3** Ultra features a ~40% taller sealing skirt than the **S_3**.

(5) **S_3** Ultra RESILIA features a proprietary bioprosthetic tissue that may mitigate valve calcification.

b. Medtronic

(1) **CoreValve** is a **self-expanding** porcine pericardial valve attached to a flexible nitinol frame.

(2) **CoreValve Evolut R** is a **self-expanding** porcine pericardial valve attached to a nitinol frame with an extended skirt to minimize the potential for paravalvular leak.

(3) **CoreValve Evolut PRO** is a **self-expanding,** repositionable, supra-annular porcine pericardial valve with a porcine pericardial tissue wrap to minimize the potential for paravalvular leak.

(4) **Evolute FX** is the newest iteration of the CoreValve self-expanding valve, with radiopaque gold markers that provide a reference for deployment depth and commissure alignment. There are also advancements in the delivery system with improved flexibility to accommodate tortuous vascular anatomies.

c. Boston Scientific

(1) **Lotus valve** is a **controlled mechanical expanding** bovine pericardial valve on a nitinol frame with polycarbonate seal to minimize the potential for paravalvular leak. The valve was taken off the market in November 2020 due to challenges with the delivery system.

(2) **ACURATE neo2** is a **self-expanding**, supra-annular porcine valve on a nitinol frame with radiopaque positioning markers designed to enhance commissural alignment upon deployment.

d. Abbott

(1) **Navitor (previously Portico) valve** is a **self-expanding** bovine pericardial valve on a nitinol frame with a porcine pericardial cuff within the stent to minimize the potential for paravalvular leak.

3. **Outcomes.** TAVR was developed to offer an alternative for patients with severe symptomatic AS who were not candidates for open surgical replacement because of either an unacceptably high estimated surgical risk or where this is prohibited because of technical challenges (ie, porcelain aorta, radiation heart disease).

Outcomes data from recent studies are summarized later. However, **it is always important to keep in mind that morbidity and mortality figures from clinical trials, although useful, should not replace knowledge of these risks for individual procedures at one's own institution**. When choosing between SAVR and TAVR consideration of surgical risk, comorbidities including patients with severe CAD who may be best served with SAVR and coronary artery bypass grafting (CABG), and patient preference should be taken into account. In addition, there is a relative lack of data on the long-term durability of TAVRs compared with SAVR.

a. **TAVR versus medical therapy in inoperable patients.** The Placement of Aortic Transcatheter Valves (PARTNER) cohort B trial was performed with the Edwards SAPIEN valve compared to medical therapy including PABV. The results of this study showed that the SAPIEN valve met noninferiority criteria with a significant reduction in mortality (20% absolute survival advantage) that persisted out to 5 years and a higher percentage of patients with New York Heart Association (NYHA) class I or II symptoms at 1-, 2-, 3-, and 5-year follow-up. The Medtronic CoreValve underwent a prospective, nonrandomized trial, which showed favorable outcomes at both 1- and 2-year follow-up and with outcomes being driven by the patients' underlying comorbid conditions rather than valve performance.

b. **TAVR in high-risk patients.** PARTNER cohort A trial compared the SAPIEN valve (transapical or transfemoral approach) to SAVR in high-risk patients (mean Society of Thoracic Surgeons predicted risk of mortality [STS-PROM] 11.7%). The results showed similar mortality rates at 1 and 5 years with a stroke risk that was significantly higher at 1 year in TAVR but did not remain significant at 3 and 5 years. The CoreValve high-risk trial compared the CoreValve to SAVR showing noninferiority as well as superiority for 1- and 2-year mortality data based on prespecified criteria. The CoreValve

had similar stroke risk at 1 year with a trend toward a lower stroke risk at 2 years compared with SAVR.

c. **TAVR in intermediate-risk patients.** Three major trials have evaluated the outcomes of TAVR in an intermediate-risk population. The PARTNER IIA trial was a large randomized trial of over 2,000 patients comparing the SAPIEN XT valve to SAVR and showed similar rates for both 2-year mortality and risk of disabling stroke. The SAPIEN 3 valve was evaluated as an observational study via propensity score analysis with the SAVR population in the PARTNER IIA trial. These results showed that the SAPIEN 3 valve was noninferior and superior to SAVR for the primary composite end point at 1 year for all-cause mortality, disabling strokes, and moderate or severe AR. Last, the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial evaluated the combined results of the CoreValve (84%) and CoreValve Evolut R (16%) valves compared with SAVR and found it to be noninferior for the primary composite end point of all-cause mortality and disabling stroke at 2 years.

d. **TAVR in low-risk patients.** TAVR in low-risk patients was studied in the PARTNER 3 trial comparing TAVR with SAPIEN 3 versus SAVR. At 1 year, TAVR was superior to SAVR for the primary end point of composite death, stroke, or rehospitalization. At 2 years, the primary end point remained significantly lower in TAVR. However, initial differences in death and stroke were diminished, and patients with TAVR had increased valve thrombosis. The longevity of TAVR versus SAVR in this population is yet to be determined. Longer term outcomes in low-risk patients are available from the Nordic Aortic Valve Intervention trial, which randomized patients in this cohort to TAVR with the Medtronic CoreValve self-expanding valve versus SAVR. The results of the trial at 5 years suggest similar outcomes in terms of all-cause mortality and stroke. However, pacemaker rate and presence of

moderate-to-severe paravalvular leak was higher in the TAVR group.

e. **BAVs.** TAVR in BAVs is challenging because of association with a dilated aortic annulus, elliptical and eccentric opening complicating frame apposition, and increased risk of damage to the aorta. On the basis of registry data, BAV has been associated with a higher rate of moderate-to-severe paravalvular leak, which may be improved with the use of CT-guided valve sizing as compared with echocardiography.

f. **Prosthetic dysfunction treated with valve-in-valve.** To date, no trial has evaluated valve-in-valve TAVR but a multinational registry has reported outcomes matched of 757 cases of valve-in-valve compared with native valve TAVR placed between November 2011 and September 2015. These results showed that valve-in-valve TAVR had superior safety outcomes including lower all-cause mortality (2.3% vs 4.1%, $P = .03$), all-cause 1-year mortality (13.3% vs 23.1%, $P < .001$), in-hospital stroke (0.4% vs 2.1%, $P = .002$), stroke at 1 year (2.0% vs 4.3%, $P = .002$), and lower rate of complication including major bleeding, vascular complication, and new-onset atrial fibrillation. Overall, the results show that valve-in-valve TAVR is a safe procedure and should be considered in inoperable patients and possibly in those with high surgical risk.

g. **Future TAVR trials** include TAVR in asymptomatic severe AS (EARLY-TAVR) and moderate AS in patients with symptomatic heart failure (NYHA ≥ II) and reduced ejection fraction (LVEF <50%; TAVR UNLOAD).

D. **Surgical therapy.** AVR is the surgical treatment of choice. It is preferred over repair because debridement of the aortic valve calcification often results in early postoperative AR from leaflet fibrosis and retraction, a process that progresses over time.

1. **Recommendation for the use of SAVR** in patients with AS has become a nuanced decision with the advent of TAVR. The indications for AVR according to the 2020 ACC/AHA valvular

heart disease guidelines are given in **Table 15.3**. Generally, SAVR is preferred in patients who are <65 years of age or have life expectancy >20 years, while TAVR is recommended in patients at high or prohibitive surgical risk. Choice of SAVR or TAVR may be considered in low- or intermediate-risk patients based on characteristics summarized in **Tables 15.3** to **15.5**. The concept of long-term valve planning is important in shared decision-making as the option for valve-in-valve is a relatively safe option for patients in the future. Valve-in-valve is only an option for patients with bioprosthetic valve, which may influence the decision to pursue mechanical or bioprosthetic valve in patients who are surgical candidates.

2. **Surgical mortality rate** varies among patients with AS, depending on age and other comorbidities including concomitant CAD. In an otherwise healthy individual, mortality rate for isolated AVR in experienced centers should be <1%. Successful AVR is feasible and improves life expectancy, even in very older patients without multiple comorbidities. Surgical options include pulmonary valve autograft (ie, Ross procedure), aortic valve homograft conduit, a pericardial or porcine bioprosthesis, mechanical valve, or rarely surgical repair. The relative advantages, disadvantages, and indications for the use of different prostheses are outlined in Chapter 18.
    a. **Bioprostheses** include porcine heterografts and bovine pericardial prostheses. These valves are most often used to treat patients older than 60 years because structural deterioration is much slower in this age group compared with younger patients. These valves have a low risk for thromboembolism and do not necessitate long-term anticoagulation. Because of the sewing ring and struts, all prostheses, both mechanical and biologic, have a pressure gradient across them, even with normal function. The largest possible valve should be inserted to minimize this pressure gradient. The threshold to insert a bioprosthesis at a younger age continues to decline given the

excellent quality of life these afford and with the developing innovation of valve-in-valve TAVR.

b. **Mechanical valves.** The most commonly used mechanical prostheses include the St Jude, Onyx, and CarboMedics prostheses. These all require anticoagulation to minimize the risk of valve thrombosis and thromboembolism. These valves are durable if anticoagulation is maintained, and careful antibiotic prophylaxis is used over the years. Mechanical valves are used with caution in older patients (>65 years) given the substantial increase in anticoagulation-related hemorrhage and resultant mortality in this population. Warfarin is the only approved anticoagulation strategy for patients with mechanical valve. The Randomized, phase II study to evaluate the safety and pharmacokinetics of oral dabigatran etexilate in patients after heart valve replacement. Rivaroxaban in mechanical valves is currently under investigation in patients with unstable international normalized ratio (INR). Non–vitamin K antagonist oral anticoagulants (NOACs) are not approved for use in mechanical valves and should not be employed outside of investigational studies. FDA has approved the use of lower INR range for anticoagulation with the Onyx valve at the aortic position.

c. In the **Ross procedure**, the pulmonary valve and main pulmonary artery are removed as a unit and placed in the aortic position with reimplantation of the coronary arteries. A pulmonary homograft is placed in the pulmonic position. This procedure is best suited for pediatric and adolescent patients with growth potential because the autograft is capable of growth, does not require anticoagulants, and has an excellent hemodynamic profile. The procedure, however, is long and technically difficult and subsequently turns a single-valve problem into a double-valve problem. Problems with pulmonary homograft are common in adults who underwent this operation as are subsequent dilation of the aorta in those with aortopathy such as with bicuspid valves.

Aortic valve homografts have been used to treat younger patients, especially those who wish to avoid anticoagulation, in the hope that greater durability of this valve might result than with a bioprosthesis. Unfortunately, more recent data suggest that any durability advantage of a homograft over a bioprosthesis in a middle-aged patient is slight. Moreover, the homograft tends to calcify and is often difficult to remove at subsequent reoperations. Therefore, enthusiasm for homografts has waned, except in the setting of endocarditis of native or prosthetic valves with pyogenic complications such as abscess or fistula or when the LVOT is small, in which case homografts maximize the flow area and minimize the pressure gradient.

d. Ozaki procedure is a surgical technique involving aortic valve neocuspidization using fixed autologous pericardium to treat AS, regurgitation, or endocarditis. While this is a highly specialized approach, it may portend improved valve hemodynamics compared to biologic or mechanical valves, and obviate the need for lifelong anticoagulation compared to the latter. The procedure is performed via median sternotomy, and involves harvesting and preparing the pericardium, removing diseased aortic cusps and calcified leaflets, preparing the neocusps using the harvested pericardium, and completing the aortic valve neocuspidization.

VII. SPECIAL CONSIDERATIONS

A. Management of asymptomatic patients with severe AS

1. High-risk patients. Most patients with asymptomatic AS have low mortality and morbidity rates. A minority of asymptomatic patients, however, may die suddenly or have rapid progression of disease. These patients may benefit from AVR in the absence of symptoms. Accurate identification of such patients has been difficult. A transaortic flow velocity of >4 m/s predicts a 70% likelihood of needing an AVR within the subsequent 2 years, whereas a velocity of <3 m/s corresponds to a low likelihood (<15%) of needing an AVR in the subsequent 5 years. Patients

with highly calcified valves and a rapid progression of disease (aortic velocity ≥0.3 m/s/y) or critical AS (aortic velocity ≥5.0 m/s or mean pressure gradient ≥60 mm Hg) may be considered for elective AVR if the transaortic flow velocity is >4 m/s. Other reasonable indications for AVR in patients with severe asymptomatic AS include LV dysfunction attributed to AS, exercise-induced hypotension, pulmonary arterial systolic pressure (PASP; >60 mm Hg), a high likelihood of rapid progression, and before pregnancy. Additional high-risk features on exercise testing include an increase in mean gradient ≥18 to 20 mm Hg with exercise, an increase in PASP ≥60 mm Hg with exercise, a lack of contractile reserve, and impaired functional capacity. Operating on an asymptomatic patient with severe AS is only reasonable when the surgical center performing the operation has a low mortality and morbidity for this procedure.

2. **CABG and moderate AS.** Studies suggest a benefit of concomitant AVR in patients undergoing CABG who have an AVA of <1.5 cm^2. Although concomitant AVR increases the risk of the initial surgery, the need for reoperation is significantly lower in these patients, and this may provide a survival benefit.

B. Patients with AS and severely reduced ejection fraction. LV systolic dysfunction in patients with AS can result from afterload stress imposed on the LV by the stenotic valve or from primary contractile dysfunction (eg, results from other causes of cardiomyopathy; see **Figure 15.2**). When LV systolic dysfunction results primarily from afterload mismatch, AVR often results in improvement or normalization or LV function. In contrast, patients with primary contractile dysfunction have an overall poor prognosis and are unlikely to benefit from AVR. It is important to determine the cause of LV dysfunction in patients with severe AS for prognostic and therapeutic purposes. These patients should be considered in two groups: high transvalvular gradients (mean gradient >40 mm Hg) and low transvalvular gradients (mean gradient <30 mm Hg). The patients with low transvalvular gradients consist of three entities: **true severe AS with systolic dysfunction, pseudosevere AS, and paradoxical**

AS with preserved systolic function with reduced stroke volume index due to marked LVH and small LV size.

1. **High transvalvular gradient.** A high transvalvular gradient is a surrogate measure of high afterload mismatch. When the transvalvular gradient is substantial (eg, mean gradient >40 mm Hg), AVR can result in normalization of LV function and a relatively low procedural mortality.
2. **Low transvalvular gradient**
   a. **Low-flow, low-gradient severe AS.** Patients with true anatomically severe AS (AVA <1.0 cm^2) and low transvalvular gradients (mean gradient <30 mm Hg) have a very poor prognosis without surgery. In the past, these patients had a substantial operative mortality; but despite this, survival was improved in those treated surgically compared with medical management, especially if they demonstrate **contractile reserve** when challenged with dobutamine. Contractile reserve is defined as the ability to increase stroke volume by >20% from baseline. However, in the current era, most of these patients undergo TAVR rather than SAVR, and outcomes are reasonable in TAVR in this population regardless of contractile reserve.

      DSE may still be useful in differentiating cardiomyopathy from significant AS with LV dysfunction. When administered dobutamine, patients with severe AS typically experience an increase in both cardiac output and transvalvular pressure gradient, and the calculated valve area increases by <0.3 cm^2 with the valve area remaining <1.0 cm^2. These patients are typically older, have CAD, and may have significant mitral regurgitation (MR) and pulmonary hypertension. Unfortunately, if stroke volume does increase with dobutamine, it may be impossible to differentiate significant AS from predominant cardiomyopathy. In this situation, the CT calcium score may be helpful in assessing the likely severity of AS.

   b. **Pseudosevere AS** is identified in patients with an inappropriately low AVA <1.0 cm^2 arising secondary to

impaired LV function and submaximal opening of a mild-to-moderate stenotic valve. Dobutamine infusion will generate an increase in cardiac output without a significant increase in the transvalvular pressure gradient. As a result, the calculated AVA increases significantly (≥0.3 cm^2) and the valve area increases to more than 1 cm^2. These patients are less likely to benefit from an AVR.

c. **Paradoxical AS with preserved LV systolic function.** This is where a valve area of <1 cm^2 is measured but the transvalvular gradients are lower than expected (mean gradient <40 mm Hg) despite preserved systolic function. This is often secondary to reduced stroke volume index (<35 mL/m^2) resulting from a small, hypertrophied ventricle or concomitant increase in afterload for another reason such as hypertension or impaired aorta compliance. It is important to ensure that the measurements have been recorded correctly in this population and that the LVOT diameter has not been underestimated. When correctly classified, patients with paradoxical low-flow AS with preserved systolic function benefit from AVR once they become symptomatic. Corroborative evidence of severe AS in this population includes heavy valve calcification on CT.

C. Subaortic stenosis. Surgical removal of the membrane leading to subaortic obstruction is indicated for symptomatic patients or for asymptomatic patients with a peak pressure gradient >50 mm Hg. In patients with peak pressure gradient <50 mm Hg, surgical intervention can also be considered if there is evidence of LV systolic dysfunction, concomitant moderate/severe AR, or a ventricular septal defect (VSD). Surgery can also be considered in asymptomatic patients with peak gradient >30 mm Hg if they are planning to become pregnant or wishing to participate in competitive sports.

AORTIC REGURGITATION

I. INTRODUCTION. AR can develop from primary disease of the valve leaflets or from abnormalities of the aortic root or ascending aorta. The

chronic and acute forms of AR are distinct disease entities, with different causes, clinical presentations, natural histories, and treatment strategies.

II. ETIOLOGY

A. Chronic AR. Disease of the valve leaflets can cause AR by inadequate leaflet coaptation, leaflet perforation, or leaflet prolapse. The most common causes of leaflet abnormalities and aortic root abnormalities that lead to the gradual development of AR are given in **Table 15.7**, and often are associated with connective tissue disease or aortopathy. Subaortic stenosis can also cause AR because of a high-velocity jet of blood that is a result of the outflow obstruction hitting the aortic valve, causing damage to the leaflets. Perimembranous VSDs are associated with AR as well. In addition to disease of native valve leaflets, structural deterioration of bioprosthetic or homograft valve leaflets is an important cause of chronic AR.

TABLE 15.7 Major Causes of Chronic Aortic Regurgitation

Leaflet Abnormalities
Rheumatic fever
Infective endocarditis
Trauma
Myxomatous degeneration
Congenital aortic regurgitation
Systemic lupus erythematosus
Rheumatoid arthritis
Ankylosing spondylitis
Takayasu arteritis
Whipple disease
Crohn disease
Drug-induced valvulopathy
Aortic Root or Ascending Aorta Abnormalities

Age-related aortic dilation
Annuloaortic ectasia
Cystic medial necrosis of the aorta (isolated bicuspid aortic valve or Marfan syndrome)
Systemic hypertension
Aortitis (syphilis and giant cell arteritis)
Reiter syndrome
Ankylosing spondylitis
Behçet syndrome
Psoriatic arthritis
Osteogenesis imperfect
Relapsing polychondritis
Ehlers-Danlos syndrome

B. Acute AR. Acute AR can also result from abnormalities in the valve leaflets or in the aortic root. The causes of acute AR are limited and often occur in cases of endocarditis with possible aortic root abscess, or prosthetic valve degeneration (**Table 15.8**).

TABLE 15.8 Major Causes of Acute Aortic Regurgitation

Leaflet Abnormalities
Acute infective endocarditis
Traumatic rupture of the valve
Acute prosthetic valve dysfunction
Post-aortic balloon valvuloplasty
Perivalvular leak or dehiscence of prosthetic valves
Aortic Root or Ascending Aorta Abnormalities
Acute aortic dissection
Traumatic injury to aortic root

III. PATHOPHYSIOLOGY

A. Chronic AR. AR results in diastolic regurgitation of LV stroke volume. This produces an increase in LV end-diastolic volume, thereby raising wall tension (ie, Laplace's law). The ventricle responds to the added wall tension by compensatory eccentric hypertrophy of myocytes. As a result, during the chronic compensated phase of AR, the LV is able to adapt to an increase in diastolic volume without a significant increase in end-diastolic pressure. The LV produces a larger total stroke volume with each contraction, preserving normal effective forward stroke volume. Over time, however, progressive interstitial fibrosis reduces LV compliance, leading to the chronic decompensated phase. Chronic volume overload results in impaired LV emptying, an increase in LV end-systolic volume and LVEDP, further cardiac dilation, and a fall in the ejection fraction and forward cardiac output.

B. Acute AR. Acute AR is usually a hemodynamic emergency because the LV does not have sufficient time to adapt to the rapid increase in LV volume. The effective forward stroke volume and cardiac output fall acutely, potentially resulting in hypotension and cardiogenic shock. The sudden increase in LV diastolic pressure initially causes preclosure of the mitral valve in early diastole, protecting the pulmonary vasculature from elevated diastolic pressure. However, further LV decompensation leads to diastolic MR, which allows transmission of elevated diastolic pressure to the pulmonary vascular bed, resulting in pulmonary edema. The tachycardia that accompanies cardiac deterioration helps shorten the diastolic filling period during which the mitral valve is open.

IV. HISTORY AND CLINICAL PRESENTATION

A. Chronic AR is usually asymptomatic for a long time. The natural history of disease progression in asymptomatic severe AR is much slower compared with AS, with an estimated annual progression (requiring AVR or death) rate of ~6%. After the development of LV dysfunction, patients gradually experience symptoms related to pulmonary congestion, including increased dyspnea with exertion, orthopnea, and paroxysmal nocturnal dyspnea. LV enlargement

frequently produces an uncomfortable sensation in the chest that is exaggerated after premature ventricular contractions and in the supine position. Although angina is uncommon, it can be produced by latent CAD, decreased diastolic coronary perfusion pressure, nocturnal bradycardia and fall in arterial diastolic pressure, marked LVH, and subendocardial ischemia.

B. Acute AR. Patients with acute, severe AR usually present with signs of sudden hemodynamic deterioration such as weakness, altered mental status, severe shortness of breath, or syncope. If left untreated, these patients quickly progress to total cardiovascular collapse. When severe chest pain is part of the initial clinical presentation, aortic dissection must be strongly suspected.

V. PHYSICAL FINDINGS

A. Chronic AR. Patients with chronic AR can have a wide array of physical findings, especially during examination of the peripheral pulses and cardiac auscultation. The physical examination may yield clues about the cause of AR. Patients with AR should be examined for the peripheral manifestations of IE, signs of Marfan syndrome, evidence of chronic aortic dissection, and signs of collagen vascular disorders.

1. Peripheral pulse examination. The increased total stroke volume in chronic AR leads to an abrupt increase in arterial pressure during systole, followed by a rapid fall in arterial pressure during diastole. The widened pulse pressure accounts for a number of physical findings associated with chronic AR (**Table 15.9**). Patients with chronic AR may exhibit a bisferiens pulse, characterized by double systolic peaks with increased amplitude. The signs of hyperdynamic circulation are not specific to AR and can be seen in conditions that cause high-output heart failure, including sepsis, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula.

TABLE 15.9 Physical Signs Associated With Hyperdynamic Pulse in Chronic Aortic Regurgitation

Physical Sign	Description
Water hammer pulse	Rapid upstroke followed by quick collapse
de Musset sign	Head bob with each heartbeat
Traube sign	Pistol shot sounds heard over the femoral arteries in both systole and diastole
Müller sign	Systolic pulsation of the uvula
Duroziez sign	Systolic murmur over the femoral artery when compressed proximally and diastolic murmur when compressed distally or systolic-diastolic murmur with increasing compression over femoral artery
Quincke sign	Capillary pulsations visible in the lunula of the nail bed
Hill sign	Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by >60 mm Hg
Becker sign	Arterial pulsations visible in the retinal arteries and pupils

2. **Palpation.** With severe AR, the apical impulse is typically enlarged and displaced lateral to the midclavicular line in the fifth intercostal space because of LV enlargement. The impulse may be sustained and hyperdynamic. A diastolic thrill may be palpable in the second left intercostal space, as may a systolic thrill caused by increased aortic flow.
3. **Auscultation.** The main auscultatory findings are outlined in **Figure 15.7**.

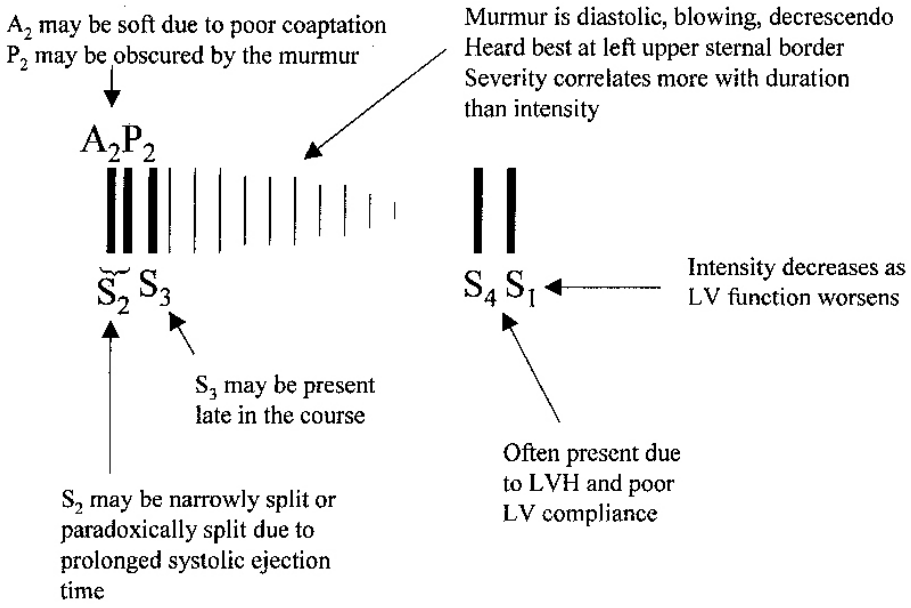

FIGURE 15.7 Physical findings in aortic regurgitation. LV, left ventricle; LVH, left ventricular hypertrophy.

a. **Heart sounds.** S_1 may be diminished in the presence of PR-interval prolongation, LV dysfunction, or preclosure of the mitral valve. S_2 may be soft, singly split (P_2 obscured by the diastolic murmur), or paradoxically split. An S_3 may be heard with severe LV dysfunction. An S_4 is often present and represents left atrial contraction into a poorly compliant LV.

b. **Diastolic murmur.** The hallmark murmur of AR is a blowing, diastolic, decrescendo murmur that starts immediately after A_2 and is best heard in the left upper sternal border with the patient sitting up and leaning forward slightly in full expiration. In general, the severity of AR correlates with the duration of the murmur more than with its intensity. Early in the course of disease, the murmur is typically short. As the disease progresses, the murmur may become pandiastolic. In the end stages of AR, the murmur may shorten again because of rapid equilibration of pressures in the aorta and LV from an elevated LVEDP. In this situation, other signs of severe AR are usually present.

c. A **second diastolic murmur** may be audible at the apex in severe AR. The Austin Flint murmur is a middle-to-late diastolic rumble that is believed to be caused by vibration of the anterior mitral leaflet as it is struck by the regurgitant jet or by turbulence in the mitral inflow from partial closure of the mitral valve by the regurgitant jet. Unlike the murmur of true valvular mitral stenosis, the Austin Flint murmur is not associated with a loud S_1 or with an opening snap.

d. A short **midsystolic ejection murmur** may be audible at the base of the heart, radiating to the neck. It reflects the increased ejection rate and large stroke volume traversing the aortic valve.

B. Acute AR. The physical examination of patients with acute AR differs considerably from that of patients with chronic AR. The physical examination may be most notable for signs of hemodynamic compromise, such as hypotension, tachycardia, pallor, cyanosis, diaphoresis, cool extremities, pulmonary congestion, and altered mental status.

1. **Peripheral examination.** The signs of hyperdynamic circulation that characterize chronic AR are often absent in acute AR. The pulse pressure may be normal or only slightly widened. The heart size is often normal, and the point of maximal intensity is not displaced laterally. When aortic dissection is suspected, blood pressures should be taken in all extremities to detect the differences.
2. **Heart sounds.** S_1 may be diminished because of preclosure of the mitral valve. An S_3 often accompanies cardiac decompensation.
3. **Murmurs.** The early diastolic murmur of acute AR is shorter and lower in pitch than the murmur of chronic AR. In severe, acute AR, the murmur may not be audible when the diastolic pressure in the LV and aorta equilibrates. The systolic murmur reflecting increased flow across the aortic valve may be heard but is usually not loud. The Austin Flint murmur, if present, is short.

VI. LABORATORY EVALUATION

A. ECG. The typical ECG in chronic AR shows LVH, left-axis deviation, and left atrial abnormality. Conduction abnormalities are unusual but can occur after the development of LV dysfunction. Premature atrial and ventricular beats are common. Sustained supraventricular or ventricular tachyarrhythmias are uncommon in the absence of LV dysfunction or concomitant mitral valve disease. In acute AR, the ECG is usually notable only for nonspecific ST–T-wave abnormalities.

B. Chest radiograph. In chronic AR, the chest radiograph may reveal marked cardiomegaly, with the heart being displaced inferiorly and leftward. Dilation of the aortic knob and root may be seen. In acute AR, the LV and left atrial dimensions are usually normal. Aortic dissection can lead to a widened mediastinum and/or a widened cardiac silhouette due to pericardial effusion. The chest radiograph is notable for signs of pulmonary congestion.

C. Laboratory testing. Chronic AR may lead to *increased natriuretic peptides* and evidence of their elevation is helpful when a decision about surgical timing is equivocal. Other blood tests may help in elucidating suspected underlying conditions such as connective tissue disorders or if endocarditis is possible.

D. Echocardiography. 2D and M-mode echocardiography are useful in determining the cause of AR, evaluating the aortic root, and assessing the overall LV size and function. Doppler echocardiography is useful for detecting AR and estimating severity. There are several different methods of estimating the severity of AR with color Doppler, pulsed wave Doppler, and continuous wave Doppler ultrasonography.

1. **2D and M-mode echocardiography.** The cause of AR can be assessed using 2D echocardiography. Rheumatic AR typically causes thickening and retraction of the leaflet tips, leading to failure of cusp apposition. Bacterial endocarditis, which can cause leaflet fibrosis and retraction, leaflet perforation, or flail of the valve cusp, should be suspected if a vegetation is detected. Prolapse of the aortic valve cusps can occur in many conditions, including IE, BAV, myxomatous degeneration, and Marfan

syndrome. Aortic root abnormalities are also well visualized in the parasternal long-axis view. Aortic root dilation is most often idiopathic, although Marfan syndrome, Ehlers-Danlos syndrome, ankylosing spondylitis, Reiter syndrome, rheumatoid arthritis, syphilis, and giant cell arteritis are other potential causes. Symmetric dilation of the aortic root produces a central jet of AR, and focal dilation causes an eccentric jet. In the parasternal long axis, the transducer should be moved up one interspace to assess the ascending aorta. Infective destruction of the aortic wall and proximal aortic dissection flaps may occasionally be visualized on transthoracic images. M-mode echocardiography may reveal **premature closure of the mitral valve in severe, acute AR**. In acute AR and chronic AR, the regurgitant jet can strike the anterior mitral valve leaflet, causing it to reverberate or "flutter" in diastole. Reversed doming of the anterior mitral leaflet may be seen on 2D imaging and generally indicates grade 3 to 4+ AR. In chronic severe AR, the LV is dilated.

2. **Doppler and color-flow imaging.** Doppler and color flow echocardiography is used to detect AR and to assess its severity. AR is identified by Doppler imaging as high-velocity pandiastolic flow originating immediately under the aortic valve. Color-flow imaging allows the assessment of jet origin, size, and direction. Continuous wave Doppler provides measurement of jet velocity and timing of flow. The maximum length of the AR jet correlates poorly with severity of regurgitation when assessed angiographically. Several other Doppler measures are used to estimate the severity of AR (**Table 15.10**). The ratio of the jet width to LVOT diameter is measured in the parasternal long-axis view and correlates well with the angiographic severity of AR. The pressure half-time of the aortic regurgitant velocity is defined as the time required for the pressure gradient across the aortic valve to fall to half of its initial value. The pressure half-times of patients with mild, moderate, and severe AR have demonstrated considerable overlap. In general, shorter pressure half-times are associated with increased severity of AR, and a pressure half-time

of <200 ms is nearly always associated with severe AR. Quantitation of regurgitant volume and regurgitant fraction provides the most direct correlation with quantitative angiographic estimates of AR severity. Regurgitant volume is the difference between the stroke volume across the LVOT (representing the sum of forward flow and regurgitant flow) and that across the mitral valve inflow (representing forward flow), provided there is no significant MR. The regurgitant fraction is the ratio of the regurgitant volume divided by the LVOT stroke volume. The proximal isovelocity surface area (PISA) method is also used for estimating AR severity. The PISA method is used to calculate the effective regurgitant orifice (ERO) area. An ERO area ≥0.30 cm^2 is indicative of severe AR. The presence of a proximal convergence area on transthoracic echocardiogram at the aortic valve is indicative of at least moderate AR. Pulsed wave Doppler echocardiography should be performed in the proximal descending aorta to establish the presence of diastolic flow reversal. Some degree of flow reversal is normally seen early in diastole because of reflux of blood into the coronary vasculature, but if this is >40 cm/s and continues throughout diastole, then severe AR is likely, especially if this persists in the abdominal aorta. Flow reversal may also be seen with other conditions that cause blood to leak out of the arterial system such as PDA or sizable arteriovenous fistula.

TABLE 15.10 Echo Doppler Assessment and Stages of Aortic Regurgitation

	Aortic Regurgitation			
	Mild	**Moderate**	**Severe, Asymptomatic**	**Severe, Symptomatic**
Stage	**B**	**B**	**C1/C2**	**D**
Qualitative				
Angiographic grade	1+	2+	3-4+	3-4+

	Aortic Regurgitation			
	Mild	**Moderate**	**Severe, Asymptomatic**	**Severe, Symptomatic**
Stage	**B**	**B**	**C1/C2**	**D**
Color Doppler jet width	<25% of LVOT	25%-64% of LVOT	≥65% of LVOT	≥65% of LVOT
Doppler vena contracta width (cm)	<0.3	0.3-0.6	>0.6	>0.6
Quantitative (Cath or Echo)				
Regurgitant volume (mL/beat)	<30	30-59	≥60	≥60
Regurgitant fraction (%)	<30	30-49	≥50	≥50
Effective regurgitant orifice area (cm^2)	<0.10	0.10-0.29	≥0.30	≥0.30
Additional Essential Criteria				
LV size	Normal	Normal	Requires evidence of LV dilation C1 = LVEF (≥50%) and LVESD ≤50 mm C2 = LVEF <50% or LVESD >50 mm or indexed >25 mm/m^2	Requires evidence of LV dilation

LV, left ventricle; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVOT, left ventricular outflow tract.

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3. **TEE** is used to rule out vegetation or aortic valve ring abscess in patients who may have bacterial endocarditis. In pure AR, vegetation typically occurs on the LV side of the aortic valve. TEE is also used to visualize congenital valvular abnormalities (eg, bicuspid valve, subaortic membrane) and to exclude aortic dissection. TEE is often optimal in defining the AR jet, with the deep transgastric view being particularly useful.
4. **Stress echocardiography** is useful for assessing functional capacity and unmasking symptoms in patients previously classified as being asymptomatic or with equivocal symptoms. It can also assess for contractile reserve, which if absent is predictive, or the development of systolic dysfunction both at follow-up (medical therapy) and postoperatively. Recent research also suggests that exercise tricuspid annular plane systolic excursion (TAPSE) <21 mm Hg is associated with right ventricular dysfunction and independently associated with the need for earlier AVR. Although contractile reserve and exercise TAPSE are not included as indication for AVR, they can be considered for use to help anticipate surgical timing in higher risk patients nearing recommendations for AVR including LVEF 50% to 55% or left ventricular end-systolic dimension (LVESD) approaching 50 mm or 25 mm/m^2 (**Table 15.10**). It is also important to acknowledge that afterload increases substantially with exercise, which can precipitate a fall in ejection fraction. This exercise-induced fall in LVEF is nonspecific and it should not of itself be used to indicate need for surgical intervention.
5. **Newer techniques.** Strain imaging is increasingly used to define LV dysfunction before this is apparent using LVEF. Abnormalities in global longitudinal strain may indicate early decompensation in patients with AR. 3D echocardiography has the potential to provide more accurate LV volumes and dimensions in AR but is not yet widely used for this purpose.

E. Cardiac catheterization. Cardiac catheterization is not necessary for all patients with chronic AR unless there are concerns about AR severity, hemodynamic abnormalities, or LV function, despite

noninvasive testing and the physical examination. All patients older than 50 years with severe AR should undergo coronary cineangiography before any definitive surgical procedure on the valve to detect CAD. The decision to perform cardiac catheterization in younger patients should be made on an individual basis after assessment of the patient's cardiac risk profile. Catheter manipulation in patients with AR may be difficult because of dilation of the ascending aorta. Caution should be exercised when manipulating catheters in patients with Marfan syndrome or cystic medial necrosis of the aortic wall to minimize the risk of vascular trauma. In addition to conventional coronary cineangiography, aortography may be performed to evaluate the degree of AR when doubt about true severity remains after noninvasive testing. The grading of AR by angiography is given in **Table 15.11**. Right heart catheterization may be helpful in certain circumstances, such as new-onset heart failure or combined AR and AS.

TABLE 15.11 Angiographic Grading of Aortic Regurgitation

Degree of Aortic Regurgitation	Left Ventricular Opacification	Rate of Clearing
Mild (1+)	Faint, incomplete	Rapid
Moderate (2+)	Faint, complete	Rapid
Moderate to severe (3+)	Equal to aortic opacification	Intermediate
Severe (4+)	Greater than aortic opacification	Slow

F. Advanced cardiac imaging. If echocardiographic imaging is inadequate, such as poor acoustic windows, cardiac CT or cardiac MRI can be used to better evaluate both the cause and severity of AR as well as the aorta. Either modality can be used to better define the anatomy including but not limited to mechanism of AR, anatomic morphology of the valve (ie, BAV), providing a more complete evaluation of the thoracic aorta including the degree of aortic dilation or presence of a vascular connective tissue disorder, and using cardiac magnetic resonance (CMR) to show evidence of early myocardial

fibrosis. In addition to an anatomic evaluation, CMR can also provide a functional assessment including an accurate calculation of LVEF, LV volumes, and quantification of regurgitation with flow mapping through calculation of regurgitant fraction. The assessment of LV volumes is especially helpful in chronic severe AR when the LV becomes spherical and linear dimensions may not be as representative of the degree of dilation. CMR is highly reproducible and thus may be used in serial assessment of AR, which has a long asymptomatic period.

II. NATURAL HISTORY. Traditionally, moderate-to-severe AR is thought to have a good prognosis for many years, provided the patient is asymptomatic and does not exhibit signs of LV dysfunction or severe dilation. Much of this information has been derived from older series of younger patients. Recent data suggest that the outcomes in older patients and in women may not be as favorable in part due to the differences in LV compliance and geometry in women and older patients versus younger ones. Older patients and women tend to have smaller ventricles than younger patients for the same degree of AR and may have worse outcomes in the absence of earlier surgical intervention than younger patients.

III. THERAPY

A. Medical therapy

1. Chronic AR. Vasodilators, such as ACEIs, angiotensin receptor blockers (ARBs), calcium channel blockers, and hydralazine, have historically been used in the treatment of chronic AR to reduce the severity of regurgitation. However, there is conflicting evidence that vasodilators reduce the severity of AR or alter the disease course. Therefore, the 2020 ACC/AHA valve guidelines suggest vasodilator use in (1) asymptomatic patients with chronic AR and hypertension when systolic blood pressure >140 mm Hg (class I indication) or (2) patients with severe AR who are symptomatic and/or have LV dysfunction but prohibitive surgical risk (class I indication). In the latter case, GDMT with ACEIs, ARBs, and/or sacubitril/valsartan is recommended. Beta-blockers are also

reasonable to use in these nonsurgical candidates, although it is important to avoid bradycardia, which increases diastolic filling time and increases the regurgitant volume in severe AR.

2. **Acute AR.** The goal of **medical therapy** in acute AR is hemodynamic stabilization before proceeding with surgical correction. For patients presenting with cardiogenic shock, intravenous vasodilators are used to reduce the afterload stress on the LV, to lower LVEDP, and to augment forward cardiac output. In severe cases, temporary transvenous atrial/ventricular pacing and/or intravenous inotropic agents may be required for temporary hemodynamic support. Beta-blockers may be used with caution when acute AR is caused by an aortic dissection. Beta-blockers help reduce arterial d*P*/d*t*, which reflects the transmission of force from LV ejection to the arterial wall. Although this is an essential component of the treatment of acute aortic dissection, beta-blockers increase the length of diastole by slowing the heart rate, which can exacerbate acute AR and contribute to cardiovascular collapse. If acute AR is associated with **endocarditis**, antibiotic therapy should be instituted as soon as all culture specimens are obtained. Patients with severe acute AR who are being triaged to surgery may be treated with rapid pacing to reduce the duration of diastole if therapeutic modalities such as intravenous vasodilators fail to produce a significant tachycardia. A **surgical evaluation** should be performed emergently for a patient with AR caused by aortic dissection or chest trauma. The goal of medical therapy in this setting is to maximize forward cardiac output and minimize propagation of aortic dissection if present.

B. Percutaneous therapy

1. **Insertion of an intra-aortic balloon counterpulsation device in patients with more than moderate AR or in the presence of aortic dissection is contraindicated.**
2. Patients with combined severe AS and at least moderate AR are poor candidates for PABV because the degree of AR is likely to increase after the procedure.

3. **Native AR.** There is an evolving role for TAVR in native severe AR with existing and investigational TAVR valves. The JenaValve was developed as a transfemoral self-expanding transcatheter valve to treat pure AR. The JenaValve is a porcine root valve sewn to a nitinol self-expanding stent fitted with an outer porcine pericardial patch or skirt. The device also features a fixation clip to firmly anchor the valve despite the absence of calcification. The first in-human case was described in 2017, published 30-day outcomes show promise in feasibility, and clinical trials are ongoing. The challenge associated with the off-label use of commercially available TAVR valves for AR is the lack of a calcified annulus that may serve as a scaffold for implantation. That being said, there are case reports suggesting this is feasible in certain anatomic conditions, particularly with supra-annular self-expanding designs. Still, SAVR remains the treatment of choice in operable patients.

C. Surgical therapy

1. **Chronic AR.** The 2020 ACC/AHA guidelines on the indications for AVR in patients with chronic AR are given in **Table 15.12**.

TABLE 15.12 Recommendations for Aortic Valve Replacement in Patients With Chronic Aortic Regurgitation

Class I
• Symptomatic patients with severe AR • Asymptomatic patients with severe AR and LVEF <55% (not attributed to another cause) • Severe AR and having heart surgery for another indication
Class IIa
• Asymptomatic patients with severe AR, normal LV function, and severe LV dilation (LVESD >50 mm or indexed LVESD >25 mm/m^2) • Moderate AR and having heart surgery (mitral valve or CABG) or surgery on the ascending aorta
Class IIb

- Asymptomatic patients with severe AR, normal LV function, and progression of LV dilation (LVEDD >65 mm) if low surgical risk

AR, aortic regurgitation; CABG, coronary artery bypass grafting; LV, left ventricle; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension.
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a. Symptomatic patients. The 2020 ACC/AHA guidelines recommend AVR symptomatic patients with severe AR regardless of the ejection fraction.

b. Asymptomatic patients

(1) LV systolic dysfunction. Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (ejection fraction <55%) secondary to aortic valve disease are at high risk for the development of symptomatic heart failure within 2 to 3 years and, therefore, should be considered for prompt surgical intervention. The likelihood of LV dysfunction normalizing after surgery decreases with increased duration of dysfunction.

(2) LV dilation. Asymptomatic patients with normal LV systolic function at rest and evidence of severe LV dilation have an increased risk of sudden cardiac death and perioperative mortality increases significantly once they develop symptoms or LV systolic dysfunction. However, their prognosis after AVR is excellent and they should be referred for valve replacement if surgical risk is low. It is reasonable to send patients for AVR if their LVESD is >50 mm or indexed >25 mm/m^2. Surgery can also be considered in patients with left ventricular end-diastolic dimension (LVEDD) >65 mm if their surgical risk is low (<1%).

(3) **Other cardiac surgery.** AVR is recommended for patients with chronic severe AR undergoing another cardiac surgery. AVR is also reasonable for patients with moderate AR if undergoing surgery on the mitral valve, ascending aorta, or CABG.

(4) **Aortic valve repair.** Many patients with prolapse of bicuspid valve as the cause of AR may be candidates for surgical repair of the aortic valve. Some patients with leaflet perforation caused by infectious endocarditis may also be candidates for repair in which a pericardial patch is sewn over the defect. Aortic valve repair has good durability when the initial result is excellent (minimal residual AR), but further surgery will be needed usually at 12 to 20 years. Leaflet sparing surgery on the aorta is increasingly feasible, and if the cause of the AR is impaired coaptation due to annular dilation, then experienced surgeons may be able to replace the aorta and reduce the severity of AR concomitantly without the need for an AVR.

(5) **Postoperative.** Patients with severe AR may show initial worsening in LV function despite relative normalization of LV size. This is likely due to the hemodynamic changes produced by eradicating the regurgitation. Slow improvement with normalization or at least stabilization of function at about 6 months is common in these patients. Afterload reduction is indicated postoperatively in patients with impaired LV systolic function at least until there is normalization of LV systolic function.

IX. KEY SUGGESTIONS

A. Acute, severe AR is usually a surgical emergency. Signs of congestive heart failure and mitral valve preclosure are ominous in acute AR.

B. Valve replacement can be performed without infection of the prosthesis in active endocarditis, even when antibiotics have only

recently been started. An aortic valve homograft is the preferred prosthesis in the setting of prosthetic endocarditis.

C. Aortic dissection should be suspected in any patient with chest pain and AR.

D. If LV systolic dysfunction is present for <12 months, LV function is likely to improve postoperatively.

E. Heart rate is usually normal until late in the course of disease, when a low effective stroke volume is compensated with tachycardia to maintain cardiac output.

F. Rapid atrial or ventricular pacing may be used as a temporary measure to manage acute AR caused by endocarditis or trauma to improve cardiac output. The diastolic filling phase is shorter at higher heart rates; therefore, there is less time for valvular regurgitation.

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SUGGESTED READINGS

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CHAPTER 16

Mitral Valve Disease

Aditya Mantha, Anirudh Kumar, and Saberio Lo Presti Vega

I. INTRODUCTION

A. Mitral valve anatomy

1. The **mitral valvular apparatus** consists of the anterior and posterior leaflets, the mitral annulus, the chordae tendineae, and the papillary muscles (PMs) (**Figure 16.1**). Mitral valve pathology occurs when one of these elements is compromised and may result in regurgitation (MR), prolapse (MVP), or stenosis (MS).

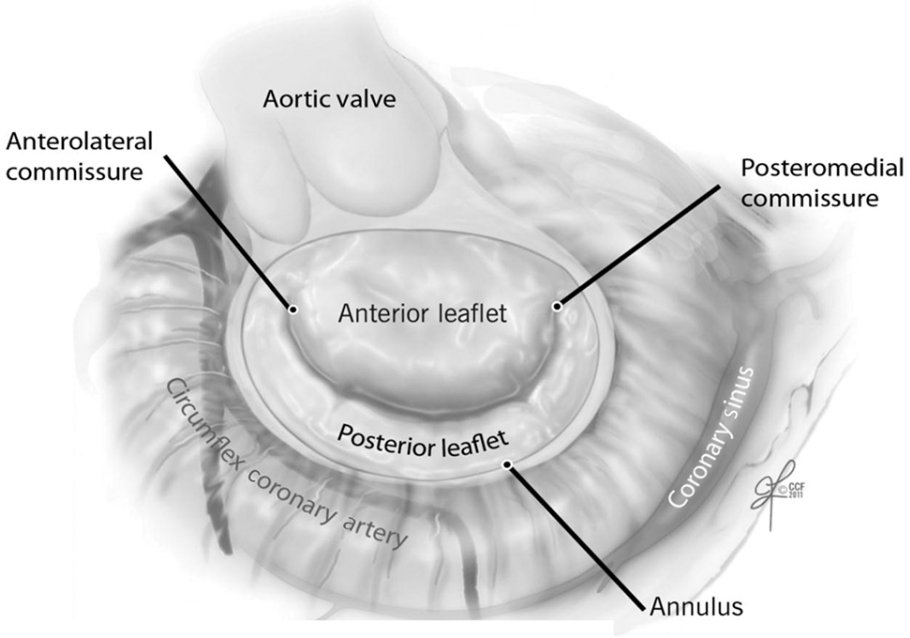

FIGURE 16.1 Anatomy of the mitral valve apparatus. (Copyright © Cleveland Clinic Foundation. Reprinted with permission, Cleveland

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2. **Valve leaflets**
    a. The apparatus brings both leaflets together in systole, creating the **coaptation zone**.
    b. The leaflets are typically described by the **Carpentier classification**, which delineates three segments separated by natural clefts in the free edge of the posterior leaflet. The lateral, middle, and medial scallops of the posterior leaflet are designated P1, P2, and P3, respectively. Correspondingly, the opposing areas of the anterior leaflet are designated A1, A2, and A3.
3. **Annulus**
    a. The mitral annulus is a semilunar ring dividing the left atrium (LA) and ventricle with a hyperbolic **paraboloid** ("saddle") shape thought to mitigate systolic forces on the leaflets. The anterior portion is in continuity with the **fibrous skeleton** of the heart at the right and left trigones, making it less prone to dilation than the posterior annulus.
    b. Congenital anomalies affecting annular geometry or leaflet insertion may cause either stenosis (supravalvular ring) or be associated with regurgitation (mitral annular disjunction [MAD]).
4. **Chordae.** The mitral valve leaflets are attached via the **chordae tendineae** to the PMs. There are several types of chordae that are classified by their attachments:
    a. At the free margin, **primary or marginal chordae** prevent prolapse and support coaptation.
    b. **Secondary or intermediary chordae** prevent billowing of the leaflets providing structural support.
    c. **Tertiary or basal chordae** insert at the annulus and base of the posterior leaflet.
    d. **Commissural chordae** insert onto the free margins of both commissures and support cusp approximation.

5. **Papillary muscles**
   a. The **PMs** supply chordae to the ipsilateral side of both leaflets.
   b. The anterolateral papillary muscle (APM) originates from the left ventricular (LV) free wall and typically has two heads (anterior and posterior) supplied by both the left anterior descending and left circumflex arteries.
   c. The **posteromedial papillary muscle (PPM)** typically has three heads and is only supplied by the **posterior descending artery**.
   d. Congenital abnormalities in PM number (parachute valve) and insertion (hypertrophic cardiomyopathy [HCM]) or attachments (arcade valve, parachute-like) that lead to restricted mobility and dysfunction
6. **Adjacent vasculature**
   a. The **left circumflex artery** and the **coronary sinus (CS)** course through the atrioventricular groove adjacent to the annulus. Injury during intervention is rare.
7. **Coaptation zone**
   a. Both leaflets come together in systole in a semilunar line at the posterior one-third of the valve orifice called the coaptation zone.
8. **LV geometry**
   a. The LV is a **bullet-shaped (prolated ellipsoid)** contractile chamber. It is **sensitive to loading conditions** and is both affected by and influences the function of the mitral valve. Thus dilation, regional wall motion abnormalities, and hypertrophy affect the valve apparatus and function.

B. Valve physiology and hemodynamics

1. **Area.** The **normal area** of the mitral orifice is 4 to 6 cm^2. The **mitral valve orifice area** is a load-independent parameter used in the assessment of both regurgitant and stenotic lesions. Restriction of the orifice to ≤1.5 is considered **severe stenosis**. In MR, the effective regurgitant orifice is estimated to quantify severity.

2. **Pressure:** The normal transmitral gradient is <2 mm Hg. When the valve area is <2.0 cm^2, a pressure gradient between the LA and the LV in diastole occurs. As the orifice area declines, both the transmitral pressure gradient and the LA pressure increase.

3. **Blood flow**

   a. **Systole**

      (1) Ventricular systole closes the **mitral valve** preventing regurgitation into the LA. **PM tension** prevents leaflet prolapse.

      (2) Myocardial contraction **deforms the fibrous mitral annulus** reducing the effective area by 20% to 25%, creating a **saddle shape**.

   b. **Diastole**

      (1) The pressure gradient between the LA and ventricle drives blood flow across the mitral valve. After the initial **rapid filling**, the flow rate decreases. Just before the mitral valve closes, **atrial contraction** results in an additional "kick."

4. **LA pressure**

   a. The **driving pressure** for flow across the mitral valve comes from the difference between the LA and LV end-systolic pressure.

   b. **LA pressure** has a major influence on the clinical manifestations of mitral pathology. **Acute pressure overload** without sufficient atrial dilation or compensatory LV compliance can lead to a sudden rise in pulmonary venous hydrostatic pressure, causing pulmonary edema manifest by dyspnea, orthopnea, and respiratory failure.

5. **LV compliance**

   a. Comorbidities that affect the atrial and ventricular myocardium contribute to the development of valvular disease by influencing **contractility, compliance, and chamber geometry**.

   b. **LV compliance** plays a key role in the chronic adaptation to regurgitation. **Eccentric hypertrophy** accommodates

increased regurgitant volume while minimizing the increases in diastolic filling pressure. Such hypertrophy maintains cardiac output by increasing **ventricular stroke volume**.

c. Over time, **progressive dilation** can lead to systolic dysfunction and impaired contractility, resulting in low-output syndrome and overt heart failure.

C. Valve assessment

1. Clinical examination

a. Auscultation

(1) Mitral lesions present with **typical murmurs**, enabling prompt diagnostic evaluation. The valve is best auscultated at the point of maximal impulse corresponding to the ventricular apex, typically at the **fifth to sixth intercostal space along the mid-clavicular line**.

b. Jugular venous assessment

(1) **Jugular venous distention** (JVD) may indicate severe impairment in forward flow acutely or the development of chronic valvular heart failure with **pulmonary hypertension** and **right-sided dysfunction.**

c. Pulse

(1) Arrhythmias (ie, atrial fibrillation [AF]) or variations in heart rate affect **loading conditions** and cardiac output in mitral disease. Thus, transvalvular gradients should always be reported with the heart rate.

2. Electrocardiogram (ECG)

a. The ECG may reflect **sequelae of chronic mitral disease**, including LA enlargement (p-mitrale), AF, and ventricular hypertrophy with axis deviation.

3. Chest radiography

a. Chest films can quickly demonstrate features of mitral disease and their sequelae, including changes in **chamber size**, development of **vascular congestion**, distribution of

calcification, and associated findings (ie, effusions, bronchus elevation).

4. Echocardiography

a. Echocardiography is the **first-line** diagnostic tool for mitral assessment providing structural and functional assessment of the valve, subvalvular, and cardiac chambers. The specific physics of echocardiography, optimization of Doppler imaging, and derivations of specific calculations such as continuity, proximal isovelocity surface area (PISA), effective regurgitant orifice area (EROA), and regurgitant fraction (RF) calculation are covered in **Chapters 66** and **67**.

b. Due to the complexity of image acquisition, mitral anatomy, and pathophysiology, there is **no single echocardiographic parameter** that consistently identifies the severity of a lesion. The integration of multiple visual and quantitative measures is necessary to assess valve function.

c. Planimetry refers to direct visualization and assessment of the annular plane and leaflets in the parasternal short-axis view at the leaflet tips. The valve orifice area provides a relatively load-independent measure of valve stenosis.

(1) Poor-quality two-dimensional (2D) images and a thick, calcified subvalvular apparatus limit accurate measurement. Oblique short-axis angles may overestimate of valve area, while dense fibrosis or calcification at the margins of the valve orifice underestimates it.

d. Doppler echocardiography

(1) Doppler echocardiography relies on shifts in emitted frequencies caused by backscatter from moving objects such as red blood cells (RBCs) to visualize flow. The three primary Doppler methods are **continuous wave, pulsed wave, and color flow**.

(a) In continuous wave Doppler, the **density** of the waveform is directly proportional to the number of RBCs reflecting ultrasound. Variations in the **timing**,

duration, or **contour** of the waveform correlated to the ECG can characterize lesions and identify other pathologies (ie, outflow obstruction in HCM).

(b) Pulsed wave Doppler (PWD) enables localized assessment at the level of the valve orifice or in the ventricular outflow tract.

(c) Color Doppler (CD) provides a visual representation of the **direction and intensity of blood flow** to help identify the underlying mechanism and severity of valvulopathy.

5. Advanced imaging

a. Transesophageal echocardiography (TEE)

(1) TEE is the **preferred modality** for detailed evaluation of the mitral valve apparatus providing excellent spatial and temporal resolution.

(2) Techniques and instrumentation

(a) The mitral valve is conventionally imaged at the mid-esophageal level scanning from 0° to 120° in 30° increments. The **anterior mitral leaflet** is identified by its association to the **aortic valve**. **Medial-to-lateral discrimination** can occur at 50° to 70° where the P1, A2, and P3 segments can be identified under normal conditions.

b. 3D echocardiography

(1) 3D TEE provides high-quality diagnostic and functional assessment of valvular heart disease, allowing planning and intraprocedural guidance for transcatheter and surgical interventions. Multiplanar 3D transthoracic echocardiography (TTE) is useful in finding the smallest opening of the mitral valve in stenosis (**Figure 16.2**).

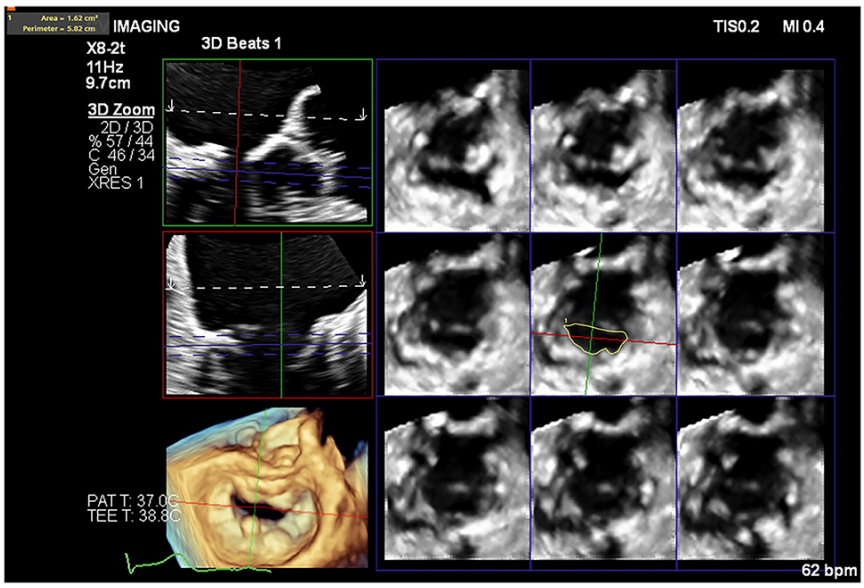


FIGURE 16.2 Two-dimensional planimetry of the mitral valve from the surgeon's view using transesophageal echocardiography. (Image Courtesy of Dr Harb MD.)

c. Cardiovascular computed tomography angiography (CCTA)

(1) A detailed discussion of the techniques and indications for cardiac CT is provided in **Chapter 51**.

(2) CCTA has emerged as an essential preprocedural planning tool, providing high spatial resolution of valve anatomy and functional assessment with retrospective 4D imaging over the cardiac cycle. **ECG gating** is used to identify phases of the interest in the cardiac cycle. Gating can be completed **prospectively or retrospectively** with pharmacologic support to attain optimal heart rate. The ideal scan balances optimal image quality while mitigating radiation and contrast dose. Retrospectively gated 4D CT enables evaluation of annular and leaflet motion and mitral valve planimetry, along with cardiac chamber size and function quantification.

(3) CT provides reproducible and accurate multiplanar reconstructions, enabling **coaxial measurement** of the mitral annulus and leaflets.

(4) CT also allows prediction and co-registration of the optimal **intraprocedural fluoroscopic angles** that can be adjacent or overlaid with the intraprocedural fluoroscopic viewer.

(5) Specifically for preoperative planning for mitral valve disease, CT can measure the mitral valve annulus, model neo-LVOT (left ventricular outflow tract) dimensions and obstruction, assess for coronary artery disease (CAD), and assess thoracoabdominal aorta and pelvic arteries for access patency, aneurysms, and other arterial pathologies.

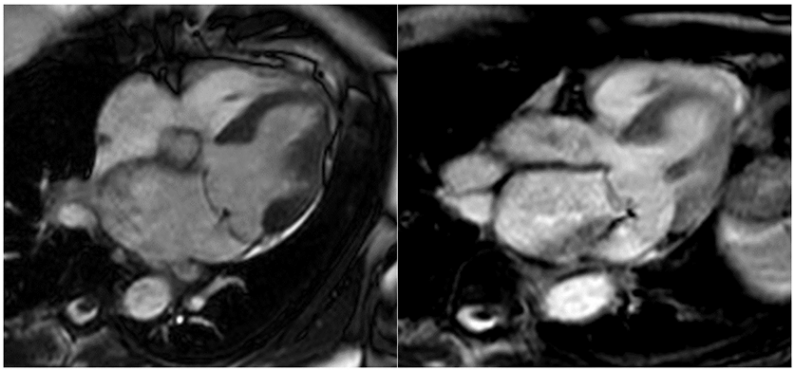
(6) Commercial multidetector energy-integrating CT scanners suffer from **calcium blooming and cone beam hardening artifacts** that can limit evaluation around the annulus. Photon-counting CT is an emerging potential solution.

d. Cardiac magnetic resonance imaging (CMR)

(1) **Chapter 52** provides a thorough introduction to the physics, indications, and interpretation of CMR.

(2) CMR is the gold standard for assessing cardiac chamber size and function and can be used to accurately calculate mitral regurgitant volume (**Figure 16.3**).

(3)



(4) **FIGURE 16.3** Assessment of mitral regurgitation by cardiac magnetic resonance imaging. (Image Courtesy of Dr Harb MD.)

(5) Contrast CMR with late-gadolinium tissue enhancement, which can indicate ischemic damage or nonischemic interstitial fibrosis, has widespread prognostic significance across a range of cardiovascular diseases, including valvulopathies and cardiomyopathies.

e. Stress echocardiography

(1) Stress echocardiography can be used in the assessment of both stenotic and regurgitant lesions and is **recommended ancillary testing** to establish the severity of MR by the 2020 American College of Cardiology (ACC) Focused Update of Expert Consensus Decision Pathway on the Management of Mitral Regurgitation.

(2) **Exercise stress echocardiography** is indicated when there is a discrepancy between resting Doppler findings and patient-reported symptoms to objectively assess functional capacity and the impact of valvular pathology on hemodynamics. Modalities include **supine or recumbent bicycle** or an upright treadmill.

6. Laboratory evaluation

a. While laboratory evaluation plays a supportive role, there is no direct laboratory measurement that accurately reflects the severity of valvulopathy. Further research is needed to determine the prognostic value and thresholds for these assays in mitral disease.

(1) **Troponin**

(a) High-sensitivity troponin (HST) assays have enabled the diagnosis of **chronic myocardial injury** to manifest as elevated low, but significant titers.

(2) **Natriuretic peptides**

(a) Natriuretic peptides are conventionally used to detect **myocardial remodeling** in the setting of chronic volume overload. As severe MS and MR can both manifest with heart failure, the brain natriuretic

peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) may guide medical therapy.

II. MITRAL REGURGITATION

A. Introduction. MR describes the pathologic reversal of blood flow from the LV to the LA through the mitral valve. Moderate-to-severe regurgitation occurs in an estimated 10% of older patients >75 years of age in the United States. The prognosis and management of MR vary significantly based on the etiology of the lesion. Common causes of MR are summarized in **Table 16.1**.

TABLE 16.1 Causes of Mitral Regurgitation

Leaflet Abnormalities
Myxomatous degeneration of leaflets with excessive motion (most common)
Rheumatic disease: scarring and contraction lead to the loss of leaflet tissue.
Endocarditis: can cause leaflet perforations and retraction in the healing phase
Aneurysms: usually from aortic valve endocarditis; aortic insufficiency produces jet lesion on the mitral valve
Congenital
Cleft mitral valve: isolated or with ostium primum atrial septal defect
Double-orifice mitral valve
Hypertrophic cardiomyopathy: systolic anterior motion of the mitral valve
Mitral Annular Abnormalities
Annular dilation
From left ventricular dilation: dilated cardiomyopathy, ischemic disease, hypertension
Normal 10 cm in circumference
With sufficient dilation, loss of adequate leaflet coaptation
Tethering of leaflet and chordae can occur and produce relative restriction of leaflet motion.
Mitral annular calcification
Degenerative disorder, most commonly seen in the older patients

Accelerated by hypertension or diabetes
Also seen in renal failure with dystrophic calcification
Also seen with rheumatic heart disease
Marfan syndrome and Hurler syndrome
MR results from immobility of the annulus and loss of sphincter activity
Chordal Abnormalities
Chordal rupture (most severe form is flail leaflet) results in loss of leaflet support usually with myxomatous degeneration.
Rheumatic heart disease (chordal fibrosis and calcification)
Papillary Muscle Abnormalities
Rupture with myocardial infarction
Complete rupture typically not survived
Partial rupture more typically encountered
Dysfunctional papillary muscle
Ischemia
Posteromedial papillary muscle, single blood supply through posterior descending artery
Anterolateral papillary muscle, supplied by left anterior descending artery and left circumflex artery
Infiltrative processes: amyloid and sarcoid
Congenital: malposition, parachute mitral valve

MR, mitral regurgitation.

B. Classification

1. MR is broadly differentiated by etiology into primary (degenerative) or secondary (functional) regurgitation. **Primary MR** involves lesions of the leaflets, annulus, and subvalvular apparatus itself. **Secondary MR** is broadly driven by leaflet tethering or malcoaptation due to ventricular dilation, disruption in ventricular synchrony, or atriogenic annular dilation in the setting of chronic AF and heart failure with preserved ejection fraction

(HFpEF). MR can also be stratified as an **acute or** chronic process.

2. The **Carpentier system** is commonly used to describe valve pathology in MR:
   a. **Class I (normal leaflet motion).** Isolated annular impairment of coaptation of leaflet
   b. **Class II (excessive leaflet motion).** Myxomatous disease resulting in excessive mobility or displacement as in prolapse or flail leaflet
   c. **Class IIIa (restrictive leaflet motion, entire cardiac cycle).** Rheumatic valve disease or secondary to systemic process resulting in fibrosis or damage to the subvalvular apparatus
   d. **Class IIIb (restrictive leaflet motion, systole).** Ischemic (IMR) or functional MR resulting in PM displacement or tethering of leaflets
3. MR can further be stratified by acute or chronic regurgitation guiding diagnostic evaluation, clinical urgency, and anticipated sequelae.
   a. **Acute mitral regurgitation (AMR)**
      (1) In acute regurgitation, the regurgitant volume returning from a **noncompliant LA** causes a sudden increase in **left ventricular end-diastolic volume (LVEDV)**. The LV attempts to compensate by increasing sarcomere length (preload) and enhancing LV contraction (inotropy), resulting in a hyperdynamic state.
      (2) Blood is ejected into the LA acutely raising **LA and pulmonary pressures**, which drive the clinical presentation.
      (3) Eventually forward cardiac output declines, resulting in hypoperfusion and **progressive shock**.
   b. **Chronic MR**

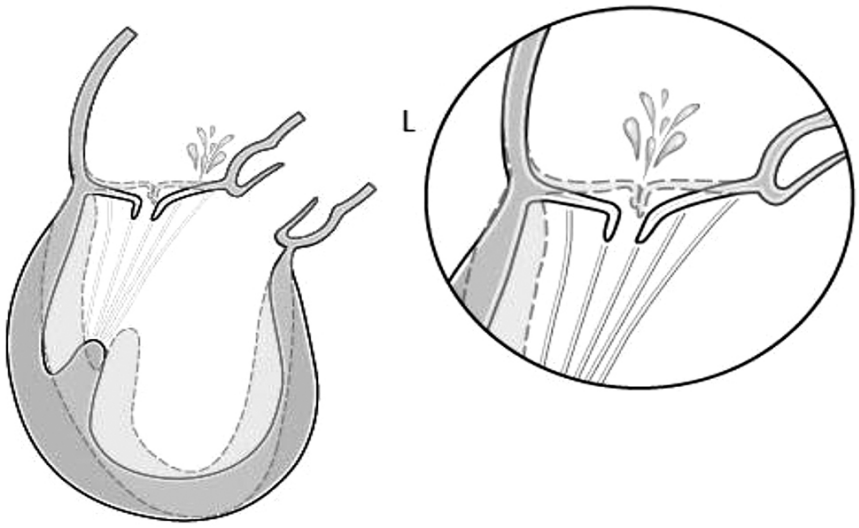


FIGURE 16.4 Larger view (L). As evident in the figure, there is distortion of the left ventricular geometry with resultant annular dilation and papillary muscle displacement causing tethering of the chordae and restricted leaflet closure. All these changes lead to ischemic mitral regurgitation.

(1) In **chronic compensated MR**, dilation of the LV or wall motion abnormalities and LV dysfunction secondary to ischemia distort annular geometry and **leaflet dynamics** as seen in **Figure 16.4**

(2) **Eccentric hypertrophy** and **increased atrial compliance** due to dilation develop to mitigate the **wall stress** and elevated **preload** from the regurgitant volume. LV function is **less hyperdynamic** than AMR in the high-normal range or may even be reduced.

(3) Patients often remain asymptomatic or minimally symptomatic for years. **Contractile dysfunction** may develop insidiously as the compensatory mechanisms to augment the ejection fraction (EF) fail. **The expected ventricular ejection fraction (LVEF) is ≥60% in severe MR, and an LVEF less than that is suggestive of contractile impairment.**

(4) In **decompensated chronic MR**, LV dysfunction results in a positive feedback cycle of dilation and progressive regurgitation. **Irreversible LV contractile dysfunction** may be present by the time overt symptoms develop, conferring poorer prognosis with higher rates of postoperative heart failure and increased mortality.

C. Clinical presentation

1. Physical examination

a. Inspection and palpation

(1) When LV function is preserved, carotid upstrokes are sharp, and the cardiac apical impulse is brisk and hyperdynamic. An **early diastolic LV filling wave** may be palpable because of the large volume of blood traversing from the LA to the LV. A late-systolic parasternal thrust reflects systolic expansion of the LA.

(2) LV dilation results in the lateral displacement of the apical impulse. An right ventricular (RV) heave and a palpable P2 are present with pulmonary hypertension. An elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema indicate RV dysfunction.

b. Auscultation

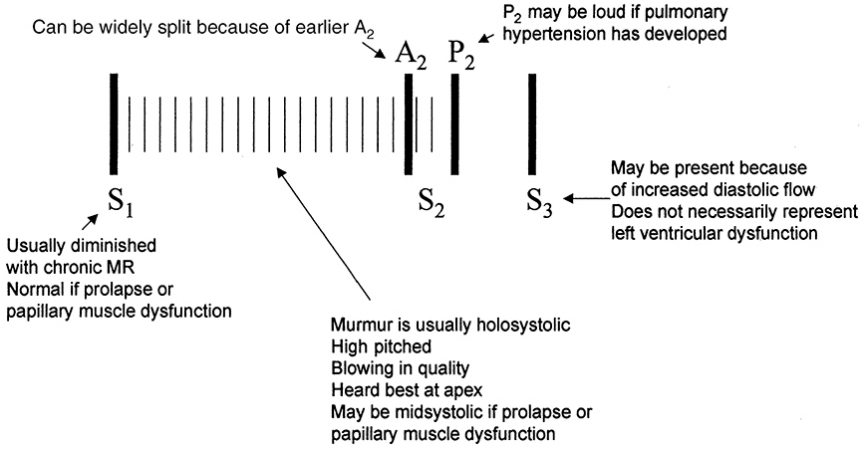


FIGURE 16.5 Auscultatory findings in mitral regurgitation. MR, mitral regurgitation.

(1) MR presents with a **holosystolic murmur** at the apex that radiates to the axilla but lacks the harsh quality and high pitch of a ventricular septal defect (VSD) or tricuspid regurgitation (TR). The main auscultatory findings in MR are shown in **Figure 16.5**.

(2) A **loud S_4** (not illustrated) can be heard, particularly with AMR. In acute severe MR, the systolic driving pressure across the mitral valve is reduced due to a high LA pressure; thus, the murmur is short and relatively soft. If the LA pressure is markedly elevated, **the murmur of AMR may be inaudible**.

2. Diagnostics

a. Chest radiography

(1) Cardiomegaly with LA and LV enlargement may be seen in chronic MR.

(2) Interstitial edema, manifest as Kerley B lines, followed by alveolar edema may develop in acute cases or with progressive LV failure.

b. Transthoracic echocardiography

(1) The recommended 2017 American Society of Echocardiography (ASE) Classification of MR severity is summarized in **Table 16.2**. MR severity is graded **qualitatively** based on the extension of the jet into the LA as follows: 1+ mild, 2+ moderate, 3+ moderately severe, and 4+ severe. Increasingly, MR is quantified where feasible.

(2) **Doppler echocardiography** should be used to determine the mechanism and severity of MR, to assess the LA and LV size and function over time, to assess the pulmonary artery (PA) pressures, and monitor postoperative function.

(3) **Qualitative estimation**

(a) **Jet profile**

i. The direction of the MR jet can aid in assessing the cause of MR (**Table 16.3**). Regurgitation caused

by prolapse or flail results in a jet **direction opposite to the affected leaflet** (ie, posterior jet with anterior leaflet prolapse). MR caused by leaflet restriction (rheumatic and ischemic) is **directed toward** the affected leaflet.

ii. As a jet directed against the atrial wall appears **smaller** than a free jet of the same regurgitant volume (**Coandă effect**), the estimated severity of MR is commonly increased by at least one grade.

iii. MR is not always holosystolic. Seemingly severe MR by peak flow may not cause structural changes as the MR occurs only in late systole, causing a smaller regurgitant volume.

(4) Semiquantitative estimation

(a) Jet area

i. Central jets with an area >**10 cm_2 or >50% of the LA area** suggest severe disease, while area <4 cm^2 or <20% LA area suggests mild MR. Underestimation of MR may occur with eccentric jets.

(b) Mitral inflow

i. A pattern of **E>A wave**, where **E wave measures >1.2 m/s** is characteristic of severe mitral insufficiency. **A-wave dominance** can effectively exclude severe MR.

(c) Pulmonary vein flow

i. **Blunting of the systolic component** of pulmonary venous flow in the presence of normal LV function suggests at least moderately severe MR. **Systolic flow reversal** suggests severe MR (**Figure 16.6**).

ii. Pulmonary venous flow is a less reliable indicator of substantial MR in the setting of **AF** or **severe**

LV dysfunction because these conditions can also cause systolic blunting.

(5) Quantitative assessment

(a) Vena contracta

i. The **vena contracta width of ≥0.70 cm** suggests severe MR.

ii. Overestimation can occur due to limited lateral resolution; thus, high resolution, zooming, or TEE may be required.

(b) PISA and EROA

i. The detailed derivation of peak flow, EROA, and volume is discussed in Chapter 66.

ii. EROA is prognostically powerful in MR of ischemic or degenerative origin and **proportional to MR severity**. An EROA of ≥0.40 cm_2 is consistent with severe MR. In IMR, **EROA of ≥0.20 cm_2** is associated with poorer long-term outcomes, reflected in the European guidelines. However, the ASE and ACC/AHA (American Heart Association) guidelines continue to use **≥0.40 cm_2**, given the concern for underestimation of MR and the desire to distinguish prognostically versus quantitatively severe disease. The calculation of EROA may be **simplified** by assuming (1) a pressure difference of approximately 100 mm Hg between the LA and LV, and thus, the MR velocity to be 5 m/s and (2) the aliasing velocity set at 40 cm/s. With these simplifications, ROA is **calculated as r2/2**.

iii. The PISA method may overestimate regurgitation in **nonspherical orifices, eccentric or multiple jets, or constrained flow convergence zone** (ie, flail leaflet). Angle-correction formulas or **TEE** may be used instead.

(c) Regurgitant volume

i. The regurgitant volume may then be calculated by three different methods: the PISA, the volumetric, and the continuity method.

   a. **The PISA method** is the most popular and uses the following equation: EROA × VTI_{MR}, where VTI_{MR} is the **velocity-time integral** of the regurgitant jet on continuous Doppler (**Figure 16.7**).

   b. **The volumetric method** utilizes **conservation of flow** to directly estimate the regurgitant volume as the difference between the total forward transmitral flow into the ventricle and the systemic flow out through the LVOT.

   c. **The continuity method** is based on the **conservation of mass** and is commonly used in the evaluation of aortic stenosis discussed in **Chapter 15**. The regurgitant volume is the difference between inflow and outflow stroke volume of the same ventricle using the velocity-time integral and cross-sectional areas of the mitral annulus and LVOT. This method assumes circular geometry and cannot be used with concomitant aortic regurgitation or intracardiac shunts.

(d) Regurgitant fraction

i. Finally, the RF can be calculated by dividing the calculated regurgitant volume if the **forward stroke volume or mitral inflow volume** is known.

ii. An RF >50% is considered severe regurgitation.

(e) Strain

i. 2D strain imaging can detect subtle changes in ventricular function that precede reductions in EF.

c. Transesophageal echocardiography

(1) Preoperative. Preprocedural TEE helps to confirm the severity and mechanism of MR prior to surgery. In some estimates, up to 15% of patients may have a change in surgical strategy based on preoperative imaging.

(2) Intraoperative. TEE provides immediate identification of the success of surgical or transcatheter intervention, allowing the detection of unsuitable **persistent MR, perivalvular leak, new systolic anterior motion (SAM), or wall motion abnormalities**. Patients undergoing open-heart surgery (OHS) can be put back on cardiopulmonary bypass (CPB) without de-cannulation for the appropriate corrective intervention.

d. 3D echocardiography

(1) Procedural guidance

(a) The "**en face**" or "**surgeon's view**" of the mitral valve orients annulus and leaflets along the optimal coplanar angulation with the aortic valve in the 12 o'clock position from the LA. The ventricular aspect may be used for the assessment of structures, such as the chordae tendineae and PMs.

(b) In regurgitation, 3D TEE can reliably identify the location and direction of regurgitating jets, as well as plan for potential grasping planes for clip devices. Measurements of regurgitant, volume, and fraction correlate well with quantitative flow data from CMR.

(c) During transcatheter clip deployment, 3D TEE can confirm freedom from the subvalvular apparatus and assessment of residual MR for additional clip placement.

(d) In percutaneous balloon mitral valvuloplasty (PBMV), 3D TEE allows for real-time visualization of

commissural splitting, identification of mechanical complication, and qualification of postprocedural regurgitation.

e. CT. Cardiac CT with contrast enhancement is essential for preprocedural native and prosthetic valve anatomic and functional assessment. 4D retrospective gating of the entire cardiac cycle enables a complete assessment of the cardiac chambers, leaflets, annular dimensions, and planimetry.

Advanced simulation software can be used to estimate the size and orientation of transcatheter mitral valve replacement (TMVR) prostheses and estimate the neo-LVOT and the iatrogenic narrowing of the ventricular outflow tract by anterior mitral leaflet after valve deployment (**Figure 16.8**).

TABLE 16.2 Echocardiographic Assessment of Severity of Mitral Regurgitation

	Mild	Moderate	Severe[a]
Qualitative			
Angiographic Grade	1+	2+	3-4+
Color Doppler jet area	Small, central jet (<4 cm_2 or <20% LA area)	Signs of MR> mild present, but no criteria for severe MR	Vena contracta width >0.7 cm with large central MR jet (area >40% of LA area) or with a wall-impinging jet of any size
Doppler vena contracta width (cm)	<0.3	0.3-0.69	≥0.70
Quantitative (Echo)			
Regurgitant volume (mL/beat)	<30	30-59	≥60
Regurgitant fraction (%)	<30	30-49	≥50

	Mild	Moderate	Severe[a]
Regurgitant orifice area (cm_2)	<0.20	0.2-0.39	≥0.40

LA, left atrium; LV, left ventricle; MR, mitral regurgitation.
[a]In severe MR, evidence of LA and LV dilation is essential.

TABLE 16.3 Mechanisms, Direction of Color Jet, and Surgical Management of Mitral Regurgitation

Jet Direction	Leaflet Motion	Likely Cause	Surgical Method
Anterior	Excessive	Posterior leaflet prolapse	Quadrilateral resection Annuloplasty Chordal shortening Shortening of papillary muscle
	Restricted	Anterior leaflet restriction	Debridement
Posterior	Excessive	Anterior leaflet prolapse	Chordal transfer or shortening
			Synthetic chords
	Restricted	Posterior leaflet restriction	Debridement, annuloplasty
	Normal	Ventricular dilation	Annuloplasty
Central	Excessive	Bileaflet prolapse	Resection, chordal transfer, synthetic chords
	Restricted	Bileaflet restriction	Debridement
	Normal	Ventricular dilation	Annuloplasty
Commissural	Papillary muscle dysfunction		Reattach or fold papillary muscle
	Eccentric	Perforation or cleft	Pericardial patch

Reprinted with permission from Stewart WJ. Adapted from Intraoperative echocardiography. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine* Lippincott-Raven Publishers; 1998.

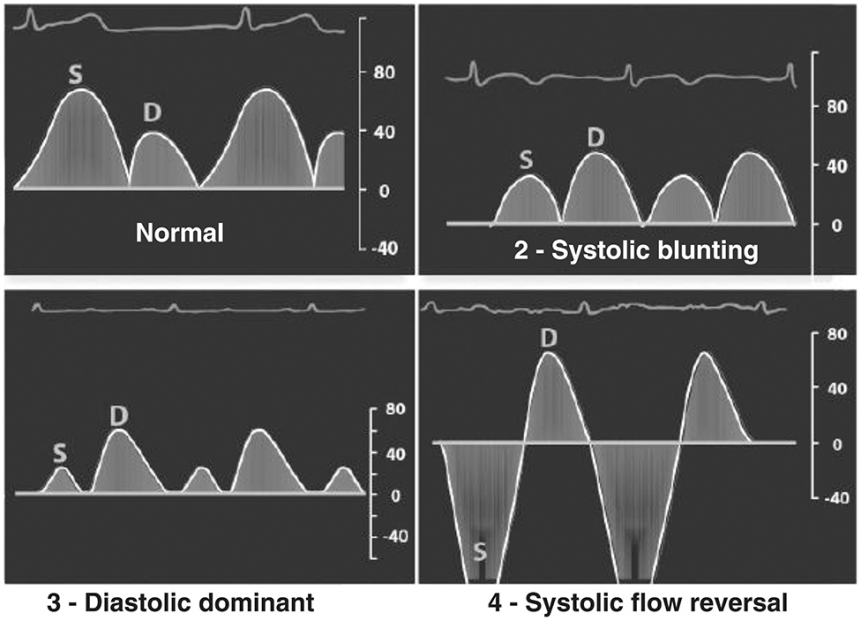


FIGURE 16.6 Pulmonary venous flow changes with increasing mitral regurgitation severity.

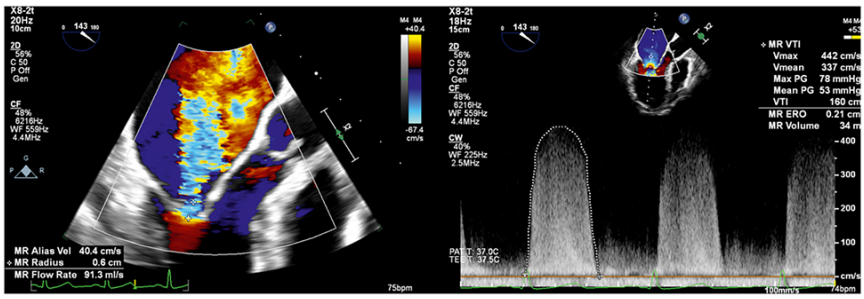


FIGURE 16.7 Calculation of the regurgitation effective orifice area by proximal isovelocity surface area and mitral regurgitation velocity-time integral using transthoracic echocardiography. (Image Courtesy of Dr Harb MD.)

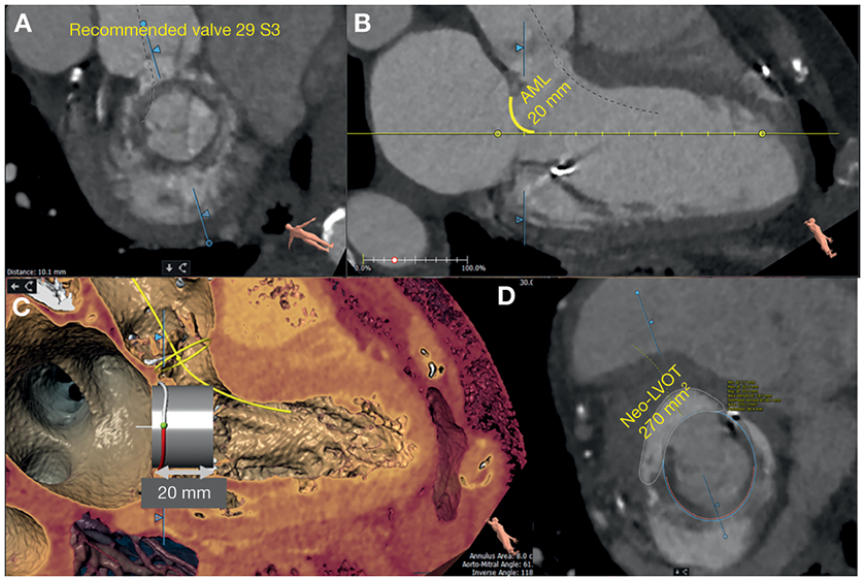


FIGURE 16.8 Computed tomographic angiographic simulation of prosthetic transcatheter mitral valve implant and estimation of residual neo-left ventricular outflow tract. (Image Courtesy of Dr Harb MD.)

f. CMR. CMR provides quantitative assessment of jet morphology, chamber volume, and regurgitant volumes/fractions. It can estimate regurgitation in the setting of comorbid multivalvular or shunt physiology. Several studies have shown that CMR assessment has **excellent reproducibility** and low variability, independent of jet characteristics (**Figure 16.9**).

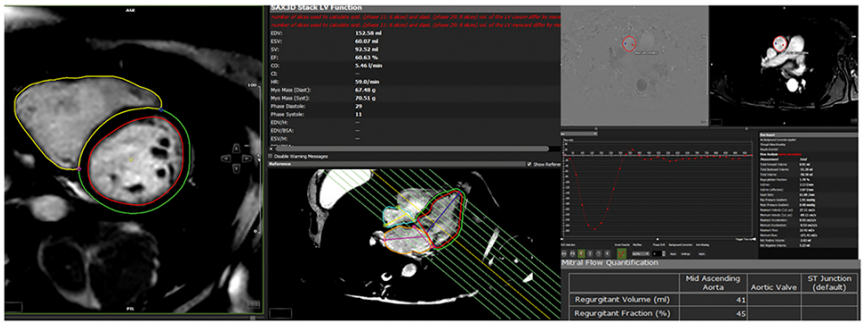


FIGURE 16.9 Acquisition, segmentation, and volume calculation of cardiac chambers utilizing a series of contiguous short-axis cine images from the base to the apex. Quantification of flow with phase-contrast imaging enables accurate assessment of

regurgitant volume across a valve. (Image Courtesy of Dr Harb MD.)

(1) Mitral regurgitant volume is calculated by the LV stroke volume minus aortic forward flow, and regurgitation fraction is regurgitant volume divided by stroke volume.

(2) **Late-gadolinium enhancement (LGE).** LGE can detect irreversible myocardial fibrosis that has prognostic significance for adverse cardiovascular outcomes, particularly among patients with mitral valve disease such as prolapse, along with functional MR in both ischemic and nonischemic cardiomyopathies discussed below.

g. Cardiac catheterization

(1) **Left heart catheterization.** The severity of MR is based on the **reflux of contrast** into the LA and is graded as follows:
1+ (mild): Contrast clears with each beat, but the entire LA is never opacified.
2+ (moderate): Contrast does not clear with a single beat and may faintly opacify the entire LA.
3+ (moderate to severe): Contrast fills the entire LA over 2 or 3 beats with complete opacification of the LA, equal in intensity to the LV.
4+ (severe): Complete opacification of the LA occurs in 1 beat or contrast material refluxes into the pulmonary veins.

(2) **Pressure-volume loops.** Ventricular impairment can be occult in severe MR. **Elastance** is the best load-independent measure of contractile function in MR. However, because a series of **pressure-volume loops** must be constructed, it is rarely performed in clinical practice.

(3) **Right heart catheterization.** The amplitude of the **v waves** on wedge pressure hemodynamic tracings reflects LA filling from the pulmonary veins during ventricular

systole and can provide clues to the severity of MR, particularly in AMR.

D. Acute primary MR

1. Introduction

a. AMR often presents with rapid onset of symptoms and **dramatic deterioration** meriting prompt diagnosis and management categorized into ischemic versus nonischemic etiology.

2. Specific clinical presentation

a. Acute regurgitation into a noncompliant LA raises **LA pressure**, causing backflow into the pulmonary circulation, resulting in **pulmonary edema** with dyspnea, orthopnea, and hypoxia. Despite compensatory increases in heart rate and contractility, **forward flow can be severely diminished**, resulting in shock.

3. Ischemic mitral regurgitation (IMR)

(1) Etiology

(a) Common mechanisms in the acute setting include:

i. The **PPM** rupture due to a compromised **single-vessel supply** (typically right coronary artery [RCA]). PPM rupture 6 to 12 times more common than the APM, which has a dual blood supply.

ii. **Altered LV motion** displaces the PM. Prompt revascularization may correct the MR.

iii. The infarcted PM can also elongate, while the noninfarcted PM demonstrates exaggerated contraction.

(2) Clinical presentation

(a) Most patients with PM rupture are having their first myocardial infarction (MI).

(b) Rupture occurs in 1% to 3% of cases occurring **2 to 7 days after infarction**.

(c) Notably, there have been cases described of papillary rupture secondary to **cardiac trauma**.

(3) **Specific diagnostics**

(a) ECG in acute IMR typically demonstrates an **inferior or inferolateral MI.**

(b) Echocardiography can often reveal PM rupture, leaflet restriction, mitral valve tethering, and relevant regional wall motion abnormalities. **Urgent TTE or TEE** should be performed when AMR is suspected.

i. In **hemodynamically compromised** patients with compensatory **tachycardia**, the recognition of AMR may be challenging. But a **sharp, early peaking MR jet** on spectral Doppler suggests early equalization of pressure between the LV and LA should raise clinical suspicion.

4. Nonischemic regurgitation

a. Nonischemic etiologies of AMR include **acute complications** of myxomatous disease, rheumatic heart disease (RHD), endocarditis, dynamic outflow tract obstruction, acute aortic regurgitation, or spontaneous rupture.

b. Iatrogenic nonischemic MR has been described with transcatheter structural interventions, temporary mechanical support, and LV assist device (LVAD) removal.

(1) **Chordal rupture**

(a) Rupture of the chordae can occur spontaneously, resulting in a flail leaflet. Chordal rupture is usually identified as **a linear, mobile, free echo density** associated with the flail leaflet.

(b) Chordal rupture is a known complication of MVP and may present with acute severe MR.

(2) **Leaflet perforation**

(a) Leaflet perforation and rupture may occur in the setting of **endocarditis**. Perforation appears as

discontinuity in the valve with normal closing mechanics on echocardiography.

(3) Iatrogenic

(a) Rare cases of **iatrogenic chordal rupture** and leaflet perforation have been described with the implantation of temporary mechanical circulatory support, and even **aberrant pacemaker lead placement** through atrial septal defect (ASD) has been described.

5. Complications

a. Acute hypoxic respiratory failure

(1) Severe pulmonary edema and respiratory failure may require **mechanical ventilation**. Invasive positive pressure ventilation may improve LV dynamics by also reducing **preload and afterload**, which support leaflet coaptation.

b. Cardiogenic shock

(1) The rapid drop in forward flow may not be adequately compensated by compensatory tachycardia and inotropy depending on the severity of regurgitation, resulting in hemodynamic collapse.

6. Management

a. Medical therapy

(1) If there is adequate mean arterial pressure, pharmacologic therapy with afterload-reducing agents such as intravenous **nitroprusside** and **nitroglycerin** may reduce pulmonary pressures and maximize forward flow. Angiotensin-converting enzyme inhibitors (ACEi) and direct-acting vasodilators (such as hydralazine) help maximize forward output and reduce RF if a transition to oral agents is pursued.

b. Intervention

(1) Temporary mechanical support

(a) Clinical stabilization until definitive surgical intervention remains the priority when feasible and

can be facilitated by temporary mechanical circulatory support.

(b) Placement of an **intra-aortic balloon pump (IABP)**, especially in postinfarction PM rupture, may temporarily stabilize hemodynamics.

(c) Options for upgrading temporary ventricular support include the use of percutaneous or surgically placed **microaxial continuous flow pumps** or **extracorporeal membrane oxygenation** with concomitant **transseptal drainage**. See Chapter 62 for further discussion regarding temporary options and management of valve shock.

(2) Surgical therapy

(a) The definitive management for most cases of acute severe MR is surgery. **Chordal-sparing mitral valve replacement** or **mitral valve repair with ventricular reshaping or artificial chordae material using expanded polytetrafluoroethylene (neo-chordae)** can be deployed while attempting to preserve as much of the native architecture.

(3) Transcatheter therapy

(a) **Transcatheter edge-to-edge repair (TEER)** has been safely used for severe AMR secondary to PM rupture and functional IMR in nonsurgical candidates based on limited reports only of short and medium (~1 year) outcomes.

E. Chronic primary MR

1. In chronic MR, there is often **compensatory cardiac remodeling** in response to valve incompetence.

2. Clinical presentation

a. Chronic MR is usually asymptomatic for years. The most common presentation is an asymptomatic murmur. **Exercise intolerance and exertional dyspnea** are followed by

orthopnea and paroxysmal nocturnal dyspnea and fatigue as cardiac output decreases.

b. Long-standing severe MR may cause **pulmonary hypertension**, with symptoms of RV failure. Progressive LA dilation may lead to AF.

3. Primary MR

a. MVP and myxomatous disease

(1) Introduction

(a) Prolapse exists when either leaflet protrudes >2 mm beyond the annulus into the LA during systole, raising the coaptation zone **above the annular plane**. A wide spectrum of disease exists from mild incidental prolapse to clinically symptomatic severe MR.

(b) MVP is the most common cause of MR in the United States, affecting approximately 2% of the population. About 10% to 15% of patients eventually develop progressive MR, particularly those with **redundant and thickened leaflets**. Chordal rupture is a contributing factor among these patients.

(2) Pathophysiology

(a) Prolapse may exist because of valvular abnormalities, primary prolapse, or occur in the setting of normal leaflets, secondary prolapse.

(b) Primary prolapse

i. Primary prolapse results from **myxomatous proliferation** of the leaflets with prominence of the spongiosa layer and chordae tendineae because of abnormal accumulation of **mucopolysaccharides**. Tensile strength of the chordae is affected, resulting in **elongation, prolapse, and loss of leaflet coaptation**. **Thickening** of the leaflets ≥5 mm is considered "classic" MVP and is associated with increased complications.

ii. Typically, this occurs in **men aged >45 years** and is more likely to cause complications and require surgical intervention than secondary prolapse.

iii. Two histologically distinct subtypes of myxomatous degeneration are (1) **Barlow disease**, seen in younger patients with greater annular dilation and more marked leaflet redundancy causing multisegment prolapse, and (2) **fibroelastic deficiency**, occurring in older patients, typically in the posterior middle scallop (P2) with thinning and rupture of chordae.

iv. An **autosomal dominant** mode of inheritance with variable penetrance has been postulated. Three loci, on chromosomes **11, 13, and 16**, have been identified in families with multiple affected members. MVP is also common in patients with connective tissue disorders, such as Marfan, Loeys-Dietz, Ehlers-Danlos, and osteogenesis imperfecta.

(c) Secondary prolapse

i. In **secondary prolapse**, valvular structure is relatively normal. A disproportion between dilated LV cavity size and normal leaflets produces **mechanical forces** that may lead to prolapse.

ii. This is seen in younger women and may occur with atrial septal defect, hyperthyroidism, emphysema, and HCM.

iii. The incidence appears to decrease with age.

iv. Secondary prolapse is usually of little clinical significance without significant MR.

(3) Clinical presentation

(a) Symptoms

i. Most patients are diagnosed incidentally and remain asymptomatic. Symptoms previously

attributed to **isolated MVP**, including chest pain, panic attacks, and autonomic instability, occur at a similar frequency in the general population.

ii. In patients with MVP without significant MR, the prevalence of **arrhythmias** is similar to the general population. However, this increases with the development of significant MR and appears to be related to the degree of MR rather than MVP itself.

(b) Physical examination

i. Patients with MVP have a higher incidence of **pectus excavatum, scoliosis,** and **straight back**. Low body weight and relative hypotension can be seen.

ii. The main auscultatory findings are shown in **Figure 16.10**. The **mid-systolic click** is the classic finding in prolapse. Systolic click occurs at **least 0.14 seconds after S_1**, after the onset of carotid upstroke. Multiple clicks can be heard later in systole from snapping taut of chordae at the lower sternal border.

iii. A click that responds to provocative maneuvers is **sufficient for diagnosing prolapse**.

a. Maneuvers that **decrease LV size** (decreased venous return, increased contractility, or decreased systemic volume) lead to **earlier occurrence** of prolapse, an earlier click, and increased duration of the murmur. These include standing, the Valsalva maneuver, dehydration, and exposure to amyl nitrite.

b. Maneuvers that **increase LV size** (increased venous return, decreasing contractility, or increasing systemic volume) shift the click and murmur **later into systole**. Examples

include squatting and infusion of phenylephrine.

iv. A mid- to late-systolic murmur is present with MR. The intensity typically decreases with conditions that result in a later click. However, exposure to **amyl nitrite** reduces LV systolic pressure and the gradient that drives the regurgitant flow. Thus, it causes a less intensity early systolic murmur.

v. **Aortic and pulmonic ejection** can produce systolic clicks earlier in systole than the click of mitral prolapse and may be differentiated based on timing with the **carotid upstroke**. **Septal and free wall aneurysms** and mobile tumors such as **myxoma** can produce clicks that do not change with maneuvers.

(4) Specific diagnostics

(a) Electrocardiogram

i. The role of ECG in identifying high-risk lesions is an area of research. **Inverted T waves** in the inferior leads appear to be associated with up to 75% of patients with MVP who suffer cardiac arrest.

ii. PM and fascicular premature ventricular contractions (PVCs) appear to implicate the Purkinje system in **arrhythmogenic mitral bileaflet prolapse**.

(b) Echocardiography

i. With primary causes of prolapse, increased **leaflet thickness** (≥5 mm) and redundant leaflets and chordae are seen. M-mode demonstrates late or holosystolic bowing of the mitral valve leaflet 3 mm or more below the C-D line. In an apical **four-chamber view**, normal valve leaflets may

appear to prolapse due to the saddle shape of the annulus. Thus, prolapse should only be diagnosed based on the long-axis echo views (parasternal, apical).

ii. Patients with elevated **peak systolic lateral mitral annulus** velocity >16 cm/s and the presence of **MAD (>8 mm gap)** appear to have a higher rate of malignant ventricular arrhythmias (VA).

(c) Cardiac magnetic resonance imaging

i. **Ventricular fibrosis** identified by LGE on CMR is independently associated with VA and sudden cardiac death (SCD) in MVP. Thus, CMR can be used for risk stratification.

ii. **CMR** is more sensitive and specific in detecting MAD, which is associated with a higher incidence of VA.

(5) Complications

(a) Sudden cardiac death

i. The risk of sustained **VA** has been reported as high as 2% annually in observational studies.

ii. **Gender, bileaflet prolapse, and greater valve thickening** appear to be associated with malignant life-threatening arrhythmias in MVP. Some reports estimate 70% to 90% of affected individuals are females.

(b) Stroke

i. MVP does not appear to confer additional risk of transient ischemic attack **(TIA)/CVA** among young patients.

(6) Treatment

(a) For most patients, MVP carries a benign prognosis, and periodic clinical follow-up examinations and reassurance are sufficient.

(b) **Endocarditis prophylaxis** is not routinely indicated in patients with MVP.

(c) Patients with evidence of primary MVP should avoid situations that might **increase the stress on the chordae**, such as sudden heavy lifting.

(d) For patients with a history of TIA, antiplatelet therapy with aspirin (81-325 mg/d) is indicated.

(e) Patients who experience palpitations should be advised to abstain from caffeine, alcohol, and tobacco use. **Beta-blockers** are useful in the management of premature atrial or ventricular contractions (VCs) and often alleviate symptoms. **Ambulatory electrocardiographic monitoring** is recommended for persistent palpitations.

(f) Ventricular tachycardia is an indication for **electrophysiologic testing** to assess the risk of sudden death and the possible need for implantation of a defibrillator device.

b. Infective endocarditis

(1) Chapter 19 provides a comprehensive perspective of the pathophysiology, diagnosis, and treatment of endocarditis.

(2) Pathophysiology

(a) Endocarditis primarily manifests as vegetation around endothelial defects, providing **platelets and fibrin** that promote the growth of microorganisms. Left-sided native valve endocarditis commonly involves primary degenerative mitral lesions with associated regurgitation.

(b) Among younger patients, **MVP** is commonly seen. Among older patients, **mitral annular calcification (MAC)** is believed to serve as a nidus for infection.

(c) Microorganisms are particularly adherent to foreign materials such as prosthetic valves, which have an

estimated 50 times higher likelihood of infection than native valves. The **prosthetic sewing ring** is often the site of infection and abscess formation.

(d) Invasive disease describes both tissue disintegration and extension of infection into the valvular annulus. Cellulitis may cause abscess and cavity formation and result in pseudoaneurysm or fistulae.

(3) Clinical presentation. The **Modified Duke Criteria** is used to estimate the likelihood of endocarditis. In addition to fever and sepsis, new-onset murmurs and embolic phenomenon are common in endocarditis. Valve damage erosion can result in symptoms of dyspnea, chest pain, and volume overload.

(4) Diagnostics

(a) TEE may be able to identify and diagnose infective endocarditis while providing better assessment of anatomic complications and valve involvement than TTE, particularly among patients with bacteremia without a clear source.

(b) TEE may be repeated **7 to 10 days after negative TEE** if the index of suspicion remains high.

(c) CT and positron emission tomography can also be used to identify **anatomic lesions/vegetations** or detect **metabolic activity** consistent with an infective process, respectively.

(5) Treatment specifics

(a) Definitive management requires an evaluation for intervention or surgery. Standard antibiotic treatment tailored to pertinent microorganisms is essential. If possible, the mitral valve should be repaired. **Autologous pericardial patch repair** may be used in perforations of the anterior mitral leaflet.

c. Rheumatic heart disease

(1) **See the section on rheumatic heart disease in the Mitral Stenosis and the Chapter on Rheumatic Fever for more detailed information.**

(2) **Pathophysiology**

(a) Rheumatic fever (ARF) secondary to **group A** β-**hemolytic *Streptococcus*** (*Streptococcus pyogenes*) infection may cause valvulitis in the acute setting and fibrotic changes chronically.

(b) MR most often occurs in younger patients. While a **mixed valvulopathy** with concomitant MS appears to develop in older patients.

(3) **Diagnostics**

(a) Echocardiography may show **restricted motion** and **diastolic doming** of leaflets, anterior MVP with minimal leaflet redundancy, leaflet thickening and small verrucous vegetations along the free margin, and commissural fusion.

(4) **Specific treatment**

(a) The indications for valve surgery are similar to typical secondary nonrheumatic regurgitation. **Progressive fibrotic thickening** of the leaflets and chordae may limit the durability of repair, with an estimated 20% reoperation at 10 years.

d. Inflammatory, connective tissue diseases

(1) **Several inflammatory diseases** have valvular manifestations, including systemic lupus erythematosus (SLE), rheumatoid arthritis, connective tissue diseases, and collagen vascular diseases.

(a) Connective tissue disorders associated with valvulopathy include Marfan syndrome, Ehlers-Danlos syndrome and subtypes, and osteogenesis imperfecta. Antiphospholipid syndrome (APLS) also appears to be associated with MR.

(2) **Pathophysiology**

(a) The presentation of valvulopathy varies significantly based on the underlying condition, but MVP occurs commonly.

(b) SLE also presents with **nonbacterial valvular vegetations** consisting of thrombi, immune complexes, mononuclear cells, and fibrin that vary in size, termed *Libman-Sacks endocarditis*.

e. Congenital mitral disorders

(1) **MAD** describes the atrial displacement and separation of the posterior annulus from the LV myocardium, typically 5 to 10 mm. It occurs with MVP and is associated with VA.

(2) **Cleft mitral valve** describes a spectrum of leaflet lesions ranging from focal indentation to discontinuity of the leaflet, typically involving the **anterior leaflet.** It is often associated with an **atrioventricular septal defect (ASD)** and has been described in up to 6.5% of neonates with **trisomy 21**. Surgical repair often has good outcomes and should be considered to prevent thickening and retraction of the leaflet edges.

(3) **Double-orifice** mitral valve (DOMV) has two orifices in the atrioventricular valve area, with separate chordal attachments to PMs. Usually, patients are asymptomatic and may not require repair in isolation. However, most cases are associated with other congenital malformations.

(4) **Intracardiac blood cysts** are rare and most commonly involve the mitral valve. They are diagnosed incidentally during routine echocardiography. They can result in **leaflet malcoaptation** or dynamic left ventricular **outflow tract obstruction (LVOTO)**. CCTA and CMR can be used to help differentiate blood cysts from solid tumors.

f. Drug-induced fibrosis

(1) Anorectic drug-induced valvulopathy appears to be mediated by **serotonin** in patients exposed to ergot

derivatives through stimulation of 5-hydroxytryptamine **(5-HT) 2B receptors**.

(2) **Fenfluramine and dexfenfluramine** have been identified as offending agents. Most cases of MR were reported in patients taking the combination of fenfluramine and phentermine.

(3) The use of **ergot derivatives** used in the treatment of migraine, hyperprolactinemia, and previously in Parkinson disease has also been associated with dose-related valvular disease. Cabergoline and pergolide were voluntarily withdrawn from the United States.

(4) While **selective serotonin reuptake inhibitors (SSRIs)** augment serotonergic activity, they are **not associated** with valvular disease.

4. Chronic secondary MR

a. Introduction

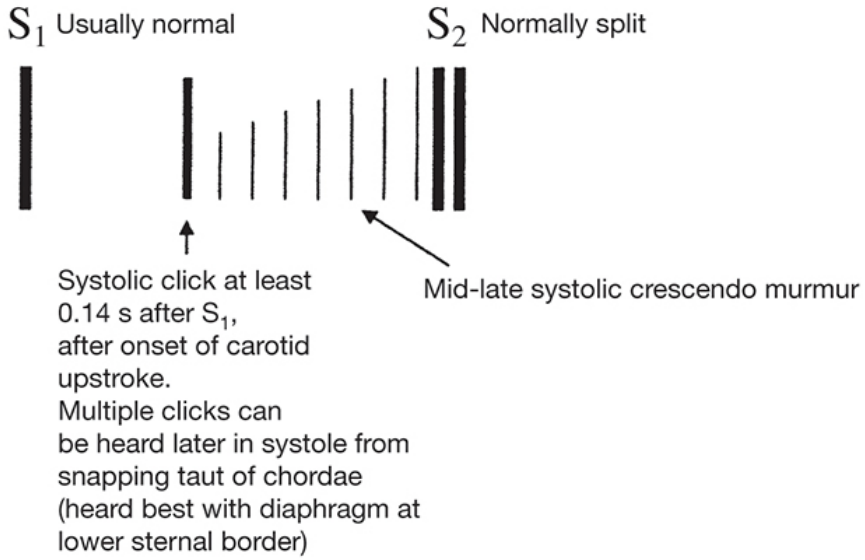


FIGURE 16.10 Auscultatory findings in mitral valve prolapse.

(1) Secondary or functional regurgitation occurs due to changes in **the geometry of the LA, LV, or both**

chambers including dilation or abnormal wall motion that impairs valve function. The mitral valve leaflets and subvalvular apparatus typically remain macroscopically normal.

b. Ischemic mitral regurgitation

(1) IMR can occur after prior infarction or chronic obstructive CAD and portends a poorer global prognosis. The clinical presentation of chronic IMR also parallels that of other etiologies of chronic MR.

(2) Pathophysiology

(a) Mechanisms common in chronic IMR are diagrammed in **Figure 16.4** and include:

i. PM necrosis and segmental dysfunction of **inferolateral wall** causing leaflet tethering and poor coaptation

ii. **Decreased mitral valve closing forces** because of LV systolic dysfunction

iii. LV cavity dilation causing mitral valve annular dilation

(3) Diagnostic specifics

(a) Electrocardiogram

i. In chronic IMR, LA abnormalities, AF, nonspecific ST changes, and evidence of prior infarction such as Q waves and loss of forces may be seen.

(b) Echocardiography

i. Surveillance echocardiography is recommended to monitor response to medical therapy and the progression of secondary regurgitation. The interval development of new wall motion abnormalities may enable the identification of progressive concomitant coronary lesions that could benefit from revascularization.

(c) Cardiac magnetic resonance imaging

i. Cardiac chamber size and shift in valve geometry can be evaluated directly by CMR.

ii. Late-gadolinium accumulation in fibrosed and necrosed scar tissue can identify and quantify the degree of ischemic damage or interstitial fibrosis with important prognostic implications.

(4) Treatment specifics

(a) Medical management of chronic IMR with preserved EF remains controversial. If LV dysfunction is present, guideline-directed medical therapy (GDMT) of heart failure management is essential.

(b) Concomitant mitral valve surgery is recommended at the time of coronary artery bypass grafting (CABG) in patients with **LV dysfunction and severe IMR**.

c. Nonischemic MR

(1) Dilated cardiomyopathy (DCM)

(a) Functional MR is common in DCM and is frequently present in patients with severe LV dilation.

(b) Pathophysiology

i. In DCM, **annular dilation** secondary to LV enlargement leads to a failure of coaptation. As the LV remodels, the PMs become displaced, leading to tethering and excessive leaflet tenting.

ii. While the regurgitant flow is variable in DCM, there is often an early systolic peak, a mid-systolic decrease, and a late smaller systolic peak, which reflects dynamic changes in the EROA.

(c) Diagnostic specifics

i. In addition to the utility of echocardiography and CMR described earlier for ischemic secondary MR, **left ventricular global longitudinal strain (LV-GLS)** has been shown both to be a sensitive indicator of LV dysfunction and to have

prognostic value identifying patients with higher 5-year mortality using a cutoff of >−7.0%.

(2) Restrictive cardiomyopathy

(a) The diagnosis, evaluation, and management of infiltrative cardiomyopathies are reviewed in **Chapter 11**. Infiltrative diseases resulting in restrictive cardiomyopathy have been associated with valvulopathy:

i. **Cardiac amyloidosis** (CA) may involve protein deposition into the valve apparatus itself with concomitant LA and annular dilation. Concomitant MR appears to occur in an estimated 12% to 30% of cases of CA. Amyloid cardiomyopathy is covered in depth in Chapter 9.

ii. In **hypereosinophilic syndrome**, Loeffler endocarditis may develop with myocardial infiltration, resulting in scarring and fibrosis of the chordae tendineae and abnormal coaptation.

(3) Hypertrophic cardiomyopathy

(a) Introduction

i. Mitral valve abnormalities play a significant role in LVOTO in patients with **HCM**, independent of the degree of hypertrophy. Variations in leaflet length, papillary insertion, and abnormal chords commonly predispose to SAM.

(b) Pathophysiology

i. Regurgitation occurs with **SAM of the mitral valve** toward the distorted hypertrophic septum obstructing the LVOT with an associated coaptation defect.

ii. The **primary mechanism** of obstruction and regurgitation appears to be a **drag effect** whereby posteriorly directed blood flow pushes mitral

valve apparatus and the elongated leaflet into the outflow tract.

iii. Mitral valve **elongation** may be part of the primary phenotypic expression of HCM rather than sequelae of abnormal chamber structure.

(c) Treatment specifics

i. Concomitant **mitral valve surgery, whether valve repair or PM repair** at the time of **surgical myectomy**, requires careful evaluation on the precise mechanism of MR and LVOTO.

ii. **Myectomy is generally favored over alcohol septal ablation (ASA),** except for patients with high or prohibitive surgical risk. **Concomitant valve or coronary disease with severe MR** would also favor myectomy. See HCM chapter with regard to medical therapies.

(4) Atrial functional mitral regurgitation (AFMR)

(a) Introduction

i. AFMR occurs secondary to **LA enlargement** and **annular dilation** in AF or HFpEF. It is estimated that 4% to 7% of patients with AF have significant MR.

ii. In the ATTEND (Acute Decompensated Heart Failure Syndromes) Registry, almost 18% of patients admitted for HFpEF had moderate-to-severe MR on discharge.

iii. The presence of AF and HFpEF appears synergistic in the development of AMR.

(b) Pathophysiology

i. Proposed mechanisms for the development of AFMR include annular dilation, reduced annular contractility, LA dysfunction, and conduction variability.

a. Typically, the mitral leaflet area exceeds the annular dimension by 1.5 to 2 times to allow sufficient coaptation during systole. Annular enlargement and dilation reduce this ratio, leading to regurgitation. In patients with intermediate range of annular dilation, between 5 and 8 cm_2/m_2, the extent of **adaptive leaflet remodeling** mediates the severity of regurgitation. Thus, insufficient remodeling may play a role in MR.

b. HFpEF may similarly cause functional regurgitation through **LA and annular dilation**.

c. Compensatory leaflet remodeling and elongation are thought to **mitigate the impact** of annular dilation or leaflet tethering due to chamber distortion in chronic MR.

d. Several studies have reported LA enlargement, causing **displacement** of the base of the posterior leaflet beyond the crest of the LV free wall. This results in **atriogenic leaflet tethering (ALT)** and malcoaptation, resulting in a posteriorly directed eccentric jet. The evidence for ALT, however, remains controversial and may be considered a rare subtype of AFMR.

(c) Diagnostics

i. Echocardiography

a. When leaflet symmetry is preserved, the MR jet remains centrally directed. As **annular enlargement** progresses, the jet may become more eccentric.

b. Quantification of regurgitation is challenging in AMR. The VC and EROA calculated from

PISA are limited due to the **elliptical regurgitant orifice** shape. 3D assessment of PISA and TEE provide better anatomic and morphologic assessment of the regurgitation and orifice.

c. **Beat-to-beat variation** in cycle lengths and loading conditions also impacts measure MR in AF. An average of five or more heart beats is used for chamber quantification.

d. LV systolic function and volumes are typically preserved.

e. Diastolic dysfunction is common but may be difficult to diagnose in the setting of AF or severe MR.

(d) Treatment specifics

i. There are **no specific guidelines** regarding the management of AFMR.

ii. **Heart failure**

a. **GDMT** and diuresis for HFpEF remain the standard of practice and have been shown to benefit patients with secondary functional MR.

b. Therapies that **target LA remodeling** and the development of AF in HFpEF may mitigate the risk of developing AFMR.

iii. **Angiotensin receptor blockers (ARBs)**

a. Angiotensin II receptor blockers (ARBs) may inhibit **leaflet fibrosis** due to cellular proliferation and valvular thickening after **MI**.

b. Limited data suggest patients with AFMR prescribed **angiotensin II receptor inhibitors (ACEi) or ARBs** had lower MR severity.

iv. Early sinus restoration

a. Several studies have found lower rates of MR in patients who have successfully undergone **ablation for AF**. LA volume improvement and peak atrial longitudinal strain with less MR have been reported after cardioversion.

b. Results from the EAST-AFNET 4 Trial suggest that **early rhythm-control strategy** is superior to rate-control therapy care in patients with newly diagnosed AF. The impact on the long-term development of valvular disease, however, remains unclear.

5. Management

a. Multidisciplinary pathway

(1) Multiple guidelines from the ACC and European Society of Cardiology (ESC) have emphasized the importance of multidisciplinary approach in managing mitral disease, the **Heart Team** that should include heart failure specialists.

(2) The recommendations for valve intervention in primary and secondary MR are summarized in **Table 16.4**.

TABLE 16.4 Indications for Valve Intervention in Primary and Secondary Mitral Regurgitation

Class I
a. In symptomatic patients with severe primary MR (stage D), mitral intervention is indicated regardless of LV systolic function.
b. In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF ≤60% or LVESD ≥40 mm, stage C2), mitral valve surgery is recommended.
c. In patients who require surgery for severe primary MR, mitral valve repair is preferred to replacement when the anatomic cause is degenerative disease, and a successful and durable repair is possible.
Class IIa
a. In asymptomatic patients with severe primary MR (stage C1) and normal LV systolic function (LVEF ≥60% and LVESD ≤40 mm), mitral

valve repair at a primary or CVC is reasonable when the likelihood of durable repair is >95% with an expected mortality <1% (LOE: B-NR).

b. In symptomatic patients (NYHA III-IV) with primary severe MR (stage D) and a life expectancy of at least 1 y, transcatheter edge-to-edge (TEER) is reasonable if operative risk is high or prohibitive and anatomy is favorable for repair (LOE: B-NR).

c. In symptomatic patients (NYHA II-IV) with severe secondary MR (stage D) associated with LV dysfunction (LVEF 20%-50%, LVESD ≤70) despite optimal GDMT, TEER is reasonable if anatomy is appropriate on TEE and PASP ≤70 mm Hg (LOE: B-R).

d. In patients with severe secondary MR (stage C,D), concomitant mitral surgery is reasonable at the time of CABG for myocardial ischemia (LOE: B-NR).

Class IIb

a. In asymptomatic patients with severe primary MR (stage C1) and normal LV systolic function (LVEF >60% and LVESD <40 mm), mitral valve surgery may be considered when there is a progressive increase in LV size or decrease in EF on ≥3 serial imaging studies (LOE: C-LD).

b. In symptomatic patients with severe primary rheumatic MR (stage D), mitral repair may be considered at a CVC when surgery is indicated if a durable and successful repair is likely (LOE: B-NR).

c. In symptomatic patients (NYHA III-IV) with severe secondary MR secondary (stage D) due to atrial annular dilation with preserved LV systolic function (LVEF ≥50%) refractory to medical therapy for HF and AF or other comorbidities, mitral valve surgery may be considered (LOE: B-NR).

d. In symptomatic patients (NYHA III-IV) with severe secondary MR (stage D) due to LV systolic dysfunction (LVEF <50%) refractory to GDMT, mitral surgery may be considered (LOE: B-NR).

e. In symptomatic patients (NYHA III-IV) with severe secondary MR (stage D) due to ischemic LV systolic dysfunction (LVEF <50%) refractory to GDMT undergoing mitral surgery, chordal-sparing replacement may be reasonable over downsized annuloplasty repair (LOE: B-R).

Class III

In patients with severe primary MR, mitral valve replacement should not be performed unless mitral repair has been attempted at a primary or CVC and was unsuccessful if the pathology is limited to less than one-half the posterior leaflet.

CVC, central venous catheter; EF, ejection fraction; LV, left ventricular; MR, mitral regurgitation; MV, mitral valve; PASP, pulmonary artery systolic pressure.
Data from 2022 valve disease ACC/AHA valve disease guidelines.

b. Primary chronic MR

(1) Introduction

(a) Primary MR is managed with surgical or transcatheter intervention. In asymptomatic MR, multiple factors should be considered, including (a) LV size and function; (b) exercise capacity and LV size and function at peak exercise; (c) repairability of the valve; (d) severity of MR, including the presence of flail leaflet; (e) PA pressures; (f) AF; and (g) age and (h) other comorbidities.

(b) The timing of intervention is important, with the goal to identify patients before **ventricular contractile dysfunction** becomes irreversible and the prognosis is poor.

(2) Considerations

(a) Diagnostics

i. **Exercise echocardiography** can determine the presence of latent LV contractile dysfunction and impaired contractile reserve. **Poor functional capacity** is important to assess during evaluation for surgical treatment.

ii. Failure to increase LVEF or a decrease in end-systolic volume with stress appears to predict **postoperative LV dysfunction** better than resting LVEF.

(b) Complications

i. **LV dysfunction**

a. When **LV end-systolic diameter (LVESD) is >4.0 cm** or **LVEF <60%**, surgical intervention is indicated.

b. In severe primary MR with preserved contractile function, LVEF should be in the high-normal range. Once the LVEF is <60%, the likelihood of impaired survival and

permanent **LV dysfunction** postoperatively is high. **Higher EF thresholds** indexed to body habitus and gender are being investigated.

c. Increased LV size and volume in end systole also predicts mortality and LV dysfunction postoperatively.

ii. **Pulmonary hypertension** due to severe MR and impaired survival is considered an indication for surgical intervention.

(c) Valve anatomy

i. The feasibility of repair depends on the etiology of MR.

ii. A **flail leaflet** usually implies severe MR. A retrospective study suggested that earlier surgical intervention was associated with better long-term survival in patients with a flail leaflet, even if asymptomatic. Once ROA is ≥0.4 cm^2, survival may be better among asymptomatic patients undergoing surgery than continued surveillance.

(d) Comorbidities

i. Concomitant **AF** with severe MR is an indication for surgical intervention. A **MAZE** or **modified MAZE** procedure (pulmonary vein and great vein isolation) may be performed with mitral valve repair.

ii. Patients aged >75 years, those with concomitant **CAD**, or those with renal dysfunction have worse outcomes after mitral surgery.

iii. Patients with IMR have a worse prognosis than those with regurgitation from other causes.

(3) Surgical therapy

(a) Chordal preservation with primary repair by leaving the subvalvular structures intact has been

shown to reduce LV volumes and wall stress postoperatively and is now the technique of choice.

i. Repair in an experienced center is usually successful in MVP unless chordae to both leaflets are severed, severe damage from endocarditis has occurred, or there is extensive leaflet calcification. Repair is usually feasible for a cleft valve and in less extreme forms of endocarditis, such as leaflet perforation without chordal disruption.

ii. Repair is more difficult to achieve in rheumatic involvement and when the valve leaflets or chordae are severely disrupted from any cause.

(b) Improvements in mitral valve repair have reduced the morbidity and mortality associated with severe MR. Mitral valve repair almost always involves placement of an undersized **annuloplasty ring**, which reduces annular diameter, improves leaflet coaptation, and significantly decreases MR. Additional components may include a pericardial patch at the site of leaflet perforation, chordal shortening or transposition, leaflet resection, and sliding valvuloplasty of the posterior leaflet to reposition the coaptation line. **Artificial chordae** are increasingly used in the repair of anterior leaflet prolapse.

(c) Comparative contemporary data suggest better postoperative LV function and survival with repair. Long-term risk of thromboembolism and endocarditis is reduced with repair versus replacement, and the need for **reoperation** is similar. Excellent 20-year outcomes following repair have been reported from multiple large-volume centers, with the estimated risk of reoperation approximating 10% at 20 years.

(d) Minimally invasive video-assisted (robotic) approaches employing **hemi-lower sternotomy or right thoracotomy incisions** may be options in

experienced centers and selected patients. Preprocedural CCTA provides precise measurement of mitral valve orifice and systemic arterial and venous anatomy for peripheral CPB cannulation and may be used to assess coronary arteries.

(e) Mitral valve replacement is indicated when repair is not technically possible, or repair has been attempted at a Comprehensive Valve Center. The choice of mechanical or bioprosthetic valve replacement depends on the risk of chronic anticoagulation required with mechanical valves against the reduced longevity of the bioprosthetic valves. **Structural degeneration** of bioprosthetic mitral valves typically affects 20% to 40% patients at 10 years and over 60% at 15 years but is highly related to patient age at the time of surgery. In older patients, a bioprosthesis will last longer, and this is the valve of choice in those over age 70.

(f) MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (EF >60%) in whom significant doubt about the feasibility of repair exists.

(g) Complications

i. Intraoperative echocardiography helps in the assessment of complications of valve repair or replacement.

ii. Residual MR is the most common problem after a pump run. If further repair is feasible, a second pump run should be considered to correct residual MR (if 1+ or greater). Otherwise, valve replacement may be needed. A second pump run does not appear to increase in-hospital mortality.

iii. Dynamic LVOTO is caused by anterior displacement of mitral leaflet coaptation point when the posterior leaflet is redundant (typically

>1.5 cm in height). The resultant SAM is exacerbated by increased inotropy and small LV size. Cessation of the use of sympathomimetic agents and volume repletion should be attempted in the operating room. If these efforts fail, further surgery to reduce the height of the posterior mitral leaflet (sliding annuloplasty) or mitral valve replacement may be necessary.

iv. In postoperative LVOTO, volume repletion and judicious use of beta-blockade are often sufficient. Occasionally, surgical "take-back" for revision of the repair is needed.

(h) Postoperative follow-up

i. Echocardiography should be performed postoperatively around 4 to 6 weeks. Often, it is performed prior to hospital discharge (within 3-4 days).

ii. MR can recur because of failure of the repair or because of progression of the underlying disease. Patients should undergo clinical evaluations annually with echocardiography and if a new apical systolic murmur is detected.

(4) Transcatheter therapies

(a) See Chapter 65 for a detailed introduction to transcatheter mitral valve interventions.

(b) Repair

i. **Percutaneous mitral valve repair** uses catheter-based devices to improve coaptation of the mitral leaflets. Current techniques emulate the existing surgical procedures classified into two functional approaches.

ii. **Edge-to-edge repair (TEER)**

a. A clip can be used to approximate the center of the mitral valve leaflets resulting double-

orifice valve modeled after the **surgical Alfieri stitch repair**.

b. TEER is recommended for the treatment of severe symptomatic (New York Heart Association [NYHA] III-IV) chronic regurgitation in patients with suitable anatomy and >1 year expected survival at a prohibitive surgical risk (IIA-B-NR).

c. Two Food and Drug Administration (FDA)-approved TEER devices systems are currently marketed for severe chronic MR, the MitraClip (Abbot Vascular) and the PASCAL Precision System (Edwards Lifesciences).

d. In 2013, the FDA approved the MitraClip system for commercial use based on the results of the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) trial, which randomized 279 patients with 3 to 4+ MR to MitraClip (Abbott Vascular) versus mitral surgery. At 4-year follow-up, the overall rates of mortality and of 3+ or 4+ MR remained similar. Notably, the need for subsequent mitral valve surgery for valvular dysfunction was higher in the percutaneous group.

e. The FDA approved the PASCAL system as the second device for TEER therapy in 2022 after the CLASP IID (Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical) trial demonstrated similar effectiveness of TEER using the PASCAL to the MitraClip systems among patients with symptomatic severe primary MR at prohibitive surgical risk. Patients receiving

PASCAL device had higher rate of sustained ≤1+ MR at 6 months by echocardiography.

iii. **Annuloplasty**

a. A flexible ring can be deployed and tightened in the **CS** to effectively reduce the mitral annulus area. Concerns regarding this procedure include the variable relationship between the CS and mitral annulus, as well as the proximity to the circumflex artery.

b. Investigational devices include two stents deployed into the CS, with the connecting coil bridge being tightened over time called the Monarc (Edwards Lifesciences); a fixed length, double-anchor CS device called the Carillon Mitral Contour System (Cardiac Dimensions); and a CS anchor that is attached to the interatrial septum via a cord under tension called the Percutaneous Septal Shortening System (Ample Medical).

c. Annular remodeling is may be suited for the repair of functional regurgitation.

(c) Replacement

i. Several registries have emerged to evaluate the feasibility and impact of **TMVR** at prohibitive surgical risk. Carefully selected patients with a very calcified mitral annulus or who have had a prior mitral valve ring or surgical prosthetic valve may benefit from percutaneous mitral valve replacement. In 2017, the Sapien S3 (Edwards Lifesciences) was approved for **valve-in-valve (ViV), valve-in-ring (ViR), and valve-in-MAC (ViMAC)** transcatheter mitral replacement among patients with severe valvulopathy at prohibitive surgical risk. 4D CT evaluation is critical for

annulus and device sizing along with determining the risk of neo-LVOTO.

(d) Active trials

i. The **PRIMARY Trial** (NCT05051033) is a prospective multicenter open-label randomized trial comparing mitral valve TEER to open surgical repair in patients >65 years of age with severe primary MR in the absence of severe LV dysfunction (EF <25%), chronic ischemia or concomitant secondary MR, or significant concomitant valvulopathy who are candidates for either therapy strategy across the spectrum of surgical risk (low, intermediate, high). The trial aims to follow patients through 5- and 10-year follow-up. The primary outcomes will be a **composite score** of all-cause mortality, valve-reintervention, hospitalizations, and onset of 3+ MR.

ii. **REPAIR** MR (NCT04198870) is a randomized controlled multicenter noninferiority trial comparing MitraClip to open valve repair in patients with severe primary MR at intermediate surgical risk and NYHA II-IV with LVEF 30% to 60%, pulmonary artery systolic pressure (PASP) >50 mm Hg or LVESD >40 mm, and an STS PROM Repair Score >2%.

(5) Medical therapy

(a) Medical therapy for asymptomatic, chronic MR caused by primary valve disease is limited. No pharmacologic agents have demonstrably delayed progression of disease.

i. The success of **afterload reducers** in AMR has led to trials of vasodilators, such as ACEi and hydralazine, in chronic MR. However, these have been largely negative. As a result, the ACC/AHA

and ESC guidelines do not recommend the use of pharmacologic vasodilatation in chronic MR with preserved EF.

ii. **Sympathetic overstimulation** appears to be a key element of progression to LV failure in primary MR. **Beta-blockers** have been attempted in chronic MR but do not appear to clinically delay the need for surgical intervention.

iii. **Diuretics and nitrates** have a role in the management of pulmonary congestion.

iv. Ventricular rate-controlling agents and antiarrhythmics are used for AF. **Digoxin and beta-blockers** are the mainstay of therapy for rate control. In severe MR with AF, maintenance of sinus rhythm is unlikely if the regurgitation remains uncorrected.

(b) Endocarditis prophylaxis is not routinely indicated in patients with MR unless there has been prior valve repair or replacement.

(6) Monitoring

(a) Patients with severe MR should be evaluated semiannually with echocardiography and stress echocardiography, if indicated. Patients with moderate MR should be evaluated annually.

F. Secondary chronic MR

1. Medical therapy

a. Medical therapy targeting the underlying etiology of secondary MR has been shown to be effective in recovering valve function and improved outcomes.

(1) LV dysfunction is a major cause of secondary MR. **GDMT** indicated in patients with LV dysfunction has been shown to be efficacious in improving valve function. Therapy targets adverse long-term effects of neurohormonal activation. In some estimates, up to 40% of patients have

improvement in their MR with improvement in their LV dysfunction.

2. Cardiac resynchronization therapy(CRT)

a. CRT has been shown to significantly reduce MR in patients when **PM dyssynchrony** due to LV dysfunction.

3. Mitral valve intervention

a. Several transcatheter devices under development for secondary MR are outlined in **Chapter 65**. Approved in 2019 by the FDA, **the MitraClip system** (Abbott Vascular, Santa Clara, CA) is the only device on the market for severe symptomatic secondary MR.

(1) Transcatheter edge-to-edge repair

(a) Transcatheter therapy with edge-to-edge MV repair (TEER) is now recommended for patients with symptomatic severe secondary MR (class IIa) at prohibitive surgical risk based on the Cardiovascular Assessment of the MitraClip Percutaneous Therapy for Heart Failure in Patients with Functional Mitral Regurgitation (COAPT) trial, which randomized 614 patients with LV dysfunction and secondary MR to GDMT alone versus GDMT with TEER. Patients undergoing TEER had lower annualized rate of all-cause hospitalization and mortality up to 5 years based on follow-up data.

(b) Notably, the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) trial did not demonstrate a significant benefit in its primary combined outcome of survival or rehospitalization for HF. This trial also randomized patients with LV dysfunction to GDMT versus GDMT with TEER.

i. Differences in trial design, patient populations, medical therapy, and potential pathophysiology have been raised to explain the discrepant results.

Both studies were open-label trials with heart failure hospitalization as part of the composite primary outcome. They had significantly different methods for assessing lesion severity. Patients in COAPT also were required to be titrated to maximally tolerated GDMT including CRT as indicated.

ii. **Proportionality**

a. Baseline EROA and indexed left ventricular end-diastolic volume (LVEDVi) were significantly different between the COAPT and MITRA-FR trial populations. The concept of **proportionality**—the ratio of EROA to LVEDVi—was proposed as a physiologic explanation that postulates patients who have a greater degree of MR relative their LV dilation may be more suitable candidates for TEER. The relative contribution of severe MR to clinical outcomes is thought to be higher than patients with proportionate MR.

(c) Further RCTs are underway to better understand which patients would most benefit from TEER for secondary MR.

(2) **Annuloplasty and valve replacement**

(a) Clinical trials for early-stage percutaneous annuloplasty and dedicated mitral valve prosthetic devices systems are underway to target functional MR.

b. Mitral surgery

(1) As discussed earlier, concomitant valve surgery is recommended at the time of CABG in patients with LV dysfunction and **severe** IMR.

(2) A Cardiothoracic Surgical Trials Network (CTSN) RCT of MV repair versus replacement in severe IMR demonstrated

equivalent reduction in postoperative LV volumes with lower recurrence of MR in the replacement group.

(3) There does **not appear to be a meaningful advantage** of concomitant mitral valve repair to CABG in patients with moderate IMR based on a CTSN RCT of 301 patients through 12 months of follow-up.

III. MITRAL STENOSIS

A. Introduction

1. MS describes the pathologic narrowing of the **mitral valve orifice,** resulting in impaired LV filling and increased atrial pressure and their sequelae.

2. Although declining in incidence in the United States, rheumatic disease remains the predominant cause of MS worldwide, accounting for up to 85% of cases followed by calcific degeneration. The prevalence of calcific MS has increased in high average income countries. Other etiologic factors are listed in **Table 16.5**.

TABLE 16.5 Causes of Mitral Stenosis

Rheumatic: Most Common Cause
Congenital
Parachute mitral valve: single papillary muscle to which chordae to both leaflets attach; results in MS or MR
Supravalvular mitral ring
Systemic Diseases: Can Cause Valvular Fibrosis
Carcinoid
Systemic lupus erythematosus
Rheumatoid arthritis
Mucopolysaccharidosis
Healed endocarditis
Prior anorectic drug use
Severe mitral annular calcification

MR, mitral regurgitation; MS, mitral stenosis.

3. There is often a **long asymptomatic course**, consisting of a couple of decades. In general, once symptoms develop, there follows about 10 years before they become debilitating. Once significant limiting symptoms develop, the 10-year survival rate is <15%.

4. Classification

   a. Mitral valve stenosis is typically classified by etiology and severity. MS is staged by valve anatomy, hemodynamics, sequelae, and patient symptoms.

B. Pathophysiology

1. **Flow.** The cross-sectional area of the mitral valve orifice is mostly independent of flow considerations and thus is a more robust measure of the severity of MS. In recent guidelines, the severity of MS is determined based on the **mitral valve area (MVA)** and **diastolic pressure half-time (P1/2)** along with its hemodynamic effects on the LA (presence of LA enlargement) and pulmonary vasculature (presence of pulmonary hypertension).

2. **Transmitral pressure**

   a. Although the **transmitral pressure gradient** is a useful indicator of MS severity, it is affected by the cardiac output. Because of the variability of the mean pressure gradient with heart rate and flow, it has not been included in the severity criteria. The gradient is usually >10 mm Hg in severe MS.

   b. The increased LA pressure is transmitted to the pulmonary vasculature, resulting in symptoms of **pulmonary congestion**. The passive increase in pulmonary venous pressure may elevate pulmonary vascular resistance (reactive pulmonary hypertension). This is usually reversible if the stenosis is relieved. However, in long-standing, severe MS, obliterative changes in pulmonary vasculature and right heart failure may occur.

3. **Cardiac output**

   a. An estimated 20% to 30% of patients with severe MS progress to develop **reduced LV function**. This appears to result from

decreased preload (decreased inflow into the LV) or a rheumatic myocarditis. The former generally normalizes after a corrective procedure; the latter will not.

b. In severe MS, there may be sufficiently low cardiac output to cause symptoms of poor perfusion. Chronically depressed cardiac output causes a reflex increase in systemic vascular resistance and increased afterload. This may further diminish LV performance.

C. Etiologies

1. RHD remains the most common cause of MS worldwide. In high average income nations, nonrheumatic causes such as annular calcification, radiation-induced disease, and iatrogenic etiologies (ie, restrictive mitral repair, clip-associated) are more prevalent. See **Chapter 20** for a complete discussion of rheumatic valve disease.

2. Rheumatic heart disease

a. In rheumatic MS, up to 50% of patients are not aware of a history of rheumatic fever.

b. MR often predominates initially in RHD. Stenosis usually develops anywhere from 2 to 20 years later, and symptoms may not develop for many years thereafter. Although the incidence of rheumatic fever is roughly equal between men and women, rheumatic MS develops **2 to 3 times more frequently in women**.

c. **Thickening of leaflets with fibrous obliteration** is a characteristic finding. Commissural and chordal fusion and chordal shortening contribute to the development of stenosis. **Calcium deposition** occurs on leaflets, chordae, and annulus, further restricting valvular function. These changes produce a funnel-shaped mitral valve with a fish-mouth orifice.

3. Mitral annular calcification

a. MAC describes the **chronic degeneration** of the fibrous skeleton, particularly around the **posterior annular base**. Most patients with MAC do not have significant mitral valvular

dysfunction, but the presence of MAC has been associated with major adverse cardiovascular events (MACE), mortality, and the development of clinical heart failure. Among patients with severe bulky annular calcification, regurgitation or stenosis may be develop.

b. Pathophysiology

(1) The pathophysiology of MAC remains unclear. Progression of disease appears to be associated with the pathogenesis of **atherosclerosis**.

(2) Progressive noninflammatory calcium deposition along the mitral annulus that spares the **commissures** and **base of the anterior mitral leaflet** defines MAC. Calcific infiltration of the annulus and the infravalvular apparatus can result in leaflet tethering, chordal malfunction and elongation with impaired contraction, insufficient closing forces, and malcoaptation.

(3) Conditions such as hypertension, aortic stenosis, and HCM accelerate calcific degeneration through excess annular tension secondary to **elevated LV peak systolic pressure** and possible LV hypertrophy.

(4) MAC is also commonly found among patients with chronic kidney disease, suggesting that abnormal **calcium phosphorus metabolism** contributes to MAC.

(5) **Inherited conditions** that cause prolapse (Marfan syndrome) and abnormal fibroblasts and collagen degradation (Hurler syndrome) are associated with MAC.

(6) Several studies have also found older female patients have an increased risk of developing MAC. **Ectopic calcium deposition** related to osteopenia and osteoporosis in postmenopausal patients is suspected to be a mediating factor.

c. Epidemiology

(1) In the EuroHeart Survey, MAC was associated with MS in up to 60% of patients over 80 years of age. There is

conflicting evidence regarding differences in prevalence of MAC between female and male patients. However, the Multi-Ethnic Study of Atherosclerosis (MESA) and Framingham Heart Study also noted a higher proportion of female patients with MAC.

d. Diagnostics

(1) Chest radiography

(a) Chest x-ray may demonstrate calcification of the mitral annulus in a curved shape often described as a **C-, D-, O-, or U-shape** oriented toward to the aortic outflow tract.

(2) Echocardiography

(a) Calcification in MAC appears as an echo-dense, band-like lesion with irregular borders around the mitral annulus associated with acoustic shadowing. Qualitatively, the distribution and extent of echo density in relation to the annulus is used. Severe disease constitutes calcification of more than half the circumference or with intrusion into the LV inflow tract or a plaque lesion greater than 4 mm.

(3) Cardiac CT

(a) Cardiac CT is effective for preprocedural measurement of the distribution and extent of MAC. Virtual simulation of possible prosthetic valve deployment and orientation with fluoroscopic co-registration can be performed. The Agatston method can reliably quantify MAC.

e. Clinical implications

(1) The presence of MAC confers a significantly **elevated operative risk** for patients undergoing cardiac surgery. Higher mortality, greater conversion from repair to replacement, and increased risk of myocardial rupture and circumflex artery injury have been associated with the

presence of MAC among patients undergoing mitral surgery.

(2) Intervention in severe MAC by either transcatheter or open surgical intervention is challenging. High rates of **operative complications** such as free wall rupture, injury to the circumflex artery, and conversion from valve repair to replacement have been described.

(3) Outcomes after TMVR are worse patients with severe MAC in comparison to those undergoing bioprosthetic ViV or ViR replacement.

4. Radiation-induced heart disease (RIHD)

a. Introduction

(1) **Mediastinal radiation** for the treatment of Hodgkin lymphoma and breast cancer can result in a broad spectrum of cardiovascular disease, including accelerated proximal CAD, arrhythmia, cardiomyopathy, and valvulopathy, including mitral valve fibrosis and calcification. The **latency** period is 1 to 2 decades after radiation exposure. The risk of valvulopathy has significantly decreased with advancements in radiation techniques and dose control.

(2) Mitral manifestations include accelerated leaflet and annular thickening and calcification, particularly along the aortomitral curtain, which is almost pathognomonic.

(3) Chest radiation is also associated with accelerated atherosclerotic disease, myocardial dysfunction, and the development of arrhythmias.

b. Clinical manifestation

(1) RIHD presents with typical features of MS, including exertional dyspnea, orthopnea, and heart failure. While the prevalence of **valvular thickening** among patients is high, the estimated proportion of valve dysfunction ranges between 10% and 20% across observational studies. These estimates are limited, however, due to the lack of baseline echocardiography and detection bias. The true rate of

clinically significant undiagnosed valvular disease remains unclear.

c. Specific diagnostics

(1) Aortomitral curtain thickness on echocardiography appears to be the strongest predictor of postoperative mortality, though the significance of the association is unclear.

d. Treatment

(1) Due to the concomitant involvement of the aortic valve, proximal ascending aorta, and proximal coronary arteries, intervention on the mitral valve usually necessitates **extensive multivalvular surgery** with bypass grafting. Postoperative mortality and morbidity burden is significantly higher over time than matched patients without RIHD undergoing primary and particularly with **redo surgery**.

5. Congenital lesions

a. Primary congenital mitral malformations are rare and estimated to account for less than 0.4% to 0.5% of congenital disease, based on limited data. Isolated stenosis is rare, and thus, evaluation for concomitant cardiac and vascular abnormalities is imperative. Typically, surgical repair is preferable to valve replacement. Percutaneous therapies can be effective and, in some instances, safer, but have a high rate of reintervention in the intermediate term. Several congenital lesions can result in anatomic or functional MS.

(1) Hypoplastic mitral valve may be the result of annular or leaflet hypoplasia, typically of the posterior leaflet, that may cause congenital obstruction. Early case reports from the 1950s identified congenital mitral atresia in patients with hypoplastic left heart and concomitant aortic atresia. The incidence of asymptomatic hypoplasia is estimated to be about 0.01% of adults in one echocardiographic survey of 8,800 adults.

(2) **Supravalvular ring** describes a fibrous connective tissue ridge positioned above the mitral valve inferior to the LA appendage, which distinguishes it from cor triatriatum sinister. This is associated with VSDs and is part of the Shone syndrome described below.

(3) **Intramitral ring** is a membranous congenital structure connected to the leaflets in the setting of an abnormal subvalvular apparatus.

(4) **Parachute mitral valve** refers to the attachment of all chordae tendineae from the anterior and posterior leaflets to a centrally located single PM resulting in restricted leaflet motion. An echocardiographic survey estimated the incidence at about 0.17%.

(5) **Anomalous mitral arcade** involves the direct insertion of the PMs into the mitral leaflets or by pathologically short thick chordae believed to result from the arrested development of the mitral valve. When viewed from the surgeon's view from the atria, it appears similar to a hammock and is thus called a **Hammock valve**.

(6) **Shone complex** typically refers to a set of four congenital left heart lesions: (1) supravalvular mitral membrane, (2) parachute mitral valve, (3) subaortic stenosis, and (4) coarctation of the aorta. Complete or incomplete Shone complex was present in 0.67% of patients with adult congenital heart in one retrospective study.

D. Clinical presentation

1. Symptoms

a. The severity of the stenosis needs to be assessed in terms of symptomatology and exercise capacity. When symptoms do develop, **dyspnea** is common. Predominant symptoms are exertional dyspnea initially, followed by paroxysmal nocturnal dyspnea and orthopnea, which reflect elevated pulmonary venous pressure.

b. **Hemoptysis** can occur and likely represents rupture of small bronchial veins from elevated LA pressure.

c. **Hoarseness** occurs when the dilated LA impinges on the recurrent laryngeal nerve (Ortner syndrome).

d. Patients with elevated pulmonary pressures may have **angina-like chest pain**, as a reflection of increased RV oxygen demand.

e. With long-standing MS and elevated pulmonary pressure, symptoms of **RV failure** may develop.

f. Mixed MS/MR is often associated with greater **symptomatic impairment** than might be predicted from the severity of either lesion alone.

g. Precipitating factors, such as exercise, emotional stress, pregnancy, infection, or AF with a rapid ventricular response, can produce or dramatically worsen symptoms by generating **increased transvalvular gradients** and LA pressure, causing dilation. AF with a rapid ventricular response is a classic exacerbating factor and may produce pulmonary edema, even in those with **mild MS.**

2. Complications

a. **LA dilation and stasis** may cause thrombus formation and embolic events. Cerebrovascular events, coronary embolization, and renal emboli and infarction are all possible sequelae. The malformed valve is predisposed to the development of endocarditis.

b. Mortality increases substantially as symptoms progress. Young symptomatic patients with severe MS have about 40% mortality at 10 years and almost 80% at 20 years. Older patients have 60% to 70% mortality at 10 years.

3. Physical examination

a. **Inspection and palpation**

(1) Patients may have a **malar facial flush**. The jugular venous pulse can demonstrate a prominent a wave if there is elevated **pulmonary vascular resistance** and the patient

is still in sinus rhythm. Jugular venous pressure is elevated with RV failure. In advanced cases, peripheral cyanosis occurs. The carotid upstrokes are usually normal but are of low amplitude if there is diminished cardiac output.

(2) The apex beat is **not displaced**, and the impulse can have a **tapping quality** because of a palpable first heart sound. An apical diastolic thrill may be felt in the lateral decubitus position ("purring cat"). If there is pulmonary hypertension, a parasternal RV lift with a palpable P2 is present.

b. Auscultation

(1) The main auscultatory findings are shown in **Figure 16.11**. The opening snap is the hallmark of MS. However, as the mitral valve becomes more calcified and immobile, the opening snap may be lost (just as S_1 becomes softer).

(2) The murmur of MS is typically a **low-pitched rumbling mid-diastolic murmur**, heard best with the bell of the stethoscope with the patient in the left lateral decubitus position.

(a) **Presystolic accentuation** can be present, independent of sinus rhythm. Auscultation after a brief period of **exercise** may accentuate the murmur of MS.

(b) The **length of the murmur** correlates better with the severity of MS than the loudness. The longer the murmur and the shorter the time interval from S_2 to the opening snap, the more severe the MS.

(3) Concomitant conditions that result in **decreased flow** across the valve, such as congestive heart failure (CHF), pulmonary hypertension, and aortic stenosis, may reduce the diastolic murmur. The **presence of a loud S_1** may be the only clue to the presence of MS in these cases, particularly if pulmonary hypertension exists.

(4) Auscultation of the lungs may reveal fine inspiratory crackles. Notably, patients with severe MS can have **clear**

lung fields postulated from lymphatic hyperfunction clearing the transudative alveolar due to elevated LA pressures.

(5) LA myxoma and cor triatriatum can mimic MS. The tumor plop of myxoma may be mistaken for an opening snap, and tumor obstruction of the valve leads to a diastolic murmur. In MS, the physical findings will vary with changes in position and from examination to examination. Other conditions in which a diastolic rumble may be present include atrial septal defect or VSD, the Austin-Flint murmur of aortic regurgitation, and tricuspid stenosis (Carvallo sign).

E. Diagnostics

1. Chest radiography

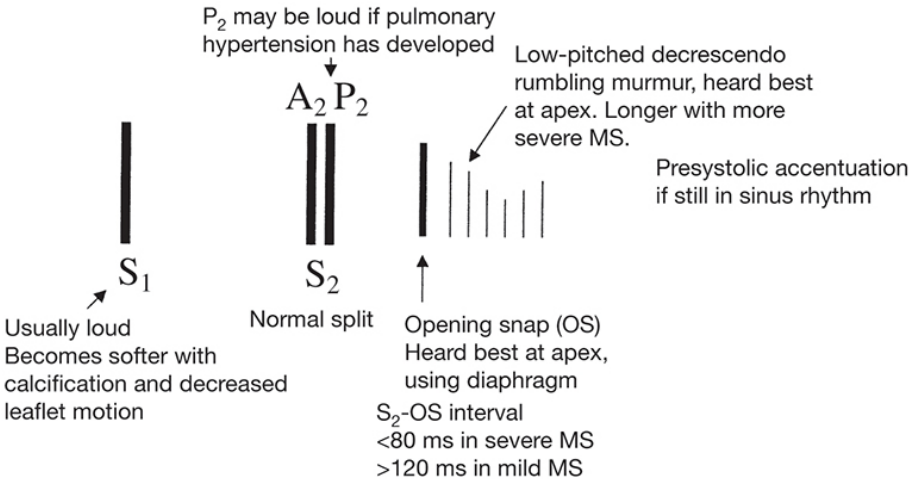


FIGURE 16.11 Auscultatory findings in mitral stenosis (MS).

a. LA enlargement is apparent with a **double density** along the right heart border. A convexity can be apparent below the PA, representing the LA appendage. Splaying of the carina with the elevation of the left main bronchus and posterior displacement of the esophagus at barium swallow examination reflects LA enlargement.

b. Kerley B lines may be present from increased pulmonary venous pressure. RV enlargement (decreased retrosternal air space on the lateral radiograph) may be present.

c. Evidence of mitral valve calcification or rarely **LA calcification** (McCallum patch) may be present.

2. Echocardiography

a. Transthoracic Echocardiography

(1) TTE is critical for the diagnosis, determination of severity, evaluation of suitability for PBMV, and identification of concomitant valve lesions. Limitations of specific methods are described earlier.

(2) The criteria for severe MS are:

(a) Progressive MS (mild to moderate) is associated with an MVA >1.5 cm^2 and a P1/2 <150 ms. There is usually mild-to-moderate LA enlargement, and the pulmonary pressures are typically normal at rest.

(b) Severe stenosis is defined by an MVA ≤1.5 cm^2 with a P1/2 ≥150 ms, also commonly accompanied by severe LA enlargement and pulmonary hypertension (PASP >30 mm Hg).

(c) Very severe stenosis is defined by an MVA ≤1.0 cm^2 with a P1/2 ≥220 ms, accompanied by severe LA enlargement and pulmonary hypertension (PASP >30 mm Hg).

(3) 2D findings include restricted motion and **diastolic doming of leaflets** (hockey stick sign) (**Figure 16.12**). The leaflets and chordae are thickened and are often calcified in older patients.

(4) A **transmitral peak velocity** >1 m/s suggests MS. However, this is not specific because tachycardia, increased inotropy, MR, and VSD may cause increased flow in the absence of MS.

(5) The **transvalvular mean gradient** can estimate mitral valve severity but should be reported with heart rate at

time of acquisition as it is highly dependent on flow and filling time.

(6) **M-mode** findings include dense echoes on the mitral valve and decreased excursion of the mitral valve. Poor leaflet separation in diastole, anterior motion of the posterior leaflet, and decreased E-F slope on the anterior leaflet are M-mode hallmarks of MS.

(7) The **Wilkin score** is a valuable tool based on echocardiography evaluation of mitral valve leaflet mobility, calcification, thickening, and subvalvar thickening to determine the chance of success with balloon mitral valvuloplasty.

b. Transesophageal echocardiography

(1) 3D planimetry by TEE enables more accurate assessment of valve area, valve shape, distribution of commissural fusion, and concomitant scarring, which may all impact the risk of MR after valvuloplasty. TEE is indicated **to exclude LA thrombus and assess MR** prior to valvuloplasty, or if the TTE data are suboptimal.

(2) Visualization of the mitral valve **"en face" view** is possible at the time of PBMV, allowing **accurate planimetry** of the valve area, optimization of balloon position, rapid detection of complications including tamponade, dissection, entrapment of the valvular apparatus, and measurement of commissural opening after inflation.

(3) If thrombosis is present, anticoagulation for at least 1 month is undertaken with repeat TEE before valvuloplasty.

c. Stress echocardiography

(1) Stress echocardiography with Doppler is useful in the evaluation of patients with symptoms when **the resting study is discrepant** with symptoms. Measurement of TR velocity is used to estimate pulmonary pressures with stress.

3. Cardiac catheterization

a. Cardiac catheterization is indicated in the evaluation of patients when Doppler and clinical findings are discrepant or when echocardiographic findings are internally discordant or if pulmonary hypertension is disproportionate to MS severity noninvasively.

b. Simultaneous measurement of **LV end-diastolic pressure, LA pressure** (either directly or more commonly with pulmonary capillary wedge pressure [PCWP] as a surrogate), **cardiac output** (Fick method or thermodilution), **heart rate, and diastolic filling period** (seconds per beat) is required. LV pressure and PCWP (or LA pressure) tracings are made simultaneously (**Figure 16.13**). A mean transmitral gradient is derived from the preceding measurements (planimeter area between the LV and PCWPs during diastole; this area is multiplied by the **scale factor** of the tracing in millimeters of mercury per centimeter to obtain the gradient). The PCWP tracing ideally should be realigned by 50 to 70 ms to the left (with tracing paper) to account for the time delay in transmission of LA pressure to the pulmonary venous beds.

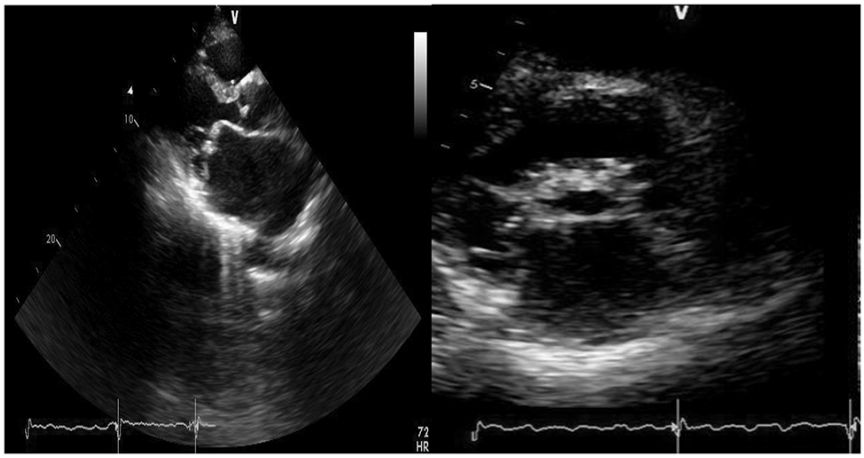


FIGURE 16.12 Severe mitral stenosis—the parasternal long-axis view on the left shows the typical doming of the anterior mitral leaflet (with the so-called “hockey stick” appearance) with associated leaflet thickening. The parasternal short-axis view on the right shows the typical “fish-mouth” appearance with restricted mitral leaflet opening.

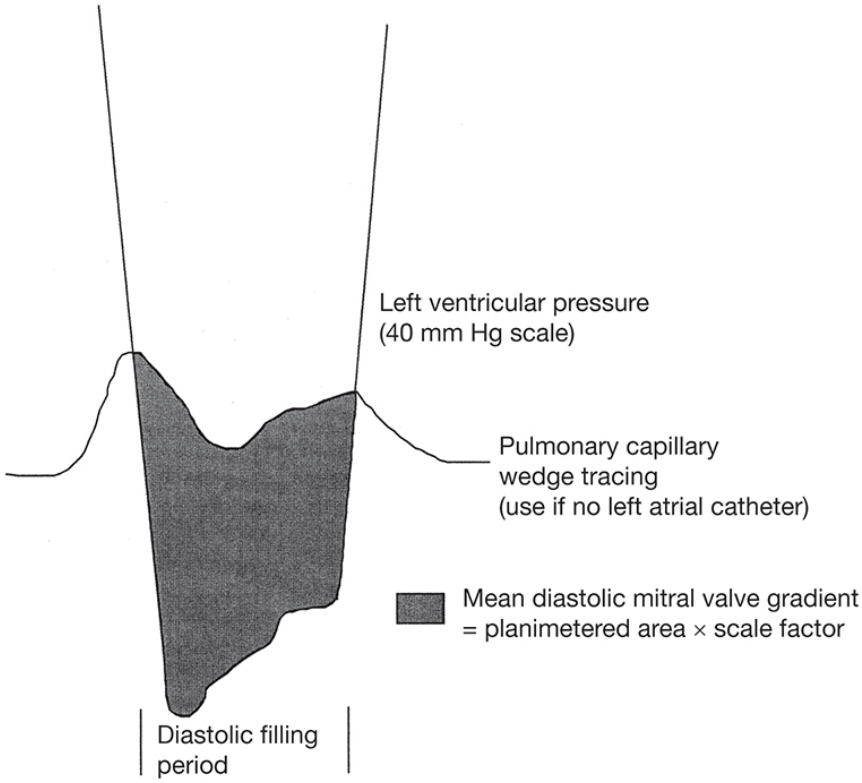


FIGURE 16.13 Simultaneous left ventricular and pulmonary capillary wedge pressure tracings used to measure the mean gradient across the mitral valve during diastole.

(1) The Gorlin formula can be used to estimate MVA and is presented in Chapter 69.

(2) Gorlin derived the empirical constant of 37.7, which is the Gorlin constant (44.3) multiplied by 0.85 (the correction factor for the mitral valve).

(3) A **simplified version** of the Gorlin formula proposed by Hakki et al has been validated and provides a reasonable approximation of the valve area. MVA is equal to the cardiac output divided by the square root of the mean mitral gradient.

c. Limitations

(1) PCWP cannot be used if the patient has pulmonary venous occlusive disease or cor triatriatum. The catheter must be properly wedged. In addition, thermodilution cardiac

output is less accurate if there is severe TR or low cardiac output. Immediately after valvuloplasty MR or atrial septal defect, flow may lead to inaccurate estimations of mitral flow.

F. Treatment

1. The management of MS should integrate symptomatic status, degree of stenosis, and suitability of the valve for PBMV.

2. **Rheumatic heart disease**

   a. **Medical therapy**

      (1) Patients without symptoms who have mild MS (valve area >1.5 cm^2 and mean gradient <5 mm Hg) need no specific treatment and do not require endocarditis prophylaxis.

      (2) In patients with rheumatic valve disease, guidelines for the prevention of rheumatic fever should be applied. Annual reevaluation is recommended, with an echocardiogram if there is a clinical change.

      (3) Patients with only mild symptoms of exertional dyspnea can be treated with diuretics and salt restriction to **lower LA pressure**. **Beta-blockers** blunt the chronotropic response to exercise and **may improve exercise capacity**. Arterial vasodilators should be avoided.

      (4) Cardioversion or rate-control measures for AF are important to maintain diastolic filling time. Embolism occurs in up to 20% of patients, particularly with advancing age and AF.

         (a) **Digitalis and beta-blockers** are the preferred agents to achieve rate control.

         (b) Anticoagulation with **warfarin** is imperative for patients with MS with paroxysmal, persistent, or chronic AF; prior venous or pulmonary embolism; or known LA thrombus. The INVICTUS trial demonstrated the **lower composite rate of MACE and death** with vitamin K antagonist (VKA) therapy over rivaroxaban with similar rates of major bleeding.

(c) Antiarrhythmic drug therapy may be used to restore sinus rhythm, but long-term efficacy may depend on correction of the MS.

(d) **PBMV** may be considered in asymptomatic patients with new-onset AF and severe MS who have a favorable valve morphology and no contraindications.

b. Balloon valvuloplasty

(1) **PBMV** is considered the treatment of choice for symptomatic patients with severe MS who have favorable valve morphology in the absence of LA thrombus and less than moderate MR. A **balloon-tipped catheter** via transseptal puncture is placed across the mitral valve. The hourglass-shaped balloon (Inoue balloon) is inflated and deflated to increasingly larger diameters until the desired result is obtained. Typically, there is an increment in valve area of 1 cm^2, due to splitting of the fused commissures. The mean valve area usually doubles with a 50% to 60% reduction in transmitral gradient.

(2) Indications for percutaneous or surgical therapy are listed (**Table 16.6**). If more than mild symptoms (NYHA class II or greater) are present due to MS, the patient should be evaluated for intervention. An asymptomatic patient with severe (or very severe) MS and evidence of pulmonary hypertension at rest or with exercise should also be referred for percutaneous therapy if the valve is suitable.

(a) Marked **pulmonary hypertension** (PASP >60 mm Hg) is an indication for mechanical treatment, even in the absence of symptoms in severe (or very severe) MS. Surgical or balloon intervention may be warranted in asymptomatic patients with severe MS prior to pregnancy, concomitant surgery with massive fluid shifts, or those with repeated embolism despite anticoagulation.

(3) PBMV is contraindicated in patients with ≥**3+ MR** or in whom there is an **LA or appendage thrombus**. Severe TR

and severe pulmonary hypertension due to shunting across iatrogenic ASD are relative contraindications to the procedure.

(4) An echocardiographic score (Wilkins) has been developed to help select patients who may be candidates for percutaneous valvuloplasty consisting of leaflet mobility, leaflet thickening, subvalvular thickening, and calcification (**Table 16.7**).

- **(a)** **Optimal** results of balloon valvuloplasty are usually achieved when the total echocardiographic score (sum 4 categories) is 8 or less.
- **(b)** Scores of 9 to 11 represent a **gray zone** in which some patients have good results with valvuloplasty. Others have suboptimal results.
- **(c)** Score higher than 11 is associated with a poorer outcome and a **suboptimal** increase in valve area, a higher incidence of heart failure and restenosis, and higher mortality. Patients with high scores should not undergo valvuloplasty unless surgical treatment is impossible.
- **(d)** In general, **extensive subvalvular disease** results in a poorer outcome with valvuloplasty. Patients with extensive fluoroscopically visible mitral valve calcification also have a worse outcome after percutaneous therapy.

(5) TEE can also help guide balloon positioning; after each inflation, the degree of MR and the gradient can be assessed. The degree of **residual MS** can be estimated with planimetry of the valve orifice before and after inflation. The pressure half-time method is **unreliable until 24 to 48 hours** after the procedure.

(6) Echocardiography is useful in the determination of immediate postprocedural complications (**Table 16.8**). Among these is MR with an incidence estimated at 3% to

8%. The echocardiographic score is less predictive of the severity of postprocedural MR, which is associated with poor long-term outcomes.

(7) The frequency of **restenosis of the valve** is variable, depending on the age of the patient and the immediate procedural increment in valve area. Data from the National Heart, Lung, and Blood Institute (NHLBI) registry of all functional classes of patients show an 84% survival rate 4 years after treatment.

(a) Advanced age, high NYHA functional class, presence of AF, smaller initial MVA, higher PA pressure, and substantial TR are associated with poorer long-term results.

c. Surgical therapy

(1) Closed commissurotomy was the earliest surgical approach performed through a thoracotomy (without CPB) and atriotomy with a valve dilator.

(2) **Mitral valve surgery** is recommended in patients with severe rheumatic MS who are not candidates for PMBC or have failed previously or require other procedures. Open mitral valvotomy involves debridement of calcium and splitting of fused commissures and chordae.

(3) Severe subvalvular disease or valvular calcification **or comorbid valvulopathy** (ie, aortic valve stenosis or regurgitation, aortopathy, multivessel CAD) favors surgical intervention.

(4) Mitral valve replacement is often required in **mixed MS/MR disease**, especially when there is extensive fibrosis and calcification or concomitant MR.

(5) A **combined MAZE procedure** (either surgical or an intraoperative ablation catheter) and **LA appendage ligation (LAAL)** may also be added to treat AF and reduce future cardioembolic risk.

(6) Balloon valvuloplasty and commissurotomy provide comparable improvements in valve area and symptoms immediately postprocedure and in medium-term outcomes in appropriately selected patients.

d. Postprocedural care

(1) After balloon valvuloplasty or valve replacement, patients should undergo baseline echocardiography, preferably >72 hours after the procedure.

(2) In patients with a history of AF, warfarin should be restarted 2 to 3 days after the procedure.

(3) Clinical follow-up examination should be performed at least once a year and more often if symptoms develop. It has become common practice at many centers for patients to undergo annual surveillance echocardiography.

3. Calcific MS

a. Medical therapy

TABLE 16.6 ACC/AHA Indications for Percutaneous Mitral Balloon Valvotomy

Class I
1. In symptomatic patients (NYHA functional class II, III, or IV), with severe RMS and favorable valve morphology in the absence of LA thrombus and less than moderate MR by Doppler (less than moderate) or Seller (2+) criteria, PBMC is recommended at a Comprehensive Valve Center (LOE: A).
2. In severely symptomatic patients (NYHA class III, IV) with severe RMS (MV ≤1.5 cm^2, stage D), who are not candidates for PMV, or failed prior PMV, or do not have access to PMV and possibly require other cardiovascular procedures, mitral surgery is indicated (LOE: B-NR).
Class IIa
1. In asymptomatic patients with severe RMS (MV area ≤1.5 cm^2, stage C) who have elevated pulmonary pressures (PASP >50 mm Hg), PBMC is reasonable if it can be performed at CVC based on favorable valve morphology with less than moderate (2+) MR in the absence of LA thrombus.

Class IIb
1. In asymptomatic patients with severe RMS (MV area ≤1.5 cm^2, stage C) who have new-onset AF, PBMC may be considered if performed at a CVC based on favorable valve morphology with less than moderate (2+) MR in the absence of LA thrombus (LOE: C-LD).
2. In symptomatic patients (NYHA II-IV) with RMS (MV area >1.5 cm^2), PBMC may be considered if performed at a CVC if there is evidence of hemodynamic impairment based on PAWP >25 mm Hg or mean mitral gradient >15 mm Hg during exercise (LOE:C-LD).
3. In severely symptomatic patients (NYHA III-IV) with severe RMS (MV area ≤1.5 cm^2, stage D), PBMC may be considered if performed at CVC if valve anatomy is suboptimal or the operative risk is prohibitively high (LOE: B-NR).
4. In severely symptomatic patients (NYHA III-IV) with severe nonrheumatic MS (MV area 1.5 cm^2) due to extensive MAC, intervention may be considered after discussion of the patient's values, preferences and the high procedural risk (LOE: C-LD).
Class III
1. PMV is not indicated for patients with mild MS.
2. PMV should not be performed in patients with moderate or severe MR or LA thrombus.

ACC, American College of Cardiology; AHA, American Heart Association; CVC, central venous catheter; LA, left atrial; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PMV, percutaneous mitral valvotomy; RMS, rheumatic mitral stenosis.

TABLE 16.7 Echo Score Assessment for Percutaneous Valvuloplasty in the Management of Mitral Stenosis

Mobility (Grade 0-4, 0 Being Normal)
1. Highly mobile with only leaflet tips restricted
2. Mild leaflet restriction; base portions have normal mobility
3. Valve moves forward in diastole, mainly from base
4. No or minimal diastolic movement of valve
Subvalvular Thickening (Grade 0-4, 0 Being Normal)
1. Minimal thickening below leaflets
2. Chordal thickening up to one-third of chordal length

3. Thickening extending to distal one-third of chords
4. Extensive thickening to papillary muscles
Thickening of Leaflets (Grade 0-4, 0 Being Normal)
1. Near normal (4-5 mm)
2. Marginal thickening (5-8 mm) with normal thickness of mid-leaflets
3. Thickening of entire leaflet (5-8 mm)
4. Extensive thickening of all leaflet tissues (>8-10 mm)
Calcification (Grade 0-4, 0 Being Normal)
1. Single area of echo brightness
2. Scattered areas of increased brightness along leaflet margins
3. Brightness extending to the midportion of leaflets
4. Extensive brightness throughout the leaflet tissue

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TABLE 16.8 Complications of Balloon Valvuloplasty

Mitral regurgitation
Cardiac perforation: incidence as high as 2%-4%
Embolization: incidence 2% in the National Heart, Lung, and Blood Institute registry
Residual atrial septal defect: most close within 6 mo; can persist long term among as many as 10% of patients; generally small and well tolerated

(1) There is no established medical therapy for the prevention or treatment of MAC. Current therapeutic recommendations focus on **guideline-based management** of sequelae, including heart failure, thrombotic, and antiarrhythmic therapy.

(2) **Antibiotic prophylaxis** is not recommended for the presence of MAC as it has not independently been associated with high-risk adverse events.

b. Surgical therapy

(1) Patients with severe symptomatic mitral valve stenosis secondary to MAC should undergo evaluation for valve intervention. However, a range of technical and clinical factors must be considered, given the high operative morbidity and mortality rates. **Center volume** has been associated with operative success, with higher mortality in centers that performed less than 50 mitral valve surgeries per year.

(2) Alternative surgical therapies include the creation of left atrioventricular bypass conduits and hybrid strategies that rely on anterior leaflet resection via transatrial approach followed by implantation of a balloon-expandable prosthetic valve.

c. Transcatheter therapy

(1) Valve replacement

(a) The Sapien S3 is a balloon-expandable trileaflet transcatheter valve (THV) (Edwards Lifesciences, Irvine, CA, USA) approved by the FDA for **severe bioprosthetic mitral valve stenosis** with ViV and ViR deployment or ViMAC) of the in high-risk patients.

(b) Careful patient selection is essential as ViMAC is associated with higher rates of periprocedural complications including embolization, outflow obstruction, and mortality than ViV or ViR. ViV and ViR rely on the integrity of a **circular or semilunar prosthetic structure** to anchor the THV unlike the heterogeneity of **calcium distribution** in severe MAC. The first case of successful ViMAC was performed in 2012. Several active registries and trials are underway to identify the optimal patient, anatomic, and technical factors for successful TMVR.

(c) **LVOTO** remains a major complication associated with significant mortality in patients undergoing ViMAC. Techniques such as intentional **laceration of the anterior mitral leaflet (LAMPOON)** and

periprocedural or rescue ASA may mitigate the risk of LVOTO.

(2) Hybrid approach

(a) Several hybrid techniques have been developed that integrate surgical exposure with balloon-expandable transcatheter bioprostheses in anatomically suitable candidates who at prohibitive risk for open repair.

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CHAPTER 17

Tricuspid Valve Disease, Pulmonary Valve Disease, and Drug-Induced Valve Disease

Mohammad Zmaili and Tom Kai Ming Wang

TRICUSPID VALVE DISEASE

I. INTRODUCTION. The **tricuspid valve (TV) apparatus** is generally considered to consist of three valve leaflets—septal, anterior, and posterior—along with the tricuspid annulus, the chordae tendineae, and the papillary muscles, each connected to two valve leaflets. However, recent transesophageal echocardiogram (TEE) studies have revealed that only 54% of patients have three valve leaflets, while the remainder had two, four, or five leaflets. It is the right ventricle (RV) inlet valve separating it from the right atrium. Normally, the TV has an orifice area of 5 to 7 cm^2. The normal TV annulus is a three-dimensional (3D) saddle-shaped structure elliptical in cross section but becomes more circular and planar with pathologic dilation. It lies somewhat inferiorly and anterolaterally compared with the mitral valve (MV) annulus and is more apically displaced than the MV along the septum. The noncircularity and nonplanarity of the TV have important mechanistic and therapeutic implications for correction of TV anomalies. Both tricuspid stenosis (TS) and tricuspid regurgitation (TR) can produce typical symptoms of right-sided congestive heart failure in their advanced stages. TV dysfunction can occur in both anatomically normal and abnormal valves.

II. TRICUSPID STENOSIS. TS is rare as an isolated entity and is most commonly part of a multivalvular process. TS is usually organic in nature and is commonly encountered in conjunction with TR.

A. Etiology. **Table 17.1** lists the causes of TS.

TABLE 17.1 Causes of Tricuspid Stenosis

Congenital
• Tricuspid atresia • Atypical Ebstein anomaly (more likely to cause TR)
Acquired
• Rheumatic • Infective endocarditis • Nonbacterial thrombotic endocarditis • Prosthetic valve failure • Carcinoid syndrome • Malignancy (eg, myxoma and metastases)—Usually cause functional TS • Radiation heart disease (more likely to affect left-sided valves. When TV is affected, TR is more common than TS) • Whipple disease • Fabry disease

TR, tricuspid regurgitation; TS, tricuspid stenosis; TV, tricuspid valve.

1. **Rheumatic heart disease (RHD)** is the most common cause of TS, accounting for >90% of cases. The majority of patients with rheumatic TS have concomitant TR, and this is almost always associated with concurrent MV and aortic valve (AV) involvement. Rheumatic TS is characterized by thickening and fibrosis of the valve leaflets, eventually culminating in marked leaflet contracture and commissural fusion.
2. **Carcinoid heart disease** is encountered in the setting of primary intestinal carcinoid tumors with secondary metastatic spread to the liver. Once metastatic to the liver, this neuroendocrine malignancy

secretes numerous vasoactive substances (eg, serotonin, histamine, bradykinin), which directly affect the right-sided heart valves. Carcinoid valvular disease is characterized by thickened, retracted, shortened, and even fixed tricuspid leaflets, causing a mixed picture of regurgitation and stenosis. Unless there is a significant right-to-left shunt (via an atrial septal defect or patent foramen ovale), the left-sided heart valves are usually spared, owing to the clearance of vasoactive substances by the lungs. Left-sided valves can also be involved in the setting of a primary bronchial carcinoid.

3. **Prosthetic TV stenosis** is another cause of TS, although it is overall rare as even if TV surgery is necessary, valve repair is much more common than replacement. The pathophysiology of the stenosis, as in any prosthetic valve, may result from valve degeneration, pannus, thrombus, or vegetations associated with endocarditis.

B. Pathophysiology

1. TS produces a **diastolic pressure gradient** between the right atrium and the RV, which is augmented when transvalvular flow increases—such as during inspiration. This typically occurs once the valve area falls below 1.5 cm^2.
2. A modest elevation of mean diastolic pressure gradient (ie, ≥5 mm Hg) can raise right atrial pressure (RAP, ie, >10 mm Hg) sufficiently to produce signs of **systemic venous congestion**, including hepatomegaly, ascites, and edema.
3. The right atrial *a wave* may be very prominent and may approach the level of the right ventricular systolic pressure (RVSP).
4. Resting cardiac output may be markedly reduced and may fail to augment with exercise, due to limited RV preload.

C. Clinical presentation

1. **Symptoms.** The presentation of TS varies depending on the **severity of stenosis**, the presence of **concomitant cardiac lesions**, and the **etiology of the valvular disease**.

a. **Fatigue** is common and related to low and relatively fixed cardiac output. Other symptoms include leg and abdominal swelling, effort intolerance, and shortness of breath. **Right upper quadrant pain** can result from high systemic venous pressure and concomitant hepatomegaly, ascites, and abdominal distention.

b. Occasionally, patients will experience a **fluttering discomfort** in the neck, caused by the giant *a waves* transmitted to the jugular veins.

c. Severe TS may mask the typical symptoms of other coexisting valvular lesions, such as mitral stenosis (MS). In the case of MS, the flow limitation across the TV can minimize the pulmonary congestion, orthopnea, and paroxysmal nocturnal dyspnea usually associated with MS.

2. **Physical findings.** The diagnosis of TS is often missed without a high index of suspicion. Clues that should raise suspicion of TS include the presence of **elevated jugular venous pressure** and **accentuation of a diastolic murmur along the left sternal border with inspiration** (not present in MS).

a. Elevated central venous pressure may lead to marked hepatomegaly, ascites, and peripheral edema. In sinus rhythm, a giant a wave in the jugular venous pulse results from impaired right ventricular diastolic filling during atrial systole.

b. **Diastolic murmur.** The murmur of TS is **low pitched**, **diastolic**, and best heard along the left lower sternal border in the third to fourth intercostal space or over the xiphoid process. If the rhythm is sinus, the murmur is prominent at end diastole (presystole). The low-pitched diastolic murmur may be obscured by the usually associated MS murmur. Accentuation of the murmur **intensity with inspiration (Rivero-Carvallo sign)** or other preload augmenting maneuvers (eg, leg raising and squatting) may serve to differentiate the two murmurs or at least identify a component of TS in the setting of concurrent MS.

c. An **opening snap** (OS) may be heard at the left lower sternal border. This can help to differentiate a true TS from a functional TS that may result from increased flow across a nonstenotic valve, which can occur with a large left-to-right atrial shunt. In the latter situation, an OS would not be audible.

d. Despite elevated neck veins and venous congestion, the patient may be comfortable lying flat due to the absence of pulmonary congestion. This apparent discrepancy between the severity of peripheral edema and the paucity of pulmonary congestion can help discriminate and identify TS from other valvular lesions.

e. Respiratory variation in splitting of the second heart sound (S_2) may be absent in patients with TS due to the relatively fixed diastolic filling of the RV despite respiration.

D. Diagnostic testing. The hemodynamic expression of TS is a pressure gradient across the TV in diastole. A mean diastolic pressure gradient of 2 mm Hg across the TV establishes the diagnosis of TS during catheterization. Nowadays, hemodynamic diagnosis is rarely required, as the diagnosis is usually apparent on Doppler echocardiography.

1. **Electrocardiogram (ECG).** TS is suggested by the presence of right atrial enlargement on the ECG (peaked P waves, for example, in inferior leads).

2. **2D echocardiography.** The **echocardiogram is the most useful tool** in identifying TS, and both transthoracic echocardiography (TTE) and TEE echocardiography may be used. Typical findings **include reduction in the diameter of the TV orifice** and **thickening and diastolic doming of the tricuspid leaflets** (especially the anterior leaflet). Echocardiography parameters of significant TS **include mean pressure gradient ≥5 mm Hg using continuous wave (CW) Doppler**, tricuspid inflow velocity time integral >60 cm, pressure halftime >190 ms, and valve area ≤1.0 cm^2. Of note, the thresholds for significant TS may differ in the setting of prior TV repair or replacement.

3. **3D echocardiography.** Given the complex 3D structure of the TV, 3D echocardiography (transthoracic or transesophageal) may prove to be a useful adjunct to standard 2D echocardiography. Using this modality, all TV leaflets can be simultaneously imaged, potentially allowing for more accurate direct planimetry of TV area and precise visualization of leaflet motion.
4. **Cardiac computed tomography (CT).** CT may also play a role in the evaluation of TS, especially for prosthetic TV using 4D retrospective ECG-gating techniques for valve assessment during the entire cardiac cycle, to identify abnormal leaflet motion and pathologies, such as calcifications, hypoattenuated thickening (including thrombus and pannus), and vegetations. It is important that the images are acquired at the time when contrast opacification is optimized for visualization of the right heart structures.
5. Given the accuracy of modern echocardiographic techniques, cardiac catheterization can often be bypassed. **Right heart catheterization can be used to confirm the diagnosis already suggested by Doppler echocardiography** and can serve as a prelude to therapeutic balloon valvuloplasty. The RAP is elevated, and the *a wave* may be very tall, sometimes approaching the RVSP in magnitude. The *y* descent is attenuated or absent. Simultaneous measurement of the RAP and RV pressure with dual catheters (or a dual-lumen catheter) enables the calculation of the diastolic pressure gradient (**Figure 17.1**). The measured gradient is highly dependent on cardiac output and heart rate. Maneuvers such as lifting the legs or administration of atropine may accentuate the gradient.

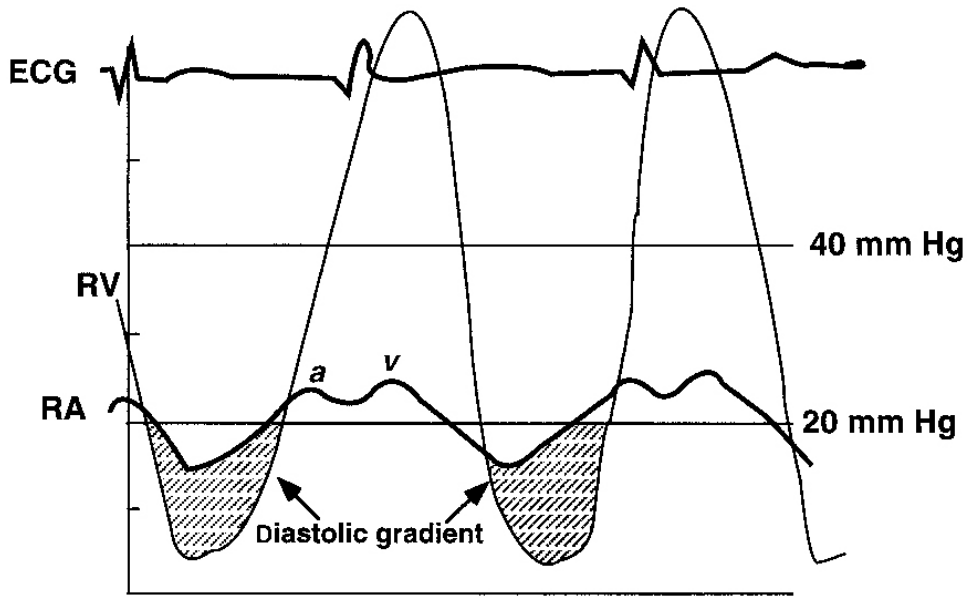

FIGURE 17.1 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid stenosis.

E. Therapy

1. **Medical therapy** consists of intensive sodium restriction, diuretics, and heart rate control, especially in the setting of an associated atrial fibrillation.
2. **Defining coexisting valvular lesions** is critical to properly managing TS. For instance, in patients with combined TS and MS, the former should not be corrected alone, as this may produce pulmonary congestion. If other valvular surgery is planned, concomitant treatment of TS should be considered if the gradient exceeds 5 mm Hg.
3. **Severe stenosis requires balloon valvuloplasty or TV replacement.** The indications for surgery or balloon valvuloplasty are usually determined by the severity of concomitant MV or AV disease. Limiting symptoms due to predominant TS are considered an indication for valvuloplasty or surgery. Balloon valvuloplasty appears to be successful from both a symptomatic and a hemodynamic standpoint, but can result in significant TR, potentially necessitating valve replacement.

4. **Bioprostheses are favored** when valve replacement is necessary at the tricuspid position, as **mechanical prostheses are more prone to thrombosis** at this location and are thus rarely used.
5. **Percutaneous or transcatheter intervention** may offer an alternative for intervention, especially for high-risk patients. Balloon valvuloplasty has occasionally been performed with success dependent on valve anatomy. Transcatheter valve-in-valve tricuspid replacement may be considered for patients with prior bioprosthetic TV replacement, but not for mechanical valve replacement.

III. TRICUSPID REGURGITATION

A. Etiology and pathophysiology. Any disease process that causes derangement of the TV apparatus (annulus, leaflets, chordae, and papillary muscles) can lead to TR. The most common cause of TR is not intrinsic valvular disease but rather dilation of the RV, causing secondary (functional) TR. **Table 17.2** lists the causes of TR, **Figure 17.2** shows the prevalence of primary and secondary etiologies of isolated TR.

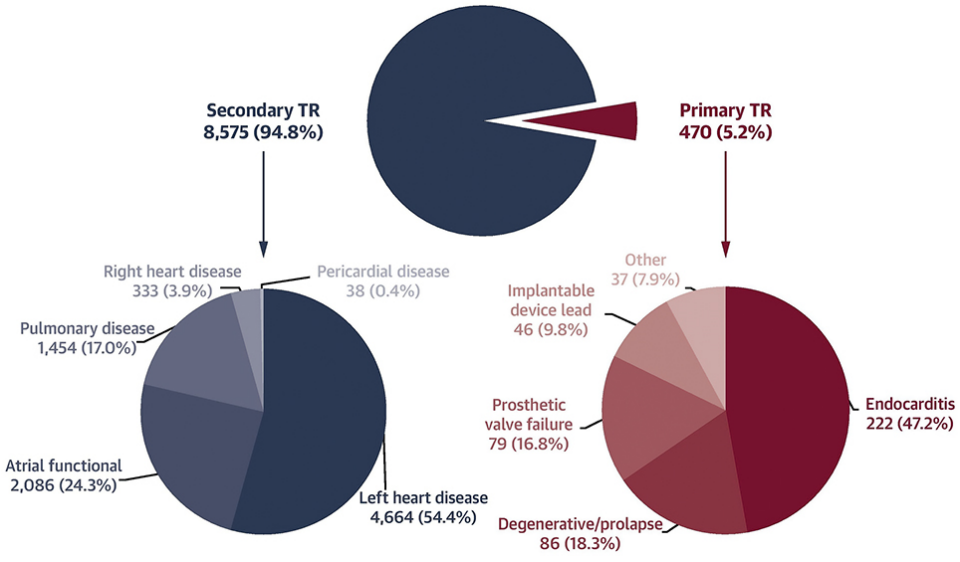

FIGURE 17.2 Breakdown and prevalence of primary and secondary etiologies of isolated tricuspid regurgitation (TR). (Reprinted from Wang TKM, Akyuz K, Mentias A, et al. Contemporary etiologies, outcomes,

and novel risk score for isolated tricuspid regurgitation. *JACC Cardiovasc Imaging*. 2022;15(5):731-744.)

TABLE 17.2 Causes of Tricuspid Regurgitation

Primary Causes
Rheumatic
Ebstein anomaly
Carcinoid
Connective tissue disease (eg, Marfan syndrome)
Tricuspid valve prolapse
Trauma • *Blunt/penetrating injuries* • *Iatrogenic secondary to pacemaker lead insertions, leaflet damage in setting endomyocardial biopsy*
Tumors (myxoma, tumors of tricuspid valve leaflet)
Infective or marantic endocarditis
Papillary muscle dysfunction
Radiation injury
Toxic secondary to phen-phen or methysergide valvulopathy
Secondary (Functional) Causes
Right ventricular dilation (dilated annulus) Dilated right atrium (atrial fibrillation)
Pulmonary hypertension
Right ventricular dysfunction • Global: Cardiomyopathy, myocarditis, infarction • Segmental: Ischemia, infarction, fibrosis, arrhythmogenic right ventricular dysplasia

1. The most commonly encountered type is the **functional or secondary TR, which constitutes about 85% to 95% of TR.** In secondary TR, the TV has normal morphology and structure, and

TR arises from other causes. The most common of these is **left heart disease** that increases the filling pressures, leading to pulmonary hypertension, RV dilation, and/or dysfunction and, therefore, TR. Examples of left heart diseases that lead to TR include MV and AV stenosis and/or regurgitation, cardiomyopathies and heart failure with reduced or preserved ejection fraction, and coronary heart disease. **Chronic lung disease** of any cause that leads to pulmonary hypertension, and cor pulmonale is another cause of functional TR. An increasingly recognized cause of functional TR is termed **atrial functional TR** (or sometimes isolated TR; however, an alternative definition of isolated TR is TR in the absence of other significant valve diseases), whereby there is no left heart, right heart, or chronic lung disease; however, the tricuspid annulus and often the right atrium are dilated. Many patients with atrial functional TR have atrial fibrillation. **Primary right heart diseases** such as arrhythmogenic RV cardiomyopathy, RV myocardial infarction, constrictive pericarditis, and cardiac sarcoidosis are uncommon. Lastly, TR has been increasingly observed early or late after left heart surgery or interventions, although the mechanism is likely associated with left heart disease or ischemic injury during surgery.

2. TR with an **anatomically abnormal valve (ie, primary TR)** may be a manifestation of congenital heart disease (eg, Ebstein anomaly, defined as apical displacement of the septal leaflet from the MV by >8 mm/m^2, atrioventricular [AV] canal defects, and ventricular septal defect [VSD]). In addition, a variety of acquired conditions such as infective endocarditis, RHD, myxomatous degeneration/prolapse, carcinoid heart disease, radiation, endomyocardial fibrosis, trauma, and the hypereosinophilic syndrome may directly damage the TV, resulting in poor leaflet coaptation and TR. Similar to prosthetic TS, prosthetic TR can develop due to valvular degeneration, thrombus formation, or endocarditis with resultant valvular destruction, dehiscence, and/or

perforation. Endomyocardial biopsy, which may cause leaflet flail or perforation, can occasionally lead to iatrogenic primary TR.

3. TR in association with **pacemaker or implantable cardioverter-defibrillator (ICD)** leads is increasingly recognized and classified separately to primary TR. **This may occur due to direct interaction between the pacemaker leads and the tricuspid valvular apparatus, which can lead to restricted leaflet mobility, valvular malcoaptation, leaflet perforation, or leaflet/chordal entrapment.** The septal leaflet tends to be more commonly affected than the other two leaflets. **Careful imaging evaluation is critical to confirm that the lead is contributing to the TR as opposed to being a bystander.** Management may involve **extraction of the leads** and alternative placement sites such as coronary sinus or epicardial lead placement, if the patient remains device dependent, along with surgery (or in high-risk patients with transcatheter interventions).

B. Clinical presentation

1. **Symptoms.** The spectrum of symptoms of TR is wide and depends on its etiology and chronicity. Therefore, enquiring about TR risk factors is important to identify the etiology. **Many patients remain asymptomatic for many years, until late or end-stage TR develops, by which time intervention risk may be too high, so early identification is important.** When TR and pulmonary hypertension coexist, cardiac output declines and patients may manifest symptoms of right heart failure. **Symptoms include leg and abdominal swelling, fatigue, weakness, shortness of breath, and exercise intolerance, as well as those associated with the underlying etiology (eg, fever for infective endocarditis, palpitations for atrial fibrillation).** On the other hand, Isolated TR is usually well tolerated.
2. **Physical findings**
    a. On general examination, patients with severe TR may have signs of weight loss, cachexia, and jaundice related to congestive hepatopathy and bowel edema.

b. The neck veins will show loss of the usual *x* wave and a prominent systolic wave, usually referred to as a *cv* wave, followed by a rapid *y* descent. The characteristics of the large *cv* wave in the jugular venous pulse are dependent on TR severity. With significant TR, the prominent *cv* wave has maximal height at S_2, and the rapid *y* descent is most prominent on inspiration. A venous systolic thrill and murmur in the neck may be present in severe TR. The RV impulse is often hyperdynamic.

c. TR typically produces a **pansystolic murmur** at the third to fourth intercostal space along the left sternal border that increases with inspiration.

d. TR causes an increase in diastolic flow across the TV. This may be heard as an **early diastolic rumble** (short and low pitched) along the left sternal border.

(1) With **severe, long-standing TR**, there is **ventricularization of the right atrium** (the pressure gradient across the TV is minimized), and the TR murmur **may be barely audible or absent**.

(2) **Other findings.** A **right-sided third or fourth heart sound (S_3 or S_4) is often present along the left sternal border, which augments with inspiration. If pulmonary hypertension coexists, P_2** is accentuated. **Systolic pulsation** of the liver is often an associated physical finding, although this may be diminished once congestive cirrhosis develops.

C. Diagnostic testing

1. **ECG.** The findings are usually nonspecific. Incomplete right bundle branch block may be seen. Atrial fibrillation is commonly found in association with severe TR.
2. **Echocardiography.** The most common views used for the detection of TR are the parasternal RV inflow, basal short axis, and the apical four-chamber views.

a. Physiologic TR. A small degree of TR is observed in about 70% of patients with structurally normal hearts, and the prevalence increases with age. Physiologic TR is usually represented by a small jet that does not extend >1 cm into the atrium.

b. 2D echocardiography

(1) Leaflet thickening may be seen in TR due to rheumatic or carcinoid disease. In functional TR, the leaflets usually appear normal. Tricuspid prolapse often occurs in patients with MV prolapse and may cause significant TR, while flail is typically associated with severe TR. In Ebstein anomaly, the septal leaflet of the TV is displaced apically. Vegetations are evident with endocarditis, and a flail valve leaflet may be seen with iatrogenic damage (eg, after endomyocardial biopsy) or following papillary muscle rupture with RV infarction. TEE often has superior spatial resolution in identifying the etiology and clarifying the severity of TR, especially when transthoracic echocardiography is suboptimal. **TEE is also a critical tool when combined with 3D and multiplanar reconstruction techniques for the preoperative evaluation and intraprocedural guidance of transcatheter tricuspid valve interventions (TTVIs).**

(2) Right heart evaluation is important in TR, especially when severity is at least moderate, and those that should be routinely performed are indicated in **bold.** RV size measurements include **basal diameter,** mid diameter, longitudinal diameter, wall thickness, and end-diastolic/end-systolic areas and volumes if possible. RV functional measurements include Doppler measurements of **tricuspid annular plane systolic excursion (TAPSE)**, **RV annular systolic tissue Doppler velocity (RVS'), right ventricular free wall longitudinal strain (RVFWLS), fractional area change,** myocardial performance index, and ejection fraction (3D if feasible).

TAPSE and RVFWLS hold significant prognostic value, with RVFWLS below −19% being of surgical consideration in patients with asymptomatic TR. With moderate-to-severe TR, an **RV volume overload pattern** is seen, characterized by RV enlargement, ventricular septal flattening or shift to the left in diastole, and paradoxical motion in systole. There is often associated dilation of the right atrium and inferior vena cava (IVC).

c. Doppler analysis. Assessment of TR involves incorporation of all of the qualitative, semiquantitative, and quantitative Doppler information obtainable alongside 2D findings: size of the color jet, presence or absence of a proximal convergence zone, velocity profile, and eccentricity of the TR jet. Eccentric, wall-hugging jets may lead to underestimation of jet severity. An integrated multiparametric approach is necessary to grade TR as individual parameters have their own limitations.

(1) TR direction and severity are assessed with color-flow Doppler. The severity of TR is estimated in several ways, including:

(a) Jet area: This measure is highly dependent on echocardiographic settings, particularly the pulse repetition frequency, and the direction and eccentricity of the jet.

(b) Vena contracta width (VCW): The narrowest portion of the jet just downstream from the valve orifice gives a rough estimate of the effective orifice area. Moderate and severe TR are defined as VCW of 0.3 to 0.69 cm and ≥0.7 cm, respectively.

(c) Proximal flow convergence method (see Chapter 16), to assess the **proximal isovelocity surface area (PISA) radius** (moderate 0.6-0.9 cm, severe >0.9 cm), then **effective regurgitant orifice area (EROA)** (**moderate 0.20-0.39 cm_2, severe ≥0.40 cm_2**—note these are same thresholds as mitral regurgitation [MR]), and finally **regurgitant volume** (**moderate**

30-44 mL, severe ≥45 mL—note these are lower thresholds than for MR). Again, EROA and regurgitant volume have important prognostic implications in TR and, when severe, suggest the need for intervention.

(d) **CW Doppler:** The signal intensity and contour of the TR jet on CW Doppler can help define TR severity. Severe TR produces a dense spectral recording along with a triangular signal early peaking velocity.

(e) **Hepatic vein flow:** Systolic flow reversal in the IVC or hepatic veins is consistent with severe TR.

i. The RVSP is estimated using the modified Bernoulli equation after measuring the peak TR jet velocity by CW Doppler. In the absence of pulmonary stenosis (PS), the pulmonary artery systolic pressure (PASP) can then be estimated as PASP = RVSP = 4 (TR V_{max})² + RAP. Another increasingly recognized prognostic parameter in patients with TR is the RV-to-pulmonary artery coupling ratio, typically calculated by TAPSE divided by RVSP. Lower ratio and lack of afterload reserve are associated with worse survival.

3. **Cardiac magnetic resonance imaging (MRI).** MRI has become a valuable complementary tool for TR assessment, especially when echocardiography findings are conflicting or limited due to suboptimal windows. **MRI is the reference standard for right heart size and function quantification while also being important in TR evaluation**. **It is also able to quantify tricuspid regurgitant volume (based on RV stroke volume minus pulmonary artery systolic forward flow) and regurgitant fraction (regurgitant volume divided by stroke volume)** much more easily and reliably than echo, and higher values are associated with worse outcomes (**Figure 17.3**). Lower thresholds than echocardiography for severe TR are expected because of typically lower regurgitant volume quantified by MRI

by approximately 10 mL and can contribute to decision-making toward TV interventions as well. Lastly, many etiologies of TR can also be assessed on MRI, including left heart quantification and myocardial tissue characterization.

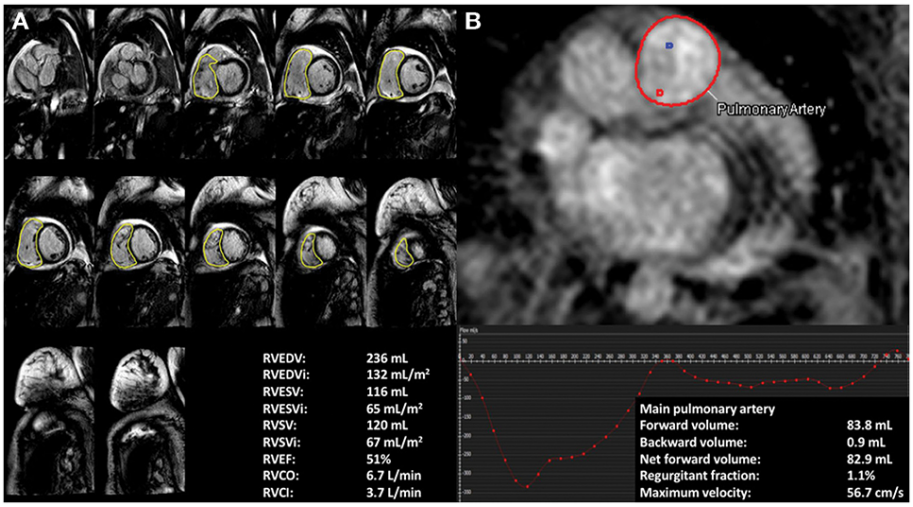

FIGURE 17.3 Tricuspid regurgitation quantification by cardiac magnetic resonance imaging (**A**) right ventricular stroke volume (120 mL) on steady-state free precession sequence and (**B**) main pulmonary artery forward flow (84 mL) by phase contrast sequence (regurgitant volume 120 - 84 = 36 mL, fraction 36/120 × 100% = 30%). (From Wang TKM, Akyuz K, Reyaldeen R, et al. Prognostic value of complementary echocardiography and magnetic resonance imaging quantitative evaluation for isolated tricuspid regurgitation. *Circ Cardiovasc Imaging*. 2021;14(9):e012211.)

4. **Cardiac CT**. CT has several niche roles in TR assessment and often requires the use of 4D retrospective ECG-gating techniques for valve assessment during the entire cardiac cycle. It is important for TTVIs to measure tricuspid annulus for device sizing; evaluate adjacent structures such as the right coronary artery, systemic veins, and their access routes; quantify right heart size and function; delineate valve geometry, including leaflet length, tenting, coaptation gap, and orifice area; and support fusion imaging with fluoroscopy, and other imaging modalities, and 3D printing.

5. **Cardiac catheterization.** Invasive hemodynamic assessment can be useful if noninvasive findings are insufficient or discordant with the clinical presentation. In the presence of moderate-to-severe TR, right heart catheterization will show a dominant *v* wave in the RAP curve (**Figure 17.4**), an RAP curve resembling that of the RV, increased RV end-diastolic pressure, and low cardiac output by thermodilution and Fick techniques.

D. Therapy

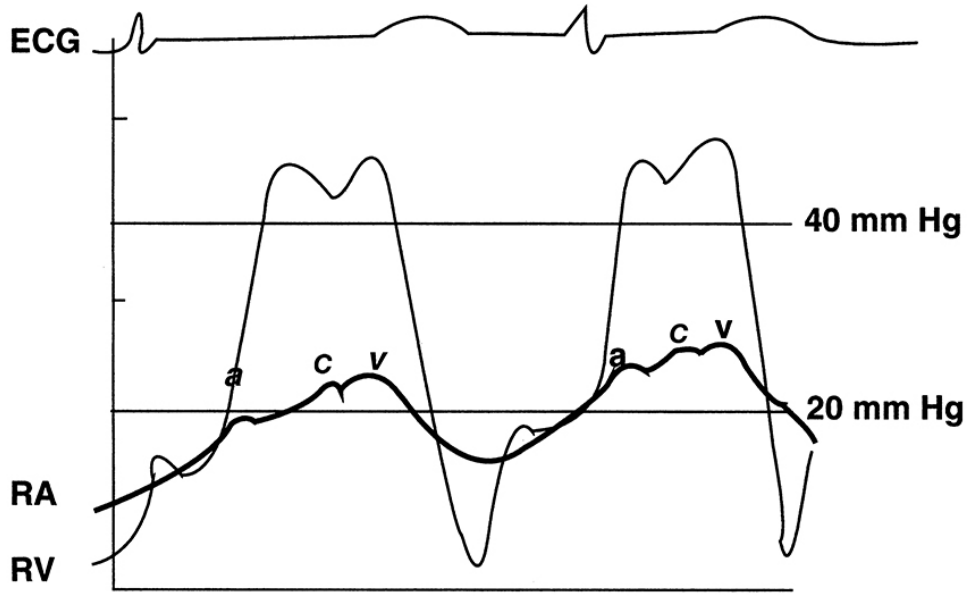

FIGURE 17.4 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid regurgitation.

1. TR is known to be associated with worse survival, even when of mild or moderate severity. Although there is no medical therapy proven to improve survival in significant TR per se, it is still an important part of treatment. Diuretics are important in the setting of right and/or left heart failure for afterload reduction and diuresis to euvolemic levels and, in some circumstances, reduce functional TR severity**. Underlying etiologies of TR need to be addressed with the appropriate therapies.** Guideline-recommended heart failure medical and device therapy needs to be maximized for

heart failure with reduced and preserved ejection fraction. Rate control, rhythm control, and/or catheter ablation need to be implemented for atrial fibrillation or other arrhythmias. Timely and aggressive antibiotic therapy is vital for infective endocarditis. Revascularization may be indicated for significant coronary heart disease. Appropriate pulmonary treatments are necessary for chronic lung disease.

2. **Surgical therapy. According to the 2020 American College of Cardiology/American Heart Association (ACC/AHA guidelines), TV surgery is recommended for severe TR in patients undergoing left-sided valve surgery (class I),** and this is the commonest indication. Several studies have demonstrated a significant improvement in the outcomes among individuals undergoing concomitant TV repair with MV or AV surgery in comparison with those undergoing left heart valvular surgery alone. In addition to multivalvular disease, **TV repair is recommended for progressive or moderate TR in patients undergoing MV surgery when there is significant TV annular dilation (>4.0 cm) or prior signs and symptoms of right-sided heart failure** (class IIa). In patients with MS and TR, a decision to repair the TV should be based on the severity of the TR, as well as the duration and severity of pulmonary hypertension (ie, TR in the setting of long-standing pulmonary hypertension and MS is unlikely to improve with MV surgery alone). Usually, **tricuspid repair or annuloplasty is favored over prosthetic valve replacement implantation where this is feasible based on observational studies**. An important operative risk associated with tricuspid surgery is the significantly **higher pacemaker rates** than without TV surgery. **In isolated TR without the need for other concomitant heart surgery, surgical indications are more controversial.** In primary TR, surgery is recommended for severe TR with signs and symptoms of right heart failure (ACC/AHA class IIa). For secondary TR, severe TR again with signs and symptoms of right heart failure with poor response to medical therapy in the absence of left-sided disease or pulmonary

hypertension has indication for surgery (ACC/AHA class IIa), and those who are asymptomatic but with progressive RV dilation and dysfunction may be considered for surgery also (ACC/AHA class IIb). Surgical outcomes for isolated TV surgery are poor even in contemporary registries, with operative mortality rates of 8% to 10%. Methods to improve these adverse surgical outcomes include earlier intervention, preferring valve repair to replacement, and performing surgery at expert centers of excellence with higher surgical volumes. In these scenarios, observational studies have demonstrated improved survival for surgery versus medical therapy; however, randomized trials are awaited. **Table 17.3** summarizes the ACC/AHA and European Society of Cardiology (ESC) guidelines for the surgical management of TR.

TABLE 17.3 AHA/ACC Versus ESC Guidelines for Surgical Management of Tricuspid Regurgitation

Management of Tricuspid Regurgitation			
2020 ACC/AHA Guidelines		**2021 ESC Guidelines**	
Recommendations	**COR/LOE**	**Recommendations**	**COR/LOE**
Tricuspid valve surgery concomitant to left-sided valve surgery			
In patients with severe TR (stages C and D) undergoing left-sided valve surgery, tricuspid valve surgery is recommended.	I-B	Surgery is recommended in patients with severe primary/secondary TR undergoing left-sided valve surgery.	I-C
In patients with progressive TR (stage B) undergoing left-sided valve surgery, tricuspid valve surgery can be beneficial in the context of either (1) tricuspid annular dilation (tricuspid annulus end-diastolic diameter >4.0 cm) or (2) prior signs and	IIa-B	Surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery.	IIa-C
		Surgery should be considered in patients with mild or moderate secondary TR with a dilated annulus (≥40 mm or >21 mm/m^2 by 2D	IIa-B

Management of Tricuspid Regurgitation			
2020 ACC/AHA Guidelines		**2021 ESC Guidelines**	
Recommendations	**COR/LOE**	**Recommendations**	**COR/LOE**
symptoms of right-sided HF.		echocardiography) undergoing left-sided valve surgery.	
Isolated tricuspid valve surgery			
		Surgery is recommended in symptomatic patients with isolated severe primary TR without severe RV dysfunction.	I-C
In patients with signs and symptoms of right-sided HF and severe primary TR (stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations.	IIa-B		
In patients with signs and symptoms of right-sided HF and severe isolated secondary TR attributable to annular dilation (in the absence of pulmonary hypertension or left-sided disease) who are poorly responsive to medical therapy (stage D), isolated tricuspid valve surgery can be beneficial to reduce symptoms and recurrent hospitalizations.	IIa-B		
In asymptomatic patients with severe primary	IIb-C	Surgery should be considered in	IIa-C

Management of Tricuspid Regurgitation			
2020 ACC/AHA Guidelines		**2021 ESC Guidelines**	
Recommendations	**COR/LOE**	**Recommendations**	**COR/LOE**
TR (stage C) and progressive RV dilation or systolic dysfunction, isolated tricuspid valve surgery may be considered.		asymptomatic or mildly symptomatic patients with isolated severe primary TR and RV dilatation who are appropriate for surgery.	
In patients with signs and symptoms of right-sided HF and severe TR (stage D) who have undergone previous left-sided valve surgery, reoperation with isolated tricuspid valve surgery may be considered in the absence of severe pulmonary hypertension or severe RV systolic dysfunction.	IIb-B	Surgery should be considered in patients with severe secondary TR (with or without previous left-sided surgery) who are symptomatic or have RV dilatation, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension.	IIa-B
		Transcatheter treatment of symptomatic secondary severe TR may be considered in inoperable patients at a heart valve center with expertise in the treatment of tricuspid valve disease.	IIb-C

HF, heart failure; LV, left ventricle; RV, right ventricle.

3. Percutaneous or transcatheter approaches have been increasingly utilized to manage significant TR, especially in patients who have prohibitive surgical risk. Transcatheter options available include edge-to-edge repair coaptation devices, annuloplasty, placement of caval-stented valves, and valve replacement. A number of clinical trials for TTVI are ongoing to evaluate the efficacy of such

interventions, and early results are promising for reducing TR severity, heart failure admissions, and mortality compared to medical therapy alone in propensity-matched studies. Randomized trials are awaited.

PULMONARY VALVE DISEASE

I. INTRODUCTION. The pulmonary valve is a trileaflet valve that separates the RV from the pulmonary vasculature as the outlet valve of the RV and lies anterior to the AV anatomically. Dysfunction of the valve can have adverse effects on the RV by producing pressure and/or volume overload. A small degree of pulmonary regurgitation (PR) is a common finding in healthy adults. Acquired pulmonary valve disease is rare in comparison with other valvular disorders.

II. VALVULAR PULMONARY STENOSIS

A. Etiology

1. **Congenital.** PS is the most common pulmonary valve problem, occurring in approximately 8% to 12% of all adult patients with congenital heart disease, and is slightly more common in female patients. Congenital PS is most frequently caused by a dysplastic valve and, less frequently, a bicuspid valve. Valvular PS is typically an isolated abnormality but may be part of a congenital syndrome, such as tetralogy of Fallot (TOF) or Noonan syndrome, and is associated with atrial septal defect, VSD, and branch PS.
2. **RHD** can affect the pulmonary valve, although this is uncommon and usually occurs in the setting of multivalvular involvement. This can result in thickening and fusion of the valve leaflets, resulting in PS.
3. As with the TV, **carcinoid heart disease** (see Section II.A.2) can affect the pulmonary valve, causing the formation of typical "carcinoid plaques." The plaques may result in constriction of the pulmonic valve ring, retraction and fusion of the cusps, and usually a combination of PS and PR.

4. Rarely, pseudopulmonary valve stenosis can occur as a result of **RV outflow obstruction,** from conditions like double-chamber RV, cardiac tumors, or from an aneurysm of the sinus of Valsalva.
    a. Although most cases of isolated PS are valvular, **obstruction may occur below the valve in the right ventricular outflow tract (RVOT) or above the valve at the junction with the main pulmonary artery**. RV hypertrophy from pressure overload of the PS on the RV may cause concomitant RVOT obstruction, which usually reverses following successful dilation of the valvular stenosis. Double-chamber RV can also occur in patients with VSD from shunt blood flow leading to supraventricular crest hypertrophy, or congenitally with superior displacement of septomarginal trabeculation or moderator band with hypertrophy and, therefore, subpulmonic obstruction.

B. Clinical presentation

1. **Signs and symptoms.** Patients with isolated PS present most commonly in the fourth or fifth decade of life with signs and symptoms of right heart failure, exercise intolerance, dyspnea on exertion, and arrhythmias. Mild PS has generally a benign history, and even many patients with moderate PS remain asymptomatic. When the stenosis is severe, patients may occasionally have retrosternal chest pain or syncope with exertion. If the foramen ovale is patent, right-to-left shunting may occur, producing cyanosis and clubbing.
2. **Physical findings**
    a. PS causes a systolic crescendo-decrescendo murmur, heard best in the second and third intercostal spaces, with delayed peaking of the murmur in severe cases. The murmur typically increases with inspiration. A thrill may be felt in the suprasternal notch and at the left upper sternal border. S_2 is often split widely, and the degree of the splitting increases with worsening stenosis due to delay in P_2. The intensity of P_2 may be increased in mild stenosis but is usually diminished with severe stenosis. An

ejection click can sometimes be heard along the left sternal border, and it typically decreases in intensity with inspiration. As the severity of PS increases, the click will move closer to S_1.

b. The RV impulse may be palpated at the left sternal border and be hyperdynamic.

c. The jugular venous pressure can be normal. However, in patients with reduced RV compliance, a prominent *a* wave may be seen in the venous pulse. A right-sided fourth heart sound (RV S_4) may be heard at the left lower sternal border.

d. In advanced cases, evidence of right-sided heart failure may be present.

C. Diagnostic testing

1. **ECG.** In patients with moderate-to-severe PS, the ECG may show right-axis deviation and RV hypertrophy.
2. Chest radiography may reveal **poststenotic dilation** of the main pulmonary artery and diminished pulmonary vascular markings.
3. **Echocardiography** (2D and 3D) is useful in diagnosing pulmonary valve stenosis and for quantifying the severity of the obstruction. The best images of the pulmonary valve are obtained from the short-axis view at the level of the base from the parasternal and subcostal windows. TEE is useful when the TTE images are suboptimal.
   a. Leaflets. In adults, the leaflets can appear thickened and calcified with restricted motion. In children with congenital PS, the leaflets are noncalcified with doming of the valve.
   b. RV. The RV may be normal, especially in children. RV dilation and hypertrophy may be seen in adults, depending on the severity and duration of this disease.
4. **Doppler echocardiography** is the preferred method for grading the severity of PS. This method of quantifying the degree of stenosis is well correlated with the direct measurement obtained during cardiac catheterization. The peak gradient is measured across the pulmonary valve by using CW Doppler with the

modified Bernoulli equation. The following levels of severity have been defined in the 2018 ACC/AHA guidelines on the management of congenital heart disease:

a. **Severe stenosis: A peak jet velocity of >4 m/s (peak gradient >64 mm Hg), mean gradient >35 mm Hg**
b. Moderate stenosis: Peak jet velocity of 3 to 4 m/s (peak gradient 36-64 mm Hg)
c. Mild stenosis: Peak jet velocity of <3 m/s (peak gradient <36 mm Hg)

D. Therapy

1. Mild-to-moderate PS generally has a good prognosis, and intervention is rarely necessary. Survival is excellent among patients with mild PS, with 94% of patients alive as long as 20 years after diagnosis.
2. Patients with severe PS usually warrant a therapeutic intervention for relief of stenosis. The treatment of choice is **balloon valvuloplasty**, usually leading to a 75% decrement in the transvalvular gradient after a successful procedure. The procedure is usually successful if the valve is mobile and pliable. Prognosis and morbidity subsequent to the procedure are largely based on RV function at the time of the procedure. The hypertrophic subpulmonary stenosis that may accompany valvular stenosis usually regresses after successful valvuloplasty. Valve replacement —either percutaneously (see Section III) or surgically—may be necessary if the valve is severely calcified or if there is significant concomitant PR.
3. The **ACC/AHA guidelines for intervention** in patients with valvular PS are as follows:

   Class I: Balloon valvuloplasty is indicated in symptomatic patients with a domed valve and peak instantaneous Doppler gradient of >50 mm Hg or >60 mm Hg in asymptomatic patients.

   Class IIb: Balloon valvuloplasty may be reasonable in symptomatic patients with a dysplastic valve if the peak

instantaneous Doppler gradient is >50 mm Hg or >60 mm Hg in an asymptomatic adolescent or young adult.

Class III: Balloon valvuloplasty is not indicated in symptomatic patients whose peak instantaneous gradient by Doppler is <30 mm Hg or asymptomatic patients with a peak gradient <50 and normal cardiac output.

4. **PS secondary to carcinoid syndrome has a very poor prognosis** (with a median survival of 1.6 years), and the valve often does not respond to balloon valvuloplasty. Valve replacement is often necessary.

III. VALVULAR PULMONARY REGURGITATION

A. Etiology. Beyond trivial physiologic PR, pathologic PR is mainly associated with either sequelae of congenital heart disease (most notably, repaired TOF or PS) or secondary "functional" to dilation of the valve ring in pulmonary hypertension and other dilations of the pulmonary artery.

1. In the setting of repaired TOF, severe PR is a common and difficult problem, often contributing to progressive RV dilation and dysfunction, leading to symptoms of right heart failure and exercise intolerance. These patients may have other complications, such as RVOT obstruction, atrial and ventricular arrhythmias, heart block, residual atrial and/or VSD, left ventricular dysfunction, aortic root dilation, and aortic regurgitation. PR can develop as a later complication after pulmonary valvotomy or valve surgery in other causes of congenital PS. PR may also occur secondary to rare congenital causes, such as an absent, malformed, or fenestrated leaflet.
2. Acquired causes of pathologic PR are much more common. **The most common acquired cause is pulmonary artery hypertension**, followed by infective endocarditis. Both carcinoid syndrome and RHD may cause PR, but they are more likely to cause PS. Marfan syndrome may cause PR secondary to dilation of the pulmonary artery. Iatrogenic PR may be caused by placement of a pulmonary artery catheter.

B. Clinical presentation

1. **Signs and symptoms.** Like TR, PR causes volume overload of the RV. However, in the absence of significant pulmonary hypertension, it may be tolerated well for many years. Once symptomatic, patients with PR present with the signs and symptoms of **right heart failure, exercise intolerance, and exertional dyspnea**.
2. **Physical findings**
   - **a.** The murmur of PR is a relatively brief **low-pitched, diamond-shaped, diastolic murmur**, heard best in the third and fourth left intercostal spaces with a widening of S_2. The murmur increases with inspiration, and **P_2 is accentuated** in the presence of pulmonary artery hypertension.
   - **b.** The **Graham Steell murmur** is a high-pitched, blowing decrescendo diastolic murmur starting immediately after P_2, which is accentuated by inspiration. This characteristic murmur occurs when PASP exceeds 70 mm Hg in the presence of PR.
   - **c.** An RV S_3 may be audible in the fourth intercostal space and will be augmented by inspiration. Depending on the severity and duration of the regurgitant valve, signs and symptoms of right heart failure may also be present on examination.

C. Diagnostic testing.

The pulmonary valve is best evaluated initially with **echocardiography**, using the left ventricle short-axis view from the parasternal and subcostal windows. Minor degrees of PR are seen in 40% to 78% of normal individuals. Pathologic PR is relatively infrequent and should be diagnosed in the context of other structural abnormalities. Severe pulmonary valve regurgitation may be difficult to diagnose with Doppler as the flow disturbance is reduced because of a relatively low-pressure difference from pulmonary artery to RV in this situation. MRI is the diagnostic modality of choice in this situation or if the severity of PR is in doubt. MRI allows quantitation of the PR and the impact of the regurgitation on RV size and function and allows the assessment of important parameters in determining the need for valve intervention.

1. **Anatomic assessment.** The RVOT and pulmonary valve should be interrogated for abnormalities such as leaflet hypoplasia, increased cusp number, and abnormal valve motion (ie, doming).
2. **RV.** The size and function of the RV can provide an indicator of the severity of PR (ie, long-standing severe PR should be associated with RV dilation and/or hypertrophy).
3. **Doppler.** Doppler will reveal a regurgitant jet toward the RV during diastole. Jet length is determined primarily by the pressure difference between the pulmonary artery and RV and, therefore, is an unreliable indicator of PR severity. The **vena contracta** can be measured. **Regurgitant volume** can be calculated using the PISA method, or volumetric method (eg, stroke volume in the RVOT minus stroke volume across the TV or the left ventricular outflow tract if there is no aortic regurgitation), from which the **regurgitant fraction** can be calculated (20%-40% considered moderate, >40% considered severe). CW Doppler demonstrating dense jet and early termination of diastolic flow suggests severe PR, along with short deceleration time of <260 ms, pressure halftime <100 ms, and diastolic flow reversal in the main or branch pulmonary arteries.
4. Maintenance of the regurgitant velocity during diastole suggests that **pulmonary hypertension** is the cause of valve incompetence. Pulmonary artery pressures can be obtained using Doppler flow measurements and the following equation. Pulmonary artery diastolic pressure (PADP) is only obtainable in the setting of PR:

$$\text{PADP} = 4(V_{\text{PR–E}})^2 + \text{RA}_{\text{pressure}}$$

where $V_{\text{PR-E}}$ is the end-diastolic PR velocity.

5. **Cardiac MRI** has become the preferred method to evaluate PR, including in those with TOF and repaired TOF. The pulmonary valve or prosthesis can be visualized for thickening, restricted leaflets, and flow acceleration location to suggest the degree of PS or obstruction above or below the pulmonic valve. The regurgitant jet can be visualized as well. **MRI is the reference standard for**

right heart size and function quantification, which is important in deciding when to intervene. It can directly quantify pulmonary forward flow and peak velocity for PS, as well as regurgitant volume and fraction for PR, using traditional phase contrast or novel 4D flow techniques. It can also quantify flow in the left and right pulmonary arteries and thoracic aorta to assess differential pulmonary flow, branch PS, and flow reversal, as well as Qp/Qs shunt fraction. Associated septal defects, branch pulmonary vessels, aorta, coronaries, and left heart structures can be visualized and quantified as necessary. Finally, cardiac magnetic resonance (CMR) can uniquely evaluate for myocardial scar in the RV (and left ventricle) using late gadolinium enhancement techniques, which is associated with ventricular arrhythmias and worse prognosis.

6. **Cardiac CT** using 4D retrospective ECG-gating techniques for valve assessment during the entire cardiac cycle also has a niche role in PR evaluation, including pulmonary valve or prosthesis motion and abnormalities, device sizing for transcatheter interventions, access routes, and right heart size and function quantification. Therefore, it is frequently performed in these specific settings, especially for preprocedural evaluation.

D. Therapy

1. **Primary pulmonary valve regurgitation.** The prognosis is very good; rarely is correction of the defect necessary, except in cases of intractable right heart failure.
2. **Secondary pulmonary valve regurgitation.** The prognosis due to endocarditis, carcinoid, or pulmonary artery hypertension is dependent on the prognosis and treatment of the primary disease. Treatment of the primary condition (eg, repairing MV in the setting of pulmonary hypertension) often ameliorates the PR. Besides this, vasodilating therapies for pulmonary hypertension can reduce secondary PR. When a treatment is absolutely necessary, **the preferred approach is valve replacement with a bioprosthesis or a pulmonary allograft**. Percutaneous deployment of a prosthetic valve has been successfully

accomplished in this setting and is another option in addition to surgery. Annulus repair is ideal in patients with coexisting left-sided valvular lesions.

3. Guideline indications for pulmonary valve intervention or surgery in patients with TOF for moderate or severe PR include the presence of symptoms, or at least two of (typically MRI measurements) mild or moderate RV or left ventricular systolic dysfunction, severe RV dilation (RV end-diastolic volume index >160 mL/m^2, RV end-systolic volume index >80 mL/m^2, or RV ≥2 times left ventricular end-diastolic volume), RVSP due to RVOT obstruction ≥2/3 systemic pressure, and progressive reduction in objective exercise tolerance) and are considered when there is sustained tachyarrhythmias or concomitant surgery needed for other residual lesions.
4. **Percutaneous pulmonic valve intervention (PPVI).** A viable option for individuals with severe PS or PR from a native valve, failing pulmonic bioprosthesis, or surgical RV-to-pulmonary artery conduit.
    a. **Methods.** Valves are implanted under general anesthesia or conscious sedation using fluoroscopic guidance. Both venous and arterial access is required. After an initial right heart catheterization, angiograms are performed of the RVOT to obtain precise measurements of diameter and length to guide device selection. A balloon test inflation is performed before deploying the device to evaluate compliance of the RVOT. Concurrent nonselective aortogram is performed to exclude the potential for coronary artery compression. The conduit is usually pre-stented with a covered bare metal stent to reduce rates of PPVI stent fracture or bleeding out should a conduit rupture with high-pressure balloon inflation. The valve is then deployed via a femoral or internal jugular venous approach.
    b. **Candidacy**
        (1) Patients must have an adequate RVOT conduit size to allow seating of the device (no larger than 29 mm).

(2) Individuals must have adequate venous access to accommodate the introducer.

c. **Valve types.** There are two commercially available transcatheter pulmonic valves:

(1) **Melody:** Available in one length and can be implanted with a diameter of 18 to 22 mm

(2) **Sapien:** Available in two lengths and can be dilated to a diameter of 23 to 26 mm

d. **Results.** The procedure short and medium follow-up reveals low mortality with PPVI—outcomes for both devices seem to be similar, but the Melody valve has longer term follow-up data. Both devices also show significant reductions in regurgitant fraction and stenotic gradients as well as improvement in the New York Heart Association (NYHA) functional class.

e. **Complications**

(1) **Coronary artery compression.** Occurs in 0% to 1% of all cases but is fatal, thus necessitating balloon testing before device deployment

(2) **Conduit rupture.** Rupture requiring surgery occurs in 0.8% to 2% of cases.

(3) **Stent fracture.** Most common complication. Occurs in 20% of cases without presenting. Prestenting cuts incidence in half. May cause embolization or restenosis.

(4) **Endocarditis.** Patients require prophylaxis for all dental procedures due to increased risk compared with native valves.

DRUG-INDUCED VALVE DISEASE

I. **INTRODUCTION.** Most common forms of valve disease are inherited or acquired in response to a specific disease process. Over the past three decades, however, it has become clear that several pharmacologic agents

may produce a cardiac valvulopathy, which mimics other etiologies of valvular disease.

II. DRUGS KNOWN TO CAUSE VALVE DISEASE

A. **Ergot** alkaloid derivatives (ergotamine and methysergide) used for migraine prophylaxis have been reported to cause valvulopathy since the early 1990s.

B. **Fenfluramine** and **dexfenfluramine**, the constituents of popular diet pills as anorexigens, are associated with valvular heart disease. This led to the withdrawal of a number of common diet drugs from the market. **Phentermine** is another medication that can lead to valvulopathy.

C. More recently, valvular heart disease was reported in 24% to 28% of patients undergoing treatment of Parkinson disease with **ergot-derived dopamine agonists (pergolide and cabergoline)**.

D. There is an increased risk of valvulopathy in individuals with heavy and frequent use of the recreational drug, **3,4-methylenedioxymethamphetamine (MDMA)**—popularly known as *ecstasy*.

III. PATHOLOGY AND PATHOGENESIS

A. Valves that are surgically removed from patients using these drugs are described as having a white, glistening appearance, with histologic evidence of a plaque-like process extending along the leaflet and encasing the chordae tendineae. These findings are **very similar to the findings seen in patients with valvular disease due to carcinoid tumors**, which also secrete vasoactive amines.

B. Subsequent research has indicated that valvulopathic drugs may act via their and their metabolites' ability to stimulate the serotonergic receptors as agonists, particularly the 5-hydroxytryptamine $(5\text{-HT})_{2B}$ serotonin receptor, or may interfere with serotonin metabolism and clearance. This receptor is plentiful in normal heart valves, especially valvular interstitial cells, and appears to be essential for normal cardiac development. Stimulation of the 5-HT_{2B} receptor appears to cause an "overgrowth" valvulopathy as serotonin stimulates

fibroblast growth. Similar observations are seen in the pathogenesis of carcinoid heart disease.

IV. PREVALENCE. Estimates of the prevalence of drug-induced valvular disease have varied widely. Initial studies based on case series suggested a prevalence of valve disease as high as 20% to 30% in the setting of fenfluramine exposure, but larger population-based studies suggest a much lower prevalence of around 10% to 12% (vs 5%-6% in the control group). **Factors that appear to be associated with a greater prevalence of valvular disease include duration of treatment, use of combination agents, and shorter time from cessation of drug treatment to evaluation**. The prevalence of disease is highest in those who have been on a valvulopathic medication for >**6 months**.

V. CLINICAL PRESENTATION. Most commonly, patients seek advice on the basis of a history of taking ergot-derived medications or diet drugs, given the media attention associated with this condition and the legal action that has been mounted against the drug manufacturers. Patients may also present with symptoms of valve disease, such as dyspnea and fatigue. **The predominant findings on examination in patients with significant valve disease involve regurgitation of the AV, the MV, or the TV**. Aortic regurgitation is reported with increased frequency in those with anorexiant abuse than regurgitation at other valve locations.

VI. EVALUATION. All exposed patients should have a cardiac history and physical examination. Patients suspected of having valve lesions on examination should undergo echocardiography. The echocardiographic features simulate both rheumatic disease and carcinoid disease with **leaflet thickening and doming of the MV and thickening of the AV or the TV leaflets**. Despite the apparent restriction of motion of the leaflets, clinically significant **stenosis is rare**. TV and pulmonary valve involvement is less common. The conventional criteria for drug-induced heart valve regurgitation are new aortic regurgitation after drug exposure at least mild in severity or MR at least moderate in severity, and certainly mild-to-moderate severity is more common. Severe

regurgitation requiring surgery has been reported with diet drug-induced valve disease.

II. TREATMENT. All drugs linked to valvular heart disease should be avoided. Once drug-induced valve disease is suspected, the offending drug should be discontinued immediately. In the case of anorexiant-induced valve lesions, **mild improvement in the severity of the valvular regurgitation has been reported on medium-term follow-up after drug discontinuation**. Progression in the severity of valvular disease following drug discontinuation is relatively uncommon. Indications for the surgical intervention in drug-induced valvulopathy are similar to those of other disease processes, and valve replacement is often required as valve repair may not be feasible. However, watchful waiting is a prudent approach in these patients, given the potential for some reversibility of the valve lesions upon drug discontinuation. Endocarditis prophylaxis is not indicated in those with evidence of drug-induced valve disease.

III. FOLLOW-UP. Patients with valve disease should be evaluated both clinically and with echocardiography initially every 6 months. In those with mild stable lesions, yearly evaluation is appropriate.

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CHAPTER 18

Prosthetic Heart Valves

Zackary D. Goff and Paul C. Cremer

I. INTRODUCTION.

Severely dysfunctional heart valves may require replacement by surgical or transcatheter methods. This chapter discusses types of prosthetic valves, specific considerations for valve selection, and prosthetic valve dysfunction.

II. PROSTHETIC VALVE TYPES AND SELECTION

A. Prosthetic valve types.

Prosthetic heart valves are classified as either mechanical or bioprosthetic (**Table 18.1**). Early prosthetic heart valves were predominantly mechanical; over the last two decades, there has been a shift, with bioprosthetic valves accounting for approximately 80% of replacements. Bioprosthetic valves may be implanted by surgical or transcatheter techniques. Each valve differs in its durability, thrombogenicity, and hemodynamic performance. Various mechanical and bioprosthetic valves are shown in **Figure 18.1**.

TABLE 18.1 Types of Prosthetic Heart Valves

Biologic
Stented: pericardial or porcine bioprosthesis
Stentless: pericardial or porcine bioprosthesis, aortic homograft, pulmonary autograft (Ross procedure)
Sutureless
Transcatheter
Mechanical
Bileaflet

Single tilting disc
Caged ball

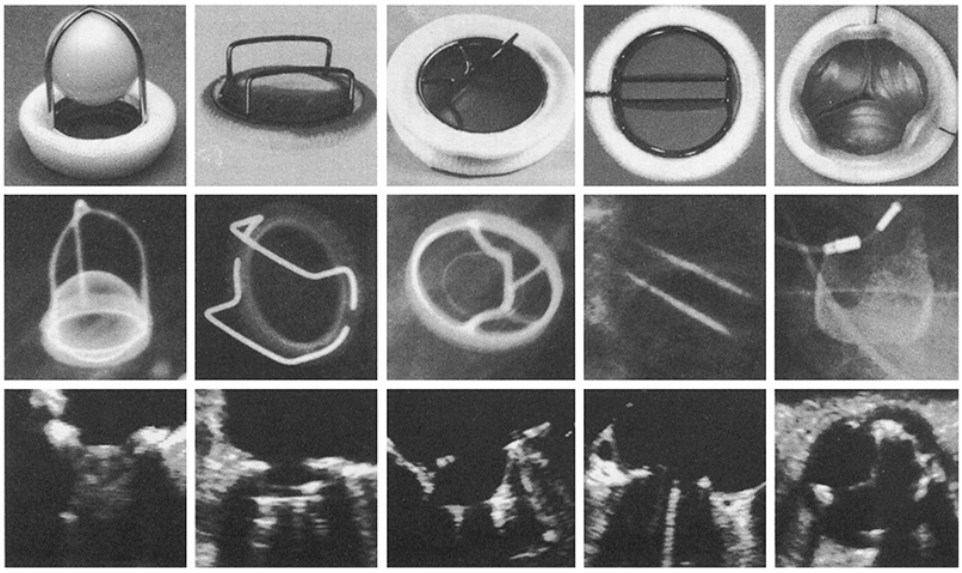


FIGURE 18.1 Photographic and radiographic appearance of different prosthetic heart valves. From left to right: Starr-Edwards caged ball, Kay-Suzuki caged disk, Björk-Shiley single tilting disk, St. Jude's bileaflet tilting disk mechanical valves, and Carpentier-Edwards xenograft. (Reprinted with permission from Garcia M. Principles of imaging. In: Topol EJ, ed. *Comprehensive Cardiovascular Medicine*. Lippincott Williams & Wilkins; 1998:610.)

1. **Bioprosthetic valves** (**Table 18.2**). These resemble native valves with leaflets composed of porcine, bovine, or cadaveric tissue.

TABLE 18.2 Surgical Biologic Valve Replacement

Stented pericardial replacement valve: Carpentier-Edwards Perimount, Carpentier-Edwards Magna, Labcor pericardial, Mitroflow Synergy, Sorin Pericarbon MORE,[a] St. Jude Biocor Pericardial, St. Jude Trifecta[a]

Stented porcine replacement valve: AorTech Aspire, Carbomedics Synergy, Carpentier-Edwards standard and supra-annular, Hancock standard and Hancock II, Labcor, Medtronic Mosaic,[a] St. Jude Biocor, St. Jude Bioimplant, St. Jude Epic

Stentless pericardial: 3F-SAVR, Freedom Solo, Sorin Pericarbon

Stentless porcine: AorTech Aspire, Cryolife-O'Brien,[a] Cryolife-Ross Stentless porcine pulmonary, Edwards Prima Plus, Labcor, Medtronic Freestyle, Medtronic-Venpro Contegra pulmonary valve conduit, Shelhigh Skeletorized Super-Stentless aortic porcine and pulmonic, St. Jude Medical Toronto,[a] St. Jude Quattro stentless mitral

Sutureless: 3F Enable (ATS Medical), Edwards Intuity, Perceval S (Sorin), Trilogy (Arbor Surgical Technologies)

[a]Withdrawn from the market.

a. Heterografts

(1) Stented bioprostheses are the most frequently implanted biologic valves. These can be porcine valves or made from bovine pericardium. The pericardium may be sewn inside or outside the stent posts. The durability of bioprosthetic bovine pericardial versus porcine valves is controversial, although the pericardial valves may have an advantage in younger patients.

(2) Stentless bioprostheses are most often composed of porcine aorta, although some are tricomposite, and others are made from bovine pericardium. The porcine aorta may be long or designed for implantation inferior to the coronary arteries. Even though the stentless valves offer a better hemodynamic profile owing to the larger effective orifice area (EOA), convincing advantages in terms of mortality, left ventricular (LV) mass regression, and durability have not been demonstrated.

b. Aortic homografts are cryopreserved cadaveric human aortic valves. These are typically implanted stentless, with a short segment of the donor's aortic root for support. The coronary arteries require reimplantation. The hemodynamic profile of the homograft is like that of the native valve. Availability of homografts of different sizes can be a limiting factor.

c. Autograft is a procedure that moves the patient's own valve from its normal anatomic position to another site. The Ross procedure moves the pulmonary valve into the aortic position,

to replace a diseased aortic valve, and a pulmonary homograft is placed at the native pulmonary position. This procedure has the advantage of placing a native valve at the hemodynamically most important position. It has been advocated for younger patients, and some reports suggest autograft growth with the patient, which is advantageous in the adolescent age group. However, the initial enthusiasm with this procedure has been tempered by suboptimal outcomes in many adult patients. Autograft implantation in adults should be considered carefully and in consultation with a surgeon with extensive experience with this procedure. The Ozaki procedure uses the patient's own pericardium to reconstruct a new aortic valve.

2. **Mechanical valves.** These consist of a valve ring, a surrounding sewing ring, and either one or two leaflets made of metal, pyrolytic carbon, or polymer (**Table 18.3**).

TABLE 18.3 Mechanical Valve Replacement

Bileaflet mechanical valves: ATS, Carbomedics (standard, reduced cuff, Optifrom, Orbis, Top Hat), Edwards (Mira, Tekna), Jyros, Medtronic Advantage, On-X, St. Jude medical (standard, HP, Masters, Regent)

Tilting disk: Björk-Shiley monostrut,[a] Medtronic-Hall, Omnicarbon, Sorin Monoleaflet allcarbon, Ultracor

Caged ball: Starr-Edwards, Smeloff-Cutter

[a]Withdrawn from the market.

a. **Bileaflet.** Bileaflet valves are the most frequently implanted mechanical valves, due to favorable hemodynamics, longevity, and low complication rates. Bileaflet valves differ in their composition of pyrolytic carbon, the shape and opening angles of the leaflets, and the design of the pivots and sewing ring. For the aortic site, these valves also differ by implantation position, which can be intra-annular, partially supra-annular, or entirely supra-annular. In the open position, bileaflet valves have two large lateral orifices and a smaller central space. A built-in

leakage volume is designed to reduce thrombus formation on disks.

b. **Single-leaflet tilting disk.** This valve consists of a metallic sewing ring attached to a tilting disk made of pyrolytic carbon that rotates about an off-centered pivot axis, with a range of about 60° to 85° from the occluded to the open position. When open, the prosthesis has two orifices separated by the occluder. The major orifice is formed as the disk swings downstream to the open position. The disk on the other side of the pivot axis swings proximally and forms the minor orifice. The Björk-Shiley valve was discontinued in 1986 due to the risk of strut fracture.

c. **Caged ball.** This valve includes a silicone ball within a cage attached to a metallic alloy ring. The ball is free to travel along the cage over 1 to 2 cm. Flow across the prosthesis is directed circumferentially around the ball. The hemodynamic profile and thrombogenicity make this valve less favorable, but this valve has the longest follow-up, over 30 years in some studies.

3. 3. Transcatheter valves

a. **Transcatheter aortic valve replacement (TAVR)** was first performed in 2002 and initially gained U.S. Food and Drug Administration (FDA) approval (2011) for severe aortic stenosis (AS) and prohibitive surgical risk, although now it has FDA approval (2019) regardless of surgical risk. The technology has evolved with lower profile catheter and delivery systems, wider range of valve sizes, more precise valve positioning, retrievable and repositionable features, and reduced paravalvular aortic regurgitation. Additionally, TAVR valves can be implanted within previously placed valves (valve-in-valve). In the United States, the Edwards SAPIEN, Medtronic Evolut, and Abbott Navitor valves are approved for commercial use (**Figure 18.2**).

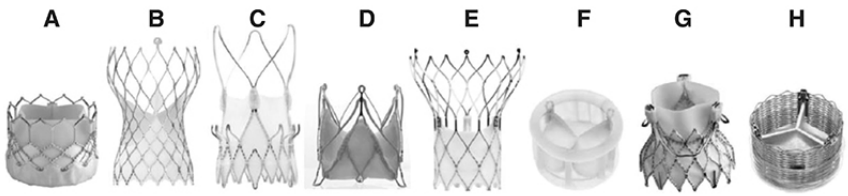


FIGURE 18.2 Transcatheter aortic valve systems. **A.** Edwards Lifesciences SAPIEN 3 valve (Edwards Lifesciences). **B.** Medtronic CoreValve Evolut R (Medtronic). **C.** Symetis Acurate *neo* valve (Symetis). **D.** JenaValve (JVT Research & Development Corporation). **E.** St. Jude Medical Portico valve (St. Jude Medical). **F.** Direct flow medical valve (Direct Flow Medical Inc). **G.** Medtronic Engager valve (Medtronic). **H.** Boston Scientific Lotus valve (Boston Scientific). Two transcatheter aortic valve replacement (TAVR) systems are approved by the U.S. Food and Drug Administration (**A** and **B**). (Adapted from Vahl TP, Kodali SK, Leon MB. Transcatheter aortic valve replacement 2016. *J Am Coll Cardiol*. 2016;67:1472-1487. Copyright © 2016 American College of Cardiology Foundation. With permission.)

b. Transcatheter mitral valve replacement (TMVR) has recently been approved (Edwards SAPIEN S3 valve, 2024) for placement within a surgically placed bioprosthetic mitral valve. Clinical trials for other TMVR valves implanted within bioprosthetic valves, rings, and mitral annular calcification are ongoing.

c. Transcatheter tricuspid valve replacement (TTVR) has also recently been approved (Edwards EVOQUE valve, 2024).

d. Transcatheter pulmonic valve replacement (TPVR) is most used in patients with congenital heart defects. The Melody valve (balloon-expandable) and Harmony valve (self-expanding) are the most common TPVR valves used.

B. Selection of valves. The selection of prosthetic heart valve type should be based on shared decision-making. **Table 18.4** summarizes the clinical factors that favor selection of a bioprosthetic versus a mechanical valve. The choice is largely dependent upon the age of the patient and the risks of anticoagulation therapy for a mechanical valve versus the risks of structural valve degeneration (SVD) and reintervention for biologic valves. Contemporary data to inform this

decision are observational. Importantly, patient preferences are emphasized, and there has been a shift toward using bioprosthetic valves.

TABLE 18.4 Clinical Factors Leading to Selection of a Bioprosthetic Versus a Mechanical Valve

Factors Favoring Bioprosthesis	Factors Favoring Aortic Homograft	Factors Favoring Mechanical Prosthesis
Age >65 y	Endocarditis	Age <50 y
High bleeding risk or inability to tolerate warfarin	Small aortic annulus in older patients	Combined multivalvular placement
High risk of trauma		Other indications for chronic anticoagulation
Poor medication compliance or inability to monitor INR levels		High risk for reoperation (eg, radiation heart disease)
Young woman considering pregnancy		Young woman completed childbearing

INR, international normalized ratio.

1. **Valve repair.** The feasibility of native valve repair instead of replacement should always be considered prior to surgery (**Table 18.5**). Currently, the greatest experience is with mitral valve repair. If feasible, mitral valve repair offers several potential advantages over replacement, including **preservation of LV function via conservation of the subvalvular apparatus, lower operative mortality, higher long-term survival rate, and freedom from anticoagulation**. An aortic valve with predominant regurgitation because of prolapse, but without severe stenosis or calcification, can also be repaired. Various open heart and catheter-based methods of mitral valve repair are as follows:

TABLE 18.5 Characteristics Favoring Valve Repair Versus Replacement

Favoring Valve Replacement	Favoring Valve Repair
Rheumatic valve disease	Mitral valve prolapse
Calcified and fibrosed valve	Excessive mitral valve leaflet mobility
Extensive leaflet destruction	Noncalcified bicuspid aortic valve with prolapse
Inexperienced surgeon	Aortic annular dilation with normal leaflets

a. **Leaflet repair with annuloplasty** typically involves quadrangular resection (triangular resection less common) of a portion of the posterior leaflet with reinforcement of the annulus with an annuloplasty band (can be complete/D-shaped, incomplete/C-shaped, rigid, semirigid, or flexible).

b. NeoChord attachment. Surgical attachment/reinforcement of the leaflet to the papillary muscles using prosthetic chord material

c. Valvuloplasty. Transcatheter expansion of a stenotic rheumatic mitral valve with a balloon to separate fused commissures

d. Mitral valve clip. Transcatheter placement of a device (MitraClip, PASCAL) that grasps the anterior and posterior leaflets

2. **Bioprosthetic valves** are indicated in patients with **a contraindication to chronic anticoagulation** and are preferred for older patients (**≥65 years for either aortic or mitral valve replacement**) because of reasonable durability, favorable hemodynamic profile, and freedom from chronic anticoagulation. Approximately 30% of heterograft bioprostheses fail within 10 to 15 years of implantation; 0-year rates of failure are inversely correlated with age: 40% in patients under 40 years, 20% in patients 50 to 59 years, and 10% in patients over 70 years. Overall complication rates for aortic bioprosthetic and mechanical valves are similar at 12 years, with a higher rate of reintervention for bioprosthetic valves and a higher rate of hemorrhage with mechanical valves. The advent of newer low-profile bioprostheses

and the apparent improved durability of later models have led to an increase in their use, especially in patients who wish to avoid anticoagulation. **Currently, for patients 50 to 65 years old, the choice of a bioprosthetic or mechanical valve is individualized**.

3. **Transcatheter aortic valve replacement**, as mentioned earlier, is now an option for patients with severe AS regardless of risk for open heart surgery. A comprehensive evaluation for procedural eligibility and candidacy is required including coronary angiography to exclude significant coronary artery disease and computed tomography (CT) angiography to size the aortic annulus and assess suitability of iliofemoral access.
4. **Homografts.** The main indication for an aortic valve homograft is **invasive endocarditis**, especially with an aortic root abscess, where the risk of reinfection is high. Durability was thought to be superior to that of heterografts, but recent studies have not confirmed this finding, and only 10% are still functioning after 20 years. The primary operation is more difficult with homografts, because the coronary arteries require implantation. Reoperation is also more complex, due to homograft calcification.
5. **Mechanical valves.** Mechanical valves have greater long-term durability than bioprosthetic valves. Mechanical prostheses are generally recommended for **younger patients** (≤50 years who require AVR and <65 years who require MVR) because of greater durability and for **patients already on permanent anticoagulation** for previous stroke or arrhythmia. The stroke risk of about 1% per annum for patients with a mechanical valve receiving appropriate anticoagulation management is similar to that for a bioprosthetic valve without anticoagulation. In **younger patients requiring combined aortic and mitral valve replacement**, mechanical valves may be preferred, given the more rapid rate of prostheses deterioration in the mitral position. **Pregnancy should be discouraged in patients with mechanical prostheses** because of the high risk to the mother and the fetus. Issues of **compliance with anticoagulation and risks of trauma** should be integrated into the selection of a mechanical valve.

C. Follow-up after valve surgery. There is a **wide spectrum of clinical practice** in the follow-up of the asymptomatic patient after valve surgery. An echocardiogram should be performed 4 to 6 weeks after implantation to establish a baseline for future reference. An echocardiogram is recommended for evaluation of change in symptoms. Annual echocardiography is reasonable **5 to 10 years after bioprosthetic surgery**. For **mechanical valves, anticoagulation** should be monitored regularly for life. **Endocarditis prophylaxis** is imperative for prosthetic valves, and patients should receive appropriate education.

D. Anticoagulation. Patients with mechanical prosthetic valves should receive a vitamin K antagonist, and oral direct thrombin inhibitors or anti-Xa agents should not be used. Current guidelines recommend a single target international normalized ratio (INR), with an acceptable window of 0.5 INR units, to minimize subtherapeutic and supratherapeutic levels. **Table 18.6** summarizes the recommended targets for anticoagulation therapy in patients with mechanical heart valves. The **embolic event rate is greater for mitral than for aortic** prostheses.

TABLE 18.6 Recommended Anticoagulation Therapy for Patients With Mechanical Prosthetic Valves

Prosthesis Type	Recommended INR
Aortic valve, mechanical bileaflet, or current generation single tilting disk without risk factors[a]	2.5
Mechanical aortic valve, with risk factors[b]	3.0
Mechanical mitral valve	3.0

INR, international normalized ratio.

[a]In patients with a mechanical On-X aortic valve replacement and no risk factors, a lower target INR of 1.5 to 2.0 may be reasonable.

[b]Risk factors include atrial fibrillation, previous thromboembolism, left ventricular dysfunction, hypercoagulable condition, or an older generation mechanical valve.

1. Immediate postoperative period

a. **Mechanical valves.** The approach to **postoperative anticoagulation** for mechanical prostheses varies widely. Early anticoagulation increases the risk of bleeding and tamponade. One approach is **warfarin, but not heparin, 3 to 4 days following surgery** when the epicardial wires are removed. Other centers recommend **low-dose intravenous heparin**, targeted for upper normal limits of activated partial thromboplastin time within 6 to 12 hours after valve replacement, and **full-dose intravenous heparin once the chest tubes are removed**. **Warfarin** is initiated within 24 to 48 hours following valve replacement. Chronic anticoagulation for mechanical valves is associated with rates of minor hemorrhage of 2% to 4% per year, major hemorrhage of 1% to 2% per year, and death of 0.2% to 0.5% per year. The bleeding risk is 5% to 6% in patients aged ≥70 years. Patient-related risk factors for thromboembolism are older age, atrial fibrillation, and LV dysfunction.

b. **Bioprosthetic valves.** The **need for anticoagulation** in bioprosthetic valves is **controversial**. The risk of embolism is greatest in the early postoperative period, declines after 3 months, and is greater for mitral (7%) compared with aortic valves (3%). In patients with a low risk of bleeding, anticoagulation with a goal INR of 2.5 is reasonable for 3 to 6 months following bioprosthetic AVR or MVR. Dual antiplatelet therapy (aspirin 75-100 mg daily and clopidogrel 75 mg daily) may be reasonable for 3 to 6 months after TAVR. After that period, aspirin monotherapy is employed.

2. **Management of anticoagulation in patients with prosthetic valves undergoing noncardiac surgery.** Although the risk of thromboembolism increases when anticoagulant therapy is briefly discontinued, the decision to suspend therapy should be individualized.

   a. For **major procedures** in which substantial blood loss is expected, **warfarin should be discontinued at least 3 days prior to the procedure** to achieve an INR of 1.6 or less.

Hospital admission for **intravenous heparin administration** is often recommended for patients with **caged ball prosthetic valves, atrial fibrillation, severe LV dysfunction, or previous embolization. Postoperatively**, intravenous heparin therapy should be **resumed when it is considered safe and continued until therapeutic anticoagulation is achieved with warfarin. Low-molecular-weight heparin (LMWH) may be considered for patients with prosthetic valves as bridging therapy**. Patients with contemporary bileaflet mechanical AVR and no other thromboembolic risk factors do not require perioperative bridging while INR is subtherapeutic.

b. For **minor procedures** (eg, dental extraction) where blood loss is minimal, anticoagulation can be continued.

c. Use of four-factor prothrombin complex concentrate (or active form) is reasonable for INR reversal in patients with mechanical prosthetic heart valves who require emergency surgery or procedures.

3. **Pregnancy**. Pregnant women have an increased incidence of thromboembolic complications, and there is no anticoagulation strategy that is consistently safe for mother and baby. Warfarin use is associated with the lowest risk of maternal complications, but highest risk of fetal complications. The use of warfarin through the entire course of pregnancy is associated with warfarin embryopathy in as many as 6.4% of live births. Given its teratogenic effects, **warfarin should be discontinued during the first trimester of pregnancy, especially if the dose is greater than 5 mg daily. However, with ≤5 mg of daily warfarin, the risk of embryopathy is low (<3%), and after careful discussion may be continued.** If warfarin is discontinued, **dose-adjusted LMWH** can be used during the first trimester with twice-daily dosing and target anti-Xa level of 0.8 to 1.2 U/mL 4 to 6 hours after the dose. **Anti-Xa monitoring is essential because the therapeutic dose can increase by 50% during pregnancy**. Alternatively, a continuous infusion of unfractionated intravenous heparin can be used. Warfarin is used in the second and third

trimesters, typically in conjunction with low-dose aspirin (75-100 mg). Prior to planned delivery, warfarin is discontinued, and continuous infusion of unfractionated heparin is used.

III. ASSESSMENT OF PROSTHETIC VALVES

A. Clinical presentation. The clinical presentations of prosthetic valve dysfunction can vary substantially. A discussion of the various entities is detailed in **Section IV**.

1. History. This should include a thorough cardiovascular review in addition to questions pertinent to the function of the prosthesis.

a. The **indication** for placement of valve prosthesis, **position** of implantation, **type** of prosthesis, and the **year of implantation** should be elicited. The model and size of the prosthesis can be verified by the identification card provided by the manufacturer.

b. Other important questions involve **compliance with anticoagulation**, previous **endocarditis, thromboembolism, fever**, and perceived **change in the quality of the valvular click**.

2. Physical findings

a. New murmur, muffled prosthetic valve sounds, or evidence of embolic events

b. Prosthetic valves are associated with **distinct auscultatory events caused by prosthesis motion or altered flow patterns**. The prosthesis sounds may mask the normal heart sounds; significant valvular dysfunction may occur without audible changes. However, familiarity with the normal auscultatory findings in the prosthetic valve examination can provide valuable clues on prosthesis dysfunction prior to a more definitive imaging examination. **Figure 18.3** summarizes the acoustic characteristics of common valve prostheses.

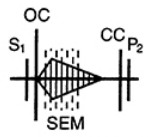
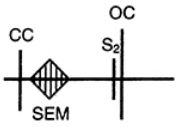
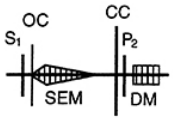
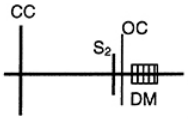
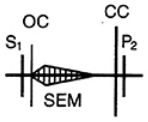
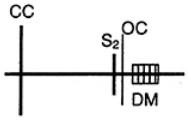
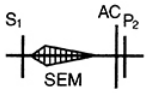
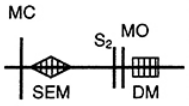
Type of valve	Aortic prosthesis		Mitral prosthesis	
	Normal findings	Abnormal findings	Normal findings	Abnormal findings
Caged ball (Starr-Edwards)		Aortic diastolic murmur Decreased intensity of opening or closing click		Low-frequency apical diastolic murmur High-frequency holosystolic murmur
Single tilting disk (Björk-Shiley or Medtronic-Hall)		Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Bileaflet tilting disk (St. Jude Medical)		Aortic diastolic murmur Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Heterograft bioprosthesis (Hancock or Carpentier-Edwards)		Aortic diastolic murmur		High-frequency holosystolic murmur

FIGURE 18.3 Acoustic characteristics of various mechanical and bioprosthetic valves. AC, aortic bioprosthetic closing sound; CC, closing click; DM, diastolic murmur; MC, mitral bioprosthetic closing sound; MO, mitral bioprosthetic opening sound; OC, opening click; P_2, pulmonary component of second heart sound; SEM, systolic ejection murmur; S_1, first heart sound; S_2, second heart sound. (From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med*. 1996;335:410, with permission from the Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

B. Diagnostic testing. The diagnosis of prosthetic valve dysfunction relies predominantly on echocardiographic findings, which can often identify degeneration prior to the onset of symptoms.

1. Two-dimensional echocardiography. Prosthetic valves have a variable degree of stenosis depending on valve type and size. Thus, it may be difficult to differentiate mild obstruction from valve design, SVD, or patient-prosthesis mismatch (PPM). Most mechanical valves and many biologic valves are associated with trace or mild transprosthetic regurgitation. The pattern of this "physiologic" regurgitation varies with the design of the replacement valve. The interrogation of the prosthetic valve requires a systematic approach to the prosthetic apparatus, peak

and mean gradients, and regurgitant flow. Oftentimes, **transesophageal echocardiography (TEE)** is performed to evaluate **symptomatic patients and patients with known or suspected endocarditis**. The two-dimensional (2D) assessment of prosthetic valves is similar to that of the native valve, but is **limited by reverberation artifacts and acoustic shadowing**. In general, echocardiographic evaluation should be done to assess the following:

a. **Occluders and leaflets.** Failure of the leaflet or occluder to open or coapt properly may result from **thrombus formation**, pannus ingrowth, or **calcification of bioprosthetic leaflets** (see Section **IV**). Imaging of leaflets and occluders may be suboptimal with transthoracic echocardiography (TTE). Multiplane TEE provides higher temporal and spatial resolution of the prosthesis than TTE and allows improved assessment of leaflet mobility and abnormalities. Although the aortic prosthesis is less well visualized relative to the mitral prosthesis, TEE still provides a better visual inspection of the posterior aspect of the prosthesis and perivalvular structures than TTE. Mechanical aortic valve leaflets can be difficult to assess when a mechanical mitral valve is also present.

b. **Sewing ring.** The orientation of the prosthetic valve in the annulus can be variable; however, **excessive motion** ("rocking") of the sewing ring is consistent with **dehiscence of the prosthesis**. Concomitant paravalvular regurgitation can be commonly identified with the use of color-flow mapping. Furthermore, adjacent echolucent structures identified in the evaluation of endocarditis may represent a pseudoaneurysm. In general, **flow into an adjacent echolucent space is pathologic**.

c. **Three-dimensional (3D) echocardiography.** 3D echocardiography is essential in the evaluation of prosthetic valves. Occluder motion and the sewing ring are often well evaluated, and the precise location of an abnormality relative to the sewing ring can be optimally demonstrated.

2. **Doppler evaluation.** Doppler evaluation complements the 2D examination and provides a **reliable indirect assessment of the prosthetic valve performance**. Pulsed-wave and continuous-wave Doppler are used to assess transvalvular gradients, from which EOAs can be derived.

   a. **Imaging planes for TTE.** Prosthetic mitral and aortic regurgitation can be visualized in the **parasternal long- and short-axis views**. Acoustic shadowing from the aortic and mitral prosthesis can interfere with the color-flow map in the proximal portion of the aortic and mitral regurgitant jets. **The apical views** allow assessment of transvalvular pressure gradients but may underestimate the size of the mitral regurgitant jets because of acoustic shadowing. Pulmonary vein flows may not be available for the same reason. **Prosthetic aortic regurgitation** is also characterized from the **apical window**.

   b. **Imaging planes for TEE.** On a short-axis view of the aortic valve (~40°), the origin of regurgitation (intravalvular or paravalvular) can be identified. The extent of the aortic regurgitant jet into the LV cavity can be visualized with a long-axis view (~120°). By systematically sweeping through the mitral valve from 0° to 120°, the origin and severity of mitral regurgitation are appreciated. Continuous-wave Doppler, usually at 0° and 120°, is used to measure the peak and mean gradients across the prosthesis.

      (1) Continuous-wave Doppler evaluation of the **aortic valve** is performed with a deep transgastric view using anteflexion to bring the aortic valve in line for Doppler interrogation.

      (2) Continuous-wave Doppler can also be used to assess **mechanical prosthetic regurgitation**. Advantages of continuous-wave Doppler include excellent temporal resolution to allow identification of specific periods in the cardiac cycle and the ability to indicate the severity of a regurgitant jet by its signal intensity. Using 2D images and the color-flow map as a guide, continuous-wave Doppler

allows interrogation of different parts of the prosthesis and can help to detect eccentric jets.

c. Normal Doppler findings

(1) Prosthetic valve clicks. The opening and closure of mechanical valve leaflets create a brief intense Doppler signal that appears as a narrow band on the spectral display.

(2) Prosthetic valve velocities/pressure gradients. The systolic spectral Doppler contour is frequently triangular, with an earlier systolic peak velocity. The expected normal velocities and pressure gradients for commonly used prosthetic valves are presented in **Table 18.7**. However, there is a large variability in these numbers depending on flow and other factors. Therefore, a postoperative baseline study is necessary for patients with prosthetic valves.

(3) Physiologic prosthetic valve regurgitation. Many prosthetic valves have regurgitant flow characterized by uniform color without aliasing. For a mechanical prosthesis, the physiologic prosthetic regurgitant flow typically has a regurgitant jet area of <2 cm^2 and jet length of <2.5 cm in the mitral position and a jet area of <1 cm^2 and jet length of <1.5 cm in the aortic position.

TABLE 18.7 Normal Doppler Values of Prosthetic Valves

Prosthetic Valve	Peak Velocity (m/s)	Mean Gradient (mm Hg)
Aortic Position		
Starr-Edwards	3.1 ± 0.5	24 ± 4
Björk-Shiley	2.5 ± 0.6	14 ± 5
St. Jude	3.0 ± 0.8	11 ± 6
Medtronic-Hall	2.6 ± 0.3	12 ± 3
Aortic homograft	0.8 ± 0.4	7 ± 3
Hancock	2.4 ± 0.4	11 ± 2

Prosthetic Valve	Peak Velocity (m/s)	Mean Gradient (mm Hg)
Carpentier-Edwards	2.4 ± 0.5	14 ± 6
Mitral Position		
Starr-Edwards	1.8 ± 0.4	5 ± 2
Björk-Shiley	1.6 ± 0.3	5 ± 2
St. Jude	1.6 ± 0.3	5 ± 2
Medtronic-Hall	1.7 ± 0.3	3 ± 1
Hancock	1.5 ± 0.3	4 ± 2
Carpentier-Edwards	1.8 ± 0.2	7 ± 2

Modified from Nottestad SY, Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM, ed. *The Practice of Clinical Echocardiography*. WB Saunders; 1997:803. Copyright © 1997 Elsevier. With permission.

d. Assessment of prosthetic valve dysfunction

(1) Prosthetic valve stenosis

(a) Transvalvular gradients. Assessment of transvalvular gradients is the mainstay of the Doppler evaluation. **Each prosthetic valve is inherently stenotic and thus has a higher than normal peak velocity across it**. The postoperative continuous-wave Doppler gradient across the prosthesis serves as a baseline for subsequent evaluations. High gradients may also be obtained in nonobstructive situations, such as high-output states, tachycardia, anemia, severe prosthetic leaks, or from the pressure recovery phenomenon. Pressure recovery occurs secondary to flow acceleration through a narrowed orifice, especially in the central orifice of a bileaflet valve in the aortic position. In this setting, the highest pressure measured through the prosthesis by Doppler overestimates the true pressure gradient by approximately one-third, and manufacturers consider pressure recovery when determining normal gradients.

(b) Valve area calculations. Calculation of orifice area in prosthetic valves is difficult given the complexity of the orifice (struts/disks), especially in mechanical prostheses. The following methods have been used to approximate orifice area:

i. Continuity equation. The continuity equation can be used to estimate the EOA of prosthetic aortic and mitral valves. For calculation of the prosthetic valve area in the aortic position,

$$\text{Area}_{\text{aortic prosthesis}} = (\text{LVOTd})^2 \times 0.785$$

$$\text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{aortic prosthesis}}$$

where TVI is time-velocity integral.

The aortic prosthesis TVI is determined from continuous-wave Doppler velocity through the prosthesis. Left ventricular outflow tract (LVOT) TVI is determined by pulsed-wave Doppler.

Mitral valve prosthesis TVI is determined from continuous-wave Doppler. For the mitral position,

$$\text{Area} = (\text{LVOT diameter})^2 \times 0.785 \times \text{TVI}_{\text{LVOT}}/\text{TVI}_{\text{mitral prosthesis}}$$

ii. Pressure half-time (PHT). For a mitral valve prosthesis, the PHT method is useful for assessing prosthetic valvular stenosis, especially in comparison to prior values obtained at similar heart rates, although it does not accurately estimate EOA. The PHT can help determine whether increased velocity is secondary to increased flow or to obstruction. If the peak velocity is increased but the PHT is not prolonged, then the increased velocity is most likely due to increased forward flow.

iii. Dimensionless index. The LVOT and aortic valve prosthesis velocity ratio is the most helpful index for the evaluation of prosthetic valve stenosis, especially in the absence of a

reliable LVOT diameter. The higher the index, the larger the EOA, and a normal aortic prosthesis has a ratio ≥0.30 to 0.35. A value ≤0.25 suggests prosthesis stenosis:
Dimensionless index = $Velocity_{LVOT}/Velocity_{aortic\ prosthesis}$ OR $TVI_{LVOT}/TVI_{aortic\ prosthesis}$
where TVI is time-velocity integral.

(2) Pathologic prosthetic valve regurgitation is larger and wider than that seen with physiologic regurgitation. Pathologic regurgitation may be related to calcified and fibrosed leaflets, disruption of the sutures securing the valve, or a perivalvular abscess with adjacent tissue destruction.

(a) Severe prosthetic mitral regurgitation is suggested by increased peak early diastolic velocity (>1.2 m/s) and normal mitral inflow PHT (≤150 m/s) (see Chapter 16).

(b) Severe prosthetic aortic regurgitation is usually present when there is diastolic flow reversal in the descending thoracic or abdominal aorta (see Chapter 15).

(3) Cinefluoroscopy. Cinefluoroscopy is useful for assessing **mechanical prosthetic valves**. The image intensifier is moved to a position with x-rays parallel to the valve ring plane to determine the occluder's excursions in a caged valve. Despite the radiolucency of pyrolytic carbon disk valves, the opening angle can be measured from positioning the image intensifier parallel to the plane of the open leaflets. **The mitral prosthesis is best visualized from the right anterior oblique (RAO) cranial projections. The aortic prosthesis can be viewed from RAO caudal or left anterior oblique cranial projection**. Diminished motion of the disks suggests valve obstruction, whereas excessive rocking of the base ring suggests partial dehiscence of the valve.

(4) **Cardiac catheterization. Invasive assessment** of the left ventricle can be performed safely in patients with bioprosthetic aortic valves. However, catheter-based evaluation of the mechanical aortic valves should be performed with a transseptal technique. Transseptal access may also be necessary for accurate measurement of prosthetic mitral valve gradients, because catheter-based assessment overestimates the mitral valve gradient because of a dampening of the pressure contour and intrinsic delay in the pulmonary capillary wedge tracing.

(5) **Magnetic resonance imaging** can be performed safely in patients with most prosthetic valves, because they are not ferromagnetic, but **imaging susceptibility artifacts** often preclude assessment of prosthetic valve leaflets. However, dedicated sequences can provide information about **blood flow velocities** and **regurgitant volumes/fractions, along with chamber quantification**.

(6) **Multislice gated cardiac CT with retrospective image acquisition (4D CT)** allows adequate evaluation of prosthetic leaflet motion and abnormalities of both bioprosthetic and mechanical valves. Like cinefluoroscopy, 4D CT can be used to measure opening and closing angles of mechanical valves. In addition, 4D CT can assess bioprosthetic leaflet thickening, thrombosis, and calcification. Unlike echocardiography, 4D CT displays only a single heart cycle.

IV. VALVE DYSFUNCTION AND COMPLICATIONS RELATED TO PROSTHETIC VALVES.

The Valve Academic Research Consortium has provided endpoint definitions and classification of prosthetic valve dysfunction. The classes of valve dysfunction are: structural, nonstructural, thrombosis, and endocarditis. (Note: Valve Academic Research Consortium [VARC] specifically addresses bioprosthetic heart valves.)

A. Structural valve degeneration (SVD) is defined as deterioration in bioprosthetic leaflets or supporting structures, not related to thrombus

or endocarditis, which eventually results in hemodynamic dysfunction. These include leaflet disruption, leaflet fibrosis or calcification, and strut fracture. As valves age, bioprosthetic SVD is expected and may manifest as stenosis, regurgitation, or both. SVD is usually gradual and due to the deposition of calcium on the leaflets. However, leaflet tears may produce a sudden clinical deterioration with the onset of severe regurgitation. Indications for reintervention are similar to those for native valve lesions, although repeat intervention is reasonable in asymptomatic patients with severe regurgitation given that further dysfunction could result in rapid clinical deterioration.

1. Failure of the current generation of mechanical prostheses is rare but may precipitate sudden hemodynamic compromise. Catastrophic failure occurs when a strut holding the occluder breaks, allowing the occluder to embolize, resulting in overwhelming regurgitation. Strut failure has been reported most commonly with the Björk-Shiley valve and results from fatigue of a metal weld.
2. In older ball-in-cage prostheses, ball variance, a structural deterioration of the occluder, can occur, giving rise to impaired occluder motion, sticking, and thromboembolism. This is rarely seen nowadays with improved prosthetic materials.

B. Nonstructural valve dysfunction is an abnormality, not intrinsic to the prosthetic valve. Paravalvular regurgitation and PPM are the most common causes. Others include leaflet entrapment by pannus formation or suture material, inappropriate positioning, or postoperative aortic root dilation.

1. **Paravalvular regurgitation**.
   a. **Paravalvular leak** (PVL) is regurgitation between the native valve annulus and the prosthetic valve annulus classified as mild (<10% of the circumference of the valve annulus), moderate (>10% and <30%), or severe (>30%). Closure is indicated for severe PVL with intractable heart failure symptoms or hemolysis. Repair is typically performed with transcatheter-placed plugs.

b. Dehiscence is detachment of the sewing ring from the annulus and may occur in the early postoperative period because of poor surgical techniques, excessive annular calcification, chronic steroid use, fragility of the annular tissue (particularly following prior valve operations), or infection. Late dehiscence occurs mainly from infectious endocarditis. Abnormal rocking of the prosthesis on echocardiography is an indication for urgent surgery.

2. **Patient-prosthesis mismatch (PPM).** All prosthetic valves, with the exception of aortic homografts, have effective orifices that are smaller than those of native valves. There is an inherent pressure gradient and relative stenosis with each prosthesis. Occasionally, when an inappropriately small prosthesis is placed, the low EOA may cause symptoms. PPM is considered moderate if indexed valve EOA is ≤ 0.85 cm^2/m^2 and >0.65 cm^2/m^2, or severe if <0.65 cm^2/m^2. The impact and prevalence of PPM are controversial. Depending on the definition, this mismatch may occur between 20% and 70% of cases after aortic valve replacement. It has been shown in some series to be associated with worse hemodynamic function, less regression of LV hypertrophy, more cardiac events, and lower survival. Unlike most of the other risk factors, PPM can be avoided or severity lessened by putting in place a prevention strategy at the time of the operation. It is rare that PPM occurs to a degree that surgical explantation is necessary.

   Some important points to consider:

- The projected indexed EOA should be systematically calculated at the time of the operation to estimate the risk of PPM.
- In a patient with a small annulus, a hemodynamically favorable prosthesis like a stentless bioprosthesis, aortic homograft, or a tilting disk valve is preferred. Alternatively, the aortic annulus may be enlarged surgically to accommodate a prosthesis of acceptable size.
- Aortic prostheses <21 mm in diameter are not recommended for a large or physically active patient.

C. Thrombosis. Mechanisms of prosthetic valve dysfunction are highlighted in **Figure 18.4**. The annual incidence of mechanical prosthetic valve thrombosis is 0.1% to 5.7%. The incidence is highest in the tricuspid position, followed by the mitral and then the aortic position. Thrombus is suspected in patients with an acute onset of symptoms, an embolic event, or inadequate anticoagulation. Thrombosis at bioprostheses is uncommon but may also occur.

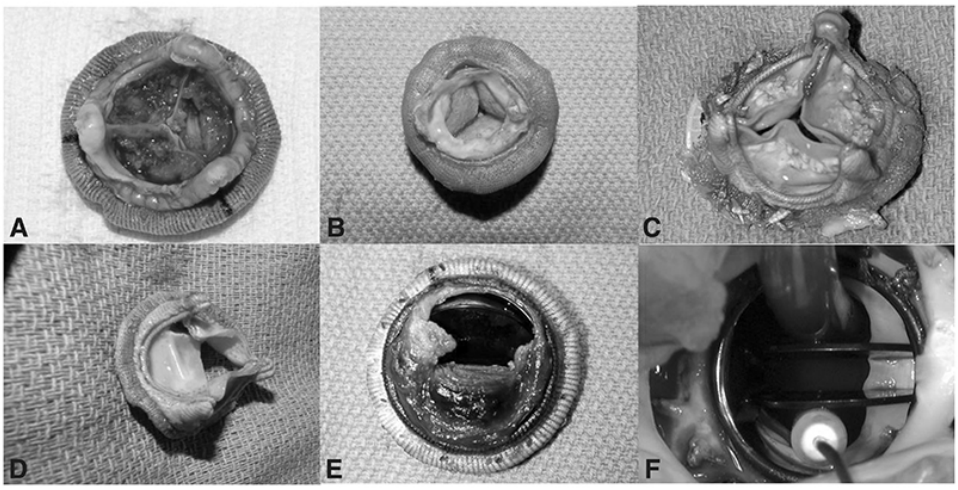


FIGURE 18.4 Modes of prosthetic valve dysfunction. **A.** Layering thrombi on the nonflow side of stented bioprosthesis. **B.** A ring of pannus on the flow side (subvalvular) of a stented bioprosthesis. **C.** Nodular cuspal calcifications of a stented bioprosthesis. **D.** Leaflet teat of a stented bioprosthesis. **E.** Thrombosed bileaflet mechanical valve. **F.** Subvalvular pannus ingrowth of a bileaflet mechanical valve. (Photos courtesy of Gosta B. Pettersson.)

1. **Laboratory examination and diagnostic testing**. TEE and 4D CT are also useful for evaluating leaflet thickening and motion. CT assessment for hypoattenuating leaflet thickening (HALT) should be considered when transvalvular gradients on echo rise earlier than expected. 4D CT or cinefluoroscopy can also be used to document restriction in occluder mobility. Echocardiographic features suggestive of thrombus include an irregular and mobile mass.
2. **Therapy**

a. Medical therapy

(1) Fibrinolytic therapy is considered the treatment of choice for right-sided prosthetic valve thrombosis because the consequences of distal embolization are less severe than in left-sided prosthesis. Low-dose, slow-infusion fibrinolytic therapy under echocardiographic guidance has been shown to have >90% hemodynamic success rates with both embolic and major bleeding event rates <2%. Therefore, systemic fibrinolysis is also acceptable therapy for left-sided heart valve thrombosis for patients with high surgical risk of reoperation, small thrombus burden, and low bleeding risk.

(a) Slow-infusion, low-dose fibrinolytic regimens with 25 mg tissue plasminogen activator (tPA) without bolus over 6 hours and repeated after 24 hours as needed have been associated with low embolic and bleeding rates and successful thrombolysis in >90%.

(b) Ultraslow fibrinolytic therapy with 25 mg tPA infusion over 25 hours (1 mg/h) without initial bolus has also been shown to be >90% successful.

(c) Thrombolysis should be stopped if there is no hemodynamic improvement after 24 to 72 hours. TEE is useful in the assessment of progress.

(2) Following successful thrombolysis, close follow-up of anticoagulation along with serial Doppler echocardiography is recommended.

(3) Anticoagulation with heparin and warfarin is generally recommended for a small thrombus (≤5 mm). The regimen consists of intravenous heparin followed by warfarin.

b. Surgery. The lowest surgical mortality reported has been approximately 5%. The risk profile of the individual patient must be balanced against the expertise and experience at each center.

(1) Valve replacement and debridement are generally preferred for left-sided prosthetic valve thrombosis, unless the thrombus is small or the patient has a prohibitive surgical risk.

(2) Surgery is also indicated in the case of unsuccessful thrombolysis 24 hours following discontinuation of the infusion.

D. Endocarditis. Approximately 3% to 6% of patients with prosthetic heart valves will experience prosthetic valve endocarditis.

1. Early prosthetic valve endocarditis (<60 days following implantation) is typically caused by *Staphylococcus epidermidis*.
2. Late prosthetic valve endocarditis has a microbiology similar to community-acquired native valve endocarditis.
3. **TEE is the imaging modality** of choice, with sensitivity of 95% and specificity of 90% in diagnosis. TEE is also useful in detecting invasive complications such as abscess, valve dehiscence, and fistula formation.
4. **Medical therapy.** Medical cure for prosthetic valve endocarditis caused by **staphylococci, gram-negative organisms, or fungi is rare. Streptococcal** prosthetic valve endocarditis responds to medical therapy alone in **50% of cases**. A high index of suspicion should be maintained for the presence of residual infection, and surgical reevaluation should be considered if medical treatment fails.
5. **Surgical therapy.** Valve replacement surgery is indicated in the setting of:
   - Persistent bacteremia despite intravenous antibiotics
   - Tissue invasion or fistula formation
   - Recurrent embolization
   - Fungal infection
   - Prosthesis dehiscence or obstruction
   - New or worsening heart block
   - **New-onset or worsening** congestive heart failure

E. Other valve-related complications

1. **Atrial fibrillation.** Up to 50% of patients undergoing valve surgery experience postoperative atrial fibrillation. Management of atrial fibrillation is discussed elsewhere. In patients without a previous history of atrial fibrillation, the arrhythmia is often self-limited. For patients with persistent atrial fibrillation beyond 24 hours, anticoagulation, direct current cardioversion, and a short course of antiarrhythmic therapy can be considered.
2. **Conduction disturbances.** High-grade heart block requiring permanent pacemaker implantation has been described in 2% to 3% of patients after valve replacement and 8% following repeat valve surgery. It is caused by trauma to the bundle of His or from postoperative edema of the periannular tissue. Aortic or mitral annular calcification, preoperative conduction disturbance, advanced age, and infectious endocarditis are associated with higher rates of postoperative conduction abnormalities, leading to permanent pacemaker implantation.
3. **Hemolysis.** Subclinical hemolysis is present in many patients with mechanical valves but **rarely results in significant anemia**.
   a. **Pathophysiology and etiology.** Clinical hemolysis occurs in 6% to 15% of patients with **caged ball valves** but is uncommon with normal bioprosthetic or tilting disk valves. Clinical hemolysis is also associated with **multiple prosthetic valves, small prostheses, periprosthetic leaks, and prosthetic valve endocarditis**. Mechanisms involved in the generation of hemolysis include high shear stress or turbulence across the prosthesis, interaction with foreign surfaces such as cloth, and rapid deceleration of erythrocytes following collision with adjoining structures (eg, struts or cardiac walls).
   b. **Laboratory examination and diagnostic testing**

      Diagnosis is made by **elevated lactate dehydrogenase, reticulocyte count, unconjugated bilirubin, urinary myoglobin**, and presence of **schistocytes on blood smear**. Echocardiographic findings consistent with mechanical hemolysis include **abnormal rocking of the prosthesis or**

regurgitant jets of high shear stress (eg, eccentric or periprosthetic regurgitant jets or those impacting a solid surface such as the left atrial appendage or sewing ring).

c. Therapy

(1) Medical therapy. Mild hemolytic anemia can be managed with **iron, folic acid supplement, and, if needed, blood transfusion**. Paradoxically, treatment of the anemia may reduce the degree of hemolysis by limiting the need for high flow through the defective valve.

(2) Surgical therapy. Repair of perivalvular leaks or valve replacement is indicated in **patients with severe hemolysis requiring repeated transfusions or in those with congestive heart failure**. Percutaneous approaches can also be considered but are not feasible with extensive dehiscence or when there is active infection.

4. Embolic stroke. Following an embolic stroke, the risk of recurrent stroke is approximately 1% per day for the first 2 weeks. If no evidence of hemorrhage is detected on CT scan at 24 to 48 hours, **intravenous heparin** may be administered after a small to moderate embolic stroke. **Maintaining anticoagulation** reduces the risk of recurrent stroke to one-third but **carries an increased risk of hemorrhagic transformation** of 8% to 24%, particularly during the first 48 hours. In patients with **larger infarcts, anticoagulation is generally withheld for 5 to 7 days**.

Anticoagulation is withheld for 1 to 2 weeks in the setting of **hemorrhagic transformation** based on recommendations from neurosurgical and neurology consultants. **Reoperation with placement of a bioprosthetic valve** may be needed for recurrent embolization.

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CHAPTER 19

Infective Endocarditis

Gregory Ogunnowo and Bo Xu

I. INTRODUCTION

A. Infective endocarditis (IE) is **an infection of the cardiac endothelium** but can also involve **intracardiac devices (including permanent pacemakers and implantable cardioverter-defibrillators) and prosthetic valves**. Macroscopically, this is manifest as vegetations. Despite modern medical and surgical therapy, IE is a serious and life-threatening condition. Mortality rates are 20% to 30% for both native and prosthetic valve endocarditis (PVE) and may be as high as 70% in certain high-risk patients. The clinical diagnosis is based on multiple elements, and **IE is best managed via multidisciplinary collaboration among cardiologists, cardiothoracic surgeons, and infectious disease specialists**. In addition, guidelines recommend involvement of cardiac anesthesiologists for surgically managed patients as well as neurologists for patients with neurologic complications.

B. The incidence of IE has increased since 2000, with approximately 3 to 14 cases per 100,000 person-years in most population-based studies. The in-hospital mortality for IE is 15% to 20%, with a 1-year mortality rate approaching 40%. An estimated 10,000 to 15,000 new cases of IE are diagnosed each year in the United States, and the incidence has increased in older patients and illicit injection drug users. There has also been an increase in the number of acute cases, prosthetic valve infections, because of gram-negative, rickettsial, chlamydial, fungal, and fastidious organisms.

C. Risk factors associated with infection include underlying cardiac structural abnormalities (congenital heart disease, history of rheumatic valve disease, degenerative valve disease, myxomatous

valve disease), intravenous drug use (IVDU), presence of prosthetic intracardiac material, immunosuppression, prolonged surgery, reoperation, catheter-related bacteremia, sternal wound infection, and history of previous IE.

II. CLINICAL PRESENTATION

A. Signs and symptoms. The clinical manifestations of IE are highly variable and influenced by factors such as virulence of the infecting organism and persistence of bacteremia, extent of local tissue destruction of the involved valve(s) and hemodynamic sequelae, perivalvular extension of infection, septic embolization to organs, and consequences of circulating immune complexes. Clinical presentation based on these factors ranges from subtle symptoms to severe valvular regurgitation and cardiogenic shock. **Acute IE** presents as a rapidly progressive infection associated with marked toxicity that can progress to valvular destruction and metastatic infection over several days to weeks. **Subacute IE** evolves over several weeks to months with mild or modest toxicity and less commonly causes metastatic infection. The rate of progression depends upon the virulence of the causative organism, age and underlying health of the patient, and nature and extent of the underlying valvular disease.

1. The **hallmarks of IE are fever and a new murmur**. Fever (>38 °C) is the most common presenting symptom in up to 95% of patients. However, fever may be absent in up to 20% of patients, namely, those who are older, uremic, patients treated with empiric antibiotics, patients with cardiac implantable electronic device (CIED) infections, or immunosuppressed. Fever typically resolves within 5 to 7 days of appropriate antibiotic therapy; however, persistence of fever may suggest perivalvular extension (abscess, pseudoaneurysm), septic embolization, antibiotic resistance, or extracardiac site of infection.
2. The patient often has nonspecific constitutional symptoms of fatigue, weight loss, malaise, chills, night sweats, and/or musculoskeletal aches.

3. The patient may also develop dyspnea. This is an important symptom to recognize as it may reflect a hemodynamically significant lesion, usually a left-sided valvular lesion. This symptom in conjunction with paroxysmal nocturnal dyspnea and orthopnea also suggests ensuing heart failure.
4. The patient may also present with pain syndromes as a consequence of septic embolization (eg, pleuritic chest pain from tricuspid valve IE, angina pectoris from coronary embolization).

B. Physical examination findings

1. A new murmur remains an important finding (85% of patients). Murmurs may be soft or absent with right-sided or mural infections or intracardiac device infections.
2. Congestive heart failure (CHF) occurs in up to 55% of cases and tends to be more common in those with aortic valve disease (75%) than in those with mitral (50%) or tricuspid (20%) valve involvement.
3. Neurologic findings may include stroke due to emboli (20%), encephalopathy (10%), mycotic aneurysm leak (<5%), meningitis, or brain abscess (<5%).
4. Additional physical findings reflecting **embolic or immune complex phenomena** include mucosal **petechiae** (20%-40%), **splinter hemorrhages** (subungual dark linear streaks: 10%-30%), **Osler nodes** (painful, tender erythematous nodules on the pads of fingers or toes: 10%-25%), **Janeway lesions** (erythematous, macular, nontender lesions on the fingers, palms, or soles: <5%), **clubbing** (10%-20%), **arterial embolism** (peripherally or centrally), **splenomegaly** (30%-50%), and **Roth spots** (retinal hemorrhages: <5%). These classic physical findings are **neither sensitive nor specific** for the diagnosis of IE, and their frequency is continuing to diminish because of a decrease in *Streptococcus* viridans IE and an increase in *Staphylococcus aureus* IE.
5. A formal **fundoscopic examination** should be routine in all patients with suspected or documented IE. It may reveal **chorioretinitis or endophthalmitis**.

6. **Systemic** embolization occurs in 25% to 50% of cases of IE and may mimic acute coronary syndrome (coronary artery emboli), peritonitis (embolization to the spleen, kidney, or bowel), acute stroke (cerebral emboli), and pulmonary embolism (from right-sided IE) or cause a cold extremity with reduced or absent pulse. Septic emboli may also cause Janeway lesions.

III. ETIOLOGY.

Table 19.1 presents the various etiologic factors.

TABLE 19.1 Frequency of Organisms Causing Infective Endocarditis

Organism	NVE (%)	IDU (%)	Early PVE (%)	Late PVE (%)
Streptococci	60	15-25	5	35
Viridans *Streptococcus*	30-40	5-10	<5	25
Streptococcus bovis	10	<5	<5	<5
Enterococci	10	10	<5	<5
Staphylococci	25	50	50	30
Coagulase positive	23	50	20	10
Coagulase negative	<5	<5	30	20
Gram negative (aerobes)	<5	5	20	10
Fungi	<5	<5	10	5
Culture negative	5-10	<5	<5	<5

IDU, intravenous drug use; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.
Data from Fuster V, Harrington RA, Jagat N, eds. *Hurst's the Heart*. 14th ed. McGraw Hill; 2017.

A. **Seventy percent to 75% of patients with IE have preexisting cardiac abnormalities. Mitral valve prolapse with regurgitation is the leading condition** underlying IE in adults. Rheumatic heart disease as a substrate for IE is decreasing, with congenital heart disease underlying 10% to 20% of IE cases. The most common congenital heart anomalies predisposing to IE are bicuspid aortic valve, patent ductus arteriosus, ventricular septal defect, coarctation

of the aorta, and tetralogy of Fallot. There is **no evidence** that the presence of secundum atrial septal defects increases the risk of IE.

B. The source of infection can only be identified occasionally (eg, dental procedures, an infected vascular catheter, or an infected skin lesion). In many patients, there is no history of an antecedent localized infection. Endocarditis is classified according to whether the native or prosthetic valve is affected and by the timing of infection after valve intervention.

C. Native valve endocarditis (NVE)

1. **The most common microorganisms** that cause native valve IE in adults are caused by **gram-positive cocci** (80%), namely, streptococcal (30%-40%) and staphylococcal (35%-40%) organisms. Viridians group *Streptococcus, Streptococcus mutans*, and *Streptococcus sanguinis*, for example, are the most common causes of community-acquired native valve IE and typically have a subacute presentation. *Staphylococcus aureus* can cause both native and prosthetic valve IE and typically has an acute presentation.
   - **a.** *Streptococcus pneumoniae* accounts for 1% to 3% of native valve IE, and it may present as part of the **"Osler triad,"** which also includes pneumococcal pneumonia and meningitis. Alcoholics are typically affected, and the mortality rate is high (30%-50%).
   - **b.** Although **coagulase-negative Staphylococcus species typically cause PVE, they can occasionally cause native valve IE as well**. Namely, two species to make note of are *Staphylococcus lugdunensis* and *Staphylococcus epidermidis*. *S. lugdunensis* is a rare but destructive cause of IE with aggressive nature and predilection for native valves. *S. lugdunensis* IE portends a high complication and mortality rate without surgical intervention. *Streptococcus epidermidis is the most commonly identified species to cause bacteremia and IE.*
   - **c.** *Streptococcus gallolyticus* (formally known as *Streptococcus bovis*). IE is often associated with colonic polyps and colon cancer; as such, a colonoscopy is recommended for patients

with positive blood cultures. Fungi and, rarely, aerobic gram-negative bacilli are seen in isolated cases.

d. **IE in injection drug users** is on the rise because of the epidemic of opioid abuse. It is **most commonly because of S. aureus** (60%), with a predilection for normal and abnormal cardiac valves. The valve most commonly affected in injection drug users is the tricuspid valve (60%-70% of cases), followed by the mitral (30%-40%) and aortic valves (5%-10%). More than one valve is involved in 20% of these patients. Despite the virulence of this organism, the disease tends to be **less severe** (mortality rates of 2%-6%) than with left-sided IE. Septic pulmonary emboli occur in up to 75% of injection drug users with tricuspid IE.

e. The HACEK group, accounting for approximately 3% of cases, includes fastidious gram-negative organisms that are normal flora in the upper respiratory tract. **HACEK organisms include** *Aggregatibacter aphrophilus* [formally *Haemophilus*], *Aggregatibacter* [formally *Actinobacillus*], *Cardiobacterium*, *Eikenella*, and *Kingella*. The diagnosis is usually delayed in this group because these organisms require several days of incubation.

f. Enterococcal IE is increasing in prevalence as well. The diagnosis must be considered in patients who have undergone recent genitourinary or obstetric procedures; these patients may not have underlying heart disease. **The most common organism causing IE in this group is Enterococcus faecalis**. Of note, patients with advanced age are at risk for developing IE from this organism. Other members of the Enterobacteriaceae (*Escherichia coli*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, *Citrobacter*, *Shigella*, and *Yersinia*) are occasionally implicated in IE. More recently, with increased health care exposure, **multidrug-resistant enterococcal species have been identified as causes of IE**, namely, *Enterococcus faecium* and vancomycin-resistant

Enterococcus (VRE). This typically has a subacute presentation.

g. Culture-negative endocarditis is most often designated when there is no obvious pathogen identified from blood cultures. Most often, this is due to recent exposure to antibiotics or pathogens that do not grow in routine blood culture media or slow growth. Organisms that have also been associated with culture-negative IE are fungi and intracellular bacteria, including *Coxiella burneti*i (often infects previously damaged valves or prosthetic valves), *Bartonella* spp. (*henselae* species associated with exposure to cats), *Brucella* spp., *Mycoplasma* spp., *Tropheryma whipplei* (this organism can be identified using periodic acid-Schiff staining of macrophages or polymerase chain reaction [PCR]), *Chlamydial* spp., *Cutibacterium* spp. (previously known as *Propionibacterium*), nutritionally variant streptococci, and *Legionella* spp.

h. **Nonbacterial endocarditis** (Libman-Sacks, marantic, and antiphospholipid syndrome) should also be considered in cases of culture-negative IE. Care should be taken to differentiate bacterial vegetations from myxomas, papillary fibroelastomas, rheumatoid nodules, inflammation involving degenerative valvular lesions, Lambl excrescences, and nonbacterial endocarditis

i. Less often, fungi can be identified as a cause of nonbacterial native valve IE. Fungal endocarditis of native valves tends to cause larger vegetations than bacterial infections, whereas in Q fever vegetations are often absent. **It is essential to interpret images in conjunction with clinical data**.

D. **PVE** accounts for about 10% to 20% of all cases of IE. The greatest risk of infection is in the first 6 months after valve implantation and appears to be **similar in mechanical and bioprosthetic valves**. Recent studies have suggested that infection occurs with similar frequencies at the mitral and aortic positions. Risk factors for surgical PVE included prolonged cardiopulmonary bypass, sternal wound infection, and multiple surgeries.

1. PVE occurring within 2 to 6 months of surgery (early PVE) is commonly associated with intraoperative contamination, hematogenous spread, and nosocomial infection, and this usually implicates **coagulase-negative staphylococci** (30% of cases). The second most common pathogen in early PVE is *S. aureus* (20% of cases). Early after valve implantation, the valve sewing ring, cardiac annulus, and anchoring sutures have not been covered with endothelium, but instead are coated with fibronectin and fibrinogen. These host proteins serve as surfaces for microorganisms to adhere, facilitating direct access to the prosthesis-annulus interface. Paravalvular abscesses are, therefore, commonly associated with early PVE.
2. The microbiology of PVE with an onset of more than 6 months after surgery (late PVE) reflects the pathogens of native valve IE. After 6 months, the sewing ring, sutures, and adjacent tissues become endothelialized following valve replacement. This alters surface flow dynamics, facilitating the deposition of microthrombi, which serve as a surface for microorganisms to adhere to. Late PVE is most commonly caused by streptococcal species, *S. aureus*, and *Enterococcus*. Coagulase-negative staphylococci cause <20% of infections in this period. Fungi account for 10% to 15% of late PVE cases and are associated with a higher mortality rate. Establishing the diagnosis of fungal PVE can be difficult because of the low yield from blood cultures. Despite aggressive antifungal therapy, these patients remain at risk for the development of PVE months or years later. *Corynebacterium* species and other coryneform bacteria, often called diphtheroids, are also the important causes of PVE during the first year after surgery (5%). Although they are often blood culture contaminants, diphtheroids in multiple cultures should not be ignored.
3. Increasingly prosthetic infections are being recognized as having a **biofilm** around them that insulates them from antibiotics within the bloodstream. Disruption of the biofilm mechanically by surgery is seen as necessary to eradicate the infection. There have

been reports of a mycobacterium (*Mycobacterium chimaera*) causing endocarditis after open heart procedures and especially after prosthetic valve implantation. The offending organism was associated with contaminated heater-cooler systems of the cardiopulmonary bypass circuit. *M. chimaera* requires molecular fingerprinting for detection.

4. As technology advances, transcatheter aortic valve replacement (TAVR) is increasingly used to address aortic valve disease. IE associated with TAVR is a serious complication associated with increased mortality. Early TAVR PVE during the periprocedural period has been associated with *Enterococcus*. As with surgical PVE, *Staphylococcus* and *Streptococcus* have a predilection for TAVR valves, causing IE as well. Risk factors include low valve placement, paravalvular leak/turbulent flow, and involvement of pacemaker leads.

E. Pacemaker/defibrillator endocarditis (commonly referred to as cardiovascular implantable electronic device IE [CIEDIE]) is increasing in frequency in clinical practice, with the burgeoning number of devices being implanted. The incidence of endocarditis following device therapy ranges from 0.2% to 7%. The infection may involve the generator or defibrillator pocket, the electrodes, and valvular or nonvalvular endocardium.

1. It is important to acknowledge that CIEDs contain both intravascular and subcutaneous components; therefore, CIEDIE is not a singular entity but rather a disease continuum that spans between the subcutaneous pocket to the endothelium.
2. When describing CIEDIE, specific terminology is used to identify the location of infection.
3. Recent studies suggest the mechanisms of CIEDIE are hematogenous spread of microorganisms from a remote site and direct seeding from skin flora contamination at the time of device implantation. Hematogenous spread is often caused by gram-positive bacteria, with *S. aureus* being the most common. Hematogenous spread by gram-negative bacteria is less common. Similar to PVE, a protective biofilm surrounds bacteria once they

have adhered to the CIED surfaces serving as antimicrobial protection.

4. The majority of infections in CIEDIE are caused by *Staphylococcus* spp., including *S. aureus* and coagulase-negative staphylococci. Several studies demonstrated an increase in the risk of in-hospital death and overall mortality in patients with device-related endocarditis. Mortality improves in device-related IE when treated with device removal and appropriate antibiotics but remains significantly higher than that of age-matched controls with similar comorbidities.

F. Fungal endocarditis (*Candida* and *Aspergillus*) usually occurs in association with **prosthetic valves, indwelling intravascular hardware, immunosuppression, or injection drug use. The most common cause is Candida species, but other causes include *Histoplasma* and *Aspergillus*. Fungal IE usually presents with large vegetations that extend into the perivalvular apparatus and embolize into large vessels and, therefore, require surgical intervention**.

IV. PATHOPHYSIOLOGY. The first step in the pathogenesis of vegetation is the formation of **nonbacterial thrombotic endocarditis (NBTE)**, which usually results from endothelial injury (the most common offender is turbulent flow), followed by focal adherence of platelets and fibrin. Microorganisms circulating in the bloodstream in turn infect this sterile platelet-fibrin nidus.

A. Vegetations classically occur along the line of closure of the valve leaflet. The endothelium may be injured by regurgitant jets, leading to vegetation formation on **the atrial surface of incompetent atrioventricular valves** or the **ventricular surface of incompetent semilunar valves**. Foreign materials, such as intracardiac devices, are not endothelialized initially and act as a formation site for platelet-fibrin thrombi.

B. Bacteremia is the event that converts NBTE to IE when host defenses fail. The foreign material also impairs host defenses, rendering them more difficult to treat.

C. Vegetations often further impair valvular coaptation or cause perforation or chordal rupture, leading to worsening of regurgitation and CHF. Furthermore, the vegetations may dislodge, causing peripheral septic-nonseptic embolization.

D. One meta-analysis showed that the **risk of embolization in patients with large vegetations (>10 mm) was nearly 3 times higher than in patients with no detectable vegetations** or small vegetations. Prolapsing vegetations and involvement of extravalvular structures increase the overall risk of heart failure, embolization, and the need for valve replacement. Vegetations that increase in size, despite appropriate therapy, are also more likely to be associated with adverse events requiring surgery.

E. The infection may extend to the surrounding structures, such as the valve ring, the cardiac conduction system, the adjacent myocardium, or the aortic-mitral intravalvular fibrosa. Consequently, once the aortic-mitral intravalvular fibrosa is violated, conduction abnormalities, abscesses, diverticula, aneurysms, or fistula may develop. Septic arterial embolization is the usual mechanism responsible for extracardiac involvement. Notably, neurologic complications, splenic infarcts, renal infarcts, and vertebral infections are the most common sites of infection arising from septic embolization. Infections involving prosthetic valves commonly invade paravalvular tissue, resulting in abscess formation or valve dehiscence.

V. LABORATORY EXAMINATION

A. Blood tests

1. Laboratory findings often reflect nonspecific acute inflammatory response, manifest as a **modest leukocytosis with a left shift seen frequently in acute IE, leukopenia associated with splenomegaly is frequently seen with subacute IE**, a **normochromic normocytic anemia**, elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), and a slightly increased or decreased **platelet count**. Other laboratory abnormalities may include an **elevated erythrocyte sedimentation rate**, C-reactive

protein, rheumatoid factor, and/or hypergammaglobulinemia. IE may also cause false-positive Venereal Disease Research Laboratory test and Lyme serologic test.

2. Decreased complement and an elevated blood urea nitrogen or creatinine may implicate renal dysfunction from an immune complex glomerulonephritis or drug toxicity.
3. Blood cultures are critical in the diagnosis and management of IE. However, if a patient is acutely ill, **therapy should not be delayed for more than 2 to 3 hours**, as a fulminant infection may be rapidly fatal. In recent reports, cultures were negative in 2% to 7% of cases with established IE, despite the best modern methods.
   a. If the clinical condition allows, three sets of cultures should be drawn at three different peripheral venipuncture sites at least/ideally several hours apart before empiric antimicrobial therapy is started. The first and last set should be drawn at least an hour apart if possible. Fungal cultures should be included when fungal infection is suspected, such as in immunocompromised hosts.
   b. Intravascular infection leads to constant bacteremia originating from vegetations. Therefore, **it is unnecessary to await the arrival of a fever spike or chills to obtain blood cultures**.
   c. The laboratory should be alerted if a **culture-negative IE or a fastidious infectious agent** is suspected, as it may be necessary to enhance the culture medium, prolong the incubation period, **or perform advanced laboratory testing, such as serology or PCR**. For example, the HACEK group (see Section III.C.1) needs prolonged incubation of up to 21 days. Serology for *Brucella*, *Legionella*, *Coxiella*, or *Psittacosis* may be revealing. Fastidious organisms can also be identified using PCR in valvular specimens. This technique does not require a culture medium; however, it does require excised valvular tissue. PCR has been shown to have a sensitivity of 41% and a specificity of 100% in recent studies, and thus, it may provide important information about the causes of IE that could not be identified by culture.

d. Special attention should be paid to cultures positive for coagulase-negative staphylococci—in particular, *S. lugdunensis*. Unlike other coagulase-negative staphylococci, it often affects native valves, is destructive, frequently causes abscesses, and is associated with high mortality without surgical intervention. Thus, in the setting of high suspicion for IE, cultures positive for coagulase-negative staphylococci should not be disregarded as a contaminant and should be further speciated.

B. Histologic evaluation. Histopathology of resected valvular tissues remains the gold standard for the diagnosis of IE. It may demonstrate valvular inflammation, vegetations, and/or specific organisms. Detection of an etiologic agent in the vegetation using special stains or immunohistology can guide the choice of antimicrobial treatment. This is particularly useful in culture-negative IE, such as Q fever, *Bartonella* spp., or *T. whipplei* (Whipple disease bacillus). **Good communication among cardiologists, surgeons, pathologists, and microbiologists helps ensure accurate diagnosis.**

C. Electrocardiogram (ECG). All patients with suspected IE should undergo baseline and follow-up ECG.

1. ECG may reveal **conduction disturbances** reflecting perivalvular extension (specifically of mitral and aortic valves) of infection to the surrounding atrioventricular node and proximal intraventricular conduction system, ranging from a prolonged PR interval to complete heart block. A **new atrioventricular block** carries a 77% positive predictive value for abscess formation with 42% sensitivity. It is important to note the presence of a new conduction abnormality is a multivariate risk predictor for death associated with IE.

2. Ischemic changes may be present as either a consequence of hemodynamic changes resulting in arterial demand mismatch or rarely coronary embolization of vegetations.

D. Chest x-ray may reveal **CHF or pleural effusions.** Right-sided IE may cause **nonspecific infiltrates or pulmonary infarcts** owing to multiple septic pulmonary emboli.

VI. DIAGNOSTIC IMAGING TECHNIQUES

A. Echocardiography has a key role in both the diagnosis and management of IE. The primary objective is to identify, localize, and characterize valvular vegetations and their effects on cardiac function. Vegetations may occur at intracardiac locations other than valves, such as the site of impact of a high-velocity jet or shunt. A limitation of echocardiography is that vegetations cannot always be distinguished from other noninfectious masses.

1. **All patients in whom IE is suspected should undergo expedited baseline transthoracic echocardiography (TTE) to define underlying cardiac abnormalities, characterize the hemodynamic severity of valvular lesions, assess ventricular function and pulmonary pressures, determine the size and location of vegetations, and explore the possibility of complications (eg, aortic annular ring abscess).** Advances in harmonic imaging and spatial resolution have increased the sensitivity of TTE imaging to detect native valve IE. TTE has a sensitivity of about 50% to 60% to as high as 89% with good imaging windows and a specificity of 90%. Moreover, the finding of morphologically and functionally normal valves on TTE decreases the likelihood of IE. In one series, 96% of patients with normal valves on TTE also had a negative transesophageal echocardiography (TEE). Benefits of TTE include wide availability, noninvasive nature, and hemodynamic valvular assessment.
2. **TEE has increased the diagnostic accuracy of IE. The sensitivity of TEE is 90% to 100% and specificity is >90%.** According to current guidelines, TTE and TEE provide complementary information, and both should be used in the evaluation of patients with suspected IE. If IE is strongly suspected and the TTE is negative, when complications have developed or are clinically suspected, or intracardiac device leads are present, then, according to current guidelines, TEE should be performed. TEE is more sensitive in detecting vegetations, especially if adequate TTE imaging windows are challenging to

obtain or image quality is poor. TEE is particularly useful for assessing posterior structures, abscesses, fistulae, perivalvular leaks, small vegetations, right-sided heart structures, masses on intracardiac devices, leaflet perforations, and prosthetic valves. The ability to detect paravalvular abscesses, fistulae, and paraprosthetic leaks has a major impact on management strategy. Intraoperative TEE can be used to evaluate the success of surgical interventions and the need for potential modification of reparative cardiac surgical procedures. A postoperative TTE should also be done as a baseline measure of cardiac anatomy/function for long-term follow-up. Although, in most cases, a TTE should be the first diagnostic test of choice, in certain circumstances, TEE may be the optimal initial test to rule out IE. These include cases that involve *S. aureus* bacteremia, prosthetic valves, prior IE, limited echo windows, and bacteremia due to an organism that is known to commonly cause IE (eg, *Enterococcus*, fungal infection). TEE is indicated in patients with suspected pacemaker or defibrillator endocarditis.

a. A negative result on TEE indicates a low likelihood of IE (provided adequate images are available). However, it does not completely rule out the diagnosis. The negative predictive value is >90%, but false negatives may occur early in endocarditis or if vegetations are small. Repeat TEE should be considered in 3 to 5 days if clinical suspicion is high or sooner if clinical findings change. Of note, a negative TEE should never override strong clinical evidence of endocarditis in the diagnosis of PVE.

b. Myocardial abscesses are more reliably detected with TEE (87% sensitive) than with TTE (28% sensitive). Detection of a perivalvular abscess is essential, as an abscess is a serious complication and a strong indication for surgical intervention.

c. The sensitivity of TTE for detecting valvular or lead vegetations is 30%, compared with 90% with TEE.

d. In the setting of PVE, TEE is superior (82% sensitive, approximately 90% specificity) to TTE (36%-69% sensitive) in

the detection of vegetations due to acoustic shadowing of prosthetic valves, especially in the mitral and aortic positions. **TEE should be performed if PVE or pacemaker endocarditis is suspected but is not evident on TTE.**

e. In patients who are being considered for an early change to oral antibiotic therapy for stable IE, a baseline TEE prior to changing therapy and a repeat TEE 1 to 3 days before completion of oral antibiotic regimen should be obtained.

B. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT): As definitive diagnosis of IE can at times be elusive, FDG-PET/CT has emerged as a valuable adjuvant imaging modality. **Strengths in diagnostic capabilities of FDG-PET/CT are particularly highlighted in PVE and CIEDIE.** Increased uptake of FDG-PET/CT has now been recognized as an imaging criterion in current guidelines for the diagnosis of PVE, helping reclassifying previously "possible" diagnoses to "definitive" IE. FDG-PET/CT can be used as an adjunct imaging modality when echocardiography is nondiagnostic and clinical suspicion is high, particularly in PVE and CIEDIE. FDG-PET/CT has reduced and limited diagnostic performance in the evaluation of native valve IE.

C. Cardiac CT: ECG-gated, multidetector row CT can be performed as complementary imaging to TEE in cases of endocarditis. This serves as an ideal imaging modality for this population as it is less invasive and readily available. CT's ability to identify vegetations demonstrates variable sensitivity ranging from 16% to 97% but a reasonably high specificity of 88% to 96%. Studies have shown that CT can help define the extent of perivalvular abscess extension or pseudoaneurysm in NVE with moderate sensitivity (66%-100%) and high specificity (88%-100%).

1. Notable difference between TEE and CT is the manner in which images are obtained. TEE images are obtained in real-time versus ECG-gated images from the CT, which are retrospectively reconstructed, limiting the ability for CT to detect independently mobile structures. To improve detection of mobile structures, thinner slices and four-dimensional (4D) analysis of the entire

cardiac cycle to improve temporal resolution to detect mobile structures.

2. In PVE, where acoustic shadowing makes characterization by TEE difficult, CT has higher specificity in detecting vegetation and perivalvular complications. In addition to detection of IE, CT also provides information useful in surgical planning, such as the degree of coronary calcification, aortic size, and proximity of thoracic vascular structures to the sternum. CT has also proven to be useful in right-sided IE by demonstrating pulmonary embolization and subsequent abscess or infarction. Recent studies have demonstrated the utility of CT in providing prognostic information when planning surgery in this high-risk population. Pseudoaneurysms, fistulas, and abscesses detected by CT have been associated with adverse outcomes following surgery.

D. **Cardiac catheterization.** Left heart catheterization with selective coronary angiography is indicated prior to surgical intervention if there is a suspicion of obstructive coronary disease. The abnormal rocking motion of a dehisced prosthetic valve may be noted on fluoroscopy. Care should be taken to avoid unnecessary coronary angiography or cardiac catheterization in aortic valve endocarditis because of the risk of embolization of vegetations. CT coronary angiography may be a useful alternative imaging modality in patients with low suspicion for obstructive coronary artery disease.

E. **Central nervous system (CNS) imaging.** CT, magnetic resonance imaging (MRI), or cerebral angiography should be considered in any patient who has sustained a CNS complication, such as an embolic infarct, intracranial bleed, or mycotic aneurysm, or in the patient with persistent headaches. Patients with endocarditis who **meet criteria for cardiac surgery should have a brain CT scan before surgery** to exclude occult cerebral embolization.

F. **Body imaging.** CT or MRI may be useful in the detection of metastatic infection. The value of CT may increase in the future as spatial resolution improves. **MRI** does not currently have a significant role in assessing cardiac manifestations of IE, owing to intrinsic problems related to temporal resolution.

III. MODIFIED DUKE CRITERIA. Given the complexity of IE, the diagnosis requires a high index of suspicion. The Modified Duke schema is currently the most sensitive and specific diagnostic set of criteria available. It is particularly useful in diagnosing endocarditis in patients with *S. aureus* bacteremia, those with right-sided endocarditis, and those with negative blood culture results. **Therefore, current guidelines suggest in patients with suspected IE, the Modified Duke Criteria should be used for diagnosis.** However, these criteria have not been validated in PVE.

A. The criteria are divided into **definite** (pathologic or clinical), **possible**, and **rejected** diagnostic groups.

B. For a **definite pathologic diagnosis**, either (A or B) of the pathologic findings listed in **Table 19.2** is sufficient.

TABLE 19.2 Modified Duke Criteria

Definite IE	Possible IE	Rejected IE
Pathologic criteria **a.** Microorganism identified through culture or histology exam of vegetation directly from the valve, an embolized vegetation, intracardiac abscess or **b.** Pathologic lesions: These are vegetations or intracardiac abscesses that are present in the setting of histology confirming endocarditis. Clinical criteria **a.** Two major or **b.** One major and three minor or **c.** Three minor	1 major and 1 minor *or* 3 minor criteria	An alternative diagnosis *or* Resolution of IE syndrome with antibiotic treatment for <4 days *or* No pathologic evidence of IE at surgery or autopsy in the setting of antibiotics <4 days *or* Does not meet criteria for possible IE

IE, infective endocarditis.

Derived from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486 and Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638.

C. For a **definite clinical diagnosis** (**Table 19.3**), two major criteria, or one major and three minor, or five minor criteria are needed.

TABLE 19.3 Duke Criteria for Definite Clinical Diagnosis: Two Major Criteria, One Major and Three Minor Criteria, or Five Minor Criteria

Major Clinical Criteria

1. Positive blood culture results for IE

A. Typical microorganisms (in two or more cultures)

- Viridans *Streptococcus*
- *Streptococcus bovis*
- HACEK group
- *Streptococcus aureus*[a]
- Community-acquired enterococci, in the absence of a primary focus

B. Persistently positive blood culture

- Recovery of a microorganism consistent with IE from two blood cultures drawn more than 12 h apart

or

- Recovery of a microorganism consistent with IE from all of three or a majority of four or more separate blood cultures, with the first and last draw at least 1 h apart

or

2. Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer >1:800[a]Evidence of endocardial involvement

A. Positive echocardiogram

- Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or on implanted material, in the absence of an alternative anatomic explanation

or

- Abscess

or

- New partial dehiscence of prosthetic valve

or

B. New valvular regurgitation (increase or change in preexisting murmur not sufficient)

Minor Clinical Criteria

1. Predisposition

- Predisposing heart condition
- Injection drug use

2. Fever >38.0 °C (100.4 °F)

3. Vascular phenomena

- Major arterial emboli
- Septic pulmonary infarcts
- Mycotic aneurysm
- Intracranial hemorrhage
- Conjunctival hemorrhages
- Janeway lesions

4. Immunologic phenomena
- Glomerulonephritis
- Osler nodes
- Roth spots
- Rheumatoid factor

5. Microbiologic evidence
- Positive blood culture but not meeting major criteria as noted above
- Serologic evidence of active infection with organism consistent with IE

HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella*, and *Kingella*; IE, infective endocarditis; IgG, immunoglobulin G.

[a]Echocardiographic minor criteria have been eliminated.
Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a scientific statement for healthcare professionals from the American Heart Association. *Circulation*. 2015;132(15):1435-1486.

D. The **possible diagnostic** group has findings consistent with IE, including one major criteria and one minor criteria or three minor criteria.

E. For a **rejected diagnosis**, there is a firm alternative diagnosis for clinical manifestations or resolution of clinical manifestations, with antibiotics for 4 days or less, or no pathologic evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days or less.

III. THERAPY. Owing to the complexity of IE, a team approach (cardiologist, cardiothoracic surgeon, infectious diseases specialist, and pathologist) in the diagnosis and management of this disease cannot be overemphasized. Effective therapy requires identification of the microbial cause, determination of a bactericidal regimen of proven efficacy, an understanding of the intracardiac pathology of IE and its implications for surgery, and effective management of extracardiac complications.

A. Medical therapy

1. Principles of therapy. Antibiotics are the mainstay of medical therapy (**Table 19.4**).

TABLE 19.4 Antibiotic Regimens for Infective Endocarditis

Medication	Dosage	Duration of Therapy (weeks)
Native valve infective endocarditis due to penicillin-susceptible viridans Streptococcus or Streptococcus bovis		
Penicillin G	12-18 million U per 24 h continuously IV or in four to six divided doses	4
or		
Ceftriaxone	2 g once daily IV or IM	4
or		
Penicillin G	12-18 million U per 24 h continuously IV or in six divided doses	2[a]
or		
Ceftriaxone *plus*	2 g once daily IV or IM	2
Gentamicin *or* if penicillin allergic	3 mg/kg once daily IV or IM	2
Vancomycin	30 mg/kg per 24 h in two divided doses	4
Native valve infective endocarditis due to penicillin-resistant or nutritionally variant viridans Streptococcus or Streptococcus bovis		
Penicillin G	24 million U per 24 h continuously IV or in four to six divided doses	6
or		
Ceftriaxone	2 g once daily IV or IM	6
with or without		

Medication	Dosage	Duration of Therapy (weeks)
Gentamicin	3 mg/kg once daily IV or IM	2-6[b]
or		
If penicillin allergic, vancomycin	30 mg/kg IV per 24 h in two divided doses	6
Prosthetic valve infective endocarditis due to penicillin-susceptible viridans Streptococcus or Streptococcus bovis		
Penicillin G	24 million U/24 h IV continuously or in four to six divided doses	6
or		
Ceftriaxone	2 g/24 h IV or IM	6
with or without		
Gentamicin	3 mg/kg per 24 h IV or IM	2
Vancomycin	30 mg/kg per 24 h IV in two divided doses	6
***Prosthetic valve infective endocarditis due to penicillin-resistant viridans* Streptococcus *or* Streptococcus bovis**		
Penicillin G	24 million U/24 h IV continuously or in four to six divided doses	6
or		
Ceftriaxone	2 g/24 h IV or IM	6
PLUS		
Gentamicin	3 mg/kg per 24 h IV or IM	2
Vancomycin	30 mg/kg per 24 h IV in two divided doses	6
Native valve infective endocarditis due to staphylococci		
Nafcillin or oxacillin	2 g IV every 4 h	6
Or for penicillin-allergic		

Medication	Dosage	Duration of Therapy (weeks)
nonanaphylactoid patients		
Cefazolin	2 g IV every 8 h	6
Or for oxacillin-resistant strains or penicillin-allergic patients with anaphylaxis		
Vancomycin[c]	30 mg/kg per 24 h in two divided doses	6
Daptomycin	≥8 mg/kg dose	6
Infective endocarditis due to oxacillin-sensitive staphylococci in the presence of prosthetic material		
Nafcillin[d] or oxacillin	2 g IV every 4 h	>6
Plus rifampin	300 mg orally every 8 h	>6
Plus gentamicin	1 mg/kg IV or IM every 8 h	2
Infective endocarditis due to oxacillin-resistant staphylococci in the presence of prosthetic material		
Vancomycin	30 mg/kg per 24 h in two divided doses	6
PLUS		
Rifampin	900 mg/24 h divided into three doses	6
PLUS		
Gentamicin	3 mg/kg per 24 h IV divided into three doses	2
Infective endocarditis due to HACEK microorganisms		
Ceftriaxone[e]	2 g once daily IV or IM in one dose	4
or		
Ampicillin	2 g IV every 4 h	4
or		

Medication	Dosage	Duration of Therapy (weeks)
Ciprofloxacin	1,000 mg orally once daily *or* 800 mg IV every 12 h	4
Native valve infective endocarditis or prosthetic valve endocarditis resulting from Enterococcus species		
Ampicillin	2 g IV every 4 h	4-6
plus		
Gentamicin	3 mg/kg in two to three equally divided doses	
or With gentamicin resistance		
Ceftriaxone	2 g IV every 12 h	6
or With penicillin resistance		
Vancomycin	30 mg/kg per 24 h IV in two equally divided doses	6
plus		
Gentamicin	3 mg/kg per 24 h in three equally divided doses	
With vancomycin resistance		
Enterococcus faecium		
Linezolid	1,200 mg/24 h IV/PO in two divided doses	≥8
E faecalis		
Imipenem/cilastatin	2 g/24 h IV in four doses	≥8
PLUS		
Ampicillin sodium	12 g/24 h IV in six doses	≥8
or		
Ceftriaxone sodium	4 g/24 h IV/IM in two doses	≥8

Medication	Dosage	Duration of Therapy (weeks)
PLUS		
Ampicillin sodium	12 g/24 h IV in six doses	≥8

HACEK, *Haemophilus, Actinobacillus, Cardiobacterium, Eikenella,* and *Kingella;* IM, intramuscular; IV, intravenous.

[a]For relatively resistant viridans *Streptococcus* or *S. bovis*, or known cardiac or extracardiac abscess, or for those with creatinine clearance <20 mL/min, penicillin G dosing is extended to 4 wk.

[b]If penicillin-susceptible strain (minimum inhibitory concentration ≤0.12 µg/mL), duration of gentamicin in combination with ceftriaxone is 2 wk; if penicillin relatively resistant or fully resistant strain (minimum inhibitory concentration >0.12 µg/mL), duration of gentamicin is extended to 6 wk.

[c]Recommended for methicillin-resistant *Staphylococcus*.

[d]For methicillin-resistant *Staphylococcus* or for the penicillin-allergic patient, vancomycin, 30 mg/kg per 24 h IV in two divided doses, is substituted for nafcillin.

[e]The third-generation cephalosporins or ampicillin-sulbactam therapy should be considered the drugs of choice. Length of therapy for prosthetic valve infective endocarditis should be 6 wk. A fluoroquinolone should be considered an alternative agent for patients unable to tolerate beta-lactam therapy.
Portions derived from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2015;132(15):1435–1486 and Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111(23):e394–e434.

a. Antibiotic regimens are most effective when the identity and sensitivities are known. Therefore, antibiotics should be specific to the infective organism, bactericidal, provided for a prolonged course (weeks), and chosen in consultation with an infectious diseases specialist. Routine empiric antibiotics not only decrease blood culture yield, thereby increasing the likelihood of culture-negative IE, but also expose the patient to potential risk from side effects of antibiotics. Empiric therapy, however, may be considered in patients with septic shock or who present with high-risk features/signs. **Measures of antibiotic effectiveness** include the minimum inhibitory

concentration of antibiotic required to inhibit growth, the minimum bactericidal concentration of an antibiotic required to kill an organism, and the serum bactericidal titer (SBT), which is the highest dilution of a patient's serum that kills 99.9% of an inoculum. The SBT is especially helpful when treating unusual organisms, when using unusual antibiotic regimens, or when treatment is failing.

b. Initiation of vitamin K antagonist (VKA) anticoagulation is not recommended routinely in patients with native valve IE. It does not prevent embolization related to IE. In fact, **simultaneous treatment with penicillin and heparin can increase the risk** of fatal intracerebral hemorrhage. According to current guidelines, for patients receiving VKA anticoagulation at the time of IE diagnosis, temporary discontinuation of VKA anticoagulation may be considered. Anticoagulation may be given in cases of IE in which there is another indication such as the presence of a prosthetic valve and in which the benefits outweigh the risks of adverse bleeding events.

2. Empiric therapy for IE is often started and continued until the etiologic organism is identified and the antibiotic sensitivities are known, especially in cases with hemodynamic compromise. Occasionally, empiric therapy is administered as a therapeutic trial to help confirm a diagnosis. Empiric therapy should cover the most likely pathogens, including staphylococci (both methicillin-sensitive and methicillin-resistant strains), streptococci, and enterococci. Vancomycin plus gentamicin is the recommended empiric regimen in NVE, with the addition of rifampin in PVE. Once an etiologic agent is identified, therapy should be narrowed (see **Table 19.4**). Unless clinical or epidemiologic clues suggest an etiologic factor, treatment for culture-negative IE is the same.

a. Renal function is an important consideration when using **aminoglycosides or vancomycin**. These antibiotics should be dosed according to estimated creatinine clearance. The following doses outlined are for normal renal function. A

vancomycin dose should not exceed 2 g per 24 hours unless serum levels are monitored.

3. When initiating therapy for coagulase-negative staphylococcal PVE, the organism should be assumed to be methicillin resistant until the laboratory definitively excludes this.
4. Antibiotic therapy **after surgery** is discussed in Section VIII.B.
5. Medical therapies for **specific organisms** are summarized in **Table 19.4**.
6. **Uncommon causes of IE.** *Coxiella burnetii* IE is treated with doxycycline and rifampin, trimethoprim-sulfamethoxazole, or fluoroquinolones for at least 3 years and requires surgical intervention in cases of prosthetic valve involvement, CHF, or refractory infection. *Brucella* IE usually requires surgical intervention in combination with doxycycline and either streptomycin or gentamicin for 8 weeks to 10 months after surgery. *Pseudomonas* IE should be treated with high doses of piperacillin and tobramycin and requires surgical intervention in cases of left-sided infection. Patients with IE due to IVDU benefit from review by addiction specialists **in the setting of recurrent admissions and reinfections**.
7. **Fungal IE.** When fungal IE is diagnosed, the standard of care involves a **combined medical/surgical approach**. Typically, fungal infection IE primarily involves prosthetic valves. *Candida* spp. and *Aspergillus* spp. are typically associated with fungal IE. *Aspergillus* spp. blood cultures are rarely positive and, therefore, are a cause of culture-negative IE, particularly in patients with prosthetic valves.
   a. The mainstay of antifungal drug therapy is **amphotericin B** with or without **flucytosine** (a synergistic effect).
      (1) Amphotericin B is infused in 5% dextrose over 2 to 4 hours at a dose of 0.7 to 1.0 mg/kg daily. Larger doses (1-1.5 mg/kg daily) are recommended for the management of PVE caused by *Aspergillus* spp.

(2) The major toxicity of amphotericin B is **renal dysfunction**. Liposomal preparations may be less nephrotoxic.

(3) The primary toxicity of flucytosine is **bone marrow suppression**; for this reason, flucytosine blood levels may be useful during therapy.

b. Surgery should be performed because effective penetration of the medicine into vegetations is unlikely. Valve replacement becomes necessary in almost all cases of fungal IE.

c. After completion of 6 weeks of parenteral therapy, lifelong suppressive therapy with an azole is recommended to prevent relapse.

B. Surgical therapy (**Table 19.5**). Approximately half of individuals with infectious endocarditis develop severe complications that require surgical treatment. There is mounting evidence that **early surgery** improves outcomes for patients with left-sided IE and refractory heart failure or intracardiac complications. Antibiotic therapy combined with valve replacement and cardiac reconstruction results in higher survival rates, fewer relapses or rehospitalizations, and lower late endocarditis-related mortality than do antibiotics alone in patients with complicated IE.

TABLE 19.5 American College of Cardiology/American Heart Association Guidelines: Intervention for Infective Endocarditis

Class I

1. Decisions about timing of surgical intervention should be made by a multispecialty Heart Valve team of cardiology, cardiothoracic surgery, and infectious disease specialists.
2. Early surgery is indicated in patients with IE who present with valve dysfunction that results in symptoms of CHF.
3. Early surgery is indicated in left-sided IE caused by *Staphylococcus aureus,* fungal, or other highly resistant organisms.
4. Early surgery is indicated in IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions.
5. Early surgery is indicated in IE with evidence of persistent bacteremia or fevers lasting longer than 5-7 d despite appropriate antimicrobial therapy.
6. Surgery is indicated in prosthetic valve and relapsing infection without other identifiable sources of infection.

7. Complete removal of pacemaker or defibrillator systems is indicated as part of early management in patients with IE and documented device infection.
8. In patients with recurrent endocarditis and continued intravenous drug use, consultation with addiction medicine is recommended to discuss the long-term prognosis for the patient refraining from actions that risk reinfection before repeat surgical intervention is considered.

Class IIa

1. Early surgery is reasonable in IE presenting recurrent emboli and persistent vegetations despite appropriate antimicrobial therapy.
2. Complete removal of pacemaker or defibrillator systems is reasonable in patients with valvular IE caused by *S. aureus* or fungi even without evidence of device infection.
3. Complete removal of pacemaker or defibrillator systems is reasonable in patients undergoing valve surgery for valvular IE.

Class IIb

1. Early surgery may be considered in patients with NVE and mobile vegetation >10 mm in length even in the absence of embolic phenomenon.
2. Operation without delay may be considered in patients with IE and an indication for surgery who have a stroke but have no evidence of intracranial hemorrhage or extensive neurologic damage.
3. Delaying valve surgery for at least 4 wk may be considered for hemodynamically stable patients with IE and major ischemic stroke or intracranial hemorrhage.

CHF, congestive heart failure; IE, infective endocarditis; NVE, native valve endocarditis.

Portions derived from Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2021 Feb 2;143(5):e35–e71 and reprinted with permission from Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159–e1195. Copyright © 2017 American Heart Association, Inc.

1. The **fundamental principles** of operative procedures for IE involve debridement of infected tissue, removal of all nonviable tissue, reconstruction of the involved area, and restoration of valve competence. There is general consensus for early surgical

intervention in any of the following situations: refractory CHF due to significant valve dysfunction; native and PVE caused by *S. aureus, fungal, or other highly resistant organisms*; uncontrolled infection despite appropriate antibiotic therapy; most cases of PVE (particularly relapsing IE after completing a course of appropriate antibiotics and subsequent negative blood cultures); and complications such as heart block, destructive, penetrating lesions, or abscess formation. Controversial indications include the presence of more than one serious systemic embolic event or one embolus with a large residual vegetation. These latter indications are not absolute and must be implemented with a careful risk-benefit analysis (see the American College of Cardiology/American Heart Association (AHA) guidelines for surgical intervention in **Table 19.5**).

2. The goals of surgical intervention for IE are total removal of infected tissues and reconstruction of cardiac morphology through either a repair or replacement of the affected valves. Surgical interventions include repair of the affected valve, valve replacement, and homograft use. Repair would be the strategy of choice, particularly for mitral and tricuspid valves, if there is limited destruction to the valves; otherwise, a valve replacement strategy can be used. In regard to IE of the aortic valve, replacement is typically the technique of choice, but valve repair can be pursued in centers with great expertise in it. Valve replacement can be achieved with mechanical or bioprosthetic without significant difference in mortality. Homografts have been suggested to reduce the risk of persistent or recurrent infection (owing to their natural biocompatibility) and are usually favored over valve prosthesis.
3. There is operative risk associated with patients with IE undergoing therapeutic surgery; however, there are limited data surrounding how to properly assess this risk. Previously, the EuroSCORE II, a risk score validated predominantly for coronary artery bypass grafting (CABG) and valve surgery, had been used to assess risk in this population. Small studies have developed risk scores

specific for patients with IE undergoing surgery curative surgery, which, when compared to the EuroSCORE II, performed better at predicting operative mortality after surgery for active IE. These are the Society of Thoracic Surgeons (STS) endocarditis score and a French scoring system developed by De Feo et al.

4. CHF (New York Heart Association class III or IV) is the strongest indication for surgery in IE, as 90% of all deaths result from CHF. It should be noted that the benefit of surgery persists even in the presence of comorbidities, such as acute renal failure, and surgery should not be delayed in the setting of life-threatening heart failure or cardiogenic shock if the patient is likely to recover after surgery.
5. PVE usually requires a combined medical/surgical approach.
6. **Patients with CNS infarcts or bleeds.** Special attention must be paid to the presurgical candidate who may have had a CNS infarct or bleed, because large doses of heparin are required for cardiopulmonary bypass. The current recommendations state that patients with IE and an indication for surgery **but also have evidence of a cerebral vascular accident (CVA) without intracranial hemorrhage or extensive neurologic damage should undergo surgery without delay.** In cases of major ischemic CVA **with extensive neurologic damage or intracranial hemorrhage,** surgery should be delayed for at least 4 weeks if the patient is hemodynamically stable. If, during evaluation of CVA, a mycotic aneurysm is found, the timing of surgery should be reconsidered, and any prosthesis that requires postoperative anticoagulation should be avoided. A mycotic aneurysm should be clipped or embolized **before** cardiac operation.
7. Metastatic infection, usually attributed to *S. aureus*, should be drained if accessible.
8. The optimal duration of **antibiotic therapy after surgery** for IE is not known.
    a. For **native valve IE** caused by an antibiotic-resistant organism with subsequent negative cultures, preoperative plus

postoperative antibiotic therapy should consist of a full course of recommended treatment.

b. For patients with **positive intraoperative cultures**, a full course of therapy should be given postoperatively.

c. Patients with prosthetic valves who are undergoing surgery for IE should receive a full course of antibiotics postoperatively when organisms are discovered in resected material.

C. The optimal management of **pacer or defibrillator endocarditis** combines complete device extraction (generator and lead extraction) and a prolonged course of parenteral antibiotics.

1. The success rate of infection resolution without removal of the entire device is low because typically the entire device is infected. Most studies suggest that the complete explantation of all hardware combined with antibiotic therapy is the optimal management.
2. The optimal route or duration of antibiotics remains unclear in the literature. Experience suggests that a prolonged course of IV antibiotics is needed.
3. The timing of device reimplantation is another important issue. It is prudent to provide sufficient duration of antibiotic therapy to eradicate bacteremia and to suppress or eradicate endocardial infection prior to reimplantation in order to minimize the risk of reinfection of the new device. Studies have shown that reimplantation is successfully performed at a median of 7 days (5-25 days) after explanation.

IX. COMPLICATIONS

A. **Table 19.6** lists the complications of IE.

TABLE 19.6 Complications of Infective Endocarditis

Cardiac complications
Congestive heart failure (leading cause of death)
Abscess (pericardial, aortic annular, or myocardial)

Conduction abnormalities (due to invasive disease)
Coronary embolism
Mycotic aneurysm (often clinically silent)
Valvular regurgitation (cusp/leaflet flail or perforation)
Valvular stenosis
Prosthetic dehiscence
Septal perforation (ventricular septal defect)
Extracardiac complications
Systemic embolism (stroke, renal infarct, splenic infarct, or ischemic limb)
Mycotic aneurysm
Abscess
Immune complex deposition (glomerulonephritis)

B. Valve ring abscess is a noteworthy complication of PVE, seen with mechanical and bioprosthetic valves and also occasionally seen in severe infection of native valves. Infection of the sutures used to secure the sewing ring to the periannular tissue may result in dehiscence of the valve. The clinical finding of a new perivalvular leak in a patient with PVE is worrisome. Risk factors for abscess formation include persistent fever, CHF, a history of IVDU, infection with a virulent organism, and PVE.

X. RESPONSE TO THERAPY. Although a reduction in the size of vegetations during antimicrobial therapy suggests therapeutic success, vegetations may persist unchanged despite microbiologic cure. Significant enlargement of a vegetation during treatment indicates possible treatment failure and constitutes a relative indication for surgery.

A. Blood cultures should be obtained during therapy for IE to ensure eradication of the organism (see Section V.A.3).

B. Defervescence usually follows 3 to 7 days of successful antimicrobial therapy. **Persistent or recurrent fever may represent therapeutic failure, drug fever, a secondary nosocomial infection, or intracardiac or extracardiac abscess formation.** Generally, if fever

persists for more than 7 days or if blood cultures are positive beyond the first week of antibiotic therapy, the treatment is considered a failure.

C. Relapses, should they occur, usually manifest clinically within 4 weeks and can be confirmed by blood cultures. With a combined medical and surgical approach, recurrent PVE occurs in 6% to 15% of patients.

D. The frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy, and the risk is considered to be greatest in the setting of large vegetations (>10 mm in diameter) and specific infections (*S. aureus* and *Candida*).

E. Medical management is successful in many patients with IE; however, surgery is required in approximately 50% of cases.

XI. PROGNOSIS. The prognosis depends on **the virulence of the causative organism, the underlying health of the patient, the valvular structures, the duration of the infection, and the presence or absence of CHF**. The overall mortality of IE is around 30% at 1 year. Notably, the mortality rates in early PVE (40%-80%) are much higher than in late PVE (20%-40%). Five-year survival rates after surgery for PVE have ranged from 54% to 87%. In *S. aureus* IE, mortality has decreased from 50% to 60% to 15% to 30% in recent years. The presence of the factors listed in **Table 19.7** should trigger an early and aggressive management plan.

TABLE 19.7 Factors and Complications That Predispose to a Poor Outcome From Infective Endocarditis

Congestive heart failure (leading adverse prognostic factor)
Nonstreptococcal disease
Aortic valve involvement
Infection of a prosthetic valve
Older age
Abscess formation

HIV with CD4 count <200 cells/mm^3
Delayed diagnosis
CNS or coronary embolization
Recurrent IE

CNS, central nervous system; HIV, human immunodeficiency virus; IE, infective endocarditis.

A. Park et al created a validated risk score to predict 6-month mortality in IE. Patient factors including older age, dialysis, PVE, left-sided IE, virulent organisms, CHF, stroke, paravalvular complications, and persistent bacteremia were independently associated with a higher 6-month mortality. Early surgery during an index hospitalization was associated with a lower risk of mortality, although it should be noted that surgery is performed less frequently in the highest risk patients.

XII. PROPHYLAXIS. Given the paucity of randomized controlled trials demonstrating the efficacy of prophylactic antibiotics preventing IE in conjunction with the uncertainty regarding which patient population will benefit, the most recent recommendations from the AHA/ACC are based on pathophysiologic considerations, limited data, and clinical expertise. A small number of cases of IE caused by viridans group strep could be prevented by antibiotic prophylaxis. If only a small number of cases will benefit, then it should be reserved for those at the highest risk. This has led to the recommendation that only those patients at highest risk of developing IE and **at high risk of developing complications from IE (as outlined in Table 19.8) receive prophylaxis prior to dental procedures that involve manipulation of gingival tissue or periapical region of the teeth or perforation of the oral mucosa.** IE caused by viridans group streptococcal infections is most likely to develop as a result of transient bacteremia from routine daily actives (brushing, chewing, flossing). Therefore, maintenance of good oral health care with routine dental visits plays a significant role in preventing viridans group streptococcal IE.

TABLE 19.8 Cardiac Conditions Associated With the Highest Risk of Adverse Outcome From Infective Endocarditis

Antibiotic Prophylaxis Against Group Streptococcal Infective Endocarditis Based on Recommendations from the AHA
Prosthetic cardiac valves (including transcatheter-implanted valves and surgical homografts)
LVAD or implantable heart
Annuloplasty rings, chords, clips—prosthetic material used for cardiac valve repair
Patients that have had infectious endocarditis in the past
CHD patients with the following: • Unrepaired (including palliative shunts and conduits) or completely repaired CHD with residual shunt or valvular regurgitation at the site/adjacent to site of prosthetic material • During the first 6 months of completely repaired CHD with prosthetic material (surgery or transcatheter) • Pulmonary artery valve or conduit placement (surgical or transcatheter)
Cardiac transplant with valve regurgitation attributable to structurally abnormal valve

AHA, American Heart Association; CHD, congenital heart disease; LVAD, left ventricular assist device.
Derived from Wilson WR, Gewitz M, Lockhart PB, Bolger AF, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2021 May 18;143(20):e963–e978 and reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association, Inc.

A. In deciding the need for antibiotic prophylaxis, two factors must be considered: the risk associated with the specific valvular lesion (**Table 19.8**) and the type of procedure to be performed (**Table 19.9**). Patients for whom antibiotic prophylaxis for IE is recommended include those with **prosthetic valves or repair material including transcatheter devices, prior IE, postcardiac transplantation valvulopathy, and certain patients with congenital heart disease** (**Table 19.8**). Routine IE prophylaxis is no longer recommended in cardiac conditions, such as mitral valve prolapse, rheumatic heart

disease, bicuspid aortic valve, calcific aortic stenosis, atrial septal defect, and ventricular septal defect.

TABLE 19.9 Recommendations for Prophylaxis of Infective Endocarditis Related to Dental or Surgical Procedures

Dental procedures that antibiotic prophylaxis against viridians group streptococcus is suggested:

- All dental procedures with manipulation of gingival tissue, the periapical region of teeth, or if there is perforation of the oral mucosa

Dental procedures that antibiotic prophylaxis against viridians group streptococcus is **NOT** suggested:

a. Injectable anesthetics through noninfected tissue

b. Dental x-rays

c. Removable prosthodontic/orthodontic appliances

d. Adjustment of orthodontic appliances

e. Brackets on teeth as part of orthodontic treatment

f. Primary teeth shedding

g. Bleeding from trauma of the mouth, lips, or oral mucosa

Derived from Wilson WR, Gewitz M, Lockhart PB, Bolger AF, et al. Prevention of Viridans Group Streptococcal Infective Endocarditis: A Scientific Statement From the American Heart Association. *Circulation*. 2021 May 18;143(20):e963–e978 and reprinted with permission from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;116(15):1736–1754. Copyright © 2007 American Heart Association, Inc.

B. Endocarditis prophylaxis following **dental or oral procedures** is directed primarily against viridans *Streptococcus*.

C. Routine antibiotic prophylaxis solely to prevent IE is no longer advised prior to gastrointestinal or genitourinary procedures. This is based upon an increasing frequency of antimicrobial-resistant strains of enterococci and a lack of evidence conclusively linking these procedures to IE.

D. Available evidence supports a shift in emphasis away from dental procedures and antibiotic prophylaxis toward a greater **emphasis on maintaining good oral hygiene** and improved access to dental care in patients at risk for IE.

E. Prophylaxis against viridans *Streptococcus* is advised in patients at highest risk of IE who undergo **invasive procedures of the respiratory tract** that involve incision or biopsy (ie, tonsillectomy or adenoidectomy).

F. Routine endocarditis prophylaxis prior to **vaginal delivery** or hysterectomy is not recommended.

G. Incision and drainage or other procedures involving infected tissue may result in bacteremia. For nonoral soft tissue infections, an antistaphylococcal penicillin or first-generation cephalosporin is an appropriate choice of prophylaxis.

H. Prophylaxis regimens are listed in **Table 19.10**. **Cardiac surgical patients** who undergo placement of prosthetic heart valves or other prosthetic material should receive perioperative antibiotic prophylaxis, primarily directed against *S. aureus*. A first-generation cephalosporin is commonly used, but the choice of antibiotic should be influenced by the antibiotic-susceptibility pattern at each hospital. Prophylaxis should be started immediately before the procedure, repeated during prolonged procedures, and continued for no more than 48 hours.

TABLE 19.10 Prophylactic Regimens for Infective Endocarditis

Clinical Situation	Antibiotic	Dose
Standard prophylaxis	Amoxicillin	2 g PO 1 h before procedure
Unable to take oral medications	Ampicillin	2 g IV or IM within 30 min before procedure
	or	
	Cefazolin or ceftriaxone	1 g IV or IM within 30 min before procedure
Penicillin allergy	Clindamycin	600 mg PO 1 h before procedure

Clinical Situation	Antibiotic	Dose
	or	
	Cephalexin	2 g PO 1 h before procedure
	or	
	Azithromycin *or* clarithromycin	500 mg 1 h before procedure

IM, intramuscular; IV, intravenous; PO, orally.
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I. A careful preoperative dental evaluation is recommended so that, whenever possible, required dental treatment can be completed before cardiac valve surgery.

J. Patients after cardiac transplantation are at moderate risk for endocarditis because of continuous immunosuppression and the tendency for acquired valvular dysfunction (tricuspid regurgitation from endomyocardial biopsy or rejection).

K. Pneumococcal vaccination is recommended for all patients with prosthetic heart valves.

III. CONTROVERSIES

A. Short courses of antibiotics (2 weeks) have shown some efficacy in the injection drug user population, as have oral antibiotics in the same population. However, IV antibiotics are recommended until conclusive data concerning alternative regimens are available. At least 5 to 7 days of inpatient therapy is advocated before considering outpatient treatment.

B. Correct timing of surgery is often the most difficult and critical decision in the management of IE. It is important to balance the need for medical stabilization with timely surgery. Kiefer et al conducted a large multicenter prospective study of over 4,000 patients with IE and heart failure and showed that surgical intervention during initial hospitalization was associated with decreased in-hospital and 1-year mortality rates. The Early Surgery Versus Conventional Treatment in

IE trial studied patients with left-sided IE, heart failure, and large vegetations randomized to either early surgery within 48 hours of diagnosis versus conventional therapy with surgery occurring some point after 48 hours but still within the index hospitalization. In patients with large mitral or aortic valve vegetations (>10 mm), early surgery was found to be associated with decreased mortality and embolic events when compared with conventional medical therapy (3% vs 23%). In this trial, patients who had surgery within 48 hours also had a decreased rate of all-cause death.

C. Valve repair is a reasonable option for mitral, tricuspid, and, less often, aortic IE in which the infection has been controlled. The choice among mechanical, bioprosthetic, and biologic devices may be made according to the usual criteria. However, in the setting of aortic prosthetic endocarditis, a homograft is less likely to become infected than either a xenograft or a mechanical valve and is considered the optimal valve substitute.

D. Some observational studies have called into question the more relaxed guidelines on antibiotic prophylaxis citing a corresponding increase in the incidence of endocarditis with decrease in prescriptions for antibiotic prophylaxis. These data have yet to be substantiated by a larger randomized trial.

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CHAPTER 20

Rheumatic Fever

Ben Alencherry and Tom Kai Ming Wang

I. INTRODUCTION. Rheumatic fever (RF) is a systemic autoimmune disorder related to prior streptococcal infection and is the leading cause of heart disease in those under the age of 40 years living in developing nations. For information on rheumatic heart disease (RHD), a long-term sequela of RF, see the corresponding section in Chapter 16.

A. The incidence of RF varies substantially among different regions, approaching 200 per 100,000 in developing nations. In the United States, the incidence is less than 1 per 100,000 and continues to decline, attributed to improving public health and living conditions, antibiotic development, and shifts in endemic strains of group A *Streptococcus* (GAS). The prevalence of RHD is estimated at 3.4 cases per 100,000 people in nonendemic countries and >1,000 cases per 100,000 in endemic countries. The highest prevalence, disability, and mortality are centered in sub-Saharan Africa, South Asia, and Oceania.

B. RF is more common among those at high risk for streptococcal pharyngitis, such as military recruits, those in close contact with school-aged children, and persons of low socioeconomic status. It most commonly occurs between 5 and 18 years of age. RF affects both sexes equally, except for Sydenham chorea, a neurologic disease manifestation more present in postpubescent females.

C. With differences in incidence worldwide, it has been recommended to risk stratify patients according to population risk to tailor the index of suspicion. Low-risk populations are those with RF incidence ≤2 per 100,000 school-aged children or all-age RHD prevalence of ≤1 per 1,000 population per year such as the case with the United States.

D. In high-risk populations, RF can present variably, including aseptic monoarthritis and low-grade fever.

E. Carditis is one of the major presentations of RF; thus, echocardiography is a key diagnostic modality. Classically, it is diagnosed by auscultation of a murmur suggesting the most common carditic presentation, valvulitis. With improvement in Doppler echocardiography, the concept of subclinical carditis has arisen, where a patient may have echocardiographic findings of valvular disease but lacks a murmur on physical examination. This subclinical carditis group comprises approximately 17% of RF cases.

F. The natural history of acute RF (ARF) includes the transition from carditis to RHD. Over the years, the valvular lesions become chronic and evolve with subsequent episodes of ARF. Although serial bacterial infections are thought to be culprit due to ongoing inflammation, repeated episodes are only recognized in 30% to 50% of cases, suggesting frequently missed infections or subclinical manifestations.

G. RF recurrence and progression to RHD is highest in the first year after the index episode, but low-level risk persists for >10 years.

II. CLINICAL PRESENTATION. The clinical manifestations of RF **develop 3 weeks after a GAS pharyngitis**. It is important to note that one-third of patients with RF do not report a history of sore throat. Patients present initially with a sudden onset of constitutional symptoms, including fever (101-104 °C), malaise, weight loss, and pallor. An exudative and proliferative inflammatory process involving collagen fibrils characterizes the acute phase of RF. **Multiple organ systems can be involved**, including the dermis, central nervous system (CNS), synovium, and heart.

A. Diagnostic criteria

1. The 2015 American Heart Association (AHA) Revised Jones Criteria, used for the diagnosis of RF, requires a recent history of pharyngitis and a combination of major and minor criteria (**Table 20.1**).

TABLE 20.1 Diagnosis of Rheumatic Fever by Revised Jones Criteria

GAS Infection	Major Jones Criteria		Minor Jones Criteria	
Culture	**Low Risk[a]**	**Moderate to High Risk**	**Low Risk[a]**	**Moderate to High Risk**
ASO titers Anti-DNAse B	Carditis[b] Polyarthritis	Carditis[b]	Polyarthralgia	Monoarthralgia Fever (≥38 °C)

GAS Infection	Major Jones Criteria		Minor Jones Criteria	
Culture	**Low Risk[a]**	**Moderate to High Risk**	**Low Risk[a]**	**Moderate to High Risk**
Other antistreptococcal antibodies Streptococcal antigens	Chorea Erythema marginatum Subcutaneous nodules	Mono- or polyarthritis Polyarthralgia Chorea Erythema marginatum Subcutaneous nodules	Fever (≥38.5 °C) ESR ≥60 mm in the first hour and/or CRP ≥3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)	ESR ≥30 mm/h and/or CRP ≥3.0 mg/dL Prolonged PR interval, after accounting for age variability (unless carditis is a major criterion)

The diagnosis of RF requires confirmation of a previous ***GAS infection*** with at least one of the methods listed above together with either ***two major criteria or one major criterion and two minor criteria***.

anti-DNase, antideoxyribonuclease B; ASO, antistreptolysin O; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A *Streptococcus*; RF, rheumatic fever.

[a]Low-risk populations are those with RF incidence ≤2 per 100,000 school-aged children or all-age rheumatic heart disease prevalence of ≤1 per 1,000 population per year.

[b]Subclinical carditis indicates echocardiographic valvulitis.

2. In some circumstances, the **diagnosis of RF can be made without strict adherence to the above criteria**, as in cases of indolent or recurrent carditis or isolated cases of chorea when other causes have been excluded. In resource-limited settings where it is not possible to fulfill criteria, "possible" RF is appropriate and warrants treatment.
3. **Echocardiography** is an integral part of the revised criteria. It is to be used in definite and suspected cases of RF. Subclinical valvulitis was a new addition to the major criteria in the latest revision, and its prompt diagnosis can lead to earlier treatment, long-term secondary prevention, and increased surveillance of cardiac involvement (**Table 20.2**).

TABLE 20.2 Doppler Findings in Rheumatic Valvulitis
Pathologic Mitral Regurgitation (All Four Criteria Met)
Seen in at least two views
Jet length ≥2 cm in at least one view
Peak velocity >3 m/s
Pan systolic jet in at least one envelope
Pathologic Aortic Regurgitation (All Four Criteria Met)
Seen in at least two views
Jet length ≥1 cm in at least one view
Peak velocity >3 m/s
Pan diastolic jet in at least one envelope

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B. Major manifestations (see **Table 20.1**)

1. **Carditis. The most serious and specific manifestation of RF, the incidence of carditis can vary from 40% to 91%.** It can manifest as a pancarditis affecting the endocardium, myocardium, and pericardium simultaneously.
   a. Cardiac involvement ranges from an asymptomatic presentation to progressive congestive heart failure and death.
   b. **The most typical manifestations include sinus tachycardia, arrhythmias, valvular insufficiency, a pericardial friction rub, cardiomegaly, and heart failure.**
   c. Heart failure is rare in the acute phase; it is usually the result of myocarditis.
   d. The most characteristic component of carditis is valvulitis and endocarditis, involving the mitral and aortic valves.
      (1) **Mitral regurgitation is the hallmark of rheumatic carditis.** Aortic insufficiency is less common and is usually associated with mitral insufficiency. Generally, patients less than 30 years old tend to present with isolated mitral regurgitation, whereas

patients develop mitral stenosis during the third decade, with mixed mitral valve disease predominating thereafter. Overall, most patients have isolated mitral regurgitation, mixed mitral regurgitation and stenosis, or mitral and aortic valve disease. Rarely is the tricuspid or pulmonic valve involved.

(2) **Subclinical carditis** occurs when no murmurs are auscultated, but valve thickening with regurgitation is present on echocardiography. This occurs in up to 17% of patients with RF.

(3) Acute mitral regurgitation produces an apical systolic murmur that may be accompanied by a mid-diastolic **Carey Coombs** murmur of relative mitral stenosis (a high-pitched early diastolic murmur that varies from day to day). Right-sided valves are rarely involved.

(4) Subclinical carditis resulting in valvular regurgitation usually persists indefinitely. If there is no progression in the subsequent month after diagnosis, the valve dysfunction is constant.

(5) Pericarditis, occurring in 10% of patients, may manifest as chest pain, friction rubs on auscultation, and distant heart sounds but is often clinically silent. Downstream sequelae, such as cardiac tamponade and constrictive pericarditis, rarely occur.

2. Arthritis. The most **common** manifestation of RF, arthritis can present as monoarthritis or polyarthritis.

a. It occurs in 80% of patients and is described as **painful, asymmetric, migratory, and transient**. **It involves large joints**, such as the knees, ankles, elbows, wrists, and shoulders.

b. It is **more common in older patients and improves markedly with nonsteroidal anti-inflammatory drugs (NSAIDs)** within 48 hours of treatment.

c. Monoarthritis, oligoarthritis, and involvement of small joints of the extremities are less common. However, arthritis of the first metatarsophalangeal joint, enthesopathy, and axial involvement have been reported.

d. This manifestation is usually benign, self-limiting, and does not result in permanent sequelae.

e. Joint fluid analysis typically shows inflammation without infection.

f. In low-risk populations, polyarthritis fulfills the arthritis criteria, whereas in high-risk populations, either polyarthralgia or monoarthritis can be considered.

3. **Sydenham chorea.** Also known as Saint Vitus dance, this **extrapyramidal disorder is characterized by purposeless and involuntary movements** of face and limbs, muscular hypotonia, and emotional lability.

   a. Initial manifestations include difficulty writing, talking, or walking.

   b. Sydenham chorea is a **delayed manifestation of RF**, usually appearing 2 months or more after an upper airway infection and can be the only manifestation of ARF. Chorea has been reported in up to 40% of affected children. Most cases tend to follow a benign course, with complete resolution of symptoms in 2 to 4 months, although persistent symptom burden has been reported.

4. **Subcutaneous nodules.** Almost always associated with carditis, arthritis, or CNS symptoms, the subcutaneous nodules of RF are firm, painless, and freely mobile, occurring in less than 10% of patients. They are usually located on the extensor surfaces of joints or bony prominences. They respond to anti-inflammatory treatment and are usually transient in nature.

5. **Erythema marginatum.** This is an evanescent erythematous macular rash with a pale center of irregular shape. It is **usually nonpruritic and tends to disappear after a few days**. It is highly specific and occurs in <5% of patients. The lesions vary in size and do not typically affect the face. Given the association, its presence is **suggestive of coexisting carditis**.

C. **Minor manifestations.** Fever and arthralgias are common, but nonspecific findings of RF can support the diagnosis when only a single major manifestation is present (**Table 20.1**).

1. Fever is encountered during the acute phase of the disease and does not follow a specific pattern.

2. Arthralgia is defined as pain in one or more large joints without objective findings of inflammation on physical examination.
3. Other clinical manifestations associated with RF, but not included in the diagnostic criteria, include **abdominal pain, epistaxis, acute glomerulonephritis, rheumatic pneumonitis, hematuria, and encephalitis**.

III. ETIOLOGY AND PATHOPHYSIOLOGY

A. The association between pharyngitis and the scarlet fever epidemics in the 1930s, the findings of high levels of antistreptolysin O (ASO) in sera of patients with RF, and the confirmation of antibiotics as an efficient mode of prophylaxis of RF provide **strong evidence that GAS is the agent causing initial and recurrent attacks of RF**.

1. While the exact mechanism is unknown, RF is plausibly caused by an immunologic mechanism. Patients demonstrate a hyperimmune response to GAS, and the level of immune response correlates with the severity of disease. Supporting evidence includes onset approximately 3 weeks following an upper respiratory tract infection, a rarity before the age of 5 years with an immature immune system, and cross-reactivity between streptococcal cellular antigens and proteins present in human connective tissue.
   a. The most important antigenic structures (M, T, and R proteins) are localized in the external layer of the bacterial cell wall.
   b. The M protein not only is responsible for type-specific immunity but also has a powerful antiphagocytic action and is classically regarded as a marker of streptococcal rheumatogenic potential. Patients with RF possess high levels of antibodies targeted against this protein. Specific M serotypes of GAS have been recognized as strong stimulators of a robust immune response and are associated with an increased risk of developing RF.
2. **In epidemics of streptococcal pharyngitis, it is estimated that approximately 3% to 6% of untreated individuals will go on to develop RF.** However, recurrence of RF is seen in about half of patients with a history of RF. For endemic GAS pharyngeal infections, the incidence of RF is much less common.

B. Numerous epidemiologic studies favor a **familial predisposition**. A monoclonal antibody to B-cell alloantigen (D8/17) is universally detected in patients with RF, whereas this antibody is present in <14% of the general population. In addition, susceptibility to RF has also been linked with D-related human leukocyte antigen 1, 2, 3, and 4 haplotypes. These genetic markers may be useful in the future to identify individuals susceptible to developing RF.

IV. DIAGNOSTIC TESTING. RF is a clinical diagnosis because there is no single laboratory study in isolation that is diagnostic.

A. Laboratory tests

1. Supporting evidence of antecedent GAS infection can be obtained through a throat swab culture, elevated ASO titer, or a positive rapid antigen detection test (RADT) in patients with a clinical story suggestive of pharyngitis.
2. Although no consensus exists regarding which tests to order at what time, ASO titers and cultures are initially obtained when RF is suspected.
3. A negative throat culture is usually sufficient to withhold antibiotic treatment in most cases, especially if clinical suspicion of RF is low.
4. Elevated or rising ASO titers provide solid evidence for recent GAS infection. **A greater than 2-fold rise in ASO titers compared with convalescent titers is diagnostic.**
5. The probability of detecting a previous GAS infection can be increased by obtaining repeated ASO tests or by looking for antibodies to other streptococcal antigens, such as **antideoxyribonuclease B**.
6. A slide agglutination test is commercially available, which measures antibodies to several streptococcal antigens. However, it is **not well standardized nor reproducible**. Therefore, it is not recommended as a definitive test.
7. Miscellaneous nonspecific tests
   a. **Leukocytosis, thrombocytosis, or anemia** may be noted.
   b. The favored tests to measure acute phase response are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP);

paradoxically, normal values are often seen in those with Sydenham chorea.

B. Chest x-ray

1. Chest radiography may identify cardiomegaly (namely, left atrium), increased pulmonary vasculature markings, or pulmonary edema.

C. Electrocardiogram (ECG)

1. In patients in whom carditis is subtle and signs of valvular involvement may be mild or transient, a baseline ECG should be obtained to help with diagnosis.
2. The most common ECG findings are **PR prolongation and sinus tachycardia**. Myocarditis may prolong the QT interval. In cases of pericarditis, low-voltage QRS complexes and ST-segment changes in the precordial leads can be observed.

D. Imaging

1. **Transthoracic echocardiography** is used to assess for rheumatic valve disease, either regurgitation or stenosis. The severity of valvular involvement follows the American Society of Echocardiography criteria, including qualitative, semiquantitative, and quantitative parameters.
   a. Leaflet calcification and subvalvular apparatus involvement are present in the chronic phase (RHD).
   b. The AHA has suggested guidelines for Doppler and morphologic features that implicate rheumatic valvulitis (see **Table 20.2**).
   c. Beyond valvular assessment, echocardiography can assess cardiac chamber size and function and estimate pulmonary pressures, especially important in mitral stenosis, pericardial disease, and congenital heart disease.
2. **Stress echocardiography** can contribute to an understanding of exercise capacity, left ventricular response to stress, and pulmonary pressure changes in moderate-to-severe lesions. This is important in considering the timing of intervention.
3. **Transesophageal echocardiography** should be pursued if image acquisition is suboptimal with transthoracic echocardiography to ensure a thorough valvular assessment is conducted, with an understanding of the risks of the invasive procedure.

4. Currently, **cardiac computed tomography, nuclear imaging, and cardiac magnetic resonance imaging** have no role in the diagnosis of ARF but may be useful in preoperative evaluation of patients who are undergoing intervention.

E. Biopsy

1. **Endomyocardial biopsy** does not help in diagnosing index rheumatic carditis events but can have a role in **distinguishing chronic inactive RHD from acute rheumatic carditis**. As such, **it is rarely indicated** in the typical diagnostic workup.
2. On pathology, Aschoff bodies, a form of granulomatous inflammation, are considered pathognomonic for rheumatic carditis. They are encountered in 30% to 40% of biopsies from patients with recurrent RF. The typical location is the interventricular septum, the left ventricular free wall, or the left atrial appendage.
3. The histologic findings of RF carditis include edema and cellular infiltration of valvular tissue. Hyaline degeneration of the affected valve results in the formation of verrucae at its edge, preventing the normal leaflet coaptation. If the inflammatory process persists, fibrosis and calcification develop, leading to valvular stenosis.

V. THERAPY. It is generally recommended that **patients with suspected RF be admitted for close observation and workup. Anti-inflammatories and antibiotics are considered the backbone of therapy**.

A. Anti-inflammatory therapy includes salicylates and NSAIDs, and if no response, then only consideration of corticosteroids for the treatment of arthritis. Aspirin in a dose of 80 to 100 mg/kg/d in children and 4 to 8 g/d for adults has been used. There is increasing experience with NSAIDs, given the risk of Reyes syndrome in children with excess aspirin administration.

1. Salicylate or steroid therapy does not appear to affect the course of carditis; therefore, the duration of anti-inflammatory therapy is somewhat arbitrary and is guided by the severity of disease and the response to therapy. Therapy should be continued until there is sufficient clinical and laboratory evidence of disease inactivity. Based on available evidence, which spans 70 years and is not of the highest

quality, neither aspirin nor corticosteroids prevent long-term valvular damage, despite relieving symptoms of inflammation.

2. For patients with severe carditis with heart failure, intravenous (IV) glucocorticoids have been recommended by some centers for a short course to treat the inflammation. Careful monitoring of side effects, including fluid retention and gastrointestinal bleeding, is paramount.

B. Antibiotic therapy is primarily penicillin, with alternatives if an intolerance is present, such as macrolides.

1. During an ARF episode, inflammation due to infection is already well established. Nevertheless, penicillin is still recommended for complete eradication of the pathogen. Oral penicillin V or a single dose of intramuscular (IM) benzathine penicillin G can be used.

2. If penicillin cannot be administered due to confirmed allergy, macrolides or cephalosporins can be given.

C. Congestive heart failure should be managed with standard therapy, including diuretics for decongestion (see Chapters 7 and 8 for further information on heart failure management).

1. For severe valvulitis manifesting as regurgitation and pulmonary edema, identification of the pathology is paramount, as cardiac surgery may be indicated if there is a ruptured chordae tendineae causing the valvular insufficiency.

VI. PREVENTION

A. Primordial prevention. RF had a dramatic fall in incidence even before the advent of antibiotics; most think this is due to an improvement in environmental, economic, and social conditions along with increased access to primary health care around the world. Successfully addressing these factors is paramount in reduction of the disease, especially in low-income countries.

B. Primary prevention. Eradication of GAS infection, which prevents chronic and repetitive exposure of antigenic streptococcal components to the host immune system, can reduce the rate of RF by up to 80%. However, **no treatment can eradicate GAS completely in all patients because of high colonization rates in endemic areas**.

1. Early therapy is advisable because it reduces both morbidity and the period of infectivity. Therapy started as late as 9 days after the onset

of acute streptococcal pharyngitis is still effective in preventing primary attacks of RF (**Table 20.3**).

TABLE 20.3 Prevention of Rheumatic Fever

Drug	Dosage	Route	Duration
Primary Prevention			
Benzathine (penicillin G)	600,000 U (≤27 kg) 1.2 million U (≥27 kg) *or*	IM	Once
Penicillin V (children)	250 mg (2-3 times/d)	Oral	10 d
Penicillin V (adolescents and adults)	500 mg (2-3 times/d)	Oral	10 d
Penicillin-allergic patients			
Erythromycin ethyl succinate	40 mg/kg/d (2-4 times/d up to 1 g/d)	Oral	10 d
Erythromycin estolate	20-40 mg/kg/d (2-4 times/d up to 1 g/d)	Oral	10 d
Secondary Prevention			
Benzathine (penicillin G)	1.2 million U	IM	q3-4 wk
Or			
Penicillin V	250 mg	Oral	bid
Or			
Sulfadiazine	0.5 g (≤27 kg) 1.0 g (>27 kg)	Oral	qd
Penicillin- and sulfadiazine-allergic patients			
Erythromycin	250 mg	Oral	bid

Bid, twice a day; IM, intramuscular; qd, every day.

2. Penicillin is the agent of choice primarily for its narrow spectrum of activity, long-standing–proven efficacy, and low cost.
   a. Best results are achieved with a **single IM dose of benzathine penicillin G**. An IM regimen is preferred in patients unlikely to complete a 10-day course of oral therapy or in patients with a

personal or family history of RF or RHD. Preparations that contain procaine penicillin are less painful than the standard formulation.

b. Oral penicillin regimens have several disadvantages, including lower compliance, complicated dosing schedules, drug interactions, and socioeconomic factors. The preferred oral antibiotic is penicillin V (phenoxymethylpenicillin) (see **Table 20.3** for dosage information). A broader spectrum penicillin, such as amoxicillin, offers no microbiologic advantage over penicillin.

c. Studies suggest the use of echocardiographic screening to identify those with subclinical findings of rheumatic valve disease and initiating penicillin therapy to prevent further RF is clinically effective and cost-effective.

3. In cases of **penicillin allergy**, alternatives include macrolides and cephalosporins.

a. Erythromycin can be used for a 10-day course, with a maximum dosage of 1 g/d.

b. Although uncommon in the United States, strains resistant to erythromycin have caused treatment failures. Other macrolides, such as azithromycin, have the advantage of shorter treatment duration and few gastrointestinal side effects. These can be used as a second-line therapy for patients aged 16 years or above with GAS pharyngitis. The recommended dosage is 500 mg as a single dose on the first day followed by 250 mg once daily for 4 days.

c. Another alternative regimen is a **10-day course of an oral cephalosporin.** A first-generation drug, such as cefazolin or cephalexin, has a narrow spectrum of action and is preferred to other broader drugs in the family.

d. Sulfa-derived antibiotics **(sulfonamides and trimethoprim) do not eradicate GAS in patients with pharyngitis**.

e. **Tetracyclines should be avoided due to highly prevalent resistant strains.**

C. **Secondary prevention.** Prophylaxis for preventing recurrences should start as soon as RF or RHD is diagnosed, as recurrences can be asymptomatic. As in primary prevention, IM is the route of choice, given adherence, cost, and level of evidence.

1. Benzathine penicillin G in doses of 600,000 IU (patient's weight <27 kg) to 1.2 million IU (patient's weight >27 kg) administered IM every 4 weeks is the recommended regimen in most circumstances. The interval is reduced to 3 weeks for individuals living in endemic areas.
2. The duration of prophylaxis depends on the situation. **Table 20.4** provides additional information.

TABLE 20.4 Duration of Therapy for Secondary Prevention of Rheumatic Fever

Disease State	Duration of Therapy
RF + carditis + residual valvular disease	At least 10 y after episode and at least until the age of 25 y. Lifelong prophylaxis may be required (for more severe valvular disease).
RF + carditis without valvular disease	10 y or at least until 25 y of age, whichever is longer
RF without carditis	5 y or until 18 y of age, whichever is longer
RF after valve surgery	Lifelong

RF, rheumatic fever.
Data from Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation*. 2015;131:1806-1818.

   a. Prophylaxis for **recurrent RF without carditis** should be continued for 5 years after the last RF attack or up to the age of 18 years, whichever is longer.
   b. For **patients with RF and carditis but no residual valvular disease**, prophylaxis should extend for a period of 10 years or until age 25, whichever is longer.
   c. Indefinite antibiotic prophylaxis is recommended in **patients with severe valvular heart disease**.
3. The success of **oral prophylaxis** depends on the patient's adherence to the prescribed regimen. Some favor switching patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of RF for at least 5 years.
   a. The preferred oral formulation is penicillin V.

b. For patients who are **penicillin allergic**, sulfadiazine or erythromycin can be used (see **Table 20.3**).

c. **Even with optimal adherence, the risk of RF recurrence is higher with an oral method compared to an IM regimen.**

D. Endocarditis prophylaxis. Updated guidelines from the AHA published in 2007 do not specify recommendations for patients with RF. Only patients with RHD who have prosthetic valves or a previous history of endocarditis should receive antibiotic prophylaxis.

E. Vaccine development. Several vaccines against GAS are currently in clinical trials. The M protein is the most promising target, but vaccine development is complicated for several reasons, including extensive genomic variation, M-protein sequence variation, and safety in development.

VIII. SCREENING

A. Screening in endemic areas. Given the significant burden of RHD, screening children and young adults has proven useful for those in endemic areas.

1. The populations to target for screening programs include school-aged children, pregnant women in endemic countries, and those with high-risk demographics.
2. Screening can include auscultation or point-of-care echocardiography, the latter being more sensitive and specific for the detection of any degree of valvular involvement.
3. Identification of patients with subclinical RHD as a result of occult or untreated RF episodes can lead to earlier initiation of secondary prophylaxis and reduce the progression of valvular heart disease.

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SECTION IV

Arrhythmias

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CHAPTER 21

Supraventricular Tachycardia

Mohammad H. Abbasi and Mandeep Bhargava

I. INTRODUCTION.

Tachyarrhythmias have been classically categorized by their location and mechanism. Tachyarrhythmias can originate from ventricular tissue (ventricular tachycardia [VT]) or, alternatively, can originate from or involve supraventricular tissue (supraventricular tachycardia [SVT]). The three mechanisms of tachyarrhythmia include abnormal automaticity, triggered activity, and reentry.

A. Mechanisms

1. **Abnormal automaticity.** Automaticity refers to the property of cardiac tissue to spontaneously generate pacemaker activity. There are both normal and abnormal sources of automaticity.

   An example of **normal** automaticity is the rapid firing rates of a normal pacemaker focus, such as the sinus node (SN), atrioventricular (AV) node, or Purkinje system because of ischemia, metabolic disturbance, exercise, or pharmacologic manipulation. A clinical example would be **sinus tachycardia** or **junctional rhythm**.

   Abnormal automaticity refers to tissues that under normal circumstances do not demonstrate automaticity but can become automatic in the setting of ischemia, metabolic disturbance, or pharmacologic manipulation. Overall, abnormal automaticity is responsible for <10% of tachyarrhythmias. These latent or ectopic loci of cells generate automatic, spontaneous impulses that usurp control of the cardiac rhythm. These usually have a warm-up and cool-down period and cannot be induced by programmed electrical stimulation. A clinical example would be **accelerated idioventricular** rhythm or **multifocal atrial tachycardia**.

2. **Triggered activity** refers to pacemaker activity that is dependent on afterdepolarizations from a prior impulse or series of impulses. Afterdepolarizations are oscillations in the membrane potential. If these reach the critical threshold for depolarization of the surrounding cardiac tissue, they may trigger an action potential, thereby precipitating further afterdepolarizations and perpetuating the pacemaker activity. The two categories of afterdepolarizations are **early** and **delayed**.

   Early afterdepolarizations (EADs) occur before repolarization of the cardiac tissue is completed (during phase 3 of the action potential) and may be the mechanism responsible for the ventricular arrhythmias of the **long QT syndromes (LQTSs)**, as well as **torsade de pointes** ("twisting of the points") produced by class I and class III antiarrhythmics, sympathetic discharge, and hypoxia. Antibiotics such as macrolides, certain azole antifungal agents, some psychotropic medications such as haloperidol, and several nonsedating antihistamines have been shown to produce EADs. Rapid heart rates and the administration of magnesium have been shown to suppress EADs.

   Delayed afterdepolarizations (DADs) occur after the repolarization of the surrounding tissue is complete (during phase 4 of the action potential) and are thought to be the mechanism of triggered atrial tachycardia, arrhythmias of **digitalis toxicity**, and rare VTs responsive to calcium channel blockers. These have been demonstrated in various cardiac issues, including parts of the conducting system, myocardial cells, and valve tissues. Increases in intracellular calcium are associated with DADs, such as those caused by digitalis preparations or excessive sympathetic stimulation. Drugs that block the influx of calcium (such as calcium channel blockers and beta-blockers) and drugs that decrease the sodium current (such as lidocaine and phenytoin) suppress the occurrence of DADs, whereas rapid heart rates augment DADs.

3. **Reentry. Reentry is the most common mechanism for tachyarrhythmias.** In order for reentry to occur, **three conditions**

must be met:

- Two functionally distinct conducting pathways must connect to form a circuit.
- Unidirectional conduction block occurs in one of the pathways because of differences in refractory periods (block occurs in pathway with the longer refractory period).
- Slow conduction occurs down the unblocked pathway (which has the shorter refractory period), allowing the blocked pathway time to recover excitability and sustain the arrhythmia.

Reentrant circuits can occur in the SN, the atrium, the AV node, between the atrium and the ventricle via accessory pathways, and within the ventricle itself. The typical substrate for malignant reentry in the ventricle is **scar or ischemia**, which can produce regions in the heart that **depolarize and repolarize heterogeneously**. Therefore, the impulse can spread to an area that has already repolarized after being previously depolarized. This can set up a circular movement of the impulse resulting in sustained tachyarrhythmias such as VT. Reentry can typically be induced by premature electrical stimulation during electrophysiologic (EP) testing.

Elucidation of the mechanisms of tachyarrhythmias has led to the development of catheter-based treatment strategies and more advanced medical therapy.

II. SUPRAVENTRICULAR TACHYARRHYTHMIAS

A. Sinus tachycardia

1. **Clinical presentation.** Sinus tachycardia manifests as sinus rhythm with a rate above 100 beats/min. Although the rate may be as high as 200 beats/min or more in younger individuals, it is generally **150 beats/min or less in older individuals**.
2. **Pathophysiology.** The SN is an epicardial structure that is located laterally near the junction between the superior vena cava and the right atrium. Under normal circumstances, the rate of SN discharge is governed by sympathetic and vagal stimulation. Sinus tachycardia generally reflects **an underlying process, metabolic**

state, or effect of medication. Fever, hypovolemia, shock, congestive heart failure (CHF), anxiety, pulmonary disease including pulmonary embolism, anemia, thyrotoxicosis, caffeine, nicotine, atropine, catecholamines, or withdrawal from alcohol or drugs (both therapeutic and illicit) can cause sinus tachycardia. Sinus tachycardia can be appropriate, where it represents a normal physiologic response, **or inappropriate**, as in defects in vagal or sympathetic tone or an intrinsic problem with the SN itself.

The **clinical consequences of sinus tachycardia vary** based on the presence or absence of underlying heart disease. Patients with significant coronary artery disease (CAD), left ventricular (LV) dysfunction, or valve disease may not tolerate sinus tachycardia. Patients with inappropriate sinus tachycardia may experience significant symptoms, such as palpitations, dyspnea, and/or chest pain.

3. **Diagnostic testing.** Electrocardiography is the primary diagnostic test. The main differential diagnosis of appropriate sinus tachycardia is sinus node reentry tachycardia (SNRT) and inappropriate sinus tachycardia. Inappropriate sinus tachycardia is characterized by the following features: **(a) heart rate >100 beats/min, (b) P-wave axis and morphology during tachycardia like or identical to that during sinus rhythm, (c) exclusion of secondary causes of sinus tachycardia, (d) exclusion of atrial tachycardias, and (e) symptoms clearly documented to be related to resting or easily provoked sinus tachycardia**. Therapy is generally directed at the elimination of the underlying cause whenever possible. If withdrawal from a therapeutic medication is suspected, then reinstitution or slow tapering of this medication can be attempted, if clinically appropriate. In the case of **inappropriate sinus tachycardia, beta-blockers and calcium channel blockers** may be necessary to control the heart rate. **Ivabradine**, a new agent that affects the I_f channel, can also be considered. In **medically refractory cases, catheter ablation for sinoatrial nodal modification** has been considered.

B. SNRT accounts for 2% to 5% of all supraventricular tachyarrhythmias.

1. **Clinical presentation.** SNRT is most frequently seen in patients with structural heart disease or CAD, especially in inferior myocardial infarctions (MIs). The rate varies from 80 to 200 beats/min. SNRT's characteristic abrupt onset and termination (paroxysmal nature) along with its ability to be induced and terminated by pacing imply that the underlying mechanism is reentry and distinguish it from sinus tachycardia and inappropriate sinus tachycardia.
2. **Pathophysiology.** Reentry occurs within or adjacent to the SN and then conducts via the normal conduction pathway to the rest of the heart. The morphology of the P wave is identical to the underlying sinus morphology. Block at the AV node may occur, but it does not slow the tachycardia. In fact, a Wenckebach-type block often occurs with this rhythm. The development of a bundle branch block does not affect the cycle length or the PR interval.
3. **Therapy.** Vagal maneuvers or adenosine may successfully terminate this arrhythmia. **Rapid atrial pacing** can be used to induce and terminate this tachycardia. Various agents such as beta-blockers, calcium channel blockers, digoxin, or amiodarone may help prevent recurrences. SN ablation or modification may be necessary.

C. Atrial fibrillation (AF) is the most common sustained arrhythmia, occurring in up to 1% of the general population. The prevalence of AF increases with age, affecting up to 10% of the population older than 80 years (see Chapter 24).

D. Atrial flutter. Atrial flutter is the **second most common of the atrial tachyarrhythmias**. Its reported incidence varies from 0.4% to 1.2% in hospital reports of electrocardiogram (ECG). The **clinical significance of atrial flutter is generally due to its association with AF** (with all of the attendant risks of AF) and/or its association with rapid rates of ventricular response.

1. **Clinical presentation.** The clinical presentation may vary widely depending on the presence of underlying heart disease, the

ventricular rate, and the overall condition of the patient. It is **occasionally reported to persist for days** and, less commonly, for weeks or longer. Careful examination of the jugular venous pulse may reveal **frequent, regular a waves** that correspond to the atrial flutter rate. Like AF, it is **commonly seen after open-heart surgery, as well as with other conditions commonly associated with AF**, such as pulmonary disease, thyrotoxicosis, atrial enlargement because of any cause including mitral/tricuspid valve disease, and SN dysfunction.

2. **Pathophysiology.** "Typical" atrial flutter is the **result of a macro-reentrant circuit in the right atrium**. Atypical atrial flutter generally involves other macro-reentrant circuits around scar tissue or surgical incisions.

   In typical atrial flutter, the reentrant circuit most commonly travels in a counterclockwise rotation (as viewed from the ventricular aspect of the tricuspid valve) down the right atrial anterolateral free wall across the cavotricuspid isthmus (area of slow conduction) and up the interatrial septum. Clockwise rotation of this circuit may also be seen and is often referred to as a reverse typical flutter.

3. **Laboratory examination.** The **diagnosis can be difficult when the AV conduction is 2:1**, because the flutter waves may be superimposed on the QRS complex and/or the T waves. When the diagnosis is uncertain, one should **consider maneuvers or medications to slow the ventricular response**, thus revealing the atrial flutter complexes.

   Vagal maneuvers include carotid sinus massage and Valsalva maneuver. **Caution must be exercised** when attempting carotid sinus massage **in patients with known or suspected carotid disease** or vagal maneuvers in **patients with CAD who are at risk for ischemia**.

   Agents for rate control include the intravenous calcium channel blockers **verapamil and diltiazem** and the intravenous beta-blockers **esmolol and metoprolol**. **Adenosine** can be administered if the diagnosis is in question: 6-mg rapid

intravenous push, followed by 12 mg if there is no response (a second 12-mg dose can be given if there is no response). The half-life of this medication is very short, approximately 9 seconds. This causes transient (lasting seconds), complete AV block. Patients should be connected to a transcutaneous pacing device during the administration of this medication for reasons of safety. The clinician can also record atrial activity or electrograms from a **temporary atrial epicardial pacing wire** (placed at open-heart surgery). This results in an ECG with clearer atrial complexes and thus simplifies diagnosis. This strategy also allows a method of delivering rapid atrial pacing in an attempt to terminate the atrial flutter.

On the surface ECG, typical counterclockwise atrial flutter shows the **classic negatively directed "sawtooth" waveform** in the inferior leads (II, III, and aVF) (**Figure 21.1**). Conversely, the atrial depolarizations are positive in these leads in clockwise atrial flutter (**Figure 21.2**).

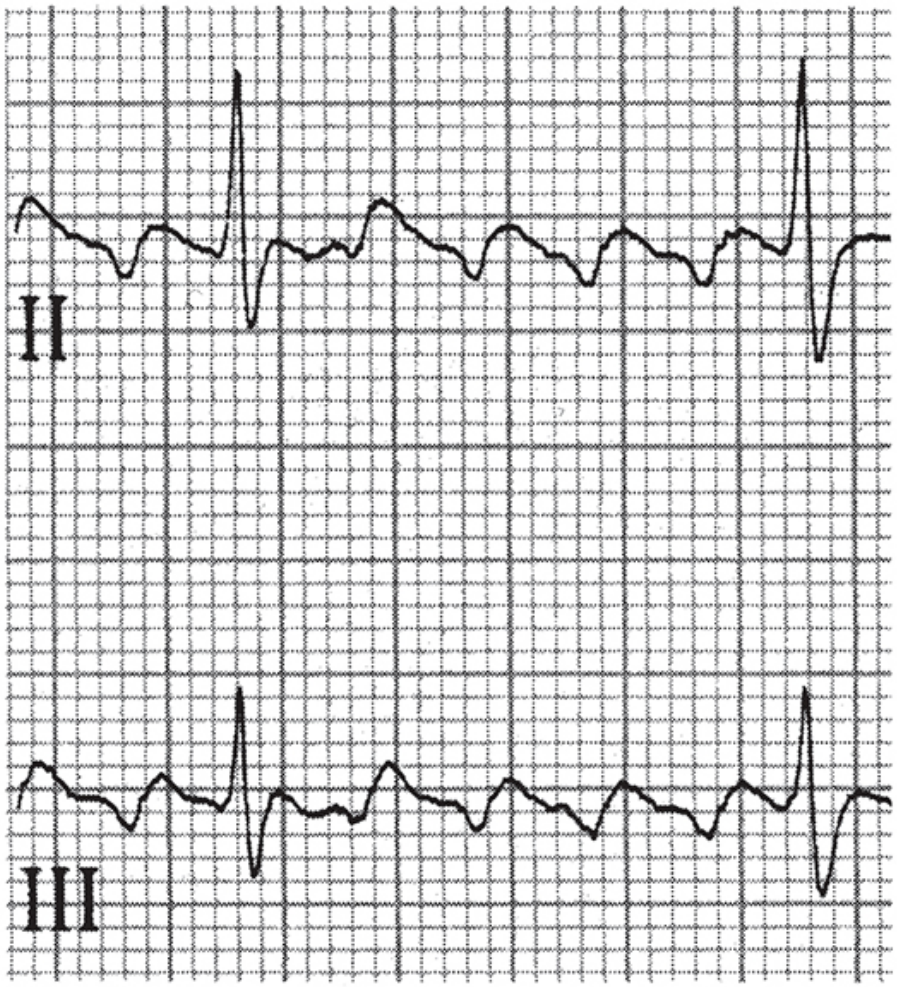

FIGURE 21.1 “Typical” atrial flutter, leads II and III.

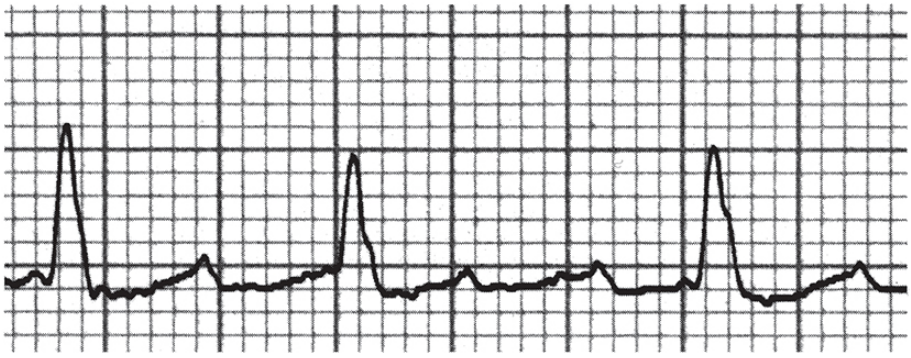

FIGURE 21.2 “Atypical” atrial flutter, lead II.

The **atrial rate** in the absence of drug therapy is **240 to 340 beats/min**. The **QRS complex should be the same as that seen during sinus rhythm,** although aberrant conduction may occur and the QRS may be slightly distorted by the atrial flutter waves. The **ventricular response** can be irregularly irregular, because of varying degrees of AV conduction (2:1, 4:1, and so on) but is more **typically regular as a fixed ratio of the flutter rate**.

4. **Therapy.** Medical therapy differs very little from that for AF (see Chapter 24). Control of the ventricular response rate with a beta-blocker, a calcium channel blocker, or digoxin is critical prior to initiating therapy with agents such as the class IA or IC agents. The class IA or IC agents may either enhance AV nodal conduction through their vagolytic effects, thereby enabling 1:1 (AV) conduction, or slow the atrial rate to a point where 1:1 conduction is facilitated. The conversion from atrial flutter to AF after cardioversion is substantially reduced by the administration of antiarrhythmic drugs prior to direct current cardioversion (DCC), thereby increasing the chance of converting to sinus rhythm.

   a. **Anticoagulation.** There are no prospective data looking at the incidence of thromboembolic events with atrial flutter. However, retrospective data suggest an increased incidence of thromboembolic events. The 2015 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HRS) Guideline statement recommends managing anticoagulation in atrial flutter in a manner similar to that for AF, including cardioversions. Direct oral anticoagulants, when appropriate, are preferred to vitamin K antagonists due to their improved safety profile. Optimal management needs to be individualized with the patients' profile for thromboembolic risk, dictating the type and duration of therapy using the CHA_2DS_2-VASc score.

   b. **DCC.** DCC is the preferred and most effective therapy for most patients. A starting energy as low as 25 to 50 J is often effective. Because DCC may result in conversion from atrial

flutter to AF, a second shock is sometimes necessary to convert AF to sinus rhythm. Rapid atrial pacing should be considered as the **first line of therapy for all patients who have epicardial atrial pacing wires in place after open-heart surgery**. It may be considered via a transesophageal pacing lead or via a transvenous pacing lead. **Before attempting to rapidly pace the atria, one should confirm the absence of ventricular capture** by first pacing at a relatively slow rate while observing for such a phenomenon. Once this is confirmed, the atrium is paced at a rate of 10 to 20 beats/min faster than the underlying atrial flutter rate. Once atrial capture is attained, the rate is increased steadily until the hallmark negative sawtooth waveform converts to a positive waveform. The pacing is then either halted abruptly or slowed rapidly to an acceptable atrial pacing rate. In cases that require extremely rapid rates of pacing (>400 beats/min) or high amplitudes of pacing stimulus strength (>20 mA), there is an increased tendency for the atrial flutter to convert to AF. **When pacing via a transesophageal lead, a higher stimulus strength (up to 30 mA) may be necessary. Because this type of pacing can be quite painful**, sufficient energy to convert the atrial flutter should be used initially to minimize the conversion attempts.

c. **Percutaneous therapy.** Radiofrequency ablation (RFA) of the cavotricuspid isthmus is often curative, with an efficacy >90% for the long-term elimination of atrial flutter. Despite the high success rate of catheter-based therapy, a significant number of patients may subsequently develop AF (>80% at 5 years).

E. **Atrial tachycardias.** This term encompasses several different types of tachycardias that originate in the atria. These tachycardias account for between 10% and 15% of the tachycardias seen in older patients, usually in the setting of structural or ischemic heart disease, chronic obstructive pulmonary disease, electrolyte imbalances, or drug toxicity (particularly digitalis).

1. **Clinical presentation.** These tachycardias are **infrequently seen in younger, healthy patients without underlying heart disease**. They are **typically paroxysmal**, but if incessant, they can lead to a tachycardia-induced cardiomyopathy.
2. **Diagnostic testing**
   a. **ECG.** The **P-wave axis** or morphology is usually different from that of sinus rhythm. One exception is atrial tachycardia originating from the right superior pulmonary vein, which is anatomically close to SN. The axis can be used to predict the origin of the atrial tachycardia. Atrial rhythm is regular, except with automatic atrial tachycardia, which displays a warm-up period. A **QRS complex that is generally identical to sinus rhythm** (QRS can be wide if aberrant conduction occurs) follows each P wave. PR interval is within normal limits or prolonged. Nonspecific ST-T–wave changes may be present. When an AV block is present, there is an **isoelectric baseline** between P waves in all leads. EP study has become critical in determining the underlying mechanism of these tachycardias, because the clinical differences are subtle and overlapping.
3. **Subclassifications.** The current subclassifications are **based on mechanisms** and include automatic atrial tachycardia, triggered atrial tachycardia, and intra-atrial reentry.

   Intra-atrial reentry is usually a disorder **seen in those with underlying heart disease or a history of atrial arrhythmia**, such as AF or atrial flutter. The mechanism is not well understood. The ventricular rate is typically 90 to 120 beats/min because of the frequent occurrence of 2:1 AV conduction, such that hemodynamic effects are generally minimal. This rhythm can be difficult to distinguish from other supraventricular tachyarrhythmias. One clue is that despite any AV conduction block, the rhythm continues. The ability to terminate with adenosine and beta-blockers is variable. **RFA may be effective**, with success rates >75%. **Antiarrhythmics** (the same drugs as for AF and atrial flutter) **have been disappointing in the prevention of recurrence**.

a. **Automatic atrial tachycardia** appears to be generated by an ectopic atrial focus, which usually arises from regions around the crista terminalis in the right atrium and around the base of the pulmonary veins in the left atrium. The mechanism is not well understood. Automatic atrial tachycardia is **seen more often in younger patients**, displays a **warm-up phenomenon** (the supraventricular tachyarrhythmia accelerates after its initiation), **does not respond to vagal maneuvers, and is more likely to be incessant**. Automatic atrial tachycardia can be induced with treadmill testing or with administration of isoproterenol. Atrial stimulation during EP has no effect on either initiating or terminating this arrhythmia. **Propranolol** has been used successfully to suppress automatic atrial tachycardia. **Catheter ablation is the preferred therapy when the tachycardia is incessant or associated with a cardiomyopathy.** Although adenosine may transiently slow automatic atrial tachycardia, it is unlikely to terminate it. Likewise, verapamil has been used without success.

b. **Triggered atrial tachycardia** is the least common of the atrial tachycardias and is virtually never incessant. It is more likely to appear in **older individuals**. It can be induced with rapid atrial pacing and is cycle length dependent. The mechanism of triggered atrial tachycardia is thought to be due to DADs secondary to digitalis toxicity or sympathetic discharge. Catecholamines may play a role in the initiation of this arrhythmia, and thus, exercise testing and isoproterenol may provoke it. Verapamil and adenosine have been shown to terminate triggered atrial tachycardia. Beta-blockers have been less effective. **RFA** is preferred when the tachycardia is very symptomatic and not responsive to medication.

c. **Multifocal atrial tachycardia**

(1) **Clinical presentation.** This atrial arrhythmia is uncommon and estimated to occur in 0.37% of hospitalized patients. The atrial rate is generally 100 to 130 beats/min. It occurs most often in older, critically ill patients and is frequently

associated with concurrent pulmonary disease, particularly chronic obstructive pulmonary disease. It may also be seen in CHF and can degenerate into AF.

(2) Pathogenesis and diagnostic tests. The mechanism appears to be abnormal automaticity or triggered activity arising from distinct atrial sites. The diagnosis requires the following criteria: (1) atrial rate >100 beats/min, (2) P waves with three or more different morphologies, (3) varying P-P, P-R, and R-R intervals, and (4) the P waves separated by isoelectric intervals. Loss of AV conduction of each P wave is uncommon, making it possible to distinguish multifocal atrial tachycardia from AF. **Therapy is directed at the underlying illness, with little role for antiarrhythmics.** Calcium channel blockers in high doses may be useful, or amiodarone when antiarrhythmic therapy is deemed necessary. Maintenance of electrolyte balance, particularly potassium and magnesium, may suppress the occurrence of multifocal atrial tachycardia.

d. Atrioventricular nodal reentrant tachycardia (AVNRT)

(1) Clinical presentation. AVNRT usually has a narrow QRS complex with a ventricular rate typically in the range of 150 to 250 beats/min, although faster rates are infrequently observed. AVNRT is generally seen in patients without underlying heart disease. Palpitations and dyspnea are common presenting complaints. Angina, CHF, and, rarely, shock may be seen in those with a history of underlying heart disease. Syncope may occur due to rapid ventricular rates or due to a prolonged pause or bradycardia seen occasionally when this tachycardia starts or terminates.

(2) Pathophysiology. The mechanism in AVNRT is a reentrant circuit composed of separate fast and slow inputs to the AV node. In 50% to 90% of patients with **"typical" AVNRT**, the antegrade conduction to the ventricles travels over the slow pathway and the retrograde conduction to the atria

occurs over the fast pathway. The initiating event may be either a premature atrial complex (PAC) or a premature ventricular complex (PVC). The PAC blocks in the fast pathway antegradely and conducts down the slow pathway, then conducts back up the fast pathway (which has now recovered) to the atria. Less commonly, a PVC conducts retrogradely to the atria via the fast pathway and then returns to the ventricles via the slow pathway. In the remaining 5% to 10% of patients, **with atypical AVNRT**, the antegrade conduction is down the fast pathway and retrograde via the slow pathway. The cycle length is thus dependent on the conduction velocity of the slow pathway because the fast pathway generally has rapid conduction. Termination of the tachycardia is often the result of a block in the slow pathway. AV dissociation may develop rarely during the tachycardia because the ventricles are not involved in the reentry circuit. This does not affect the rate of tachycardia nor does the development of bundle branch block.

(3) Laboratory features and diagnosis. P waves are generally hidden within the QRS complex or at the terminal portion of the QRS in typical AVNRT. This may be visible as a small pseudo-R′ in lead V_1 or small negative deflections in the inferior leads, as depolarization of the atria occurs simultaneously with ventricular depolarization. The RP segment is generally <100 ms. AVNRT is often induced abruptly by a PAC, and its termination, which also tends to be abrupt, is often followed by a retrograde P wave. The termination may be followed by a brief period of asystole or bradycardia before the SN recovers from its tachycardia-induced suppression. The cycle length may vary, especially at the beginning and at the end of the tachycardia. This variation reflects the variable antegrade AV nodal conduction time. Vagal maneuvers may slow or terminate this tachycardia.

(4) **Therapy.** Per the 2015 ACC/AHA/HRS Guideline statement, catheter ablation and medical therapy (specifically with beta-blockers, diltiazem, or verapamil) share a class I indication for symptomatic AVNRT. The decision about treatment approach should be individualized according to the characteristics of each patient and their preference for medication versus ablation. **RFA has the advantage of curing the arrhythmia** usually and eliminating the need for long-term suppressive therapy with medications. Cure rates with catheter ablation for AVNRT are more than 95%.

Medical therapy. Medications that suppress AV nodal conduction such as beta-blockers, calcium channel blockers, digoxin, and adenosine all slow or block conduction in the antegrade slow pathway, whereas class IA and class IC antiarrhythmic drugs slow the conduction in the retrograde fast pathway. Adenosine may be considered as first-line drug therapy for acute termination of AVNRT. This medication is available in an intravenous form only and has a very short half-life of about 9 seconds. The use of intravenous or oral beta-blockers or calcium channel blockers is an alternative if adenosine is unsuccessful. The onset of action of digoxin limits its usefulness in terminating these arrhythmias, although it may be useful to prevent recurrences. Recurrences may be prevented in patients with frequent sustained episodes with any of the abovementioned agents, except adenosine. Antiarrhythmic drug therapy is not routinely necessary or desirable for AVNRT, given the high success rates and low complication rates for catheter ablation. DCC should be considered for patients whose arrhythmia is unstable or highly symptomatic. Low energies of 10 to 50 J are usually sufficient to terminate AVNRT.

e. Atrioventricular reentrant tachycardia (AVRT)

(1) **Clinical presentation.** Similar to AVNRT, this is another example of an AV nodal–dependent SVT. AVRT usually has a narrow QRS with ventricular rates similar to those of AVNRT, although it more often tends to have a ventricular rate >200 beats/min. The clinical features are very similar to those of AVNRT but are distinct on an EP basis.

(2) **Pathophysiology.** The mechanism in AVRT relies on the presence of an accessory pathway as one portion of the circuit and the AV node as the other portion. The atrium and the ventricle on the same side as the accessory pathway are necessary components of the circuit. AVRT may be orthodromic or antidromic. Orthodromic AVRT usually has a narrow complex that uses the AV node as the antegrade limb and the accessory pathway as the retrograde limb of the circuit. Antidromic AVRT has a wide complex that is the opposite of the orthodromic variety, such that the accessory pathway serves as the antegrade limb and the AV node as the retrograde limb of the circuit. AVRT is most often of the orthodromic type. Accessory pathways may be "concealed" (inapparent by ECG) because of having only retrograde (V to A) conduction properties or "manifest" (apparent on ECG as delta waves, ie, Wolff-Parkinson-White [WPW] pattern). **Unlike AVNRT, the AVRT circuit must involve one of the ventricles; therefore, the development of bundle branch block on the side ipsilateral to the accessory pathway can prolong the ventricular to atrial conduction time and often the cycle length of the tachycardia.** Bundle branch block, particularly left bundle branch block (LBBB), occurs more commonly in AVRT than in AVNRT. AVRT can be distinguished from AVNRT by EP study. The presence of AV or ventriculoatrial (VA) block with continuation of the tachycardia should exclude the presence of an accessory AV pathway.

(3) **Laboratory features and diagnosis.** The P waves of AVRT are frequently inscribed on the ST segment or T wave, because the atrial depolarization and ventricular depolarization are in series rather than in parallel. The RP segment is generally >100 ms. Orthodromic AVRT is more common, accounting for about 95% of all AVRTs, whereas antidromic AVRT accounts for only about 5%. Orthodromic AVRT is usually characterized by a narrow QRS complex as opposed to antidromic AVRT, which is characterized by a wide QRS complex.

(4) **Therapy.** See the discussion of therapy for WPW syndrome.

III. PREEXCITATION SYNDROMES.

Preexcitation was originally used to describe the premature activation of ventricles in patients with WPW. The term has broadened to include all conditions in which antegrade ventricular activation or retrograde atrial activation occurs partially or totally via an anomalous pathway distinct from the normal cardiac conduction system. The incidence of preexcitation on ECG is approximately 1.5 per 1,000 cases, most of which occur in otherwise healthy subjects without organic heart disease. About 7% to 10% of these patients have associated **Ebstein anomaly and are those who are more likely to have multiple accessory pathways**. There is a higher rate of preexcitation in males, with the **prevalence** decreasing with age, although the **frequency** of paroxysmal tachycardia increases with age.

A. Clinical presentation. Approximately 50% to 60% of patients with preexcitation report symptoms such as **palpitations, anxiety, dyspnea, chest pain or tightness, and syncope**. In approximately 25% of the cases, the disease will become asymptomatic over time. Those patients older than 40 years whose disease has been asymptomatic are likely to remain symptom free. The absence of preexcitation on ECG despite the discovery of accessory pathways in patients with asymptomatic disease likely identifies a group of patients at low risk for developing symptoms.

B. Pathophysiology. Patients with preexcitation generally have an accessory pathway(s) that alters the conduction between the atria and the ventricles. These accessory pathways are likely congenital, because relatives of subjects with preexcitation have an increased incidence of preexcitation. AVRT is the most common mechanism associated with preexcitation (80%-85%), with permanent junctional reciprocating tachycardia, Mahaim fiber tachycardia, and Lown-Ganong-Levine (LGL) syndrome accounting for the remainder.

C. WPW syndrome. The basic abnormality lies in the existence of an accessory pathway of conducting tissue, outside the normal conducting system, which connects the atria and the ventricles. This accessory pathway permits the atrial impulse to bypass the normal pathway through the AV node to the ventricles. In the past, these accessory pathways have been referred to as "bundles of Kent." An impulse from the atria can be conducted down both the accessory pathway and the AV node, arriving at the ventricle at nearly the same time. This results in preexcitation of the ventricle, which is really a fusion beat, as a portion of the ventricle is activated via the accessory pathway (giving rise to the delta wave; **Figure 21.3**) and the remainder of the ventricle is activated by the normal activation pathway. If antegrade conduction occurs exclusively via the accessory pathway, the resultant QRS is maximally preexcited and is a wide complex. These accessory pathways may conduct rapidly but frequently have longer refractory periods than the AV node. The inciting event for AVRT is frequently a PAC that is blocked in the accessory pathway and that conducts to the ventricles via the AV node, which has recovered more rapidly. The resultant QRS complex in this instance is normal in appearance. After the QRS complex, the accessory pathway has had sufficient time to recover excitability, and the impulse thus conducts retrogradely to the atria via the accessory pathway. A small but significant percentage (5%-10%) of patients have multiple accessory pathways.

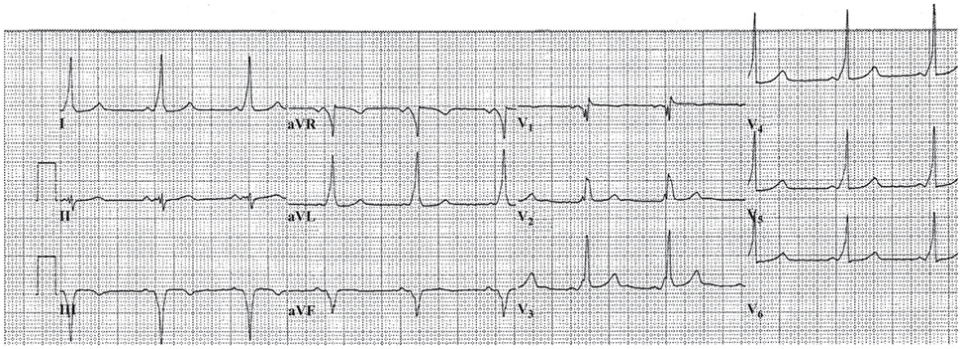

FIGURE 21.3 Wolff-Parkinson-White syndrome, with widespread delta waves seen at the upstroke of the QRS complexes.

D. Permanent junctional reciprocating tachycardia is a variant of AVRT. It is often an incessant supraventricular tachyarrhythmia with an unusual accessory pathway. Here, the accessory pathway behaves like the AV node in that it displays decremental retrograde conduction properties but conducts only retrogradely and is hence a concealed accessory pathway. Thus, the faster the stimulation of such an accessory pathway, the slower the conduction through the pathway. The accessory pathway is most often located in the posteroseptal region and acts as the retrograde limb of the reentrant circuit. The VA conduction is slowed by the decremental nature of the accessory pathway. Because of the incessant nature of this tachycardia, a tachycardia-induced cardiomyopathy may result and ablation is the therapy of choice when this occurs.

E. Mahaim fiber tachycardias are another variant of reentrant tachycardia. The two most common varieties that are recognized are **atriofascicular and fasciculoventricular pathways**. In the former, the accessory pathway is located within the right atrium and inserts into the right bundle branch. The reentrant tachycardia conducts antegrade via the accessory pathway, resulting in a typical LBBB morphology with left-axis deviation. The retrograde circuit is via the AV node. In the second form of Mahaim reentry, the accessory pathway arises in the His-Purkinje fibers and allows bypass of the distal conducting system. This second type is not associated with a clinical tachycardia syndrome, and further therapy is not needed.

LGL syndrome is diagnosed by the presence of a short PR interval and a normal QRS complex on the surface ECG. LGL syndrome likely represents one end (enhanced) of the normal spectrum of AV nodal conduction properties, but in some cases, it is impossible to exclude a distinct perinodal accessory pathway or an abnormality in conduction characteristics of the AV node. It is uncertain if this abnormality in AV conduction is itself associated with arrhythmias.

F. Diagnostic testing

1. **ECG.** The following electrocardiographic criteria are suggestive of an accessory pathway consistent with a WPW pattern. **The WPW syndrome occurs in the setting of the WPW pattern and SVT.**

   The **PR interval is short, typically <120 ms**.

   The QRS complex exceeds 120 ms, with some leads showing the characteristic slurred upstroke known as a delta wave (**Figure 21.3**) and a normal terminal QRS portion.

   The ST-T segment is directed opposite to the major delta and QRS vectors. The most seen tachycardia in WPW syndrome is characterized by a normal QRS with a regular rate of 150 to 250 beats/min. Onset and termination are abrupt.

2. **Localization of accessory pathway.** The **surface ECG** may provide information that allows localization of the accessory pathway. Using the initial 20 ms of the delta wave in leads I, II, aVF, and V_1 [classified as positive (+), negative (−), or isoelectric (±)] and the ratio of R- and S-wave amplitudes in leads III and V_1 (classified as $R \geq S$ or $R < S$) is used in the **Arruda criteria**. Step 1 uses leads I and V_1. If lead I is isoelectric or negative or if $R > S$ in lead V_1, it is a left-sided pathway. Using aVF will then help determine if the pathway is anterolateral, lateral, or posterior. Step 2 uses lead II. If lead II is negative, the pathway is located in a branch of the coronary sinus. Step 3 uses lead V_1. If V_1 is isoelectric or negative, the pathway is septal. Again using lead aVF and QRS vector will help determine if the pathway is anterior, middle, or posteroseptal. Step 4 locates all others on the

right side. Leads aVF and II will then help to differentiate anterior, lateral, or posterior locations. The **most precise localization method is EP study** with ventricular pacing or during orthodromic AVRT (the latter condition is especially helpful because there is VA conduction purely through the accessory pathway, and fusion with VA conduction through the AV node is, therefore, avoided).

3. **Risk stratification** should be considered for patients with WPW pattern or ventricular preexcitation according to ECG findings. The appearance or disappearance of preexcitation on **serial ECGs is of no predictive value**. However, **the intermittent loss or appearance of preexcitation on a beat-to-beat basis is indicative of lower risk**. This may be assessed with ambulatory Holter monitoring during usual activities or with formal exercise stress testing. Such intermittent preexcitation suggests a pathway without the ability for rapid AV conduction and, therefore, lower risk of sudden cardiac death (SCD). However, the reverse is not necessarily true in that most patients with persistent preexcitation may still be at low risk for SCD, but these patients cannot be distinguished from those at risk. Because the greatest danger to patients with preexcitation may be the development of AF, **the induction of AF may be most useful in risk stratification**. This can be done via transesophageal pacing; however, **EP study is the procedure of choice for risk stratification** in patients with persistent ventricular preexcitation.
4. **Therapy**
    a. **Emergency management of acute tachycardia episodes.** A patient **demonstrating hemodynamic instability or extreme symptomatology should be cardioverted rapidly**. Stable patients may be treated medically.
    b. **Normal QRS width.** Both types of AVRT (orthodromic and antidromic) are AV node dependent and thus respond to AV nodal blocking therapies. Although it is reasonable to use vagal maneuvers and AV nodal blocking medications acutely in patients presenting with a narrow QRS (immediate

synchronized DCC should be available should the rhythm degenerate), it is not safe in patients when they present with a wide QRS. Atrial pacing, either transvenous or transesophageal, is also quite efficacious for terminating these types of tachycardias. Adenosine, although effective in treating orthodromic and antidromic AVRTs, may induce AF in up to 15% of cases and should, therefore, be used with caution. In patients with WPW syndrome, AF is a potentially life-threatening arrhythmia, especially when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction.

c. **Wide QRS width.** Patients with accessory pathways can present with wide QRS complex resulting from **(1)** orthodromic AVRT with aberrant conduction, **(2)** antidromic AVRT, or, **most importantly**, **(3)** atrial arrhythmias (atrial tachycardia/atrial flutter/AF) with antegrade conduction down an accessory pathway. Because it is often initially impossible to determine the mechanism of a wide QRS complex in patients with an accessory pathway, they should be treated with agents that slow conduction in the accessory pathways preferentially (procainamide). Because atrial arrhythmias with antegrade accessory pathway conduction are **not** AV node dependent, AV nodal blocking therapies are ineffective and potentially dangerous. **Beta-blockers, calcium channel blockers, digoxin, and adenosine should be avoided in patients presenting with wide complex tachycardias (WCTs)**, because they may encourage preferential conduction down accessory pathways and accelerate ventricular rates, precipitating ventricular fibrillation (VF). **If the tachycardia persists, synchronized DCC** is the treatment of choice. Energies of at least 200 J are likely to be required.

If the patient develops AF, it has been observed that **definitive therapy for the AV reentrant circuit, such as ablation of the accessory pathway, often results in the decrease or even prevention of future episodes of AF**.

5. Long-term management

a. **Priority of therapy.** Patients whose disease is asymptomatic at diagnosis are at low risk for sudden death. As such, it may not be justified to pursue medical or ablative therapy in these patients unless there is a family history of sudden death or the patients are competitive athletes or are in a high-risk occupation. Patients whose disease is symptomatic or who have a history of AF or aborted sudden death may be at higher risk, and such patients warrant further study.

b. **Medical therapy.** Medical therapy may be **appropriate for those with increased risk but no prior symptoms, those with accessory pathways located near the normal conduction pathway that might develop AV block with RFA**, or those at increased risk from invasive procedures. Per the 2015 ACC/AHA/HRS Guideline statement, single-drug therapy may be attempted with flecainide or propafenone (class IIa), in the absence of structural heart disease, which may be preferred to amiodarone, sotalol, or dofetilide (class IIb). These drugs work to slow conduction in both the accessory pathway and the AV node.

c. **Combination therapy** can be accomplished with drugs that work on the AV node (calcium channel blockers, beta-blockers) and with drugs that work exclusively on the accessory pathway (class IA antiarrhythmics).

d. **Percutaneous therapy.** RFA is effective 85% to 98% of the time, depending on the location of the accessory pathway. Recurrence rates are approximately 5% to 8%. Catheter ablation should be considered for any patient at high risk, patients with symptoms or tachycardias refractory to medical therapy, those who have intolerance to medical therapy, and those with high-risk occupations such as pilots.

IV. ATRIAL PREMATURE DEPOLARIZATIONS.

Atrial premature depolarizations (APDs) are premature depolarizations that arise from a region other than the SN. The P-wave morphology and PR interval may be different from

the sinus P wave and normal P interval, depending on the location and timing of the APD and its distance from the AV node.

A. Clinical presentation. APDs are usually asymptomatic and, in isolation, benign. Some patients may feel palpitations or skipped beats. If there is atrial bigeminy with each APD causing AV block, patients may develop symptoms of bradycardia. APDs may trigger SVT (AVNRT, AVRT, and atrial tachycardia) or AF in patients with the electrical and structural substrate for these arrhythmias. APDs increase in frequency as patients age and may be more frequent in patients with mitral valve disease, LV dysfunction, hypertrophic cardiomyopathy (HCM), mitral stenosis, pulmonary disease, and renal failure. Stress, alcohol and caffeine consumption, and smoking can promote APDs. However, APDs also occur in healthy individuals with structurally normal hearts and without significant external exposures (caffeine, alcohol, and stress). Although one study showed a correlation between the frequency of APDs within a 24-hour period and the risk of stroke in men, it is unclear what percentage of these men developed AF. Furthermore, in the Atherosclerosis Risk in Communities (ARIC) study that followed patients with APDs and ventricular premature depolarizations (VPDs), only patients with APDs did not have an increased incidence of SCD.

B. Pathophysiology. APDs may be caused by a variety of mechanisms, including reentry, triggered activity, and increased automaticity. Reentry is thought to be the most common mechanism.

C. Therapy. Asymptomatic individuals do not need treatment for APDs. For symptomatic patients, beta-blockers and class IA, class IC, and class III antiarrhythmic drugs may be considered, although no randomized controlled trials have been performed in this patient population.

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SUGGESTED READINGS

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CHAPTER 22

Ventricular Tachycardia

Arshneel Kochar and Jakub Sroubek

I. INTRODUCTION.

Ventricular tachyarrhythmias, including monomorphic ventricular tachycardia (VT), polymorphic VT, and ventricular fibrillation (VF), account for a large portion of sudden cardiac death (SCD). VT is defined as three or more consecutive QRS complexes of ventricular origin at a rate exceeding 100 beats/min. Ongoing VT that requires intervention or lasts for 30 seconds is considered **sustained VT**. The occurrence of ≥3 episodes of sustained VT within 24 hours that each requires an intervention characterizes **VT storm** (albeit one should be aware that other definitions of VT storm exist). The predominant mechanisms for ventricular arrhythmias (VAs) include abnormal automaticity, triggered activity, and reentry.

II. GENERAL OVERVIEW

A. Mechanisms

1. Automaticity. Automaticity refers to the ability of cardiac tissue to spontaneously generate pacemaker activity. There are both normal and abnormal sources of automaticity.

An example of **normal** accelerated automaticity is the rapid firing rates of a normal pacemaker focus, such as the sinus node (SN), atrioventricular (AV) node, or Purkinje system because of ischemia, metabolic disturbance, exercise, or pharmacologic manipulation. A clinical example would be accelerated **sinus tachycardia** or a **junctional escape rhythm**.

Abnormal automaticity refers to tissues that under normal circumstances do not demonstrate automaticity but can become automatic in the setting of ischemia, metabolic disturbance, or pharmacologic manipulation. Overall, abnormal automaticity is

responsible for <10% of tachyarrhythmias. These latent or ectopic loci of cells generate automatic, spontaneous impulses that usurp control of the cardiac rhythm. These usually have a warm-up and cool-down period and cannot be induced by programmed electrical stimulation. A clinical example would be **accelerated idioventricular** rhythm or **multifocal atrial tachycardia**.

2. **Triggered activity** refers to pacemaker activity that is dependent on afterdepolarizations from a prior impulse or series of impulses. Afterdepolarizations are oscillations in the membrane potential. If these reach the critical threshold for depolarization of the surrounding cardiac tissue, they may trigger an action potential, thereby precipitating further afterdepolarizations and perpetuating the pacemaker activity. The two categories of afterdepolarizations are **early** and **delayed**.

   Early afterdepolarizations (EADs) occur during late phase 2 or phase 3 before repolarization of the cardiac tissue is completed and are associated with action potential prolongation. EADs are the cause of VAs in the setting of the **long QT syndromes (LQTSs)**, particularly **torsades de pointes (TdP)** ("twisting of the points"). TdP secondary to acquired LQTS can be the result of electrolyte abnormalities or medications including class I and class III antiarrhythmics, antibiotics such as macrolides, certain azole antifungal agents, some psychotropic medications such as haloperidol, and several nonsedating antihistamines. Rapid heart rates and the administration of magnesium have been shown to suppress EADs.

   Delayed afterdepolarizations (DADs) occur after the repolarization of the surrounding tissue is complete (during phase 4 of the action potential) under conditions of calcium overload. This is thought to be the mechanism of triggered atrial tachycardia, arrhythmias of **digitalis toxicity**, catecholaminergic polymorphic VT (CPVT), and idiopathic outflow tract VTs. These have been demonstrated in various cardiac tissues, including parts of the conducting system, myocardial cells, and valve tissues. Drugs that block the influx of calcium (such as calcium channel

blockers and beta-blockers) and drugs that decrease the sodium current (such as lidocaine and phenytoin) suppress the occurrence of DADs, whereas rapid heart rates augment DADs.

3. **Reentry. Reentry is the most common cause of tachyarrhythmias.** For reentry to occur, **three conditions** must be met (**Figure 22.1**):

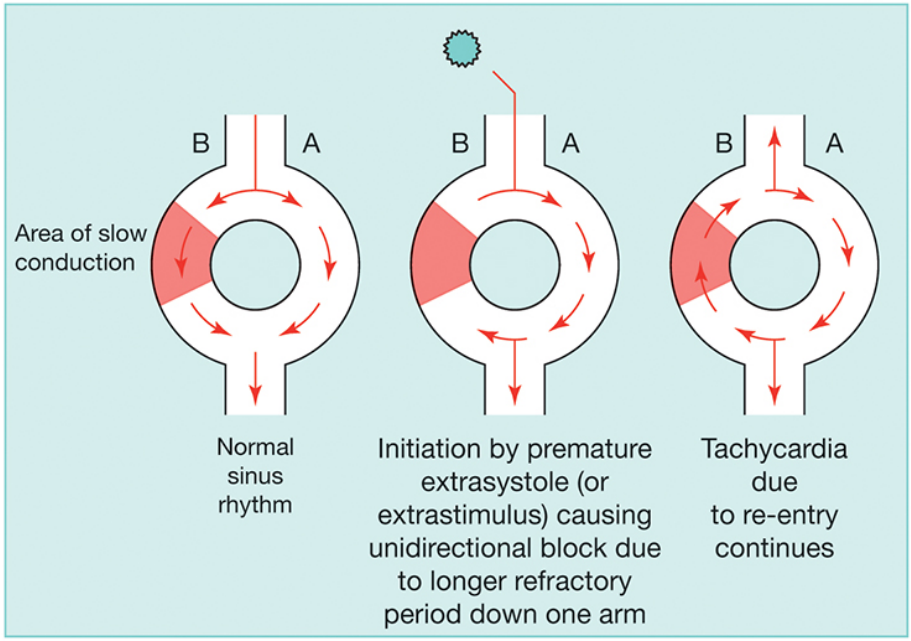


FIGURE 22.1 Mechanism for reentrant arrhythmias. Two functionally distinct conducting pathways (A and B) form a circuit. Unidirectional conduction block occurs in pathway B because of a longer refractory period and premature stimulus. Slow conduction occurs down the unblocked pathway (A) allowing the blocked pathway (B) time to recover excitability, conduct in a retrograde manner, and thus sustain the arrhythmia. (Reproduced from Kaye GC. Percutaneous interventional electrophysiology. *BMJ*. 2003;327(7409):280-283,with permission from BMJ Publishing Group.)

- Two functionally distinct conducting pathways must connect to form a circuit.
- Unidirectional conduction block occurs in one of the pathways because of differences in refractory periods (block occurs in

pathway with the longer refractory period).

- Slow conduction occurs down the unblocked pathway (which has the shorter refractory period), allowing the blocked pathway time to recover excitability, conduct in a retrograde manner, and thus sustain the arrhythmia.

Reentrant circuits can occur in the SN, the atrium, the AV node, between the atrium and the ventricle via bypass tracts, and within the ventricle itself. The typical substrate for malignant reentry in the ventricle is **scar**, which can produce regions in the heart that **depolarize and repolarize heterogeneously**. Therefore, the impulse can spread to an area that has already repolarized after being previously depolarized. This can set up a circular movement of the impulse, resulting in sustained tachyarrhythmias such as VT. Scar-related reentry often presents as monomorphic tachycardia at a regular rate. Reentry can typically be induced by premature electrical stimulation during electrophysiologic (EP) testing. Elucidation of the mechanisms of tachyarrhythmias has led to the development of catheter-based treatment strategies and more advanced medical therapy, which are discussed later.

B. Clinical presentation. The presentation is variable and depends on the clinical setting, the heart rate, the presence of underlying heart disease, and other medical conditions. Some patients have no or minimal symptoms, whereas others may present with syncope or sudden death. In general, slower rates in otherwise normal hearts are better tolerated hemodynamically. The loss of normal AV synchrony may cause symptoms in patients with decreased cardiac function at baseline. Heart rates <150 beats/min can be surprisingly well tolerated in the short term; however, exposure to these rates for more than a few hours is likely to be associated with heart failure in patients with poor ventricular function. Those with normal ventricular function may tolerate prolonged periods at such rates. The range of 150 to 200 beats/min is tolerated variably, according to the factors noted previously. Once the rate reaches and exceeds 200 beats/min, there are symptoms in virtually all patients. On electrocardiogram (ECG), VT commonly presents as a wide complex tachycardia

(WCT), which can be monomorphic (QRS unchanged from beat to beat) or polymorphic (QRS alterations from beat to beat) in appearance. In general, monomorphic VT suggests a single focus or stable reentrant circuit in a patient with or without structural heart disease. On the other hand, polymorphic VT is most commonly seen in ischemia but can also present in patients with channelopathies. TdP is a form of polymorphic VT specific to patients with congenital or acquired LQTS.

C. **Differential diagnosis.** VT needs to be distinguished from **supraventricular tachyarrhythmia (SVT) with aberrant intraventricular conduction, preexcited SVT, bundle branch block, and morphologic changes of the QRS complex secondary to metabolic derangement, pacing, or, occasionally, artifact**.

Brugada criteria. Distinguishing VT from **SVT with aberrancy** can be challenging. Various criteria have been proposed. A good rule of thumb **is that any WCT in a patient with ischemic heart disease is VT until proven otherwise**. Some have reported that >80% of WCTs in such patients are VTs. The **algorithm proposed by Brugada may be helpful in making this distinction, and the algorithm is both sensitive** (99%) **and specific** (96.5%) in patients without a preexisting bundle branch block. As shown in **Figure 22.2**, a stepwise approach is applied. In the first step, the precordial leads are examined for the presence or absence of an RS complex. If an RS is uniformly absent, VT is established. If an RS is present in at least one precordial lead, one moves to the second step, which is measuring the interval from the onset of the QRS complex to the nadir of the S wave. If this distance is >100 ms in at least one precordial lead, then the diagnosis of VT is made (note that the validity of this criterion may be affected by the presence of antiarrhythmic drugs, such as amiodarone). If there is no RS interval >100 ms, the third step is used. In the third step, one looks for evidence of AV dissociation. If there are more QRS complexes than P waves, then the diagnosis is VT. If not, then one moves to the fourth step, which involves examining the morphology of the QRS in the precordial leads V_1 and V_6. If the morphology criteria for VT

(**Figure 22.3**) are present in these leads, then the diagnosis of VT is established. If not, the diagnosis is SVT with aberrant intraventricular conduction.

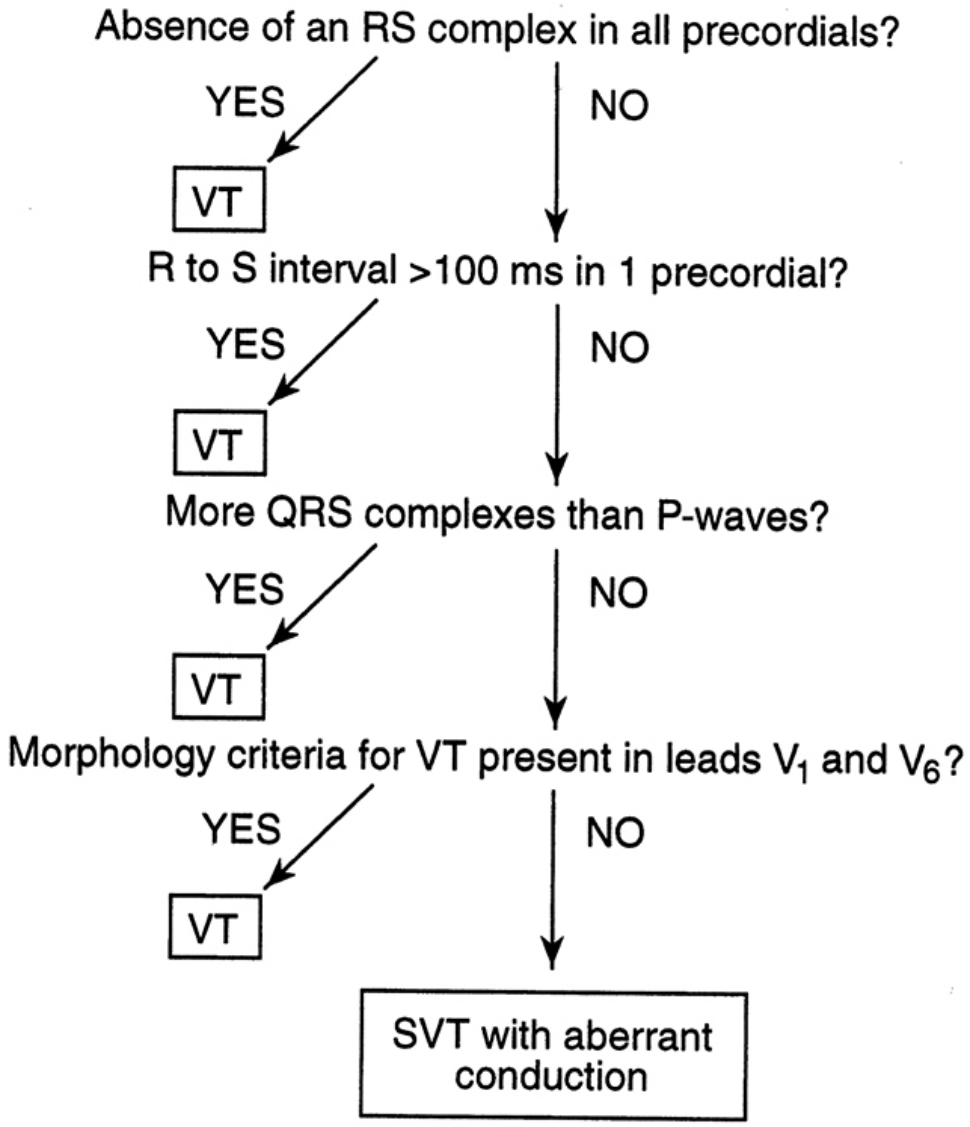


FIGURE 22.2 Brugada criteria for differentiating ventricular tachycardia (VT) from supraventricular tachycardia (SVT) with aberrant intraventricular conduction.

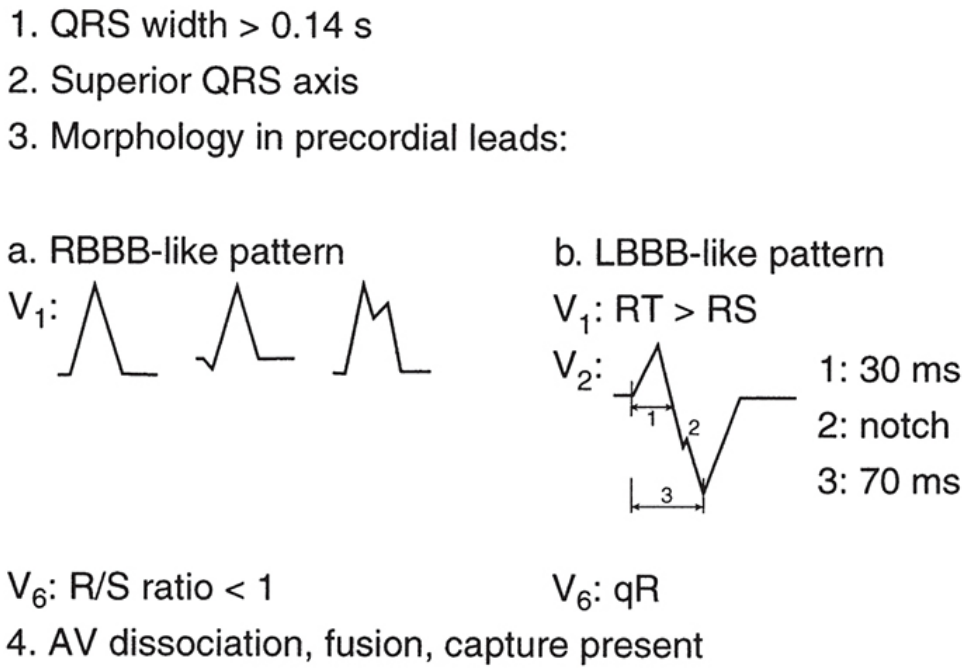


FIGURE 22.3 Classic morphology criteria for ventricular tachycardia. AV, atrioventricular; LBBB, left bundle branch block; RBBB, right bundle branch block.

The Brugada criteria have been further redefined to distinguish between VT and SVT with antegrade conduction over an accessory pathway (**Figure 22.4**). This **second algorithm has a sensitivity of 75% and a specificity of 100% to diagnose VT and exclude preexcited tachycardia**. In the first step, leads V_4 to V_6 are examined to see if the QRS is predominantly negative. If so, then VT is favored. If not, then the second step, examining leads V_2 to V_6 for the presence of a QR complex in one or more of these leads, is applied. If there is a QR complex in any of these leads, then the diagnosis is VT. The third criterion, the presence of AV dissociation, is 100% specific for VT. If there is no AV dissociation, then SVT with antegrade accessory pathway conduction is favored.

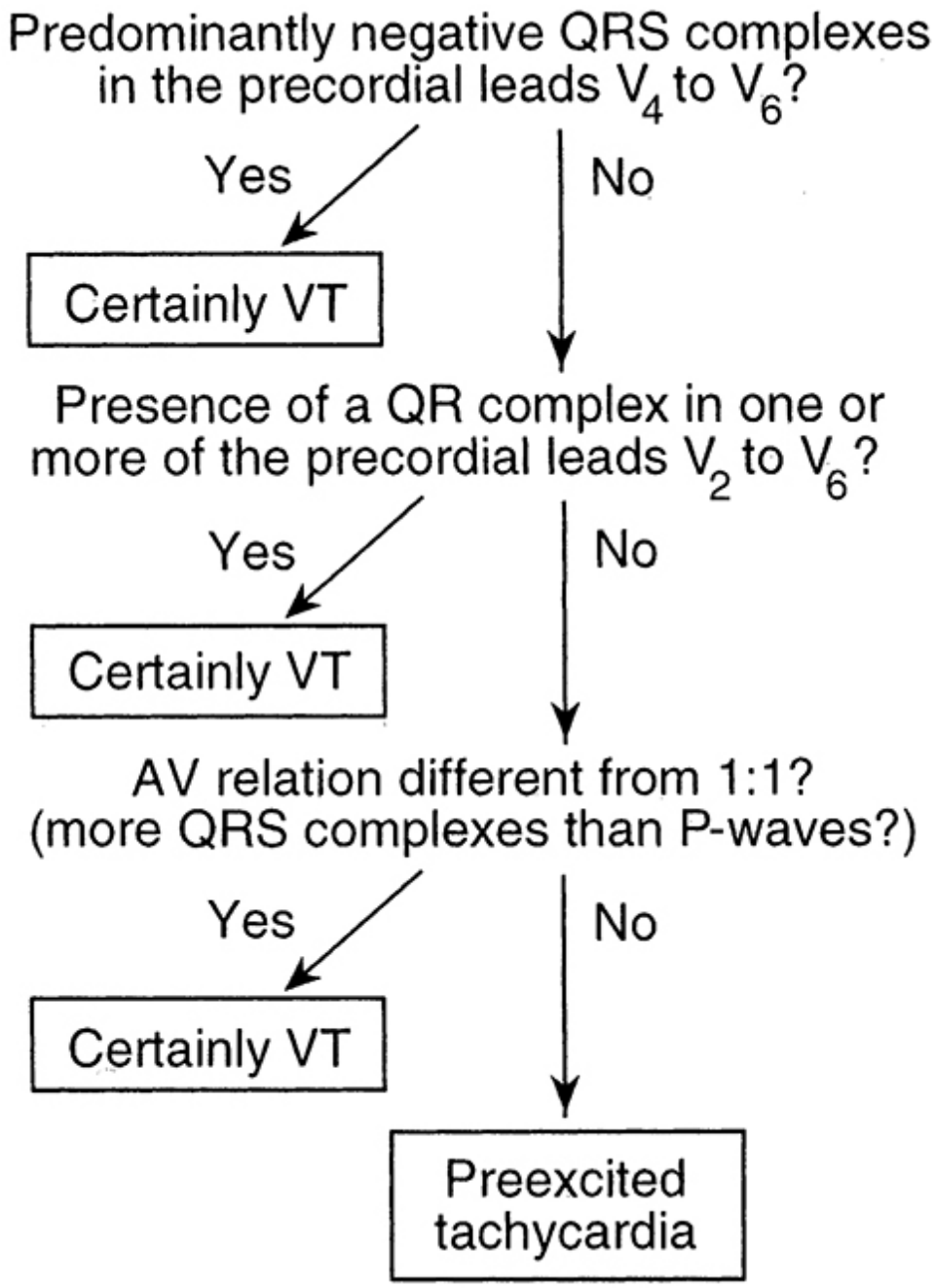
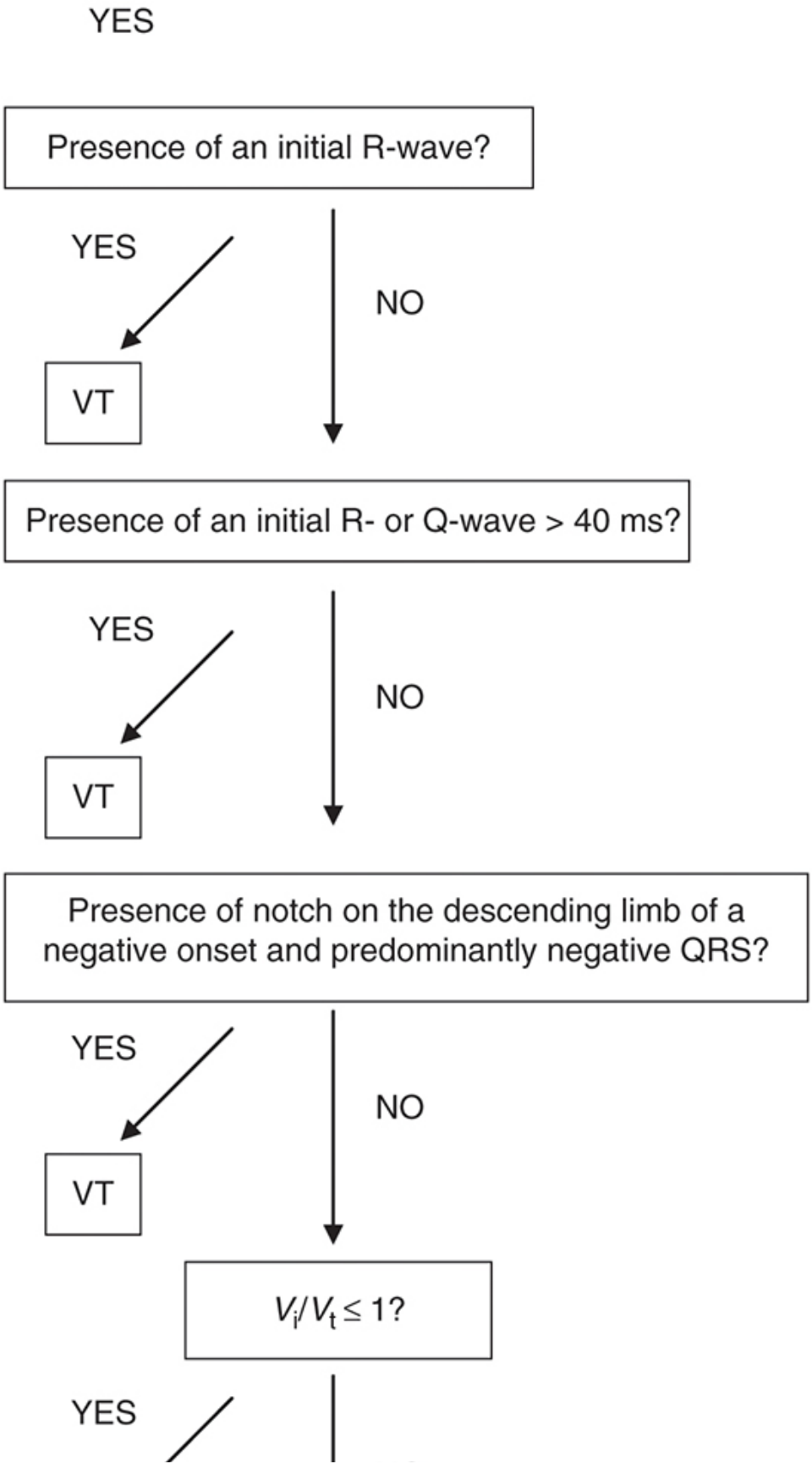


FIGURE 22.4 Brugada criteria for differentiating ventricular tachycardia (VT) from antidromic tachycardia over an accessory pathway. AV, atrioventricular.

A new criterion for differentiating VT from SVT was published in 2008 by Vereckei et al, which boasts a >90% accuracy in their cohort (**Figure 22.5**). The rationale to use the new method was to simplify

the approach by using one electrocardiographic lead (aVR) in a four-step, tree-like model. The method starts with identifying the presence of an initial R wave in aVR. If present, VT is diagnosed. If not, then the next step is to assess the presence of an initial R or Q wave >40 ms, and if present, VT is diagnosed. If this criterion is not satisfied, then the presence of a notch on the descending limb of a negative onset and predominantly negative QRS gives the diagnosis of VT. If this is not present, then one should compare the voltage of the initial 40 ms (V_i) with the voltage of the terminal 40 ms (V_t) of the QRS complex. If $V_i/V_t \leq 1$, then it is VT. If none of these criteria are satisfied, then SVT is diagnosed. One caveat is that the aVR Vereckei algorithm cannot differentiate VT from preexcited SVT.


YES
Presence of an initial R-wave?
YES
NO
VT
Presence of an initial R- or Q-wave > 40 ms?
YES
NO
VT
Presence of notch on the descending limb of a negative onset and predominantly negative QRS?
YES
NO
VT
$V_i/V_t \leq 1$?
YES

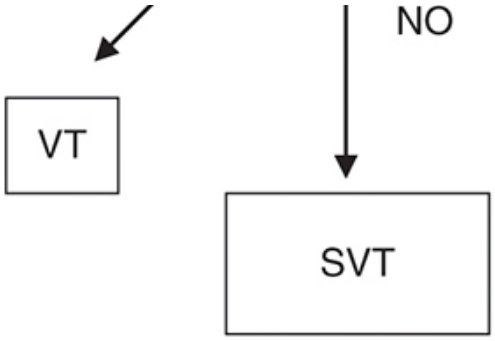


FIGURE 22.5 aVR criteria for diagnosing ventricular tachycardia (VT) V_i, vertical excursion (mV) during initial (V_i) and terminal (V_t) 40 ms of the QRS complex. SVT, supraventricular tachycardia.

D. Therapy

General management. The treatment of VT may involve direct current cardioversion (DCC), discontinuation of offending proarrhythmic drugs, specific antiarrhythmic therapy with drugs, correction of electrolyte imbalances, implantable devices, ablation, revascularization, and surgery. The appropriate selection of the preceding therapies is aided by the assessment of the patient, an understanding of the etiology and mechanism of the VT, knowledge of any exacerbating medical conditions contributing to the VT, and the risk-to-benefit ratio of the available therapies.

1. **Priority of therapy.** A patient who has no hemodynamic compromise can be treated medically, at least initially. As with most types of tachyarrhythmias, **the treatment of any unstable patient with VT is rapid DCC**. The treatment for pulseless VT is asynchronous DCC with a starting energy of 200 (biphasic) to 360 J (monophasic). If the patient is conscious but has unstable vital signs or is extremely symptomatic, **synchronized DCC** is recommended. The most recent Advanced Cardiac Life Support guidelines (American Heart Association [AHA]) currently emphasize the delivery of high-quality cardiopulmonary resuscitation (CPR): effective chest compressions (at least 100/min and compression depth of 2 in) with minimal interruptions, rescue breaths given over 1 second with visible chest rise while avoiding hyperventilation (30:2 ratio before an

advanced airway and 10 asynchronous breaths/min after airway is secured), and a **single** shock to attempt to defibrillate patients with pulseless VT followed by immediate continuation of CPR.

2. **Acute therapy.** Intravenous amiodarone, lidocaine, procainamide, beta-blockers, and other oral agents may be given initially depending on the clinical scenario. Amiodarone is the agent of choice for resistant VT causing repeated episodes (150 mg bolus, drip at 1 mg/min × 6 hours then 0.5 mg/min) and also for pulseless VT/cardiac arrest (300 mg bolus). Amiodarone and lidocaine are the preferred agents in patients with left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF] <40%). Lidocaine is effective when VT is thought to be ischemic in nature. Dosing of lidocaine is 1 mg/kg bolus followed by 0.5 to 4 mg/min, and serum drug concentrations should be monitored. Procainamide is reasonable as the initial treatment in patients with stable monomorphic VT, because it more effectively provides early rate slowing and conversion than amiodarone. Procainamide dosing is 10 to 17 mg/kg load followed by 1 to 4 mg/min maintenance. Beta-blockers may be preferred in the setting of acute coronary syndrome. Magnesium (2 g over 5 minutes) should be administered for TdP. Whenever possible, a **reversible cause for VT** should be sought. Elimination of **ischemia** and correction of **electrolyte abnormalities** are recommended. For refractory VT and VT storm, early intubation and sedation should be considered to reduce sympathetic drive. Stellate ganglion block can be considered at the bedside for patients who have ongoing VT with sedation weaning, which is suggestive of a catecholamine-sensitive VT. However, stellate ganglion block is only a temporizing measure, and if effective, subsequent evaluation for surgical sympathectomy should be performed (unilateral or bilateral). **Bradycardia** may cause frequent premature ventricular contractions (PVCs) or VT, particularly in patients with acquired LQTS and most common forms of congenital LQTS. (It should be noted that patients with some of the more uncommon forms of congenital LQTS may actually be more prone to develop

arrhythmias during sinus tachycardia.) Maneuvers including temporary pacing and agents that increase heart rate should be used. **Hypotension** should be promptly corrected. Therapy for congestive heart failure (CHF) should be optimized with the agents known to promote survival in this disorder. **Offending agents** should be stopped whenever possible, and **antidotes** should be administered in the case of overdosage and poisoning.

3. **Prevention and prophylactic treatment.** All antiarrhythmic agents to date, except beta-blockers, have not been shown in randomized clinical trials to be effective in the primary management of patients with life-threatening VAs or in the prevention of SCD. Since the Cardiac Arrhythmia Suppression Trial (CAST), there has been a shift away from the use of class Ic agents and toward the **use of class III agents and beta-blockers for prophylactic maintenance therapy** of VT. The development of **curative catheter-based therapies and surgical procedures** has somewhat reduced the role of antiarrhythmics in the prevention of recurrence, especially for VT occurring in normal hearts, which has very high cure rates with catheter ablation. The greatest impact on survival in sudden death has been made by the **implantable cardioverter-defibrillator (ICD)**. This is especially true in the setting of secondary prevention (patients with prior sustained VT). However, there is ample evidence that ICDs may be helpful in primary prevention as well (ie, patients with no history of sustained VT but at risk for SCD). For example, data from the Multicenter Unsustained Tachycardia Trial have shown that **patients with coronary artery disease (CAD), an ejection fraction (EF) <40%, and nonsustained ventricular tachycardia (NSVT) who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT—and that ICD implants favorably affect outcomes in this population.
4. **Medical therapy.** Although drug therapy continues to have a role in the prevention of VT, the mortality benefit with the use of antiarrhythmic drugs is controversial. The SCD-HeFT trial

showed no mortality benefit in New York Heart Classification (NYHA) class II or III heart failure with reduced ejection fraction (HFrEF) (EF ≤35%) compared to placebo. Amiodarone is preferred to other antiarrhythmics in reducing SCD and all-cause mortality based on a systematic review. Although less effective than amiodarone, sotalol and mexiletine can be considered alternative options, particularly in patients when there is concern for amiodarone side effects. Dofetilide is not currently recommended as first-line therapy for VAs. Beta-blockers are often first-line therapy in channelopathies and polymorphic VT in the setting of ischemia. Calcium channel blockers are used primarily in the management of SVT. However, some of the idiopathic monomorphic VTs (the VTs originating in the right ventricular outflow tract [RVOT]), fascicular VT, and the VTs of digitalis toxicity are responsive to calcium channel–blocking agents, such as verapamil and diltiazem (because of the underlying mechanism of calcium-dependent triggered activity).

5. **Combination therapy.** Drug therapy is becoming **an adjunct to ICD therapy** in this high-risk population. At present, fully half of those with ICDs remain on antiarrhythmic therapy. The rationale for this combined therapy includes preventing atrial tachyarrhythmias and reducing the frequency of VT and thus the frequency of ICD discharge.
6. **Invasive therapy**
    a. **ICDs.** It has long been established that ICDs are superior to medical therapy alone in the secondary prevention population (eg, the Antiarrhythmics Versus Implantable Defibrillator [AVID] trial). The topic of primary prevention (ie, implantation of ICDs in patients without prior sustained VT/VF) is more nuanced. The best evidence in support for primary prevention ICDs pertains to patients with infarct-related cardiomyopathy (eg, Multicenter Automatic Defibrillator Implantation Trials [MADIT I and MADIT II] the SCD-HeFT trial and the MUSTT study). Based on these studies, patients with infarct-related cardiomyopathy, who are considered to be at high risk

for SCD (risk estimated primarily by the degree of LVEF reduction and NYHA functional class), reap mortality benefit from primary prevention ICD. The evidence supporting ICD benefit in patients with nonischemic cardiomyopathy (NICM) is less convincing, especially since the most recent large-scale trial (The Danish Study to Assess the Efficacy of ICDs in Patients With Nonischemic Systolic Heart Failure on Mortality [DANISH]) was negative. This does not mean that patients with NICM are not at risk for SCD, but that a better risk stratification process is needed to identify those who would benefit from an ICD; cardiac magnetic resonance (cMR) may play a major role in this regard. With the exception of subcutaneous ICDs, transvenous ICDs have antitachycardia pacing (ATP) capabilities, which can recognize monomorphic ventricular rhythms and can rapidly pace the ventricles to restore sinus rhythm, aborting the need for countershock. In the Primary Prevention Parameters Evaluation study that evaluated the effects of ICD programming in a patient population receiving ICDs for primary prevention, using ATP as first-line therapy for fast VT (≥182 and <250 beats/min), including a monitoring zone at 167 beats/min, and applying SVT versus VT discriminators for rates <200 beats/min helped in reducing shocks without negatively affecting the mortality. Importantly, not all VTs require ICD therapy, and the specifics of ICD programming are thus vitally important. Data from the MADIT-RIT trial showed decreased inappropriate therapy and all-cause mortality with higher rate or longer detection intervals as compared with conventional programming in primary prevention patients. Programmed high rate therapy (with a 2.5-second delay before the initiation of therapy at a heart rate of ≥200 beats/min) or delayed therapy (with a 60-second delay at 170-199 beats/min, a 12-second delay at 200 to 249 beats/min, and a 2.5-second delay at ≥250 beats/min) was associated with a decrease in the number of patients with a first occurrence of inappropriate ATP or shocks, and all-cause mortality, as compared with conventional programming (with a

2.5-second delay at 170-199 beats/min and a 1.0-second delay at ≥200 beats/min). It is important to keep in mind that the MADIT-RIT data pertain to the primary prevention ICD population; in patients with prior sustained VT, ICD programming needs to be tailored to their specific situation.

b. **Catheter-based therapy.** Radiofrequency ablation (RFA) may be effective for reducing the incidence of VT. The success rate depends on the type of VT and the underlying substrate. The role of ablation is to target the source in focal VT or the critical isthmus in reentrant VT. Outcomes are very encouraging in patients with structurally normal hearts and focal VTs originating from a single site such as the ventricular outflow tracts. The outcomes are more variable in patients with structurally abnormal hearts. In ischemic cardiomyopathy, the underlying substrate tends to be subendocardial compared to mid-myocardial or subepicardial in NICM, which is why the former is thought to be more accessible for catheter ablation. Although the mortality benefit of VT ablation remains controversial, it has been shown to reduce VT recurrence and ICD shocks, particularly in patients with ischemic cardiomyopathy. In the VANISH trial, there was a 10% reduction in death, VT storm, and ICD shock in patients with ischemic cardiomyopathy who underwent ablation versus escalation of antiarrhythmic therapy; however, this was predominantly driven by a reduction in VT storm. SURVIVE-VT data further suggest that, in this population, there are fewer severe treatment-related complications with ablation compared to antiarrhythmic medications. In regard to the timing of VT ablation, there is no benefit to preventive VT ablation prior to ICD implant in patients with ICM and EF of 30% to 50% as per the BERLIN-VT trial. Although limited by a small sample size, the more recent PARTITA trial that did include patients with NICM suggests ablation should be considered within a few months after the first ICD shock to reduce recurrence of

VT. Presently, catheter ablation of VT does not obviate the need for an ICD in a patient with an indication for one.

E. Diagnostic evaluation of a patient with VT. Once the diagnosis of VT has been established and the patient has been acutely managed with either DCC, defibrillation, or medical therapy, further management depends on the underlying cardiac pathology. In broad terms, the substrate can be divided into two categories: the structurally normal heart and the structurally abnormal heart. Various modalities are available to determine the cardiac structure and function, which include ECG, cardiac catheterization, echocardiography, nuclear imaging, and magnetic resonance imaging (MRI).

III. VENTRICULAR TACHYCARDIA SUBSTRATE

A. VT in a structurally normal heart. About 20% of VT in the United States occurs in structurally normal hearts, the so-called idiopathic VT. These patients have no significant CAD, no family history of arrhythmia or sudden death, and normal surface ECGs. They can be **focal VTs or reentry VTs**. Focal VTs are a result of triggered activity, abnormal automaticity, or reentry within the Purkinje fibers.

1. Focal VT

a. Mechanism. Focal VAs can present as PVCs, NSVT, or sustained VT. Most commonly, they arise from the RVOT, which accounts for up to 70% of idiopathic VAs. Other locations of focal VAs may include the LV outflow tract (LVOT), aortic cusps, pulmonary artery, mitral and tricuspid annuli, papillary muscles, and epicardium. Outflow tract VAs may be caused by cyclic adenosine monophosphate (cAMP)-mediated EADs. ECG of RVOT VA is characterized by a left bundle morphology in lead V_1 and inferior axis. On the differential diagnosis of a patient who presents with left bundle branch block (LBBB) VT is arrhythmogenic right ventricular dysplasia (ARVD), which falls into the category of VT/PVCs in the structurally abnormal heart. The clinician should investigate for RV structural abnormalities (fatty infiltration),

ask about a family history of ARVD, and review the electrogram for the presence of T-wave inversion across the right precordial leads and/or epsilon waves (**Figure 22.6**). A cMRI or cardiac positron emission tomography scan may also be useful to rule out the presence of cardiac sarcoidosis, which also would fall into the category of the structurally abnormal heart.

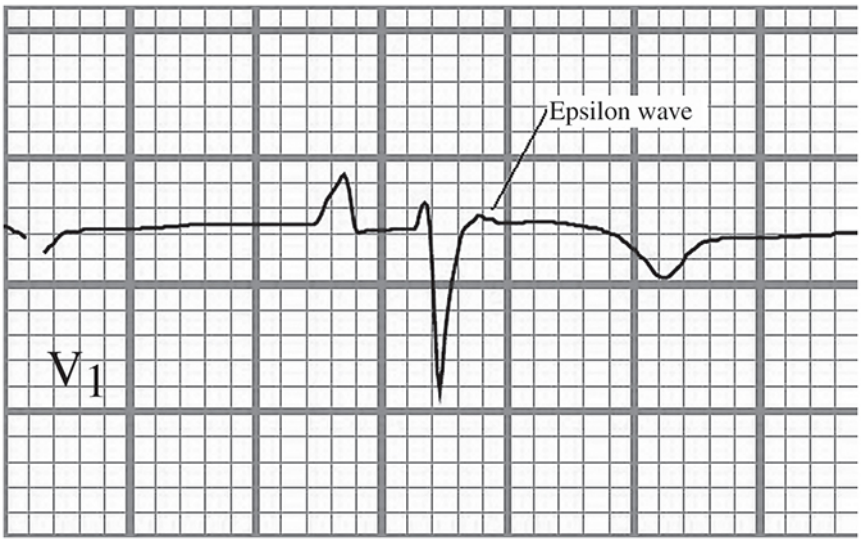


FIGURE 22.6 Epsilon wave in a patient with arrhythmogenic right ventricular dysplasia.

b. ECG. The surface ECG can be used to localize idiopathic VAs and is helpful for preprocedural planning. Noting the limitations of lead placement, body habitus, and heart rotation, four factors on surface ECG should be evaluated: (1) bundle branch morphology, (2) QRS axis, (3) precordial transition, and (4) QRS width. If the terminal forces in lead V_1 are positive consistent with a right bundle pattern, VA origin is from the LV. If the terminal forces in V_1 are negative consistent with a left bundle pattern, the VA origin is from the RV or interventricular septum. Positive forces in leads II/III indicate inferior axis, whereas negative forces in these leads indicate superior axis. Positive forces in lead I suggest rightward origin, whereas negative forces suggest leftward/lateral origin. Greater positive

forces in aVR compared to aVL can also indicate leftward origin. Positive precordial concordance suggests basilar origin compared to negative precordial concordance, which suggests apical origin. In left bundle morphology, VA later transition corresponds to more RV free wall origin. Lastly, narrow QRS width is consistent with septal VAs. These rules serve as a general guide and are summarized in **Figure 22.7**. Even if one is not facile with these localization rules, it may be helpful to develop a skill for pattern recognition of the most common form of idiopathic VT—the RVOT VT. These arrhythmias usually have a striking inferior axis (very positive QRS complex in leads II and III and very negative QRS complex in leads aVL and aVR), LBBB morphology in lead V_1 and precordial transition in lead V_3, V_4, or V_5.

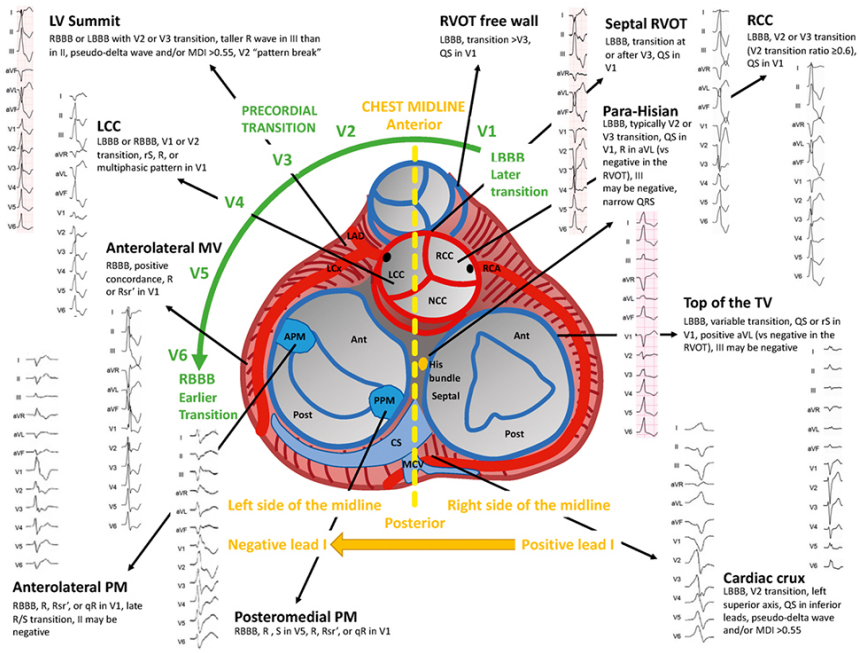


FIGURE 22.7 Summary of approach to PVC localization. Right bundle pattern in V_1 indicates origin from the LV, left bundle pattern indicates origin is from the RV or interventricular septum. Positive forces in leads II/III indicate inferior axis, whereas negative forces in these leads indicate superior axis. Positive forces in lead I suggest rightward origin, whereas negative forces suggest leftward/lateral origin. Positive precordial

concordance suggests basilar origin compared to negative precordial concordance, which suggests apical origin. In left bundle morphology, VA later transition corresponds to more RV free wall origin. Lastly, narrow QRS width is consistent with septal VAs. LBBB, left bundle branch block; LCC, left Coronary Cusp; LV, left ventricular; MDI, maximum deflection index; MV, mitral valve; PM, posteromedial; PVC, premature ventricular contraction; RBBB, right bundle branch block; RCC, right coronary cusp; RV, left ventricular; RVOT, right ventricular outflow tract; TV, tricuspid valve. (Reproduced from Muser D, Tirro M, Mariani MV, et al. Diagnosis and treatment of idiopathic premature ventricular contractions: a stepwise approach based on the site of origin. *Diagnostics (Basel)*. 2021;11(10):1840.)

c. **Treatment.** In general, focal VTs are benign, carrying a very low risk of SCD, although patients with high burden of VT may develop secondary cardiomyopathy as a result. Therefore, the treatment is predominantly guided by symptoms or presence of high VT burden (in asymptomatic patients). Given the role of cAMP in inducing this form of VT, adenosine may be effective at acute termination. For longer term therapy in the symptomatic patient, beta-blockers are typically the first-line agents and can be effective in up to 50% of patients. The nondihydropyridine calcium channel blockers may also be effective in 25% to 50% of patients. Sotalol and amiodarone can eliminate symptoms in up to 90% of cases, but potential side effects may limit their use. Patients who wish to potentially avoid lifelong medications or who are refractory to medical therapy can be considered for ablation, which has variable success rate depending on the location. RVOT VT ablation success rate may be as high as 90%. Ablation procedures, although generally safe, may be associated with infrequent but life-threatening complications, including cardiac perforation and tamponade.

2. **Fascicular VTs.** Fascicular VT involves reentry using the tissue of the LV septum as the antegrade limb and usually the posterior fascicle in the retrograde limb.

   a. **ECG.** This typically produced a right bundle branch block (RBBB) with left-axis deviation pattern. Less commonly, the

QRS pattern is an RBBB with right-axis deviation (left anterior fascicular VT).

b. Treatment. This subtype of VT may be verapamil sensitive, but catheter ablation can be considered in patients who want to avoid long-term medication or in whom medical therapy is ineffective.

3. VT/VF associated with channelopathies. Various cardiac ion channel disturbances can predispose to VAs. Patients with these channelopathies have no overt structural heart disease. They are genetically heterogeneous and have variable penetrance. They include LQTS, short QT syndrome (SQTS), Brugada syndrome, and CPVT.

a. LQTS

(1) Pathology and presentation. The QT interval on ECG represents the depolarization and repolarization portions of the cardiac action potential. Two forms of LQTS: acquired and congenital. Both are caused by changes in ion currents (the vast majority due to dysregulated outward repolarizing potassium current, but sodium, calcium, and mixed currents have also been implicated), which prolong the action potential duration of individual myocytes that, in turn, manifests as a prolonged QT interval on surface ECG. Clinical presentation includes syncope or sudden death as a result of TdP. Although best studied, congenital LQTS is less common than its acquired counterpart. While at least 15 distinct causal genetic loci have been identified, by far the most common subtypes of congenital LQTS are LQT1, LQT2, and LQT3, which are characterized by mutations in the alpha subunits of the potassium channels responsible for repolarization currents (I_{Ks} [KCNQ1, alternatively known as KVLQT1 and Kv7.1], I_{Kr} [KCNH2, also known as HERG and Kv11.1]) and the alpha subunit of the sodium channel responsible for the initial myocyte depolarization current (I_{Na} [SCN5A, also known as

NaV1.5]). Most LQT1-3 mutations are autosomal dominant and are occasionally referred to as the Romano-Ward syndrome. A small number of patients have autosomal recessive LQT1 (and LQT5) mutations that also confer sensorineural deafness; this is recognized as the Jervell and Lange-Nielsen syndrome. Patients with LQT1 typically have broad-based T waves and exercise-induced arrhythmias, especially during swimming. LQT2 syndrome is characterized by low-amplitude or notched T waves and auditory triggers such as sudden loud sounds like alarm clocks or strong emotion, and LQT3 is characterized by a long isoelectric ST segment and arrhythmias during sleep. Acquired LQTS is much more common than congenital LQTS. The vast majority of acquired LQTS cases are caused by medications interacting with the HERG channel. Therefore, the phenotype of acquired LQTS most resembles that of LQT2 syndrome.

(2) **Diagnosis.** Congenital LQTS is diagnosed in the presence of a LQTS risk score (Schwartz score) of ≥3.5 in the absence of a secondary cause for QT prolongation. The risk score incorporates ECG features, clinical, and family history. Diagnosis can also be made based on having a mutation in one of the *LQTS* genes or presence of a QTc interval ≥500 ms on repeated ECGs. In patients with unexplained syncope and QTc between 480 and 499 on repeated ECGs without secondary cause, the diagnosis of congenital LQTS should be considered. Exercise stress testing can also elicit ECG pattern changes specific to the different types of LQTS.

(3) **Treatment.** In patients with congenital LQTS, risk stratification involves assessment of age, gender, clinical history, and, possibly, the QT interval and genetic mutation. Beta-blockers are first-line therapy for patients with symptomatic AND asymptomatic LQTS with QTc ≥470 ms. However, not all beta-blockers are the same.

Typically, high doses of propranolol or nadolol are superior to metoprolol and should be used to prevent clinical symptoms. Patient with syncope despite beta-blocker therapy or history of aborted sudden death should undergo ICD implantation. Asymptomatic patients who have not been tried on beta-blocker therapy should not receive an ICD. Left cardiac sympathetic denervation can be used as an adjunctive therapy in patients who have syncope/arrhythmias despite beta-blockers and/or in those who cannot receive an ICD. For the patients with LQT3, there may be a role for sodium channel blockers (flecainide) as add-on therapy if the QTc is >500 ms and acute dosing results in a >40 ms shortening of the QTc. Patients should be advised against high-intensity sports and should be educated regarding avoidance of QT-prolonging drugs.

b. SQTS. SQTS is diagnosed by the presence of a QTc ≤330 ms. It can be diagnosed in the presence of a QTc <360 ms with a pathogenic mutation, family history of SQTS, family history of SCD ≤40, or VT/VF episode in the absence of heart disease. This syndrome is characterized by gain-of-function mutations in the potassium channels responsible for the I_{Ks}, I_{Kr}, and I_{K1} currents or CACNA1 and CACNB2 L-type calcium channel mutations. ICD therapy is the primary treatment modality (class I) in patients with aborted SCD or VT. However, particular attention needs to be given to the prevention of inappropriate shocks, because patients may have T-wave oversensing (tall T waves) and a high incidence of atrial fibrillation (AF). Quinidine or sotalol can be considered (class IIb) in asymptomatic patients with a family history of SCD.

c. Brugada syndrome. Brugada syndrome is a condition associated with SCD in the setting of a structurally normal heart. It is characterized by either a spontaneous or provoked electrocardiographic pattern of RBBB and ST-segment elevation in leads V_1 and V_2 (**Figure 22.8**). Class I

antiarrhythmics are used for drug provocation (in the United States, this is usually procainamide). It is generally inherited in an autosomal dominant pattern with a male predominance, but there is marked variable expression. Most patients do not have an identifiable, causal genetic mutation. That said, when a causal genetic mutation is identified (around 30% of total cases), it is almost always in the *SCN5A*, which encodes for a cardiac sodium channel, leading to unopposed I_{to} potassium current in the RV epicardium. This sets up a voltage gradient across the epicardium-endocardium that may have arrhythmogenic consequences. The diagnosis can be difficult because of the variable expression of the ECGs at baseline, changes in the ECG over time induced by a host of factors (fever, heart rate, autonomic tone, and medications), and the wide range of clinical manifestations. The diagnosis should be considered in patients who have documented VF, self-terminating polymorphic VT, family members with ST-segment elevation, syncope, or family history of sudden death in the setting of the electrocardiographic findings noted previously. Currently, no medication has proved effective in preventing SCD in these patients, but quinidine, which (among other things) blocks the I_{to} current, may be used as an adjunctive therapy to reduce the likelihood of arrhythmias. ICDs are recommended in (1) patients with previous cardiac arrest or VT (class I), (2) syncope felt to be from arrhythmia with spontaneous ECG pattern (class IIa), or (3) induced VF during EP study (IIb). It is generally recommended to implant an ICD in **symptomatic** patients and clinically follow **asymptomatic** patients with an abnormal ECG only on pharmacologic provocation and no inducible VAs. Catheter ablation can be considered in patients with a history of VT storm and repeated ICD shocks (class IIb). Drugs known to affect the I_{to} current should be avoided whenever possible.

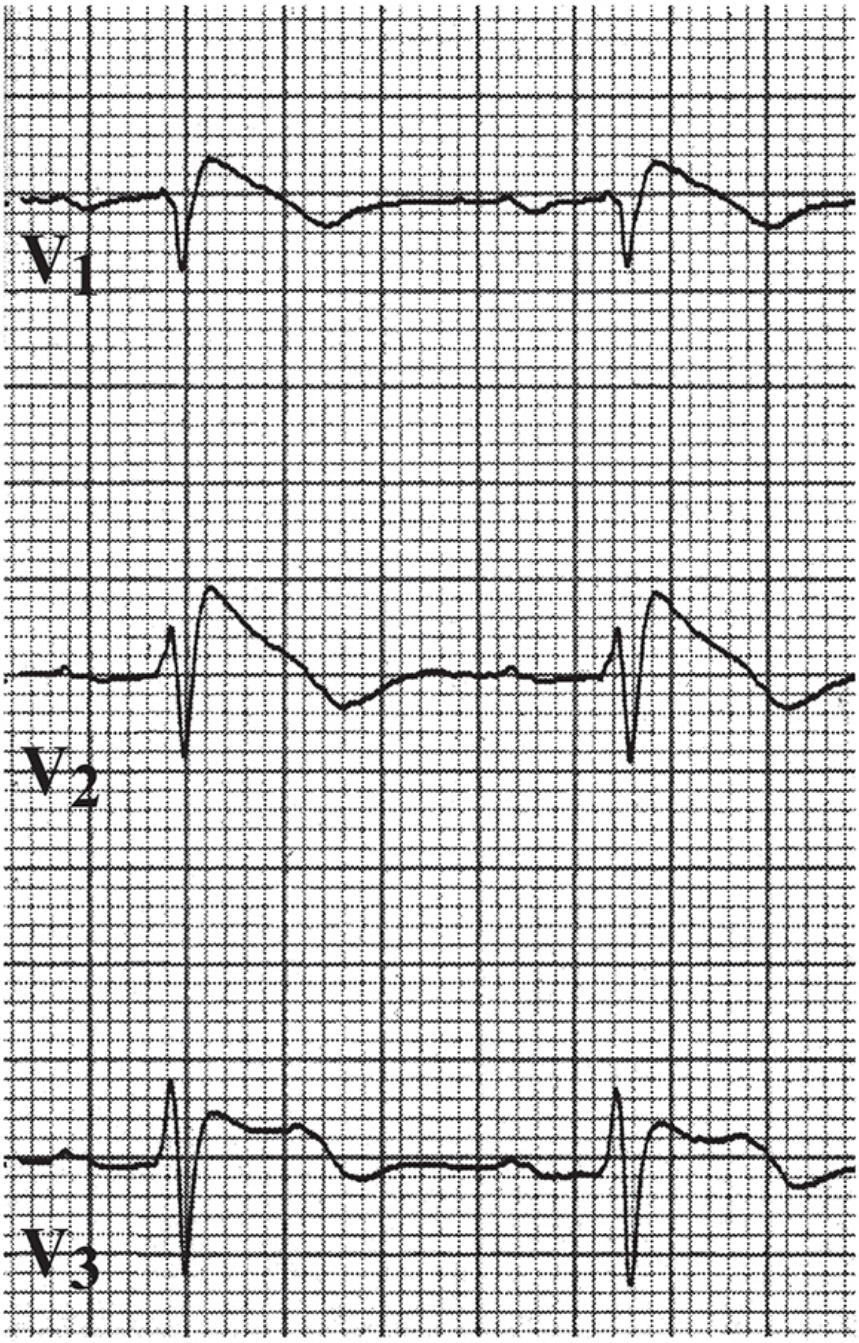


FIGURE 22.8 Leads V_1 through V_3, demonstrating type 1 Brugada pattern.

d. CPVT. This arrhythmia is more common in adolescents and children and may present with SCD or stress/exercise-induced syncope. Although usually familial, it can also occur because of de novo mutations. Triggers often include exercise, emotional,

or physical stress. The arrhythmia can present as polymorphic, bidirectional, and, less commonly, VF. Several culprit genes have been identified, but two loci account for the majority of cases: calsequestrin 2 (autosomal recessive pattern) and cardiac ryanodine receptor (autosomal dominant pattern). ICDs are indicated in patients with this syndrome who experience cardiac arrest, recurrent syncope, and/or VT despite optimal medical management. Beta-blockers can reduce the incidence of arrhythmias as well. Flecainide may be useful (class IIa), and sympathetic denervation can be considered (class IIb) in patients who have recurrent arrhythmia despite beta-blocker therapy. Patients should be counseled to limit/avoid competitive sports, strenuous exercise, and stressful environments.

4. VT in the structurally abnormal heart

a. Ischemic VT. Patients with ischemic VT may have acute ischemia leading to myocardial infarction (MI) or a history of ischemic heart disease with scar. Patients who have VF/VT within 48 hours of an acute MI have a relatively high in hospital and 30-day mortality compared with patients who do not have VF/VT.

(1) Etiology and pathophysiology. At the cellular level, ischemia may alter action potentials, prolong refractoriness of cells, and uncouple the cell-to-cell propagation of depolarization. The biochemical milieu in which the cells exist with respect to ion concentrations, acid-base balance, and so forth can be altered. Also, the myocardial damage as a result of infarction is structurally heterogeneous. Therefore, scar tissue and healthy tissue are admixed in the region of the infarction. As described before, a reentrant circuit requires two functionally distinct pathways with unidirectional block in one pathway and slowed conduction down a second pathway. The changes associated with ischemia provide the anatomic substrate for reentry. The VT in the setting of ischemia tends to be

polymorphic, whereas VT in the setting of established myocardial scar tends to be **monomorphic**. Ischemia has been shown to prolong the QT interval in some subjects, often with associated T-wave inversion. The **QT interval in ischemic-mediated polymorphic VT is not as prolonged** as that in TdP, another polymorphic VT. Ischemia is by far the **most common cause of polymorphic VT with normal QT interval**.

(2) **Predictors of VT.** As might be expected, **larger infarcts with greater resultant impairment of LV systolic function** are more likely to be associated with VT. In fact, LV systolic function is the single most important predictor of sudden death because of arrhythmia. Similarly, the presence of a **patent artery appears to reduce the occurrence of VT and other arrhythmias**. Other proposed predictors include syncope, abnormal signal-averaged electrocardiogram (SAECG) result, NSVT, absence of heart rate variability, abnormal EP study outcome, and T-wave alternans (TWA); however, currently, the LVEF remains the most accurate predictor of sudden death.

(3) **Laboratory examination and diagnostic testing.** The various tests for risk stratification (EP study, SAECG, heart rate variability, TWA, and so forth) have shown poor specificity and positive predictive value for VT **and thus should not be used alone to guide therapy but in combination with the rest of the clinical information**.

(4) **Role for ICD.** In patients who present with a VF/VT arrest in the setting of an acute MI (within 24-48 hours of infarction), revascularization should be the primary initial treatment. Based on current guidelines, an ICD should be considered after 40 days from the initial MI or 90 days after revascularization. This is especially true in patients with NYHA class II or III heart failure and LVEF is ≤35% or NYHA class I heart failure and EF ≤30% (class I). For

patients with EF ≤40% and NSVT, an EP study can be performed and ICD should be implanted if there is inducible sustained VT. Survivors of cardiac arrest or cardiac syncope warrant a secondary prevention ICD. Patients who are post-MI and are deemed to be at high risk for SCD during the waiting period of 40 to 90 days, a wearable cardioverter-defibrillator (WCD) may provide protection against cardiac arrest (class IIb). Patients with late VT/VF (ie, >48 hours after acute MI) are deemed to be particularly at high risk for recurrent VT/VF and, therefore, typically receive ICDs before hospital discharge. These patients are considered to meet secondary prevention indications for ICDs. ICD is NOT indicated in patients who have sustained VT/VF within 48 hours of initial MI.

b. Accelerated idioventricular rhythm (**Figure 22.9**) is a form of VA seen almost exclusively in ischemic heart disease, particularly during an MI and especially after reperfusion of an occluded territory. It may be seen with digitalis toxicity but can also be present in healthy adults and children with no structural heart disease.

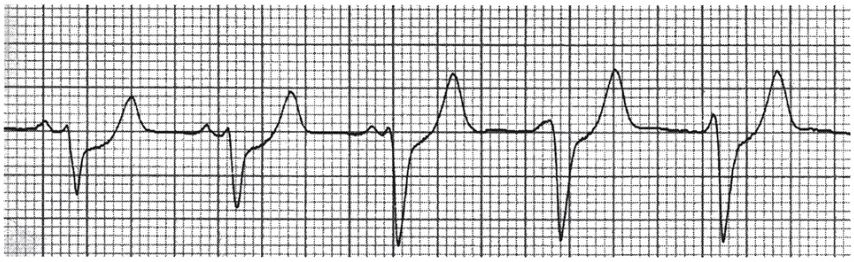


FIGURE 22.9 Accelerated idioventricular rhythm (beats 3-5), interspersed with normal sinus rhythm (beats 1 and 2).

(1) The **ECG** features include regular or slightly irregular ventricular rhythm, a rate of 60 to 110 beats/min, a QRS

morphology resembling that of PVCs, and, often, AV dissociation as well as fusion beats and capture beats.

(2) **Pathophysiology.** The ectopic ventricular pacing focus competes with the SN and takes control of the ventricular rate when the sinus rate slows or when sinoatrial or AV block occurs. Enhanced automaticity is the likely underlying mechanism.
Accelerating the sinus rhythm with atropine or atrial pacing can be useful to suppress the accelerated idioventricular rhythm.

(3) **Therapy is rarely necessary, unless** the loss of AV synchrony results in hemodynamic compromise, a more rapid VT intervenes, the accelerated idioventricular rhythm falling on the T wave of the preceding beat (R-on-T phenomenon), the ventricular rate being rapid enough to produce symptoms, or occurrence of VF.

c. **Dilated cardiomyopathy (DCM).** Primary prevention risk stratification is particularly difficult in patients with DCM because SAECG, microvolt TWA, and an EP study are not reliable predictors in this population and asymptomatic VAs are common. Moreover, several randomized controlled trials have shown a lack of mortality benefit in patients with DCM who were risk stratified primarily based on LVEF and NYHA functional class. As a result, the strongest indication for ICDs in this population is for secondary prevention (ie, patients with manifest life-threatening arrhythmias or syncope). The current primary prevention ICD indication is for patients who have an LVEF ≤35% and NYHA classes II to III. It is important to note that all patients with DCM being considered for a primary prevention ICD should be receiving chronic optimal medical therapy for at least 3 months and have a life expectancy >1 year. WCD can be considered for patients with new diagnoses with less than 3 months of optimal guideline-directed medical therapy (GDMT). These guidelines will likely change in the future, as more specific predictors of VT (eg, myocardial

fibrosis on MRI) are discovered. Bundle branch reentrant tachycardia, a specific subtype of VT that is mechanistically different from the canonical scar-dependent VT, occurs most commonly in patients with DCM for which EP testing is helpful in diagnosing and guiding ablative treatment. Although ablation may be curative if bundle branch reentry is the mechanism, such patients should still be considered for ICD implantation.

d. **Hypertrophic cardiomyopathy (HCM).** SVT and AF are particularly poorly tolerated by these patients, as is ischemia, and may lead to VT. **ICDs are recommended for patients who have cardiac arrest, VF, or sustained VT. For primary prevention, the strength of the ICD indication (classes IIa-IIb) varies depending on multiple risk factors. In general, one or more major risk factors for SCD (family history of premature SCD, unexplained syncope in the past 6 months, LV thickness ≥30 mm) confer a class IIa indication. Primary prevention ICDs are also warranted in patients with spontaneous NSVT or abnormal blood pressure response to exercise who also have additional risk modifiers, including delayed late gadolinium enhancement (LGE) on cMRI, LVOT obstruction, LV aneurysm, EF <50%, and age <30.** Several risk stratification calculators exist and may be helpful in the shared decision-making process leading up to the potential ICD implant. Again, all patients should be receiving chronic optimal medical therapy and have a life expectancy >1 year. Patients at low risk for HCM include those with infrequent or brief episodes that are asymptomatic or mildly symptomatic. Although **amiodarone** may be beneficial in this population, an ICD is increasingly used in those considered to be at high risk.

e. **Muscular dystrophies**, particularly Duchenne muscular dystrophy and myotonic dystrophy, have been associated with frequent defects in the conduction system. Heart block and bundle branch block as well as sudden death because of

ventricular tachyarrhythmias are well-recognized complications of these muscular disorders.

f. **Congenital heart disease.** Structural abnormalities such as **repaired tetralogy of Fallot** have been associated with an increased risk of VT and sudden death. In tetralogy of Fallot, the VT often originates in the RVOT, at the site of a previous repair. Risk of VT and sudden death in this population has been associated with QRS width ≥180 ms (and rate of QRS width increase) as well as the severity of pulmonary insufficiency.

g. **Mitral valve prolapse.** Mitral annular disjunction (MAD) is characterized by left atrial displacement of the mitral valve leaflet hinge point. There is increasing evidence associating MAD with later VAs likely from the development of progressive fibrosis of the mitral apparatus. The diagnosis should be considered with multimodality advanced imaging in patients with mitral valve prolapse and VA.

h. **Arrhythmogenic RV cardiomyopathy** is a cardiomyopathy that begins in the RV and often progresses to involve the LV. It results in RV dilation with resultant poor contractile function. The RV muscle becomes increasingly replaced by adipose and fibrous tissues as the disease progresses. VT arising in the RV is often an early manifestation of this disorder. The **VT is a reentrant type and has an LBBB morphology**, although, in sinus rhythm, there is often inversion of the T waves in the anterior precordial leads and a slurring of the terminal portion of the QRS complex, known as an epsilon wave (**Figure 22.6**). These patients frequently have a positive SAECG for late potentials. The combination of the scarring and the late potentials provides the anatomic substrate for reentry. During EP study, it may be possible to elicit VT of varying morphologies. The **risk of VT correlates with the extent of myocardial involvement**. Therapy with sotalol or high-dose amiodarone may be somewhat successful. Ablation via catheters is often successful, but only temporizing, because the generalized involvement tends to give rise to arrhythmias at a

different locus later in the disease course. ICDs are often the only reliable therapy to prevent sudden death in this disorder. Patients are advised against intense exercise, because this may promote the incidence and progression of arrhythmias.

i. Several inflammatory or infectious conditions have been associated with VT.

(1) **Sarcoidosis** is frequently cited as a cause of heart block and may also cause VT and VF. **Amiodarone** and **sotalol** are the most efficacious agents in this disorder. Catheter ablation may be considered for recurrent arrhythmia, especially if acute myocardial inflammation has been successfully suppressed. Primary prevention ICDs are recommended in all cardiac sarcoidosis and LVEF ≤35%.

(2) **Acute myocarditis** has been associated with both polymorphic and monomorphic VTs. It may be intractable in giant cell myocarditis. **Antiarrhythmic therapy and anti-inflammatory therapy** are generally combined in the treatment of these patients.

(3) **Chagas** disease, caused by the parasite *Trypanosoma cruzi*, is a well-known cause of cardiomyopathy, particularly in South and Central America. VT and other arrhythmias because of conduction system involvement are common complications. Therapy involves antiparasitic treatment, standard therapy for CHF, antiarrhythmics, and pacemaker or ICD implantation, as appropriate. Some patients require catheter ablation of refractory VT, which very often requires epicardial access.

j. Coronary anomalies. Anomalous aortic origin of the coronary artery is recognized as a cause of sudden death and/or exercise-induced death in young individuals. In an autopsy study of over 200 patients conducted by the Armed Forces Institute of Pathology, the most common coronary anomalies included the right coronary artery and left main coronary artery arising from the left sinus, the left main and right coronary arteries arising from the right sinus, single coronary artery from the aorta, and

the left main or left anterior descending artery arising from the pulmonary artery. Patients whose coronary arteries take an interarterial course (between the pulmonary artery and the aorta) may develop exercise-induced ischemia and/or sudden death. Surgical revascularization in patients with symptomatic coronary anomalies has been well described. Surgical treatment for patients with high-risk coronary anomalies who are asymptomatic is controversial.

5. **Drug-induced VT.** Drugs are a well-known cause of VT, both polymorphic and monomorphic VTs. This is particularly true in ischemic or infarcted hearts. Phenothiazines, tricyclic antidepressants, digitalis, epinephrine, cocaine, nicotine, alcohol, and glue (inhaled) are some of the wide varieties of drugs that have been implicated in the development of monomorphic VT. The CAST and other trials of the late 1980s showed an increase in mortality resulting from the use of class I antiarrhythmic agents employed to suppress asymptomatic ventricular ectopy after MI. NSVT and depressed LV function remain risk factors for sudden death, and the agents studied in CAST did decrease the occurrence of ventricular ectopy; however, it is believed that these drugs (flecainide, encainide, and moricizine) generated VT, causing sudden death in recipients. These agents all have in common their sodium channel–blocking activities. Other drugs in this class, including procainamide, quinidine, disopyramide, lidocaine, tocainide, and mexiletine, have all been shown either experimentally or clinically to be associated with increased mortality compared with controls in the peri-infarction period. The results of CAST caused a major shift away from the sodium channel–blocking agents (class I antiarrhythmics) in the peri-infarction period. Digitalis toxicity can propagate DADs, which generate action potentials, leading to VT. The VT of digitalis toxicity is typically monomorphic and often responds to calcium channel blockers. Rarely, digitalis toxicity manifests as a bidirectional VT, meaning that it has a regular rhythm with an axis that alternates from −60° to −90° to +120° to +130°, with a

ventricular rate from 140 to 200 beats/min (**Figure 22.10**). Because digitalis toxicity may have a narrow QRS complex and may respond to calcium channel blockers, it may be confused with SVT. This type of VT is best managed by removing the offending agent, digoxin, with administration of its binding antibody fragment. The treatment for digitalis toxicity is the same in the face of bidirectional VT.

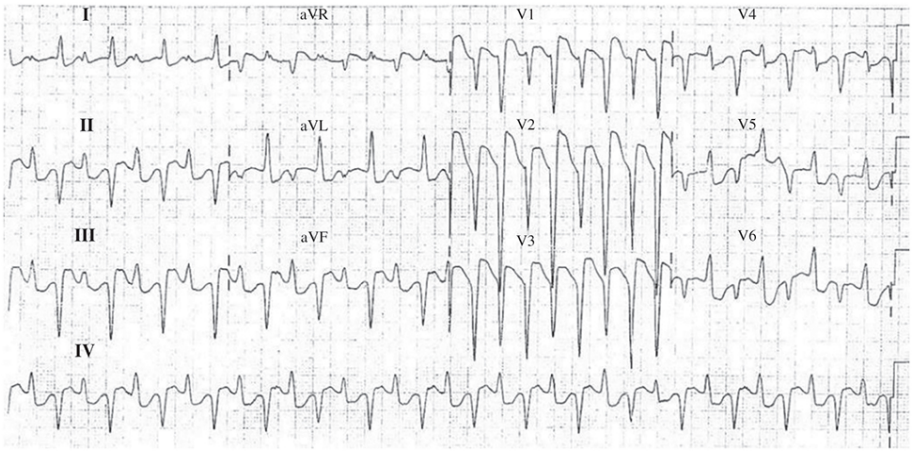


FIGURE 22.10 Bidirectional ventricular tachycardia typically seen in the setting of digitalis toxicity or catecholaminergic polymorphic ventricular tachycardia.

6. **TdP** is a type of polymorphic VT associated with delayed myocardial repolarization, most often manifested as a prolonged QT interval. Although the duration of TdP is typically brief (<20 seconds), it can be sustained and can degenerate into VF. It generally has an irregular ventricular rate (>200 beats/min) and displays a polymorphic structure with an undulating appearance. The QRS complexes appear to twist around an isoelectric axis. Characteristics that distinguish TdP from other forms of VT include (1) prolonged QT interval, (2) initiation with a short-long-short sequence, and (3) typical "twisting of the points" appearance of the VT (**Figure 22.11**).

FIGURE 22.11 Torsades de pointes, a type of polymorphic ventricular tachycardia seen in the setting of long QT.

a. Etiology. QT prolongation can be congenital or acquired.

The **congenital** forms are seen in the LQTS, which were previously discussed in this chapter. The **acquired forms are most often drug induced**, although polymorphic VT with a prolonged QT can be caused by electrolyte abnormalities, hypothyroidism, cerebrovascular events, MI or ischemia, starvation diets, organophosphate poisoning, myocarditis, severe CHF, and mitral valve prolapse.

The **most commonly implicated drugs have been the class IA drugs**, although less frequent occurrences have been reported with all subclasses of class I antiarrhythmics. The class III drugs, such as sotalol, dofetilide, and, less commonly, amiodarone, have been implicated. The incidence of TdP with sotalol is in the range of 2% to 5% and that with dofetilide is ~1%. Ibutilide is an antiarrhythmic agent for SVTs that is associated with an incidence of TdP at least as high as that of sotalol. Other drugs implicated include phenothiazines, haloperidol, and tricyclic antidepressants. Antibiotics, including erythromycin and other macrolides, as well as trimethoprim-sulfamethoxazole combinations, have been implicated. Medications associated with increasing QT interval are listed at www.torsades.org. It is maintained by the University of Arizona Center for Education and Research on Therapeutics.

Bradycardia can promote TdP in patients with prolonged QT intervals, although it is not clear if bradycardia by itself predisposes to TdP. Specifically, pause-dependent VT occurs in the setting of bradycardia and a prolonged QT interval.

Usually, a long RR interval followed by a short RR interval followed by another long RR interval initiates the VT.

Electrolyte disorders. Hypokalemia is the electrolyte disorder most reliably linked to TdP. **Hypomagnesemia** has been proposed as a logical cause, because the administration of magnesium frequently terminates TdP. However, there is scant evidence to confirm this. Likewise, although **hypocalcemia** is associated with prolongation of the QT interval, there are only rare reports of TdP associated with hypocalcemia.

Short coupled VT. Polymorphic VT is initiated <400 ms following the preceding QRS complex.

R-on-T phenomenon occurs when a defibrillation or pacing current or spike is delivered simultaneously, with the occurrence of the electrocardiographic T wave resulting in polymorphic VT.

A variety of **cerebrovascular events** have been associated with TdP, most notably subarachnoid hemorrhage. The prolongation of the QT interval sometimes seen with intracranial bleeding is usually transient, resolving within weeks.

b. Therapy. Acute management is aimed at terminating the arrhythmia.

If TdP is sustained or associated with hemodynamic compromise, prompt defibrillation should be carried out. Starting voltages are generally 50 to 100 J and can be advanced to 360 J if necessary.

Correction of hypokalemia, hypomagnesemia, and hypocalcemia should be undertaken promptly. Magnesium can be given in a bolus form at a dose of 1 to 2 g, with a total dose of 2 to 4 g given over 10 to 15 minutes. This successfully terminates TdP within 5 minutes in up to 75% of patients and within 15 minutes in virtually all patients.

Bradycardia can be corrected with either isoproterenol infusion or temporary transvenous pacing. Pacing may be preferable when readily available, because of the potential

complications of isoproterenol therapy (worsened ischemia and hypertension). Offending agents should be discontinued.

7. **Miscellaneous**

Commotio cordis. Commotio cordis is the sudden VA occurring as a result of a blunt, nonpenetrating impact to the precordial region, which is most commonly observed in young healthy persons during participation in sports. The blow likely falls within a small 10- to 30-ms window of ventricular vulnerability just prior to the peak of the T wave that results in polymorphic VT and sudden death. A 2002 case series of 128 individuals showed that only 16% of patients survived an episode of commotio cordis, with most returning to a baseline level of function. Prompt CPR/defibrillation was the only identifiable factor associated with a favorable outcome.

8. **VF.** VF is a **chaotic ventricular rhythm that reflects no organized electrical activity and hence no cardiac output** from the ventricle. It is devoid of the distinct elements that make up the usual electrical complex of ventricular activity. It is a **rapidly fatal rhythm, and if resuscitation is not begun within 5 to 7 minutes, death is virtually certain**. VF is often preceded by VT. Virtually all of the risk factors and conditions discussed for VT are applicable to VF. It may arise without any inciting cardiac rhythm or event.

   a. **Course of disease.** Of patients who experience an out-of-hospital cardiac arrest, 75% have VF as their initial cardiac rhythm. Of those successfully resuscitated, 75% have significant CAD and 20% to 30% have a transmural infarction. Patients without an ischemic etiology have an increased risk of further episodes of sudden death, whereas those who have an MI associated with sudden death have a 1-year recurrence rate of 2%. Anterior MI complicated by VF represents a subgroup at high risk for recurrence of sudden death. Predictors of SCD include evidence of ischemia, decreased LV systolic function, 10 or more PVCs per hour on telemetry, inducible or spontaneous VT, hypertension and LV hypertrophy, smoking,

male sex, obesity, elevated cholesterol, advanced age, and excessive alcohol use.

b. **Therapy.** As noted previously, VF is a rapidly fatal rhythm, which virtually never terminates spontaneously. CPR must be initiated promptly and rapid, asynchronous DCC performed as soon as possible. A **single** shock of 200 to 360 J (biphasic devices, 200 J; monophasic devices, 360 J) should be given initially followed by immediate resumption of CPR for 2 minutes before checking for a pulse. If VF/pulseless VT persists, an immediate **second** shock (biphasic devices, ≥200 J; monophasic devices, 360 J) should be given followed by a vasopressor (1 mg of epinephrine every 3-5 minutes). If VF/pulseless VT persists after two or three shocks, CPR, and a vasopressor, administration of an antiarrhythmic should be considered (amiodarone is preferred and lidocaine as an alternative). The emphasis should be on performing high-quality CPR with interruptions in chest compressions **only** for ventilation (until an advanced airway is established), rhythm checks (pulse checks only if an organized rhythm is observed), and shocks.

9. **Ventricular premature depolarizations (VPDs) and NSVT.** **VPDs** are common in patients with both structurally normal and structurally abnormal hearts. They are usually not hemodynamically significant, except in patients with depressed EF secondary to high VPD burden or those who are not optimally biventricular pacing due to frequent VPD **therapy**.

   a. **VPDs.** Although patients post-MI with VPDs have a higher mortality than patients post-MI without VPDs, suppression of VPDs with antiarrhythmic medication is associated with increased mortality. For patients with symptomatic VPDs, beta-blockers or calcium channel blockers should be the first-line agents. If this fails and the patient has no structural heart disease, class Ic agents may be effective; however, potential risks and benefits of the antiarrhythmic drug should be explained to the patient. Sotalol has been shown to reduce the

frequency of VPDs by 70% to 80%. In CAMIAT, amiodarone reduced VPDs and arrhythmic deaths, but not overall mortality. **A very high burden of VPDs (>20,000/d) may be associated with reduced EF**. In these patients with a high burden of VPDs and idiopathic DCM, treating the VPDs with either medication or catheter ablation may improve the LVEF. Ablation can be considered in very symptomatic VPDs refractory to medical therapy and/or patients with reduced EF thought to be a result of the VPDs.

b. **NSVT** is defined as VT of duration <30 seconds. It can occur in up to 4% of healthy adults and increases in frequency as people age. NSVT during exercise is not associated with a poor cardiovascular prognosis. The approach to NSVT is based on the cardiac substrate. However, patients with frequent polymorphic NSVT should undergo an evaluation for LQTS and catecholaminergic VT. One should also be mindful of repetitive monomorphic NSVT that may be of LBBB morphology in patients who have a family history of arrhythmias or sudden death, which may suggest ARVD. Monomorphic NSVT may also be a part of the spectrum of the outflow tract VTs.

   In patients in whom **structural heart disease has been excluded, NSVT does not carry prognostic significance**. Treatment should, therefore, only be guided by symptoms. A similar approach to NSVT with regard to medication choices is used as with symptomatic VPDs.

c. **NSVT in structural heart disease.** In patients with MI, NSVT within the first 24 to 48 hours has little prognostic significance. However, NSVT >48 hours after acute MI may increase the risk of sudden death by almost 2-fold, and the risk is even higher in patients with reduced LV function. **Patients with CAD, an EF <40%, and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT. In patients with HCM, NSVT on Holter monitoring is one of the major risk

factors for SCD. In patients with nonischemic DCM, NSVT is not an independent predictor of sudden death.

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CHAPTER 23

Bradyarrhythmias, Atrioventricular Block, Asystole, and Pulseless Electrical Activity

Jose Aguilera and Shady Nakhla

I. INTRODUCTION.

Bradyarrhythmias and **conduction blocks** are common electrocardiographic findings. Many of these arrhythmias are asymptomatic and do not require specific therapy, whereas others can be life-threatening, requiring rapid intervention.

II. ANATOMY

A. Sinoatrial (SA) node.

The normal sinus beat originates in the **SA node**, a focus of subepicardial automatic cells near the junction of the superior vena cava and the right atrium, the mean length of the SA node is 13.5 mm in adults.

1. The blood supply to the SA node is from the **sinus node artery**, which arises from the proximal **right coronary artery** (RCA) in 55% of the population (**Figure 23.1**) and the **left circumflex artery** (LCx) in 35%. The SA node receives a dual supply of blood from both the RCA and the LCx in 10% of the population.

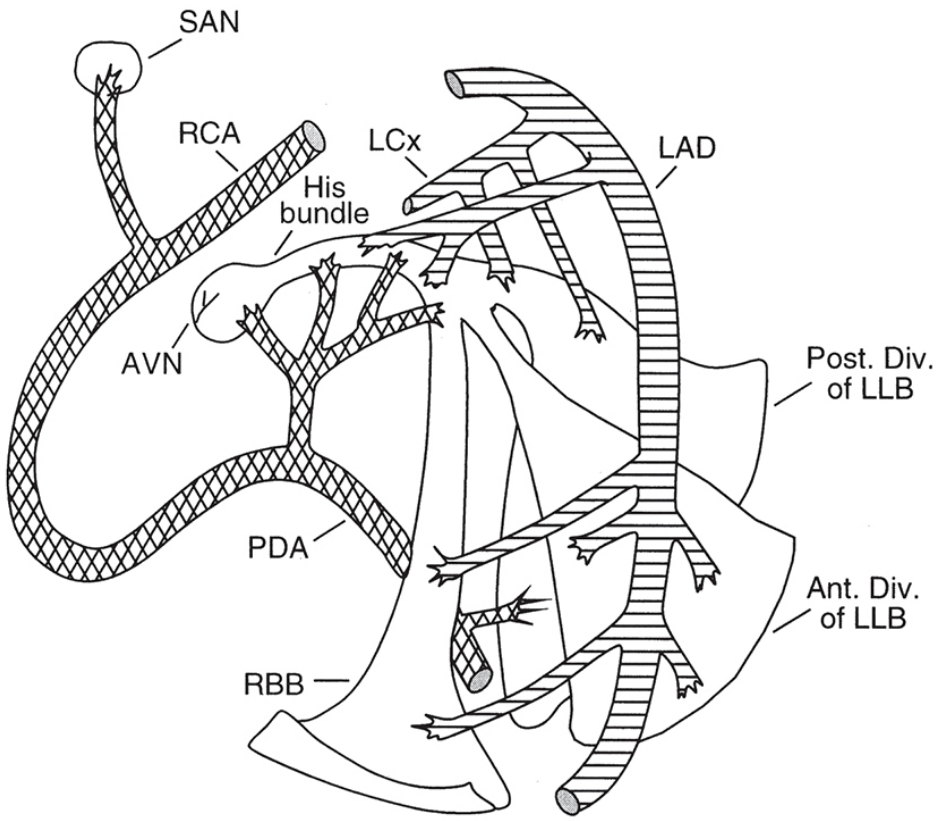

FIGURE 23.1 Diagrammatic representation of the conduction system and its blood supply. AVN, atrioventricular node; LAD, left anterior descending; LCx, left circumflex artery; LLB, left lateral branch; PDA, patent ductus arteriosus; RBB, right bundle branch; RCA, right coronary artery; SAN, sinoatrial node.

2. The automaticity of the SA node is affected by both the parasympathetic and sympathetic nervous systems to meet metabolic demands. If the SA node fails to generate an impulse, other foci in the atrium, atrioventricular (AV) node, or ventricle can act as "backup" pacemaker sites.

B. AV node. The AV node is located at the superior portion of the triangle of Koch, which is defined by the coronary sinus ostium inferiorly, tendon of Todaro posteriorly, and septal leaflet of the tricuspid valve anteriorly. The AV node is the only pathway between the atrium and the ventricles in normal hearts (without accessory pathway connections), as the fibrous skeleton of the heart acts as an insulator preventing impulses from entering the ventricle via other routes. The impulse generated by the SA node progresses through the atrium to the AV node, providing enough delay of <200 ms to allow for ventricular filling It can also limit the input to the

ventricles during rapid atrial tachyarrhythmias (ie, atrial flutter with 2:1 conduction).

1. The AV node is also innervated by both the parasympathetic and sympathetic nervous systems and can act as a subsidiary pacemaker when the sinus rate or atrial rate is too slow.
2. The AV node receives its blood supply from the **AV node artery**, which arises from the **posterior descending artery (PDA)** in 80% of the population (**Figure 23.1**), from the LCx in 10%, and from both arteries in 10%. Collateral blood supply from the **left anterior descending artery (LAD)** makes the AV node somewhat less prone to ischemic damage than the SA node.

C. His bundle and bundle branches

1. After a normal delay in the AV node, the electrical impulse is propagated down the His bundle that courses in the interventricular septum for a few millimeters before diving into the right and left bundle branches. The **left bundle branch splits further into anterior and posterior fascicles**. The autonomic nervous system does not have a major effect on conduction below the AV node.
2. The **His bundle and right bundle branch** receive their blood supply from the AV nodal artery and the septal perforating branches of the LAD. The **anterior fascicle of the left bundle branch** receives blood from the septal perforating branches of the LAD alone. The **posterior fascicle of the left bundle branch** has a dual blood supply from the septal perforating branches of the LAD and branches of the PDA.

III. SINUS NODE DYSFUNCTION.

Sinus node dysfunction (SND) encompasses any dysfunction of the sinus node resulting in a mismatch of physiologic demands. SND spectrum includes **inappropriate sinus bradycardia**, **chronotropic incompetence,** SA **exit block**, SA **arrest, sinus pauses, and tachycardia-bradycardia syndrome**.

A. Clinical presentation.

There is a wide range of presentations, and some patients' disease may be asymptomatic.

1. **Syncope** and **presyncope** are the most dramatic presenting symptoms. **Fatigue, angina, shortness of breath, and decreased exercise capacity** are more subtle consequences of SND.
2. In the tachycardia-bradycardia syndrome, the primary complaint may be palpitations or symptoms suggestive of a pause after a tachycardia

episode. Documentation of the symptomatic tachyarrhythmia may be difficult because of the sporadic and fleeting nature of the problem.

B. Etiology. The intrinsic and extrinsic causes of SND are listed in **Table 23.1**. **Idiopathic degenerative disease** due to progressive fibrosis is the most common cause of intrinsic SND, the incidence increases with age. **Acute coronary syndromes** are another common cause of bradyarrhythmias, occurring in 25% to 30% of patients with myocardial infarction (MI), especially of the inferior wall (**Table 23.2**).

TABLE 23.1 Etiologies of Sinus Node Dysfunction

Intrinsic Causes
Idiopathic degenerative disease
Coronary artery disease
Cardiomyopathy
Hypertension
Infiltrative disorders (amyloidosis, hemochromatosis, and tumors)
Collagen vascular disease (scleroderma and systemic lupus erythematosus)
Inflammatory processes (myocarditis and pericarditis)
Surgical trauma (valve surgery and transplantation)
Musculoskeletal disorders (myotonic dystrophy and Friedreich ataxia)
Congenital heart disease (postoperative or in the absence of surgical correction)
Extrinsic Causes
Drug effects
Beta-blocking agents
Calcium channel–blocking agents
Digoxin
Sympatholytic antihypertensives (clonidine, methyldopa, and reserpine)
Antiarrhythmic drugs
Type Ia (quinidine, procainamide, and disopyramide)
Type Ic (flecainide and propafenone)
Type III (sotalol and amiodarone)
Others (lithium, cimetidine, amitriptyline, and phenytoin)

Intrinsic Causes
Autonomic influences
Excessive vagal tone
Carotid sinus syndrome
Vasovagal syncope
Well-trained athletes (normal variant and not dysfunction)
Electrolyte abnormalities
Hyperkalemia
Hypercarbia
Endocrine disorders—hypothyroidism
Increased intracranial pressure
Hypothermia
Sepsis

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TABLE 23.2 Incidence of Bradyarrhythmia in the Setting of Acute Myocardial Infarction

Rhythm	Incidence (%)
Sinus bradycardia	25
Junctional escape rhythm	20
Idioventricular escape rhythm	15
First-degree AV block	15
Second-degree, Mobitz type I AV block	12
Second-degree, Mobitz type II AV block	4
Third-degree AV block	15
Right bundle branch block	7
Left bundle branch block	5
Left anterior fascicular block	8
Left posterior fascicular block	0.5

AV, atrioventricular.

C. Electrocardiographic findings

1. Inappropriate sinus bradycardia, also known as "**chronotropic incompetence**," is the inability of the heart to increase its rate with increased activity or physiologic demand. It can be defined as the inability to accelerate to >80% of the age-predicted maximum heart rate (220-age) during exercise. Inappropriate sinus bradycardia must be differentiated from a low resting heart rate, which may be normal in athletes and sleeping individuals.
2. Sinus arrest, or a sinus pause, occurs when the sinus node fails to depolarize on time. Pauses of <3 seconds may be seen on Holter monitoring in up to 11% of normal adults (especially athletes) and are not a cause for concern. This is due to high vagal tone. However, **pauses lasting longer than 3 seconds are generally considered abnormal and are suggestive of underlying pathology**, especially if the patient is awake when they occur.
3. SA exit block, although similar to sinus arrest on the electrocardiographic tracing, may be distinguished by the fact that the **duration of the pause is a multiple of the sinus PP** interval. High-grade SA exit block cannot be differentiated from prolonged sinus arrest and is treated in the same manner.
4. Tachycardia-bradycardia syndrome, also referred to as "sick sinus syndrome," is characterized by episodes of sinus or junctional bradycardia interspersed with an atrial tachyarrhythmia, usually paroxysmal atrial fibrillation. The main cause of morbidity in these patients is the presence of pauses. This happens when the atrial tachyarrhythmia suppresses the SA nodal depolarization, upon termination of the tachyarrhythmia, a diseased SA node takes a long time to recover and initiate spontaneous depolarization, and this can cause "postconversion pauses" that may result in lightheadedness, presyncope, or syncope.

D. Diagnostic testing.

Invasive testing is used when noninvasive methods have failed to yield a diagnosis and SND is still strongly suspected.

1. **Noninvasive testing**
   a. **Electrocardiogram (ECG).** In evaluating SND, the initial workup should include a 12-lead ECG, followed by **ambulatory ECG monitoring**. In some cases, 24 to 48 hours of monitoring (Holter) is sufficient, but frequently, extended monitoring for 2 to 4 weeks (event

recorder) is required for diagnosis. Rarely, in more paroxysmal cases, prolonged monitoring for months to years via implantable loop recorders is indicated. The use of a diary during the recording period can help correlate symptoms with the cardiac rhythm. **Stress testing** can help in the diagnosis and severity of chronotropic incompetence.

b. Autonomic testing includes physical maneuvers, such as carotid sinus massage and tilt table testing, as well as pharmacologic interventions to test the autonomic reflexes.

TABLE 23.3 Indications for Permanent Pacing

Indication	Class I	Class II	Class III
SND	**1.** SND documented in association with symptomatic bradycardia and because of factors that are irreversible or because of essential drug therapy **2.** Symptomatic chronotropic incompetence	IIa. No clear association between SND with heart rate <40 beats/min and symptoms can be documented IIb. In minimally symptomatic patients, chronic heart rate <40 beats/min while awake	**1.** SND with marked sinus bradycardia or pauses but *no associated symptoms*, including because of long-term drug therapy **2.** SND in patients with symptoms suggestive of bradycardia that are clearly documented as *not* associated with a slow heart rate **3.** SND with symptomatic bradycardia because of nonessential drug therapy
Acquired AV block	**1.** Third-degree or advanced second-degree (Mobitz II) AV block at any anatomic level, associated with	IIa **1.** Asymptomatic third-degree AV block with average ventricular rates ≥40 beats/min	**1.** Asymptomatic first-degree AV block **2.** Asymptomatic type I second-degree AV block

Indication	Class I	Class II	Class III
	any one of the following conditions: **A.** Bradycardia with symptoms presumed to be due to AV block **B.** Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia **C.** Documented periods of asystole ≥3.0 s, or an escape rhythm below the AV node, or any escape rate <40 beats/min in awake, symptom-free individuals in sinus rhythm **D.** Documented pauses >5 s in awake, symptom-free patients who are in atrial fibrillation **E.** After catheter ablation of the AV junction **F.** Postoperative AV block that is not expected to resolve **G.** Neuromuscular diseases with AV block such as myotonic muscular dystrophy,	without cardiomegaly **2.** Asymptomatic type II second-degree AV block with narrow QRS. Becomes class I recommendation when wide non-RBBB QRS **3.** Asymptomatic second-degree AV block at intra-His or infra-His levels found at EP study **4.** First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise IIb **1.** Neuromuscular diseases with *any* degree of AV block (including first degree) with or without symptoms **2.** AV block in the setting of drug use or toxicity when the block is expected to recur even after drug withdrawal	(Wenckebach) at the supra-His (AV node) level or not known to be intra-Hisian or infra-Hisian **3.** AV block expected to resolve and unlikely to recur (eg, drug toxicity, Lyme disease)

Indication	Class I	Class II	Class III
	Kearns-Sayre syndrome, Erb dystrophy (limb girdle), and peroneal muscular dystrophy, with or without symptoms **H.** Asymptomatic persistent AV block at any anatomic site with average awake ventricular rates of 40 beats/min or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node **I.** Present during exercise in the absence of myocardial ischemia		
Postacute MI	**1.** Persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after acute ST-elevation acute MI **2.** Transient advanced (second- or third-	IIa. None IIb **1.** Persistent second- or third-degree AV block at the AV node level, even in the absence of symptoms	**1.** Transient AV block without intraventricular conduction defect **2.** Transient AV block in the presence of isolated left anterior fascicular block **3.** New bundle branch or fascicular block in the absence of AV

Indication	Class I	Class II	Class III
	degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an EP study may be necessary **3.** Persistent and symptomatic second- or third-degree AV block		block. Persistent asymptomatic first-degree AV block in the presence of bundle branch block
Chronic bifascicular blocks	**1.** Intermittent advanced second- or third-degree AV block **2.** Type II second-degree AV block **3.** Alternating bundle branch block	IIa **1.** Syncope not proved to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia **2.** HV interval >100 ms on EP study in asymptomatic patients **3.** Pacing-induced infra-His block on EP study that is nonphysiologic IIb **1.** Neuromuscular disorders with any fascicular or bifascicular block with or without symptoms	**1.** Fascicular block without AV block or symptoms **2.** Fascicular block with first-degree AV block without symptoms
Carotid sinus hypersensitivity and neurocardiogenic syncope	Recurrent syncope caused by spontaneous carotid sinus stimulation inducing ventricular asystole >3 s	IIa Syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of >3 s IIb	**1.** Hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of clear symptoms

Indication	Class I	Class II	Class III
		1. Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at time of tilt table testing	**2.** Situational vasovagal syncope in which avoidance behavior is effective and preferred

Class I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of pacing.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.

AV, atrioventricular; EP, electrophysiologic; HV, half-value; LV, left ventricular; MI, myocardial infarction; RBBB, right bundle branch block; SND, sinus node dysfunction.

Data from Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices). *J Am Coll Cardiol*. 2008;51:2085-2105; Epstein AE, Darbar D, DiMarco JP, et al. ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2012;126:1784-1800.

TABLE 23.4 Causes of Atrioventricular Block

Drug effects
Digoxin
Beta-blockers
Certain calcium channel blockers (nondihydropyridines)
Membrane-active antiarrhythmic drugs
Ischemic heart disease
Acute myocardial infarction
Chronic coronary artery disease

- Idiopathic fibrosis of the conduction system
  - Lenegre disease
  - Lev disease
- Congenital heart disease
  - Congenital complete heart block
  - Ostium primum atrial septal defect
  - Transposition of the great vessels
  - Maternal systemic lupus erythematosus
- Calcific valvular disease
- Cardiomyopathy
- Infiltrative disease
  - Amyloidosis
  - Sarcoidosis
  - Hemochromatosis
- Infectious/inflammatory diseases
  - Endocarditis
  - Myocarditis (Chagas disease, Lyme disease, rheumatic fever, tuberculosis, measles, and mumps)
- Collagen vascular diseases (scleroderma, rheumatoid arthritis, Reiter syndrome, systemic lupus erythematosus, ankylosing spondylitis, and polymyositis)
- Metabolic
  - Hyperkalemia
  - Hypermagnesemia
- Endocrine—Addison disease
- Trauma
  - Cardiac surgery
- Transaortic valve replacement (TAVR)
  - Radiation
  - Catheter trauma
  - Catheter ablation
- Tumors
  - Mesothelioma

	Hodgkin disease
	Malignant melanoma
	Rhabdomyosarcoma
Neurally mediated	
	Carotid sinus syndrome
	Vasovagal syncope
Neuromyopathic disorders	
	Myotonic muscular dystrophy
	Slowly progressive X-linked muscular dystrophy

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(1) Carotid sinus massage distinguishes intrinsic sinus arrest from a pause because of **carotid sinus hypersensitivity**, which is a 3-second or longer pause, because of the tilt table testing as well as pharmacologic interventions to test the autonomic reflexes. The paroxysmal carotid **sinus massage should not normally precipitate sinus arrest**, although it will decrease the rate of depolarization of the SA node and slow conduction in the AV node. Carotid sinus hypersensitivity is relatively common in older patients with atherosclerotic disease and can be provoked by neck motion, shaving, or a tight shirt collar. When carotid sinus hypersensitivity is accompanied by syncope or presyncope, it constitutes **carotid sinus syndrome** and may warrant permanent pacing for nonvasodepressive subtypes (**Table 23.3**).

(2) **Tilt table testing** may help differentiate between syncope caused by SND and that because of autonomic dysfunction (**neurocardiogenic syncope**). **Bradycardic episodes precipitated by tilt table testing are usually caused by autonomic dysfunction and not by SND**.

(3) **Pharmacologic testing** may be used to differentiate between SND and autonomic dysfunction. Total autonomic blockade is achieved after administration of atropine 0.04 mg/kg and propranolol 0.2 mg/kg. The resulting intrinsic heart rate represents the sinus node rate, devoid of autonomic influences. Assuming that the normal intrinsic heart rate (in beats/min) is

defined by the formula:
Intrinsic heart rate = 118.1 − (0.57 × age), then (a) an intrinsic heart rate lower than predicted using this formula is consistent with SND and (b) an intrinsic heart rate close to the predicted rate with a clinical presentation similar to SND is suggestive of autonomic dysfunction as the cause of bradyarrhythmia.

2. Invasive testing. Electrophysiologic study (EPS) is rarely used in modern practice for the diagnosis of SND. However, when performed, the two most common tests use indirect measurements of SA node function, as direct measurement of SA node function is laborious.

a. Sinus node recovery time (SNRT) is the time it takes the SA node to recover following paced overdrive suppression of the node.

(1) A delay of longer than 1,400 ms is considered abnormal. This measurement may be corrected by subtracting the intrinsic sinus cycle length (in milliseconds) from the recovery time. **A corrected SNRT >550 ms is suggestive of SND.**

(2) The limitations of this test are as follows:

(a) It is an indirect measurement of SA node function and reflects both sinoatrial node conduction time (SACT) and automaticity.

(b) It may be falsely shortened by an SA node entrance block during atrial pacing (because of failure of the paced impulse to reset the sinus node) or falsely prolonged by an SA node exit block (the sinus node is normal, but the impulse cannot leave the node), which affects its specificity.

(c) The SNRT is not prolonged in all patients with SND, which affects its sensitivity.

b. SACT

(1) The steady-state atrial rate is determined (A_1-A_1 interval or the time between P waves). Then, premature atrial **extra stimuli** (A_2) are introduced by pacing high in the right atrium, starting in late diastole at progressively shorter intervals until atrial refractoriness is found (ie, A_2 does not result in a P wave). The duration before the next spontaneous atrial impulse (A_3) is measured, and the baseline rate is subtracted.
SACT = (A_2 – A_3 interval) – (A_1 – A_1 interval)

The test assumes that SA node automaticity is not affected by pacing, that the conduction time into the node is equal to the conduction time out of the node, and that there is no shift in the principal pacemaker site.

E. Therapy. Treatment for symptomatic SND may be pharmacologic, pacing, or a combination of both.

1. Initial management should focus on the identification and elimination of reversible causes such as metabolic abnormalities, medications, infection, or sleep disorder (**Table 23.1**).
2. Indications for pacing in SND are largely determined by symptoms (eg, correlation with a documented arrhythmia; **Table 23.3**). Patients with SND who are asymptomatic do not require treatment. Pacing in these groups of patients does not impact survival; it only improves symptoms and quality of life.
3. Pacing may also be indicated when essential drug therapy that causes SND cannot be stopped or changed.
4. For patients with **tachycardia-bradycardia syndrome**, a pacemaker is often placed for the management of the bradyarrhythmia, and antiarrhythmic or rate-controlling drugs are added for the treatment of the tachycardia episodes.
5. Acute treatment for patients with **symptomatic SND** includes the following:
   a. Atropine (0.04 mg/kg or 0.5 mg intravenous [IV] bolus). This can be repeated every 3 to 5 minutes for a maximum total dose of 3 mg.
   b. IV adrenergic agents such as isoproterenol (starting at 1 mcg/min IV), which may be used as a bridge to pacemaker placement. Isoproterenol is not indicated in most patients with cardiac arrest. Other adrenergic agent options are dopamine and epinephrine.
   c. Temporary pacing for patients whose conditions fail to respond to drug therapy
6. For patients requiring permanent pacing for SND, a dual-chamber (right atrium and right ventricle [RV]) pacemaker should be implanted and programmed to DDD or AAI modes, which have been shown to be superior to VVI mode with respect to subsequent incidence of atrial fibrillation, heart failure, pacemaker syndrome, and pacing-induced systolic cardiomyopathy. Subsequent AV block occurs in up to 35% of

patients with SND over extended follow-up, and thus single-chamber AAI pacing is typically used only in younger patient populations.

IV. ATRIOVENTRICULAR CONDUCTION DISTURBANCES. These disturbances are classified as first-, second-, or third-degree block, depending on the severity of the conduction abnormality.

A. Classification

1. **First-degree AV block** is characterized by prolongation of the PR interval beyond 200 ms. This finding may occur as a normal variant in 0.5% of asymptomatic young adults without overt heart disease. In older individuals, it is most often caused by idiopathic degenerative disease of the conducting system. Although the name contains the term "AV block," there is no real block, instead is a conduction delay almost always located in the AV node. In rare circumstances, delay within the His bundle results in the same electrocardiographic phenomenon—a narrow QRS with a long PR interval.
2. **Second-degree AV block**
   - **a.** Second-degree AV block is characterized by **a failure of one or more, but not all, atrial impulses to conduct to the ventricles**. The block may be at any level of the AV conduction system.
   - **b.** When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes (for two P waves preceding each QRS complex, 2:1 second-degree AV block is present).
     - **(1)** Lesser degrees of AV block (ie, 4:3 or 3:2) with a prolonging PR interval prior to a nonconducted atrial impulse are described as **Mobitz type I AV block** (also known as **Wenckebach** block).
       - **(a)** The conducted impulse of a **Mobitz type I block** will generally be narrow, similar to first-degree AV block, the site of block is often in the AV node, above the His bundle.
       - **(b)** A Mobitz type I block with a bundle branch block is still likely to be above the His bundle, but a His bundle electrogram is needed to confirm the level of block.
     - **(2)** High-grade AV block (3:1, 4:1, or greater) is typically described as **Mobitz type II AV block**. The conducted impulses will generally be preceded by constant PR intervals and have a wide

QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] pattern). The site of block is often below the AV node. A **Mobitz type II block** is usually intra-Hisian or infra-Hisian and has a greater propensity for progressing to **third-degree AV block**.

(3) Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II by ECG alone, and if diagnostic maneuvers (such as exercise) are not able to elucidate one type of second-degree block versus the other, an EPS may be warranted.

3. Third-degree AV block, or **complete heart block**, may be acquired or congenital and is characterized by AV electrical dissociation.

a. A total of 60% to 90% of cases of **congenital complete heart block** result from neonatal lupus. The vast remainder occurs concurrently with congenital structural heart defects.

b. Acquired AV block occurs most commonly (~50%) because of progressive degeneration of the conduction system, but the differential includes a myriad of reversible and irreversible, iatrogenic, and noniatrogenic causes (**Table 23.4**).

B. Clinical presentation

1. Signs and symptoms

a. First-degree AV block and Mobitz type I second-degree AV block are generally not a cause of symptoms. Rarely, very long PR interval (>300 ms) can cause atrial systole to occur near simultaneously to ventricular systole and cause symptoms similar to a pacemaker syndrome as the atria contract against a closed mitral and tricuspid valve.

b. Mobitz type II second-degree AV block ***may*** result in symptoms; however, high-grade second-degree AV block may progress to third-degree AV block, which can frequently cause symptoms.

c. Depending on the escape rate, patients with **third-degree AV block** may experience **fatigue** or **syncope**.

2. Physical findings. The amplitude of the arterial pulse and venous waveform varies, depending on the timing of atrial filling of the ventricles.

a. Second-degree AV block is associated with a periodic change in amplitude. In patients with **third-degree AV block**, amplitude is constantly changing, with a periodic appearance of **cannon A waves**

(large-amplitude waves in the venous pulsations seen in the neck when the atria contract against a closed tricuspid valve).

b. Heart sounds are similarly affected by the change in filling duration of the ventricles.

(1) The first heart sound (S_1) becomes softer as the PR interval is prolonged, resulting in a soft S_1 in first-degree AV block, a progressive softening of S_1 in type I second-degree AV block, and a constantly changing S_1 in third-degree AV block.

(2) Third-degree AV block may also result in a functional systolic ejection murmur.

C. Etiology. The causes of AV block are listed in **Table 23.4**; the most common cause is **idiopathic degenerative fibrosis. Acute MI** results in AV block in 14% of patients with inferior infarction and 2% of those with anterior infarction, usually within the first 24 hours.

D. Diagnostic testing. ECG can identify the presence of AV block and provide clues of the site of AV block. Response to carotid sinus massage (increase vagal tone) and exercise (increase sympathetic tone) may also be used in diagnosing and locating the site of AV block. In some patients, an EPS may be required to investigate suspected AV block.

1. First-degree AV block. Measuring a PR interval longer than 200 ms in adults and 180 ms in children makes the diagnosis. A P wave precedes each QRS, and both the P and the QRS are morphologically normal.

2. Second-degree AV block

a. The diagnosis of **Mobitz type I** is made when the following criteria are met on the ECG:

(1) Sequential and gradual prolongation of the PR interval terminated by a nonconducted P wave

(2) Prolongation of the PR interval occurring in progressively shorter increments in "typical" Wenckebach, which results in progressive shortening of the RR intervals prior to the nonconducted atrial impulse

(3) Duration of the pause following the nonconducted P wave, which is less than the sum of any two consecutively conducted beats

(4) Decreased PR interval following the pause when compared with the prepause PR interval

(5) "Grouped beating," a pattern of repeated groups of QRS complexes characteristic of Wenckebach block

b. Mobitz type II second-degree AV block is less common than type I.

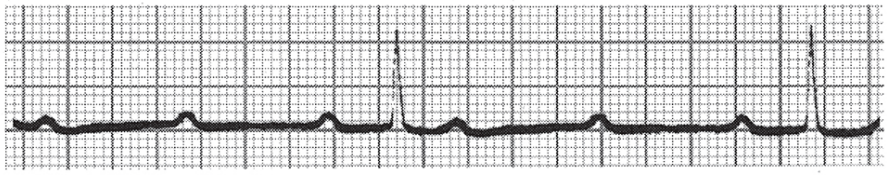

FIGURE 23.2 Mobitz type II second-degree atrioventricular block with 3:1 conduction.

(1) The PR and PP intervals are constant with a sudden nonconducted P wave (**Figure 23.2**), in contrast to nonconducted (blocked) premature atrial contractions that have varying PR and PP intervals.

(2) Each QRS complex may have multiple P waves, which are designated by the number of P waves before each conducted QRS (3:1, 4:1, etc.). The QRS complex is typically not narrow (a narrow QRS complex is suggestive of a Mobitz type I block). It is often difficult to distinguish between 2:1 Mobitz I versus Mobitz II patterns by ECG alone, particularly if the QRS complex is narrow. A commonly used discrimination tool in this scenario is exercise ECG testing. Exercise improves (decreases) AV nodal conduction time, but ***not*** infranodal conduction time, and thus may *improve* block from 2:1 to 3:2 in Mobitz I, whereas block should be unchanged to *worsened* (2:1 to 3:1) in Mobitz II.

3. Third-degree AV block (**Figure 23.3**)

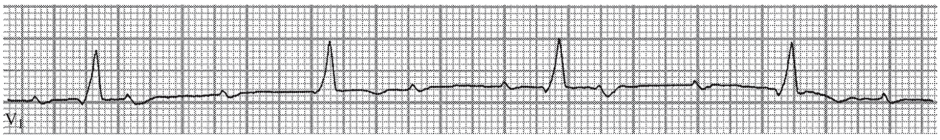

FIGURE 23.3 Third-degree atrioventricular block with sinus tachycardia and right bundle branch block.

a. Third-degree AV block is characterized by the identification of **complete dissociation of the atrial and ventricular electrical activities** (no temporal relationship exists between the P waves and the QRS complexes), with atrial activity more rapid than ventricular activity. Using calipers, it is possible to march out the progression of the P waves to determine the atrial rate.

b. Third-degree AV block is only one cause of AV dissociation; **not all AV dissociation is third-degree AV block.** For example, conditions where the ventricles are depolarizing faster than the atria—such as accelerated junctional rhythm or ventricular tachycardia—also result in AV dissociation if there is a lack of retrograde conduction over the AV node.

E. Therapy. Patients with first-degree AV block and Mobitz type I AV block usually do *not* require therapy. Permanent pacing is indicated for Mobitz type II AV block and third-degree AV block without reversible cause. (See **Table 23.3** for complete indications for pacing.)

1. Medical therapy may be used as a bridge to pacing, but it has no role in long-term treatment.

a. The principal drug used as a bridge to pacing is **atropine**:

(1) It reduces heart block because of hypervagotonia, but not because of AV nodal ischemia.

(2) It is more useful for AV block in inferior MI than anterior MI.

(3) It does not increase infranodal conduction (will not improve second- or third-degree AV block that is below the AV node).

(4) It is ineffective in the denervated hearts of transplant patients.

(5) It is used with caution (if at all) in Mobitz type II AV block because of a possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases, and a 2:1 block with an atrial rate of 80 beats/min and a ventricular rate of 40 beats/min may be converted to a 3:1 block with an atrial rate of 90 beats/min and a ventricular rate of 30 beats/min).

b. Targeted medical therapy ± temporary pacing is indicated for potential reversible causes prior to permanent pacemaker implantation. For example, cardiac Lyme should receive appropriate antibiotic therapy.

c. Overmedication with AV nodal blocking agents should receive adequate time for drug metabolism/clearance ± administration of reversal agents (eg, glucagon, IV calcium). Digoxin-specific Fab

fragments may be used to treat patients with symptomatic AV blocks related to the use of digitalis.

2. Pacing
   a. Third-degree AV block as a complication of **inferior MI** is usually temporary and thus usually only requires **temporary pacing**. However, complete heart block with **anterior MI** often requires **permanent pacing** (**Table 23.3**).
   b. Acquired third-degree AV block usually requires pacing, but patients with congenital third-degree AV block often have a sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.
   c. For irreversible third-degree AV block *without* permanent atrial tachyarrhythmia, a permanent dual-chamber pacemaker should be implanted and programmed to DDD mode. However, if the preimplant ejection fraction is ≤50%, implantation of a biventricular pacemaker (cardiac resynchronization therapy [CRT]) should be considered, due to lower composite rates of mortality, heart failure, and adverse left ventricular (LV) remodeling with CRT in this patient population (BLOCK-HF trial).
   d. Traditionally, in patients with preserved LV function, RV apical or septal pacing was considered acceptable with no adverse effects of outcomes. However, in patients with an expected high burden of RV pacing, the need for upgrade to CRT due to a pacing-induced cardiomyopathy is as high as 20%. As such, leverage of the native conduction system distal to the sites of block has been an area of growing experience.
   e. Most recently, **conduction system pacing (CSP) by capturing the His bundle or left bundle branch area pacing (LBBAP)** maintains physiologic ventricular activation. This is particularly important in those with anticipated high percentage of RV pacing or those with indication for CRT.
   f. **Permanent His bundle pacing** is an ideal site from a hemodynamic standpoint as it preserves the normal electrical activation of both ventricles; however, it is more technically challenging and has been associated with an increased rate of lead revision due to high capture thresholds and lead dislodgment.

g. **LBBAP** overcomes many of the limitations of His bundle pacing while maintaining LV synchrony. The lead captures the left bundle, typically distal to the site where the left bundle branch block develops. There are active ongoing randomized controlled trials (RCTs) investigating the long-term safety and effectiveness of LBBAP pacing.

V. JUNCTIONAL RHYTHMS. Junctional rhythms arise from the area surrounding the AV node, including the supranodal fibers, the node itself, and the bundle of His. This area has an intrinsic rate of 30 to 60 beats/min and serves as a faster escape mechanism that supersedes the automaticity of ventricular myocardium (0-40 beats/min) in the case of complete AV block. Junctional rhythm that is faster than the sinus rhythm is referred to as **accelerated junctional rhythm**.

A. Clinical presentation. Patients usually do not develop symptoms that are directly attributable to accelerated junctional rhythm. The **physical findings of AV dissociation may be noted** and are the same as those seen in third-degree AV block.

B. Etiology

1. Accelerated junctional rhythm is seen in approximately **10% of patients with acute MI**. More than one-half of these patients have inferior, and about one-third have anterior MI.
2. Digitalis toxicity by itself does not seem to cause accelerated junctional rhythm, as evidenced in persons with normal hearts who take accidental overdoses of digoxin. **Concomitant heart disease** is required to develop accelerated junctional rhythm.
3. Other causes of accelerated junctional rhythm are valve surgery, acute rheumatic fever, direct current cardioversion, cardiac catheterization, serious infection, chronic obstructive pulmonary disease, systemic amyloidosis, and uremia with hyperkalemia.

C. ECG findings

1. **Accelerated junctional rhythm**
   a. **Unless the junctional rhythm causes retrograde activation of the atria**, the P wave is normal in morphologic characteristics. The QRS complex has a normal duration, unless there is concomitant bundle branch block. The distinguishing characteristic of accelerated junctional rhythm is the AV dissociation and changing PR interval (**Figure 23.4**).

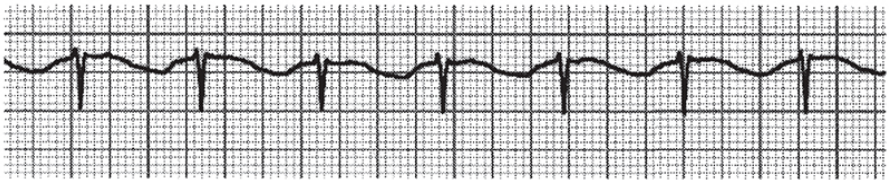

FIGURE 23.4 Accelerated junctional rhythm.

b. The difference between accelerated junctional rhythm and third-degree AV block is the fact that the ventricular rate is faster than the atrial rate in accelerated junctional rhythm and slower than the atrial rate in third-degree AV block.

2. **Junctional rhythm.** In the absence of a sinus beat, the AV node can act as a backup pacemaker. The ECG findings are classically an absence of P waves (or retrograde P waves with negative axis in inferior leads immediately before or after the QRS complex with short PR/RP intervals, respectively), a narrow QRS complex, and a rate of 30 to 60 beats/min.

D. Therapy

1. Therapy for junctional rhythm secondary to SA node failure or AV block is as previously outlined for AV conduction disturbances.
2. Patients with accelerated junctional rhythm do not usually require therapy for the arrhythmia, although management of the underlying cause is indicated.
3. Suppression of accelerated junctional rhythm may be achieved by **increasing the atrial rate with drugs** (eg, atropine and adrenergics) or **pacing**.
4. Digoxin-induced accelerated junctional rhythm is an indication to stop digoxin, but it does not usually require administration of digoxin-specific Fab fragments.

VI. INTRAVENTRICULAR CONDUCTION DISTURBANCES.

Conduction disturbances because of blockage below the AV node are classified on the basis of the intraventricular conduction system. An intraventricular conduction disturbance (IVCD) does not itself cause bradyarrhythmia, but it may be associated with any of the other rhythms that cause bradycardia. When associated with an acute MI, an IVCD predicts a worse outcome.

A. Etiology

1. The causes of IVCDs are similar to those that cause AV block (**Table 23.4**); **idiopathic degenerative conduction disease** and **acute ischemic syndromes** are the most common causes.
2. IVCDs increase with age and affect up to 2% of individuals older than 60 years.
3. The incidence of IVCDs is increased in persons with structural heart disease, especially those with coronary artery disease.

B. ECG findings

1. The ECG findings of IVCDs are summarized in **Table 23.5**, and examples are presented in **Figures 23.5** to **23.8**. As shown, **IVCDs may be further classified by the number of fascicles they affect**.

TABLE 23.5 Electrocardiographic Features for the Fascicular and Bifascicular Blocks

ECG Finding	LBBB	LAFB	LPFB	RBBB	RBBB and LAFB	RBBB and LPFB
QRS axis		≥−45°	+90° to +120°		−60° to −120°	≥+120°
QRS duration leads I/aVL	≥120 ms broad monophasic R	Normal qR	Normal rS	≥120 ms qRS with wide terminal S	≥120 ms qR	≥120 ms rS
Leads II, III, and aVF		rS	qR		rS	qR
Leads V_1 and V_2	rS or QS			rsR′ or rSR′	rsR′ or rSR′	rsR′ or rSR′
Leads V_5 and V_6		S	No Q	qRS		

ECG, electrocardiogram; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.

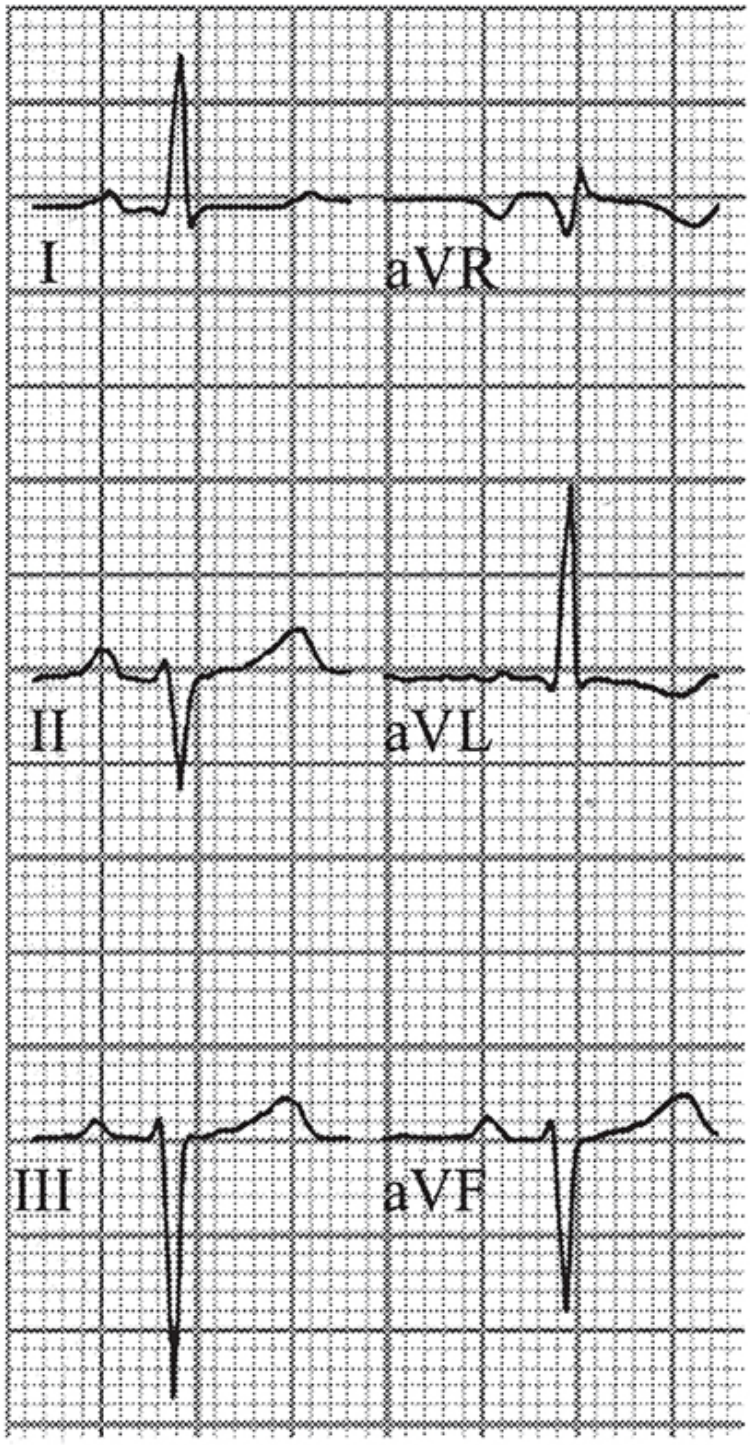

FIGURE 23.5 Left anterior hemiblock.

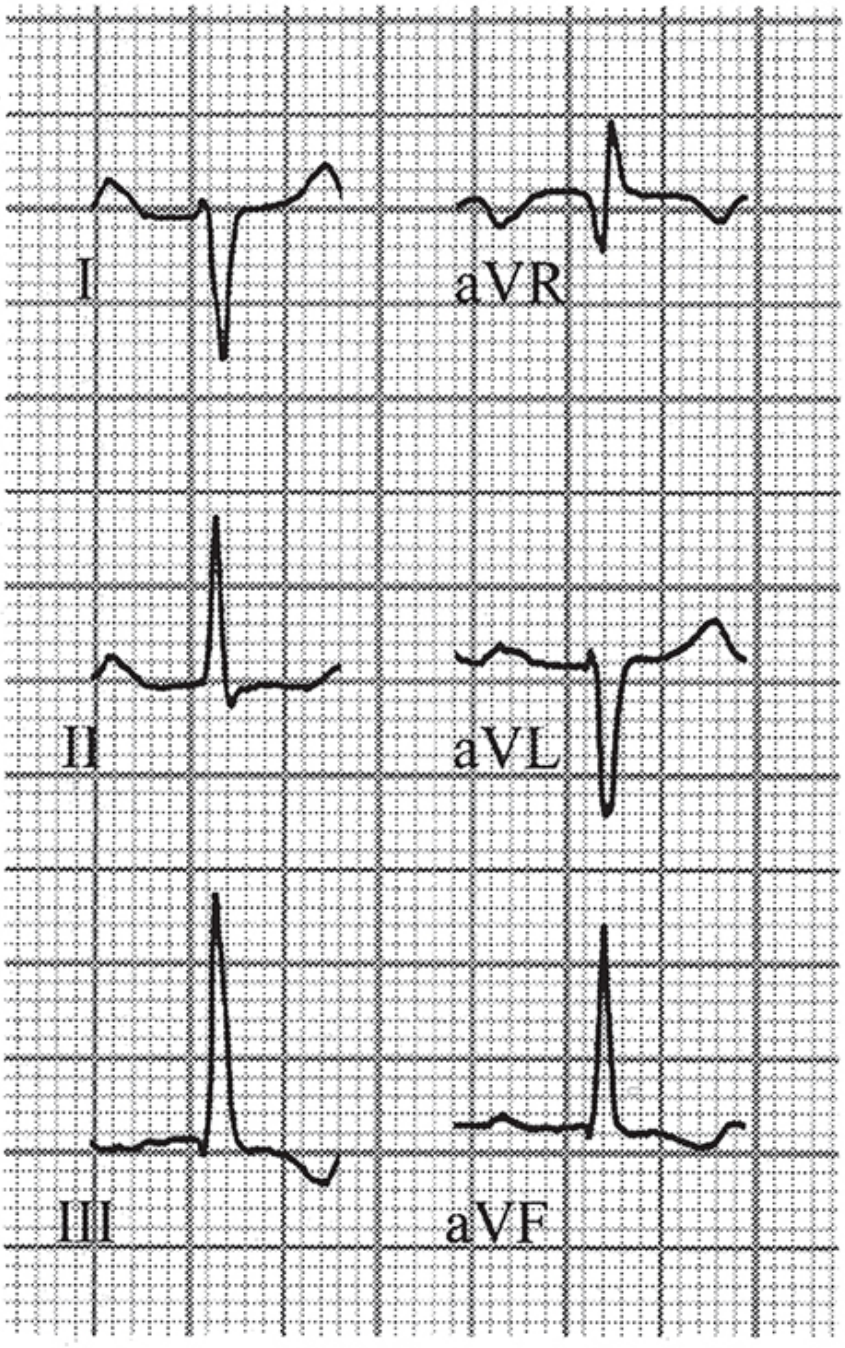

FIGURE 23.6 Left posterior hemiblock.

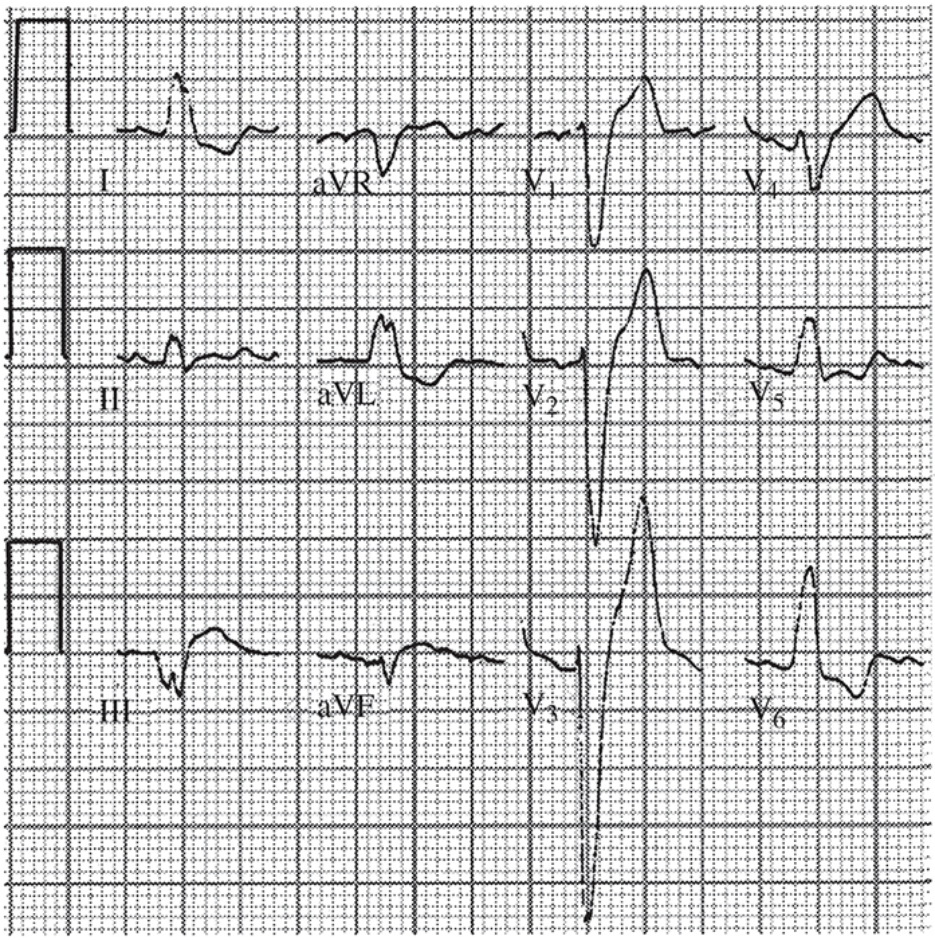

FIGURE 23.7 Left bundle branch block.

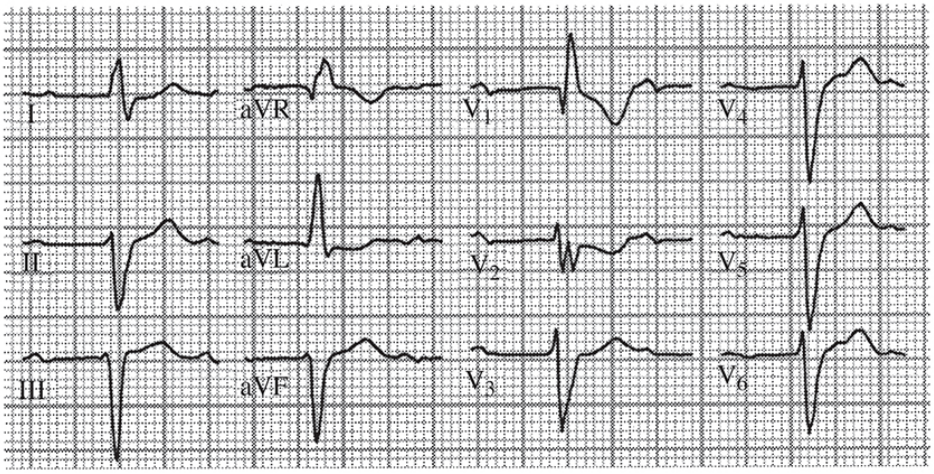

FIGURE 23.8 First-degree atrioventricular block with right bundle branch block and left anterior hemiblock.

2. **Fascicular blocks**

   a. **Unifascicular** block affects only one of the three fascicles. Examples are RBBB, left anterior fascicular block (LAFB), and left posterior fascicular block (LPFB).

   b. **Bifascicular** block is present when conduction disturbances affect two of the fascicles, most commonly the right bundle branch and the left anterior fascicle. Approximately, 6% of these patients progress to complete heart block. RBBB with LPFB is less common, but the progression to complete heart block is more common.

   c. "**Trifascicular** block" is said to be present when there is a combination of bifascicular block and first-degree AV block (**Figure 23.8**).

C. **Therapy.** Pacing is indicated in patients with bifascicular block who have advanced AV block (Mobitz II or complete heart block) or alternating bundle branch block. Whereas an EPS is not routinely performed in this setting, pacing may also be indicated in asymptomatic patients if a prolonged HV interval >100 ms or nonphysiologic infra-Hisian block is found (**Table 23.3**).

III. POSTPROCEDURAL BRADYARRHYTHMIAS

A. **Etiology.** Bradyarrhythmias following cardiac surgery and endovascular procedures are common.

1. Cardiac surgery, in particular valvular surgery and myectomy, can cause mechanical damage to the conduction system, leading to new AV block and IVCD that are variably reversible. The estimated incidence of persistent high-grade AV block requiring permanent pacemaker implantation following cardiac surgery is 2% to 7%. Prolonged ischemic time during cardiac surgery, most commonly cardiac transplantation, can similarly lead to SNDSND and subsequent permanent pacing requirement (up to 10% of post-transplant patients). The risk following transcatheter aortic valve replacement appears to be much greater, ranging from 10% to 40%. Risk factors include preexisting RBBB and is highly device specific (self-expanding valves).
2. The risk of permanent high-grade AV block following nonurgent, coronary-exclusive interventions (coronary artery bypass grafting or percutaneous coronary intervention) is comparably low.

B. Therapy. Because postprocedural bradyarrhythmias are frequently temporary and resolve with time postprocedure, temporary pacing should be utilized initially, with the decision to proceed to permanent pacing made only after extended surveillance (institution and procedure dependent, ranging from 5 to 14 days). The same criteria listed in **Table 23.3** are used to determine the indications for permanent pacing postprocedure.

III. PULSELESS ELECTRICAL ACTIVITY AND ASYSTOLE

A. Pulseless electrical activity (**PEA**) is defined as the absence of a pulse or blood pressure, yet with the continued presence of electrical activity of the heart. Asystole is defined as the absence of **both** cardiac electrical (eg, flat line) and mechanical activity. PEA and asystole exist on the same spectrum, classified by advanced cardiac life support (ACLS) as "nonshockable" rhythms and carry exceedingly poor prognoses, with survival 2% after out-of-hospital and 20% to 30% after in-hospital PEA/asystolic arrest.

B. Etiology

1. PEA results from electromechanical dissociation, a condition where cardiac electrical activation is ongoing (although not necessarily functioning normally) but produces inadequate (or absent) mechanical contraction/cardiac output. PEA can occur in a variety of **rhythm disturbances**, ranging from idioventricular escape rhythm to sinus tachycardia, although classically excluding ventricular tachycardia and ventricular fibrillation (VF) according to ACLS algorithms. PEA may degenerate to asystole, or asystole may occur directly.
2. A variety of potentially reversible clinical situations are classically associated with PEA and asystole, abbreviated as the H's and T's (**Table 23.6**).

TABLE 23.6 Conditions That Cause Pulseless Electrical Activity

Condition	Clues	Management
Hypovolemia	History of poor oral intake and/or increased blood volume/GI/insensible losses, flat neck veins and poor skin turgor on physical examination, preceding sinus tachycardia, collapsible IVC on ultrasound	Volume infusion (+ transfusion if concern for hemorrhage)
Hypothermia	History of exposure to cold, central body temperature, and ECG	Gradual warming

Condition	Clues	Management
	findings (bradycardia, Osborn waves)	
Hypoxia	Baseline pulmonary pathology, cyanosis, increasing A-a gradient, airway concerns	Increase oxygen delivery (noninvasive, positive pressure, intubation)
Hypoglycemia	History of diabetes (particularly insulin requiring), fingerstick blood glucose, recent NPO status, acute kidney injury/renal failure	Dextrose administration
Hyperkalemia	History of renal failure, ischemic presentation, uncontrolled diabetes, ECG findings (peaked T waves, QRS prolongation, sine wave)	(Immediate for electrical stabilization): Calcium chloride/gluconate, combination of IV insulin + glucose, sodium bicarbonate, albuterol (if controlled airway); (long term for potassium clearance): sodium polystyrene or dialysis
Hydrogen ions (acidosis)	History of renal failure, medical comorbidity predisposing to hypercapnia (COPD), acidosis or hypercapnia on arterial blood gas	Sodium bicarbonate, hyperventilation
Tension pneumothorax	History (asthma, ventilator, COPD, recent procedure or trauma), no pulse with CPR, neck vein distention, tracheal deviation, absent breath sounds	Needle decompression
Thrombosis (MI)	CAD history, ischemic symptoms, ST changes on ECG, elevated cardiac enzymes, ventricular arrhythmia preceding or subsequent to PEA arrest	Urgent revascularization
Thrombosis (pulmonary embolism)	Predisposing history (high Wells score), preceding hypoxia or elevated A-a gradient without clear alternative pulmonary pathology, ECG findings (sinus tachycardia, S1Q3T3, new RBBB, RV strain)	Periarrest: Consider thrombolytics if high clinical suspicion and not contraindicated; (postarrest): confirm diagnosis via CT or $\dot{V}/\dot{Q}$ scan imaging
Tamponade (cardiac)	History (recent cardiac procedure or trauma, renal failure, malignancy), vein distention; impending tamponade—tachycardia, hypotension, low	Urgent pericardiocentesis

Condition	Clues	Management
	pulse pressure with pulsus paradoxus, electrical alternans on ECG	
Toxins (drug overdose)	History of ingestion, empty pill bottles at the scene, pupils, skin, and neurologic examination. ECG findings (bradycardia or tachycardia, PR + QRS + QTc intervals, aVR elevation)	Toxicology consultation with targeted antidose administration, drug screening, airway protection (intubation)
Trauma	History of recent trauma, physical examination findings (absent breath sounds, overt fractures, ecchymoses, pupil asymmetry), FAST ultrasound findings, profound anemia	Aggressive volume resuscitation ± transfusion, targeted trauma surgery consultation

A-a, alveolar-arterial; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CT, computed tomography; ECG, electrocardiogram; FAST, focused assessment with sonography in trauma; GI, gastrointestinal; IV, intravenous; IVC, inferior vena cava; MI, myocardial infarction; NPO, nil per os; PEA, pulseless electrical activity; RBBB, right bundle branch block; RV, right ventricle/ventricular; $\dot{V}/\dot{Q}$, ventilation/perfusion.

C. Therapy

1. Rapid management targeted at the suspected underlying cause is most likely to result in a favorable outcome. The differential of PEA/asystolic arrest should always include the "H's and T's": **H**ypovolemia, **H**ypothermia, **H**ypoxia, **H**ypoglycemia, **H**yperkalemia, acidosis ("**H**ydrogen ions"), **T**ension pneumothorax, **T**hrombosis (coronary or pulmonary), **T**amponade, **T**oxins, and **T**rauma (**Table 23.6**).
2. Emergency resuscitation should be initiated at once as per ACLS protocols:
   a. Effective, uninterrupted cardiopulmonary resuscitation (CPR) prioritized over advanced airway management
   b. Epinephrine, 1 mg IV push every 3 to 5 minutes
   c. One-time IV push of 40 IU of vasopressin may be considered as an alternative to epinephrine during the first or second round of ACLS.
   d. Atropine is no longer recommended for routine ACLS administration during PEA/asystole, nor is routine defibrillation for potential coarse VF masquerading as asystole, nor routine cardiac pacing for bradycardic rhythms or asystole.

e. Although not yet integrated into ACLS guidelines, 20 IU vasopressin +1 mg epinephrine for up to the first 5 CPR cycles *and* 40 mg methylprednisolone during the first CPR cycle followed by stress-dose hydrocortisone with taper after return of spontaneous circulation demonstrated improved survival and neurologic outcomes after in-hospital PEA/asystolic arrest in a prospective RCT.

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CHAPTER 24

Sudden Cardiac Death

Robert E. Dunn and Tyler L. Taigen

I. DEFINITION AND EPIDEMIOLOGY.

Sudden cardiac death (SCD) is defined **as death following cardiac arrest in a patient with or without known preexisting heart disease in whom the mode and time of death were unexpected**. If the person survives the circulatory arrest with a return of spontaneous circulation, whether from cardiopulmonary resuscitation (CPR), defibrillation, or spontaneously, the event is deemed a sudden cardiac arrest (SCA). The incidence of SCD in the United States is estimated at 356,000 out-of-hospital cases per annum, with 209,000 in-hospital cases, accounting for **10% to 15% of all deaths** from natural causes and about 50% of all cardiac deaths. SCD exhibits a bimodal age distribution with peaks between birth and 6 months of age and then rises steadily from age 30. A male preponderance is observed in all age groups, narrowing after age 65, and is attributable to an increased incidence of coronary artery disease (CAD). Whereas the absolute risk of SCD is greater among high-risk populations, most SCDs occur in patients who have not been identified as being at risk, being the **first presentation of cardiovascular disease in approximately 25% of patients**.

It is postulated that most cases of SCA present with ventricular fibrillation (VF) or ventricular tachycardia (VT). As the time from onset of arrest and rhythm identification increases, the proportion of VF decreases. This suggests that asystole and pulseless electrical activity (PEA) are frequently the result of prolonged VT or VF and resultant ischemia and hypoxia. Bradyarrhythmias and pump failure are also responsible for a significant proportion of SCA, especially in patients with advanced heart failure.

II. CAUSES OF SUDDEN CARDIAC DEATH

A. **CAD** accounts for 80% or more episodes of SCD in Western societies, and SCD is the first presentation of CAD in 20% to 25% of patients. However, the extent to which acute ischemia plays a role in initiating a trigger for SCD is less clear. On autopsy, 40% to 70% of patients with SCD have evidence of remote coronary infarction, whereas only 15% to 20% have evidence of acute occlusive coronary thrombus. Therefore, the majority of SCD episodes in patients with CAD are considered to be primary (ie, no precipitating factor can be identified), whereas secondary causes such as acute myocardial ischemia/myocardial infarction (MI), drug toxicity or proarrhythmic agents, decompensated heart failure, or electrolyte imbalance can be identified in the minority. Patients with reduced left ventricular ejection fraction (LVEF) and frequent premature ventricular contractions (PVCs) are identified as a particularly high-risk subgroup. A study of patients implanted with a loop recorder with recent MI and ejection fraction (EF) ≤40% found that the terminal rhythm was VF in 86% of all sudden deaths.

B. **Cardiomyopathies**

1. **Dilated cardiomyopathy (DCM).** Patients with DCM represent the second largest group of patients who experience SCD, after those with CAD, accounting for approximately 10% of cases. The annual mortality from DCM is 11% to 15%, with SCD accounting for about 30% of all deaths in this population. The presence of reduced LVEF and syncope are high-risk markers for SCA in these patients. There is also a higher incidence of sudden deaths related to bradyarrhythmias and PEA in patients with advanced disease.
2. **Hypertrophic cardiomyopathy (HCM).** The incidence of SCD in patients with *HCM* is 2% to 4% per year in adults and 4% to 6% per year in children and adolescents. Risk factors for SCD in this population include prior SCA, family history of SCD, sustained or nonsustained VT (NSVT), syncope, a drop in blood pressure with exercise, and septal hypertrophy ≥30 mm. Myocardial scar, detected by late gadolinium enhancement on magnetic resonance imaging (MRI), is also emerging as a predictor of risk. SCD usually results from ventricular arrhythmias

but occasionally may be precipitated by atrial fibrillation (AF), bradyarrhythmias, or myocardial ischemia.

3. **Arrhythmogenic right ventricular dysplasia (ARVD).** *ARVD* is a rare genetic disorder characterized by heart failure, ventricular arrhythmias, and SCD. Mutations involving the desmosome result in fibrofatty infiltration of the right ventricle. The incidence of SCD is approximately 2% per year and is mainly due to ventricular tachyarrhythmia. Electrocardiogram (ECG) characteristics of *ARVD* include right bundle branch block (RBBB), T-wave inversion in V_1 through V_3, and epsilon waves. On echo or MRI, there is regional right ventricular akinesia, dyskinesia, or aneurysm, and the diagnosis may be confirmed by endomyocardial biopsy.
4. **Other inherited cardiomyopathies.** Several other cardiomyopathies also present an increased risk of SCA. These include *Pompe disease* (GAA), *Danon disease* (LAMP2), *left ventricular hypertrophy with Wolff-Parkinson-White (WPW) syndrome* (PRKAG2), *Fabry disease* (GLA), and *familial amyloidosis* (TTR).

C. The channelopathies

1. **The congenital long QT syndrome (LQTS).** *LQTS* is a familial disease with a prevalence of about 1:2,000, characterized by an abnormally long QT interval, leading to the development **of early afterdepolarizations and torsades de pointes**. It is the most common cardiac channelopathy. The two variants of the syndrome include the more common autosomal dominant form (Romano-Ward syndrome) and the less common recessive form (Jervell and Lange-Nielsen syndrome), which is associated with congenital deafness. At least 15 mutations at different LQTS susceptibility genes have been identified. The most common form is LQT1, accounting for 35% of cases. LQT1 arises from a mutation in *KCNQ1*, which encodes the **alpha**-subunit of the potassium channel conducting the slow delayed rectifier current (I_{Ks}). Clinically, LQT1 is characterized by broad-based T waves and exercise-induced arrhythmic events, especially during swimming.

LQT2, accounting for 30% of cases, and is caused by mutations in the *KCNH2* gene encoding the HERG protein (I_{Kr} current) and presents with low-amplitude, notched T waves and auditory arrhythmogenic triggers. LQT2 is also associated with postpartum SCD. LQT3 is caused by a gain-of-function mutation in the sodium channel gene *SCN5A* and manifests a long, isoelectric ST segment and SCD events during sleep.

The mortality rate for LQTS is estimated to be about 1% per year. **High-risk patients include those with a corrected QT interval >500 ms, a history of syncope or SCA, male sex in children and female sex in adults (especially after menopause), and the LQT2 or LQT3 genotype.** It has been postulated that 11% to 13% of sudden infant death syndrome cases may be caused by LQTS. All patients are treated with beta-blocker therapy; however, genotype-specific and individualized therapies are evolving. Symptomatic patients who are either refractory to or intolerant of medical therapy or who have other high-risk markers for SCD should be considered for implantable cardioverter-defibrillator (ICD) implantation and left cardiac sympathetic denervation. It seems increasingly likely that many patients who suffer cardiac events because of drug-induced or other acquired QT prolongation have a *forme fruste* of LQTS.

2. **Short QT syndrome** presents with QT interval <350 ms, with a predisposition for supraventricular arrhythmias. It is caused by mutations in genes encoding the potassium channel, resulting in shortening of the action potential duration and increasing vulnerability to VF.
3. **Brugada syndrome** is characterized by **ECG finding of incomplete RBBB with coved ST elevation >0.2 mV in >1 right precordial leads**. Although traditionally caused by mutations in the *SCN5A* gene encoding the cardiac sodium channel, which disposes to polymorphic VT or VF, more than 17 mutations in other genes have been identified to cause the characteristic ECG changes. Making the diagnosis can be challenging, as these ST elevations are often transient, occurring during stress, fever, or

provocation by class I antiarrhythmic drugs, with normalized ECG during other times. The risk of SCA is up to 30% at 3 years in untreated symptomatic patients. AF and conduction abnormalities are frequently associated. Symptomatic patients (syncope or SCA) should undergo ICD implantation. Risk stratification for asymptomatic patients is controversial.

4. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** is due to mutations in the ryanodine receptor and calsequestrin and results in a malignant phenotype of bidirectional VT during emotional or physical stress. Treatment is with beta-blockers and ICD, and recent evidence suggests an emerging role for flecainide.

D. Other causes of SCD. The risk of SCD is also higher in patients with *WPW syndrome*, especially if they have rapidly conducting accessory pathways. AF can be associated with very rapid ventricular rates and degeneration to VF. An RR interval ≤250 ms during spontaneous AF indicates a higher risk. The incidence of SCD is 0.05% to 0.1% per year and is higher in males in their second and third decades, but the phenomenon is easily identifiable and manageable. When no cause of SCA can be found, the label *idiopathic VF* is applied. In some cases, VF is triggered by a PVC, which is amenable to catheter ablation. *Early repolarization* on ECG may denote a higher risk of SCD in the presence of proarrhythmic triggers, and the clinical implications of this are still being clarified. Refer to **Table 24.1** for other cardiac and noncardiac causes of SCD.

TABLE 24.1 Some Other Conditions With an Increased Risk of Sudden Cardiac Death

Cardiac	Noncardiac
Cardiovascular	Neurologic
Coronary artery anomalies	Epilepsy
Coronary artery embolism	Hereditary muscular dystrophies
Coronary arteritis (polyarteritis nodosa and Kawasaki syndrome)	Friedreich ataxia
Coronary artery dissection	Central nervous system injury
Coronary spasm	Respiratory
Myocardial bridging	Asthma

Cardiac	Noncardiac
Valvular and great vessels	Obstructive sleep apnea
Severe aortic stenosis	Massive pulmonary embolism
Severe mitral regurgitation	Pulmonary hypertension
Prosthetic valvular obstruction or dehiscence	Endocrine and metabolic
Ruptured sinus of Valsalva aneurysm	Diabetes mellitus
Aortic dissection	Acromegaly
Electrophysiologic	Electrolyte disturbances
Progressive cardiac conduction disease (Lev-Lenegre disease)	Acid-base disturbances
Myocardial	Renal
Left ventricular hypertrophy	Chronic kidney disease
Infiltrative disease (sarcoid and amyloid)	Hemodialysis
Apical ballooning syndrome	Psychiatric/psychological
Myocarditis	Depression
Congenital	Anxiety
Eisenmenger physiology	Anorexia nervosa
Late after surgical repair, especially of tetralogy of Fallot	Intense emotion
Trauma	Situational
Cardiac tamponade	Intense exercise and athletes
Commotio cordis	Drugs
	Antiarrhythmic drugs
	Typical and atypical antipsychotics
	Other QT-prolonging drugs
	Drug-drug interactions
	Cigarette smoking
	Cocaine

III. DIAGNOSTIC AND PROGNOSTIC TESTING. Survivors of SCA should have a detailed cardiovascular evaluation. Reversible precipitating factors must be identified and corrected. Underlying diseases must be identified and managed, and the risk of recurrent SCA must be determined. Diagnostic and prognostic testing appropriate for the survivor of SCA includes the following:

A. ECG for the evidence of MI or ischemia, intraventricular conduction delay, accessory pathway (WPW syndrome), prolonged QT interval, epsilon waves, Brugada pattern, and left ventricular hypertrophy

B. Laboratory data to rule out reversible causes, such as cardiac biomarkers, abnormal electrolytes, antiarrhythmic drug levels for toxicity, and urine screening for illicit drugs such as cocaine

C. **ECG monitoring** to assess frequency, duration, and symptomatology of arrhythmias

D. **Twenty-four-hour ambulatory electrocardiography** during normal activities can be useful in predicting the risk of recurrent SCA.

E. **Echocardiography** for the assessment of left ventricular function, valvular disease, cardiomyopathy, and hypertrophy. **LVEF continues to be the strongest, independent predictor of SCD**, behaving as a continuous variable with markedly increased risk when LVEF is lower than 40%. However, non–sudden death also increases with declining EF, meaning that the likely mode of death cannot be predicted. Nuclear or angiographic determinations of left ventricular function may be used but do not provide as much information as echocardiography.

F. **Coronary angiography** for the assessment of CAD or coronary anomalies

G. **Exercise or pharmacologic stress testing** with radionuclide imaging or echocardiography if CAD is present and myocardial ischemia and/or viability is in question.

H. **Electrophysiologic (EP) testing** has a limited role in assessing the survivor of SCA. Given its low sensitivity, a negative test does not exclude recurrent SCA, and almost all patients who survive SCA are in any case candidates for an ICD. Although EP testing may be performed to guide programming of the ICD, this is rarely done in practice. Voltage mapping has been used to corroborate a diagnosis of ARVD, and mapping and ablation are essential in the management of patients with WPW and selected patients with cardiomyopathy and VT. Emerging applications of ablation in ARVD and Brugada syndrome require further study.

I. **Cardiac MRI.** Cardiac MRI may be useful for evaluating arrhythmogenic right ventricular cardiomyopathy and to investigate evidence of myocardial scar, inflammation, infiltrative process, or left ventricular hypertrophy.

J. **Drug challenge** with flecainide, procainamide, or ajmaline to provoke the Brugada pattern should be considered in all SCA

survivors where the above tests do not reveal a cause. Epinephrine infusion or exercise testing has been used to diagnose LQT1 and CPVT.

K. Genetic testing for the channelopathies, HCM, and ARVD is becoming increasingly comprehensive; however, many as-yet unidentified mutations are postulated to exist. At present, only 21% of patients with Brugada syndrome and 52% with ARVD have an identifiable causative mutation. In young patients, <40 years of age, with unexplained SCA, unexplained near drowning, or recurrent exertional syncope without ischemic or other structural heart disease, a genetic evaluation is recommended. A positive genetic test is useful and facilitates family screening, but a negative test is not.

IV. THERAPY

A. Acute therapy for SCA

1. **CPR.** Early response is crucial. The two most critical components of out-of-hospital cardiac resuscitation are the availability of a rapid response system and bystander CPR. Survivors of SCA are more likely to be discharged from the hospital if the arrest is witnessed and they receive early CPR from bystanders. There is an increasing effort to train police personnel, students, and the general public in resuscitation techniques, focusing on high-quality, uninterrupted chest compressions.
2. **Automated external defibrillator (AED) and public access defibrillation.** An AED is designed to be used by emergency personnel and lay rescuers with minimal or no training for victims of out-of-hospital SCA. The device monitors the patient's ECG via self-adhesive defibrillation electrode pads applied to the chest wall and is programmed with a VF detection algorithm. When the device detects VF, an alarm is emitted, followed by delivery of a defibrillation shock or an indicator for the rescuer to press a button to deliver the shock. Availability of these devices results in more rapid delivery of defibrillation and improved survival to hospital discharge in several large trials. Provision of AEDs for public access defibrillation in airports, sporting facilities, and shopping

malls has the potential to have a significant impact on survival of out-of-hospital SCA. Home AEDs have not been shown to increase survival.

3. **Advanced cardiac life support (ACLS).** Unlike AEDs, incorporation of ACLS techniques into prehospital care has not been shown to improve survival in out-of-hospital SCA. Continuous refinements in ACLS algorithms continue to be made, including an emphasis on high-quality CPR with minimal interruption.
4. **Post–cardiac arrest hospital care.** Initial management is focused on establishing and maintaining hemodynamic stability and supportive care. Amiodarone or lidocaine (especially if ischemia is suspected as the trigger) is often used to prevent further ventricular tachyarrhythmias. Therapeutic hypothermia for patients who remain unconscious after resuscitation; however, more research needs to be done regarding the efficacy of this therapy. Immediate coronary angiography, with revascularization if indicated, may improve survival in patients in whom an ischemic etiology is suspected. Further diagnostic testing is described above.

B. Primary prevention of SCD

1. **Identifying individuals at risk for SCD.** No single factor has been identified that accurately predicts the occurrence of SCD, although combinations of factors have been more useful. In general, the specificity and positive predictive value of these tests are poor, whereas the negative predictive value is much better (particularly for combinations of tests). Overall, the most potent predictor of survival continues to be LVEF, but other factors may aid prognostication and guide subsequent therapy. Other tools for predicting the risk of SCD, such as EP testing, ambulatory electrocardiography, signal-averaged electrocardiography (SAECG), baroreflex sensitivity, heart rate variability (HRV), and T-wave alternans, have been used to identify high-risk groups, but none have been shown to be of convincing value. Although a

combination of different tests can improve sensitivity and specificity, the positive predictive value remains modest.

2. **Pharmacologic agents and surgical/percutaneous revascularization.** Because the majority of episodes of SCD occur in patients with CAD, agents that reduce myocardial ischemia (beta-blockers) prevent or limit the extent of MI, and alter ventricular remodeling after MI (angiotensin-converting enzyme inhibitors and aldosterone antagonists) have all been shown to reduce the incidence of SCD. Although there is no direct evidence of a role for antiplatelet agents or statins in reducing SCD, such an effect is likely, given the reduction in mortality in several broad populations. Early studies of surgical myocardial revascularization showed a reduction in SCD for patients with triple-vessel CAD and left ventricular dysfunction compared with those patients treated medically. Fibrinolysis and percutaneous coronary intervention also reduce SCD in patients with MI. Catheter ablation of VT has a role in select patient populations, particularly in patients with incessant arrhythmias, despite antiarrhythmic drug and/or implantable device therapy.

More than 40 years ago, complex ventricular ectopy in survivors of MI was recognized as a risk factor for SCD. Suppression of ventricular ectopy with antiarrhythmic drugs in such patients was, therefore, thought to be beneficial. However, the Cardiac Arrhythmia Suppression Trial demonstrated that the proarrhythmic effects of class Ic antiarrhythmic drugs are greater than the benefit achieved through ectopy suppression in the post-MI population, resulting in a 2.6-fold increased mortality. Excess mortality was also demonstrated in survivors of MI with poor left ventricular function taking the class II/III agent sotalol in the Survival With Oral *d*-Sotalol study and with mexiletine.

To date, of all the antiarrhythmic drugs, only amiodarone has been shown to reduce SCD in some populations. Initial small trials of amiodarone therapy for survivors of MI, and meta-analyses of these trials, suggested reduced SCD mortality, and the larger but unblinded Grupo de Estudio de la Sobrevida en la Insuficiencia

Cardiaca en Argentina study appeared to corroborate this finding. However, several prospective, placebo-controlled trials did not. The Survival Trial of Amiodarone in Patients with Congestive Heart Failure failed to demonstrate a significant reduction in either SCD or all-cause mortality in a largely male population with heart failure, EF ≤40%, and frequent PVCs. Although the European Myocardial Infarct Amiodarone Trial demonstrated a 35% reduction in arrhythmic deaths in a population with recent MI, there was no difference in all-cause mortality. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) similarly reported a reduction in resuscitated VF or arrhythmic death in survivors of MI with frequent ventricular ectopy, but no difference in all-cause mortality. Lastly, there was no difference in the primary end point of all-cause mortality between amiodarone and placebo in the medical treatment arm of the large Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The newer benzofuran derivative, dronedarone, also reduced SCD in the pivotal ATHENA trial of patients with AF and additional risk factors, but increased all-cause mortality in patients with severe heart failure in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe congestive heart failure (CHF) Evaluating Morbidity Decrease. Mexiletine showed a trend toward increased mortality, and dofetilide and azimilide had no effect on all-cause mortality or SCD in patients with recent MI in large controlled studies.

In summary, **amiodarone reduces SCD, but not all-cause mortality in patients with heart failure or recent MI**, and several other antiarrhythmics, including class Ic agents, mexiletine, dronedarone, and sotalol, may increase mortality in this population.

3. **Implantable devices.** In light of the inefficacy and even hazards of antiarrhythmic drugs for the prevention of SCD, attention has shifted to the ICD. Since its introduction by Mirowski in 1980, technical refinements have paralleled a series of clinical trials, which extended indications to primary prevention in select

populations. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated a 54% relative risk reduction in all-cause death versus usual care in 196 patients with prior MI, New York Heart Association (NYHA) class I-III heart failure, EF ≤35%, NSVT, and inducible, nonsuppressible, ventricular arrhythmia during EP study (EPS). The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with CAD, EF ≤40%, NSVT, and inducible VT/VF to receive EP-guided antiarrhythmic drug therapy, with or without an ICD, or no therapy. The 27% reduction in arrhythmic death or cardiac arrest in the EP-guided drug therapy arm was entirely driven by a 76% reduction in patients with ICDs, with no difference between drug therapy and no therapy. Given the modest predictive value of EPS, MADIT II dispensed with inducible VT as an inclusion criterion and enrolled patients with prior MI on the basis of an EF ≤30%. This randomized comparison of ICD with usual care demonstrated a 31% relative risk reduction in all-cause mortality over an average follow-up of 20 months. MADIT, MUSTT, and MADIT II all enrolled patients with prior MI. Whereas the underpowered Amiodarone Versus Implantable Cardioverter-Defibrillator and Cardiomyopathy Trial failed to show a benefit of ICDs over medical therapy in patients with nonischemic cardiomyopathy (NICM), the results of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial extended primary prevention ICD therapy to these patients. In patients with NICM, heart failure, EF ≤35%, and NSVT or frequent PVCs, a nonsignificant reduction in all-cause mortality was observed, with a significant reduction in SCD. The larger SCD-HeFT randomized 2,521 patients with ischemic cardiomyopathy (52%) or NICM (48%), EF ≤35%, and NYHA functional class II or III heart failure to receive conventional therapy plus placebo, amiodarone, or a single lead ICD. ICD therapy reduced all-cause mortality by 23% compared with placebo, whereas amiodarone was not associated with any benefit. These trials, and SCD-HeFT in particular, ushered in the current era of primary prevention ICDs for patients risk-stratified largely on the basis of EF.

The limitations of ICDs have also been defined by clinical trials. The Coronary Artery Bypass Graft (CABG) Patch Trial demonstrated that primary prevention ICD implantation at the time of CABG in patients with preoperative left ventricular dysfunction (EF ≤35%) and an abnormal SAECG did not improve the overall survival, despite reducing arrhythmic deaths. The lower event rates in the CABG Patch Trial were consistent with earlier evidence that CABG reduces the risk of SCD in this population, negating the protective effect of the ICD.

MADIT, MUSTT, and MADIT II studied patients with remote (>3 weeks) ischemic events. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) assessed whether the benefits of ICD therapy would also be seen early after MI. The trial enrolled patients 6 to 40 days post-MI with EF <35% and impaired HRV or elevated average 24-hour heart rate and randomized them to receive an ICD or no ICD. Although ICD therapy reduced arrhythmic death, this was offset by an increase in nonarrhythmic death in the ICD group, so there was no difference in all-cause mortality over 30 months of follow-up. These results were confirmed by the larger Immediate Risk Stratification Improves Survival (IRIS) trial, which enrolled a similar population. Taken together, IRIS and DINAMIT suggest that whereas ICDs prevent SCD in high-risk patients early post-MI, this merely changes the mode of death to non–sudden death, without affecting the overall survival. This is supported by a secondary analysis of DINAMIT, which showed that the risk of non–sudden death in the ICD group was 4.8-fold higher in those who had received an appropriate shock. The above findings have been incorporated into the Centers for Medicare and Medicaid Services coverage determination for ICDs, which excludes patients with MI within 40 days and surgical or percutaneous revascularization within 3 months of ICD implantation. A wearable defibrillator is available for temporary use, while diagnostic testing is ongoing, or during periods of transient elevated risk.

4. **Cardiac resynchronization therapy (CRT).** Approximately 30% of patients with advanced heart failure (EF ≤35%) have an associated ventricular conduction delay resulting in a QRS duration ≥120 ms and are candidates for CRT. The strongest data for CRT therapy exist for individuals with left bundle branch block (LBBB) and QRS duration >150 ms with LVEF of 35% or less and at least class II NYHA symptoms. Biventricular pacing has been shown to improve survival, quality of life, exercise capacity, and EF in patients with advanced CHF. Extended follow-up data from the Cardiac Resynchronization in Heart Failure trial also reported a significant 46% reduction in SCD in patients with CRT without a defibrillator when compared with no CRT. However, a significant number of SCDs occurred in the CRT group, some of which might conceivably have been prevented by a defibrillator. The only large randomized trial comparing CRT with a defibrillator (CRT-D), CRT without defibrillator (CRT-P), and no device was the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure trial. Although not powered to detect a difference between CRT-D and CRT-P, a nonsignificant 50% decrease in SCD was seen with CRT-D in patients with NYHA class III or IV CHF, EF ≤35%, and a QRS duration ≥120 ms. These data suggest that CRT-D should be considered for most patients eligible for biventricular pacing. See Chapter 55 in this book for in-depth discussion of CRT.

C. Secondary prevention

1. **Pharmacologic agents.** As with primary prevention of SCD, the disappointing efficacy and safety of class I antiarrhythmic drugs shifted attention to other antiarrhythmic drugs for the secondary prevention of SCD. In the Cardiac Arrest in Seattle Conventional Versus Amiodarone Drug Evaluation study, amiodarone reduced cardiac death, arrest, and ICD shocks compared with conventional class I antiarrhythmic drugs in a secondary prevention population. In addition, the Electrophysiologic Study Versus Electrocardiographic Monitoring trial demonstrated that the class II/III antiarrhythmic drug sotalol was superior to six class I agents

guided by EP testing or Holter monitoring in preventing all-cause, cardiac, and arrhythmic mortality in patients with a history of VT/VF, SCA, or syncope. However, the emergence of the ICD led to randomized trials comparing the efficacy of best medical therapy and ICDs for the secondary prevention of SCD.

2. **Implantable devices.** The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial studied the efficacy of ICD therapy versus the antiarrhythmic drugs amiodarone or sotalol for the secondary prevention of SCD in patients with resuscitated VF or sustained VT plus either syncope or EF ≤40% and hemodynamic compromise during VT. Inducible arrhythmias were not required for inclusion, and only sotalol therapy was guided by EP testing (only 2.6% of patients randomized to antiarrhythmic drug therapy were discharged on sotalol). ICDs reduced all-cause mortality by 31% at 3 years of follow-up.

   Two other large trials of ICDs for secondary prevention of SCD that ran concurrently with AVID reported similar results. The Cardiac Arrest Study Hamburg found that ICDs conferred a nonsignificant 23% reduction in all-cause mortality when compared with amiodarone or metoprolol in patients with resuscitated cardiac arrest because of documented VT/VF. The propafenone arm of the study was terminated early after an interim analysis showed excess mortality compared with the ICD group. The Canadian Implantable Defibrillator Study enrolled a similar population as the AVID trial, randomizing patients with resuscitated VF, sustained VT with syncope or hemodynamic compromise and EF ≤35%, or unmonitored syncope with subsequent spontaneous or induced VT to ICD or amiodarone therapy. Over a mean follow-up period of 3 years, a nonsignificant 19.7% relative risk reduction in all-cause mortality was observed, as well as a nonsignificant 32.8% reduction in SCD. Each of the above studies excluded patients with a transient or reversible cause of ventricular arrhythmias, such as MI within 72 hours, or electrolyte imbalances. A meta-analysis of these three trials

confirmed a significant 28% reduction in the relative risk of death with the ICD, which was due largely to a 50% reduction in SCD.

Of considerable interest is evidence that patients screened for the AVID trial but thought to have a transient or reversible cause of SCA, and who were not entered in the trial but followed in a registry, had poor long-term survival similar to those patients who were also ineligible for the trial but known to be at high risk for SCD. These data emphasize the need for meticulous evaluation of every SCA survivor and careful consideration of whether SCA was due to a cause that was not only transient and reversible but also preventable in the future.

D. Summary: Antiarrhythmic drugs versus ICDs. Current guidelines for ICD therapy are summarized in **Table 24.2**. From the available data, there is good evidence that many antiarrhythmic drugs are not efficacious and may be harmful in the primary prevention of SCD, and antiarrhythmic drugs (apart from beta-blockers) are not indicated for this purpose. ICD therapy has proven to be highly effective in the termination of malignant ventricular arrhythmias and is more effective than antiarrhythmic medications for the prevention of SCD in patients with ischemic or nonischemic heart failure and an EF ≤35%. Patients with prolonged QRS duration, especially with LBBB, should also be considered for CRT. The most powerful predictor of SCD risk in this population remains LVEF, and other methods such as EP testing and SAECG may give additional information but are neither sensitive nor specific enough to select patients for ICD therapy. Specific antiarrhythmics may have niche uses in high-risk patients with genetic diseases predisposing to SCD, such as HCM, ARVD, Brugada syndrome, and LQTS, and an ICD is also indicated in select patients. The bradyarrhythmias respond well to pacemaker therapy. Radiofrequency catheter ablation is the therapy of first choice in patients with WPW syndrome and is an effective synergistic therapy in patients with VT who have recurrent ICD shocks.

TABLE 24.2 Indications for Implantable Cardioverter-Defibrillator Therapy

Class I

Primary Prevention

- LVEF ≤35% because of prior MI, at least 40 d post-MI and 90 d post-revascularization with NYHA class II or III symptoms despite GDMT
- LVEF ≤30% because of prior MI, at least 40 d post-MI, and 90 d post-revascularization with NYHA class I symptoms despite GDMT
- NSVT because of prior MI, LVEF ≤40%, and inducible VF or sustained VT during EPS
- Nonischemic cardiomyopathy, LVEF ≤35%, and NYHA class II or III symptoms despite GDMT

Secondary Prevention

- Patients with ischemic or nonischemic cardiomyopathy who are survivors of cardiac arrest because of VF/VT, hemodynamically unstable sustained VT, stable sustained VT not due to reversible causes
- IHD with syncope of undetermined origin with hemodynamically significant sustained VT or VF induced during EP study
- ARVC and an additional risk factor (SCA, sustained VT, RVEF/LVEF ≤35)
- LQTS with syncope and/or VT while receiving beta-blocker
- Catecholaminergic polymorphic VT with syncope and/or documented sustained VT while receiving beta-blocker
- Brugada syndrome with spontaneous type 1 pattern and SCA, sustained ventricular arrhythmias or syncope thought due to ventricular arrhythmia
- Hemodynamically unstable VT in association with congenital heart disease after evaluation and appropriate treatment for residual lesions/ventricular dysfunction

Class IIa

Primary Prevention

- Nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or LVAD
- NICM due to Lamin A/C mutations and ≥2 risk factors (NSVT, LVEF <45%, nonmissense mutation, male sex)
- HCM with one or more major risk factors for SCD

Secondary Prevention

- Unexplained syncope, significant LV dysfunction, and NICM +/− positive EPS
- ARVC and syncope presumed due to ventricular arrhythmia
- Cardiac sarcoid with LVEF ≥35% with syncope and/or myocardial scar on cMRI or PET with an indication for permanent pacing
- Congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction, marked hypertrophy, or inducible ventricular arrhythmias during EP study

Class IIb

Primary Prevention

- Nonischemic cardiomyopathy, LVEF ≤35%, and NYHA class I symptoms despite GDMT
- Asymptomatic LQTS with QTc >500 ms

Class III

- Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 y
- Incessant VT or VF
- NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation, LVAD, or CRT-D
- VF or VT that is amenable to surgical or catheter ablation (eg, atrial arrhythmias associated with the WPW syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease)
- Ventricular tachyarrhythmias because of a completely reversible disorder in the absence of structural heart disease (eg, electrolyte imbalance, drugs, or trauma)

ARVC, arrhythmogenic right ventricular cardiomyopathy; cMRI, cardiac magnetic resonance imaging; CRT-D, cardiac resynchronization therapy with a defibrillator; EP, electrophysiologic; EPS, electrophysiologic study; GDMT, guideline directed medical therapy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LQTS, long QT syndrome; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association; PET, positron emission tomography; RV, right ventricle; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White. Derived from the 2017 ACC/AHA/HRS guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death; American Heart Association.

Evidence from several recent randomized trials demonstrates the superiority of the ICD over antiarrhythmic drugs for the population requiring secondary prophylaxis. Antiarrhythmic drugs such as amiodarone, sotalol, and mexiletine may be of use in those patients who experience frequent ICD shocks.

V. PROGNOSIS

A. VF and pulseless VT ("shockable rhythms") are the initial rhythm in approximately one-quarter of SCA victims and are associated with more favorable outcomes than asystole or PEA. VT/VF incidence declines by ~10% with each minute after the onset of cardiac arrest;

therefore, witnessed SCA and prompt recognition and defibrillation are associated with improved survival. Only one-third of SCA victims receive bystander CPR. A recent large study of cardiac arrest incidence and outcomes in North America found that of the 60% of patients in whom resuscitation was attempted, 10.6% survived to hospital discharge, with wide regional variation. This proportion rose to 31.4% if the initial rhythm was VF. A number of factors have been identified to aid prognostication postarrest, including preexisting comorbidities, absent pupillary and corneal reflexes, extensor or no motor response to pain on day 3, and myoclonus status epilepticus; however, none are definitive.

VI. FUTURE. Large population studies are needed to better define the incidence of SCD across ethnic/racial groups and elucidate the mechanisms. The discovery of risk markers of SCD in the general population, such as clinical, molecular, and genetic factors, will facilitate to targeting of evaluation and therapy for those who need it. CAD and its consequences account for 80% of SCD, often occurring as the first presentation of CAD. Given the difficulty in identifying those with subclinical disease who are ostensibly at low risk, the focus has recently moved to primordial prevention—the prevention of the development of risk factors for CAD. This will likely have the most impact on SCD at the population level, but its effects are difficult to measure. In those at established risk, improved risk markers that refine the current LVEF-based approach will allow better targeting of ICD therapy.

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SUGGESTED READINGS

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CHAPTER 25

Atrial Fibrillation

Arwa Younis and Ayman A. Hussein

I. INTRODUCTION. Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is characterized by the degeneration of organized atrial electrical activity into a rapid, chaotic pattern. AF accounts for approximately one-third of hospitalizations for cardiac rhythm disturbances. An estimated 3 million people in the United States and 6 million people in Europe have AF. The prevalence of AF is higher in men and increases with age. AF is associated with an increased risk of stroke, heart failure, and mortality.

A. Classification. AF can be classified as **new onset** or **recurrent** (at least two episodes). AF can also be classified according to its pattern as **paroxysmal** (self-limiting), **persistent** (sustained >7 days), **long-standing persistent** (sustained >12 months), and **permanent** (no longer pursuing restoration of sinus rhythm). It is important to distinguish **nonvalvular** from **valvular AF** (rheumatic mitral stenosis, prosthetic heart valve, or mitral valve repair) because this impacts antithrombotic choice. Many of the clinical trials of the new oral anticoagulants excluded patients with prosthetic heart valves, mitral stenosis, and severe valvular disease who were likely to require imminent valve surgery. The term **lone AF** has been used to describe patients without structural heart disease and should only be used in patients at very low risk for complications of AF, such as thromboembolism.

B. Pathophysiology. Multiple disease pathways contribute to AF, and these mechanisms are incompletely understood. **The role of the pulmonary veins as a source of triggers for AF is increasingly appreciated**. A previous model has described multiple reentrant wavelets within the atrial tissue that contributed to the maintenance

of AF. More recent data support a focal mechanism involving both increased automaticity and multiple reentrant wavelets that occur predominantly in the left atrium around the pulmonary veins. A new model incorporates these mechanisms of initiation of AF and additional atrial substrate conditions for AF maintenance. In turn, this may be affected by various modulating factors, such as autonomic tone, medications, atrial pressure, and catecholamine levels. AF is a very complex arrhythmia, and this mechanistic model simply serves as a conceptual framework on which to build.

C. **Risk factors.** AF is most commonly associated with advanced age, hypertension, valvular heart disease, congestive heart failure, and coronary artery disease. AF has also been associated with physiologic stress, drugs, pulmonary embolism, chronic lung disease, hyperthyroidism, caffeine, infectious processes, alcohol intake, and various metabolic disturbances. AF has also been linked with obesity and obstructive sleep apnea. This phenomenon seems to be mediated by left atrial dilation. Other less common cardiac associations include preexcitation syndromes, pericarditis, and cardiomyopathies. Surgery, particularly cardiac surgery, is associated with a high risk of AF. Persistence of AF has been correlated with elevated C-reactive protein levels, which raises the possibility of a role for inflammation in this condition.

The very recent guidelines from the **American College of Cardiology/American Heart Association/American College of Clinical Pharmacy/Heart Rhythm Society (ACC/AHA/ACCP/HRS) 2023** recognize lifestyle and risk factor modification as a pillar of AF management to prevent onset, progression, and adverse outcomes. The guideline emphasizes risk factor management throughout the disease continuum and offers more prescriptive recommendations, accordingly, including management of obesity, weight loss, physical activity, smoking cessation, alcohol moderation, hypertension, and other comorbidities such as obstructive sleep apnea and diabetes.

D. **Clinical presentation.** The clinical presentation of AF can vary widely. Some patients may be **asymptomatic**, whereas others can

present with severe hemodynamic instability, such as those with ventricular preexcitation. The most common symptoms are **palpitations, fatigue,** and **dyspnea**. Some patients may present with **chest discomfort** or **syncope**. AF is also commonly found in patients admitted with **stroke**.

E. **Diagnostic testing.** The initial evaluation of a patient with new-onset AF includes a detailed history and physical examination to define the clinical type of AF (pattern, frequency, and duration) and to characterize the nature of symptoms associated with AF. Additional evaluation should include the following:

1. **Laboratory evaluation** should include a complete blood count, comprehensive metabolic panel, magnesium level, and **thyroid function tests**. Hyperthyroidism should always be considered, especially when the ventricular rate is difficult to control.
2. **12-Lead electrocardiogram** (ECG) should be obtained to verify AF and determine the ventricular response rate. P waves are absent and replaced by **fibrillatory (f) waves**. The atrial electrical activity is disorganized, and the ventricular response rate is usually **irregularly irregular**. The atrial rate is generally in the range of 400 to 700 beats/min whereas the ventricular response rate is generally in the range of 120 to 180 beats/min in the absence of drug therapy. Special attention should be paid to signs of underlying left ventricular hypertrophy, ventricular preexcitation, and ischemic heart disease because these features can affect management. The ECG may also be used to measure and follow PR, QRS, and QT intervals during treatment with antiarrhythmic agents.
3. **Transthoracic echocardiography** is usually performed to identify the presence of structural heart disease, to assess atrial and ventricular size and function, and to document coexistent pulmonary hypertension.
4. Additional investigation in selected patients with AF may include ambulatory ECG monitoring or a 6-minute treadmill walk test to document heart rate response to exercise. An evaluation for sleep

apnea should be considered in patients who are obese or if the index of suspicion is otherwise high.

II. THROMBOEMBOLIC RISK AND TREATMENT. Patients with AF are at increased risk of systemic thromboembolism compared with the general population, and antithrombotic therapy should be considered in all patients. Decisions regarding antithrombotic therapy should be individualized after careful consideration of the risks of stroke and bleeding as well as patient preferences.

A. Anticoagulation strategy with cardioversion. Electrical, pharmacologic, and spontaneous cardioversion carries an increased risk of thromboembolism, with most events occurring in the 10 days following restoration of sinus rhythm. Therefore, several factors should be considered when deciding upon an anticoagulation strategy with cardioversion.

1. Duration of AF

a. Patients with AF **longer than 48-hour duration** represent a particularly high-risk population. These patients merit transesophageal echocardiography (TEE) to rule out left atrial thrombus or 3 weeks of therapeutic anticoagulation prior to cardioversion, **regardless of CHA_2DS_2-VASc score**.

b. For patients with AF **less than 48-hour duration** who are at high risk for thromboembolism, anticoagulation is recommended as soon as possible before or immediately after cardioversion. For patients who are at low risk for thromboembolism, either anticoagulation or no anticoagulation may be considered.

c. Duration of anticoagulation. For patients requiring anticoagulation, they should continue therapy **for at least 4 weeks after cardioversion**. Decisions regarding long-term anticoagulation should be made after careful consideration of the risks and benefits of therapy.

d. Choice of anticoagulant. For patients with nonvalvular AF, anticoagulation with intravenous (IV) heparin, low-molecular-weight heparin (LMWH), warfarin, and new oral

anticoagulants may be considered. For those with mitral stenosis and AF, warfarin is the only proven oral anticoagulant to date. Recent ACC/AHA guidelines support the use of noncoumadin anticoagulants in other forms of valve disease associated with AF based on registry data from multiple clinical trials.

B. Long-term anticoagulation. The decision for long-term anticoagulation in patients with nonvalvular AF should be individualized after considering the risks, benefits, and patient preferences.

1. **Thromboembolic risk.** Current guidelines recommend the use of the **CHA_2DS_2-VASc risk stratification score** for the assessment of stroke risk in patients with nonvalvular AF (**Table 25.1**). The pattern of AF (paroxysmal, persistent, long-standing persistent, or permanent) should not be considered.

TABLE 25.1 CHA_2DS_2-VASc Risk Stratification Score for Patients With Nonvalvular AF

Risk Factor	Score
Congestive heart failure[a]	1
Hypertension	1
Age ≥75 y	2
Diabetes mellitus	1
Systemic thromboembolism (including TIA)	2
Vascular disease[b]	1
Age 65-74 y	1
Female sex[c]	1
Maximum score	9
Ischemic Stroke Risk[d]	
CHA_2DS_2-VASc Score	Percent per Year

Risk Factor	Score
0	0.2
1	0.6
2	2.2
3	3.2
4	4.8
5	7.2
6	9.7
7	11.2
8	10.8
9	12.2
Antithrombotic Strategy[e]	
CHA_2DS_2-VASc Score	Recommendation
0	Reasonable to omit therapy (class IIa, LOE: B)
1	No therapy or oral anticoagulation or aspirin (class IIb, LOE: C)
≥2	Oral anticoagulation (class I, LOE: A)

AF, atrial fibrillation; LOE, Level of Evidence; TIA, transient ischemic attack.

[a]Documented moderate-to-severe systolic dysfunction or recent decompensated heart failure requiring hospitalization, regardless of ejection fraction.

[b]Prior myocardial infarction, peripheral arterial disease, or aortic plaque.

[c]If age <65 years with no other risk factors, female sex does not independently increase risk.

[d]From Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182,678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J.* 2012;33(12):1500-1510.

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2. **Bleeding risk.** Multiple tools exist to predict bleeding risk; however, their clinical application is limited by imprecise bleeding estimates. The **HAS-BLED bleeding risk score** (hypertension, abnormal renal and liver function, stroke, bleeding tendency, labile international normalized ratio, older patients, and drugs/alcohol concomitant use) is the most used score, but its routine use is not included in current guidelines. Intracerebral hemorrhage is the most feared bleeding complication and has been reported to occur between 0.2% and 0.4% per year in patients taking warfarin.
3. **Choice of oral anticoagulant.** The use of most new oral anticoagulants should also be avoided in patients with severe kidney disease. For patients with AF, the antithrombotic selection should consider multiple factors, such as comorbidity, dosing frequency, patient preference, cost, tolerability of warfarin, drug interactions, and other clinical characteristics (**Table 25.2**).

TABLE 25.2 Choices of Oral Anticoagulants

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	Factors II, VII, IX, X	Thrombin	Factor Xa	Factor Xa	Factor Xa
Half-life (h)	20-60	14-17	5-9	8-15	10-14
Dosing frequency	Once daily	Twice daily	Once daily	Twice daily	Once daily
Antidote	Vitamin K	Idarucizumab	Andexanet	Andexanet	None

4. **Nonpharmacologic stroke prevention.** For patients who have an unacceptable risk of bleeding on anticoagulation, percutaneous techniques to occlude the left atrial appendage have been shown to be effective. There are several devices available, but the **WATCHMAN device** is the most used. This device was approved by the U.S. Food and Drug Administration in March 2015 based on the findings of two randomized trials that compared the device

to warfarin therapy (PROTECT AF and PREVAIL). After left atrial appendage occlusion, patients should be treated with 6 weeks of oral anticoagulation and aspirin followed by 6 months of aspirin and clopidogrel. **Surgical closure of the left atrial appendage should be considered in all patients with AF who require cardiac surgery**.

III. RATE CONTROL. Control of the ventricular response rate is an important strategy in the management of AF, and multiple drugs that slow conduction through the atrioventricular (AV) node can be utilized. **It is important to recognize signs of ventricular preexcitation in patients with AF** because AV nodal agents in this setting can facilitate increased conduction down the accessory pathway and lead to further hemodynamic compromise. **The ideal resting heart rate should be less than 80 beats/min**, although a more lenient target of less than 110 beats/min can be used if left ventricular systolic function is preserved. Heart rate during exercise should also be assessed to ensure adequate control.

A. Beta-blockers have a rapid onset of action and are available in both oral and IV forms. They can be used in both the inpatient and outpatient settings. Metoprolol succinate, carvedilol, and bisoprolol are the preferred agents if patients have concomitant left ventricular systolic dysfunction. Beta-blockers should be used with caution in patients with bronchospastic airway disease.

B. Nondihydropyridine calcium channel blockers such as diltiazem and verapamil have a rapid onset of action and are available in both oral and IV forms. **These medications should not be used in patients with decompensated heart failure or cardiac amyloidosis**. Both diltiazem and verapamil are available in short-acting and sustained-release oral formulations.

C. Digitalis is available in both oral and IV forms. It is primarily used for rate control when contraindications exist to beta-blockers and calcium channel blockers and in patients with left ventricular systolic dysfunction. It may also be used as an adjunct to beta-blockers and calcium channel blockers. It is important to remember that digoxin is

most effective at controlling the resting heart rate but less effective with activity. **Digitalis toxicity** is a serious complication of chronic therapy. Cardiac manifestations of digitalis toxicity include all arrhythmias except rapidly conducted atrial tachyarrhythmias. Patients also present with gastrointestinal and neurologic complaints. Digitalis toxicity can be treated with digoxin-specific antibody fragments.

D. Antiarrhythmic medications such as **amiodarone** can also be used for rate control because of its beta-blocking properties if other medications are unsuccessful. Patients must be anticoagulated, given the chance of pharmacologic cardioversion. Dronedarone should never be used for rate control in patients with permanent AF because of increased harm.

E. AV nodal ablation with insertion of a permanent ventricular pacemaker can be used if medical therapy is unsuccessful and should only be considered as a last resort. If possible, the device should be implanted 4 to 6 weeks before AV nodal ablation to ensure adequate pacemaker function prior to the procedure. These patients should be followed closely for the development of a cardiomyopathy because of chronic right ventricular pacing in which case a referral for cardiac resynchronization therapy may be necessary.

IV. RHYTHM CONTROL. The treatment of **any unstable patient where AF is contributing to hemodynamic instability is immediate direct current cardioversion (DCCV)**. For stable patients with AF, attempts to restore and maintain sinus rhythm utilizing cardioversion, antiarrhythmic drugs, and catheter ablation are commonly used (see **Figure 25.1**). Although rhythm control with antiarrhythmic drugs has not been shown to be superior to rate control with respect to mortality, restoration of sinus rhythm is associated with symptom relief and improved quality of life (QoL) in many patients. With the emergence of new and consistent evidence, the new updated **ACC/AHA/ACCP/HRS 2023** guidelines emphasize the importance of early and continued management of patients with AF that should focus on maintaining sinus rhythm and minimizing AF burden. Other factors such as young age, new-onset AF,

tachycardia-induced cardiomyopathy, or heart failure also favor a rhythm control strategy.

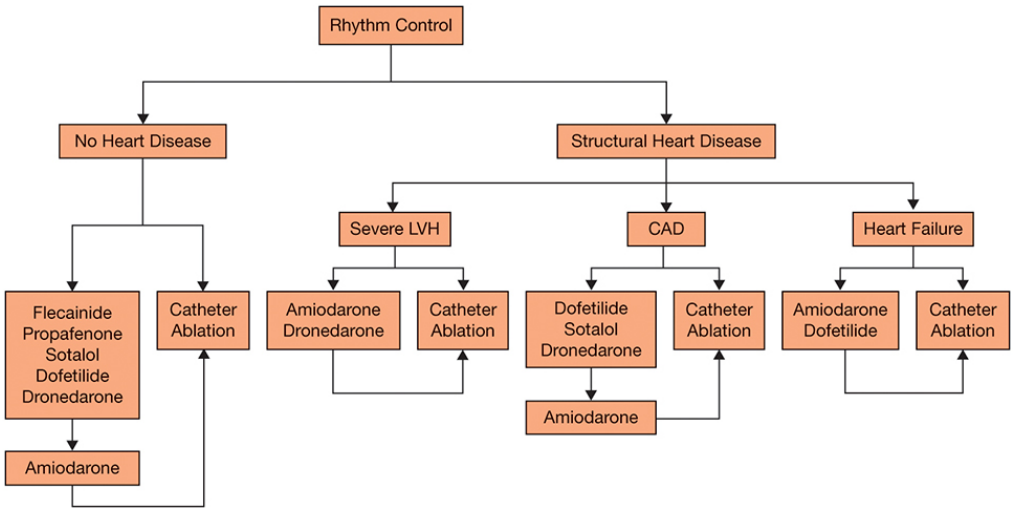

FIGURE 25.1 Approach to rhythm control for patients with paroxysmal and persistent atrial fibrillation. CAD, coronary artery disease; LVH, left ventricular hypertrophy. (Adapted from the January CT, Wann LS, Alpert JS, et al. ACC/ACC/HRS guideline for the management of patients with atrial fibrillation. *J Am Coll Cardiol*. 2014;64(21):2305-2307; American Heart Association, Inc.)

A. Electrical cardioversion. Successful restoration of sinus rhythm is most effectively accomplished with DCCV, which is successful approximately 80% of the time. Whenever possible, DCCV should be performed under sedation with appropriate hemodynamic monitoring and in the presence of personnel skilled in airway management. See Chapter 58 for more procedural details of DCCV.

B. Pharmacologic cardioversion. Flecainide, propafenone, dofetilide, amiodarone, and IV ibutilide can be used for cardioversion if no contraindications exist. However, the success rate is much lower than DCCV.

1. IV ibutilide is a class III agent that carries a 1% to 2% risk of **torsades de pointes**, and patients should be monitored after drug administration. Because of this, the use of ibutilide for pharmacologic cardioversion has fallen.

2. As needed, **flecainide** and **propafenone** can be used for selected outpatients as long as these agents have been shown to be safe in a monitored setting. **This "pill-in-the-pocket" approach should always be used in conjunction with AV nodal blocking agents** because these class IC antiarrhythmic agents can promote 1:1 ventricular conduction in patients with atrial flutter. These agents should not be used in patients with coronary artery disease, left ventricular dysfunction, or other significant heart disease.
3. **Dofetilide should always be started in a monitored inpatient** setting because of its risk for QT prolongation and subsequent torsades de pointes.

C. **Drugs to maintain sinus rhythm.** Several oral agents are available for the maintenance of sinus rhythm. It should be kept in mind that the initiation or upward dose titration of antiarrhythmic drugs should be done with caution and, in many instances, should be performed in a hospital setting with cardiac monitoring. This is particularly true for the class III agents sotalol and dofetilide. On the other hand, in patients without structural heart disease, the class IC agents flecainide and propafenone may be considered for initiation on an outpatient basis.

1. **Vaughan Williams class IA agents.** These sodium channel blockers have seen a decline in use over time primarily not only because of a high incidence of intolerable side effects but also because of the possibility of increased mortality in patients with structural heart disease.
   a. **Procainamide** is not used frequently due to its gastrointestinal, hematologic, and immunologic (ie, drug-induced lupus) side effects. An active metabolite of this drug, *N*-acetylprocainamide (NAPA), is cleared renally and has class III antiarrhythmic properties. Blood levels of both procainamide and NAPA need to be monitored to prevent toxicity, especially in patients with renal or hepatic insufficiency. **Procainamide is still used in stable patients with AF and evidence of ventricular preexcitation.**

b. **Quinidine** is not used frequently due to its relatively high incidence of gastrointestinal, hematologic, and neurologic side effects. In addition, quinidine prolongs the QT interval and has significant drug-drug interactions. Quinidine has no negative inotropic effects and can be used in patients with advanced renal dysfunction when other antiarrhythmics cannot be used.

c. **Disopyramide** is not used frequently due to its powerful negative inotropic and anticholinergic effects, although it is used in patients with **hypertrophic cardiomyopathy**.

2. **Vaughan Williams class IC agents. Flecainide** and **propafenone** are sodium channel blockers that have become the preferred agents for the maintenance of sinus rhythm in patients without significant heart disease. The Cardiac Arrhythmia Suppression Trial found flecainide to be associated with increased mortality when used for suppression of ventricular arrhythmias in patients with left ventricular dysfunction after myocardial infarction. Furthermore, these agents are negative inotropes and can prolong QRS duration. Therefore, **these agents should not be used in patients with coronary artery disease or structural heart disease and should be used with caution in patients with significant conduction system disease without a pacemaker**. In patients with atrial flutter, these agents can slow the atrial rate to the point where 1:1 ventricular conduction occurs; therefore, they should **always be administered in conjunction with AV nodal blocking agents**.

3. **Vaughan Williams class III agents.** These potassium channel blockers have become the preferred agents for most patients with structural heart disease. Sotalol and dofetilide should be avoided in patients with severe left ventricular hypertrophy.

a. **Sotalol** has beta-blocking properties and should be used with caution in patients with heart failure. This agent also causes **QT prolongation**, and drug initiation or dose increase should be performed in a hospital setting with cardiac monitoring. The dose must be reduced in patients with renal insufficiency.

b. **Dofetilide** is an effective drug for the maintenance of sinus rhythm in patients with heart failure, coronary artery disease, and sinus node dysfunction. This agent is generally well tolerated but can cause **QT prolongation**, especially in the setting of renal dysfunction. Therefore, drug initiation or dose increase should be performed in a hospital setting with cardiac monitoring. The prescription of the drug is tightly controlled, and only those certified in its use may prescribe it. Careful attention should be paid to avoid electrolyte disturbances and concomitant administration with other QT-prolonging drugs, thiazide diuretics, and verapamil.

c. **Amiodarone** has properties of all four Vaughan Williams classes and has a very long half-life (up to 120 days). It is generally reserved for patients in whom other antiarrhythmic drugs are contraindicated or ineffective because of the **significant side effects that occur in the liver**, **lungs**, **thyroid**, **and eyes**. Patients should undergo periodic screening for drug toxicity. Sinus node dysfunction is also a common side effect.

d. **Dronedarone** is similar to amiodarone but has fewer side effects. It is contraindicated in patients with New York Heart Association class III or IV heart failure as well as recently decompensated heart failure, especially those with left ventricular systolic dysfunction. It can cause bradycardia and QT interval prolongation and should not be used in permanent AF. There is potential for serious hepatotoxicity, and liver function tests should be monitored closely.

D. **Catheter ablation to maintain sinus rhythm.** The role of catheter ablation continues to expand rapidly and is currently used in many patients to maintain sinus rhythm. Recent randomized studies have demonstrated the superiority of catheter ablation over drug therapy for rhythm control in appropriately selected patients. In view of the most recent evidence, the **ACC/AHA/ACCP/HRS 2023** guidelines have upgraded the class of recommendation of catheter ablation as first-line therapy to class 1 indication. **Radiofrequency ablation** and **cryoballoon ablation** can both be utilized to isolate the pulmonary

veins. When AF is resistant to at least one class I or class III antiarrhythmic agent, current guidelines recommend the use of catheter ablation in patients with symptomatic paroxysmal AF (class I, Level of Evidence: A), symptomatic persistent AF (class IIa, Level of Evidence: A), and symptomatic long-standing persistent AF (class IIb, Level of Evidence: B). Catheter ablation can be considered before a trial of antiarrhythmics in patients with recurrent symptomatic paroxysmal AF (class IIa, Level of Evidence: B) and patients with symptomatic persistent AF (class IIb, Level of Evidence: C). **Patients must be on anticoagulation during and after the procedure**. A discussion about the risks and benefits of catheter ablation should always occur. For more details about the procedure, refer to Chapter 55.

E. Pulsed-field ablation (PFA). For many years, guidelines have suggested thermal ablation (TA) (radiofrequency or cryoballoon) for the treatment of AF. TA involves the destruction of tissue and may lead to multiple complications. Although the overall incidence of these complications is low, their clinical significance can be devastating. PFA, a nonthermal method of tissue ablation, is currently being evaluated as a more safe and efficient way to treat AF.

The ADVENT trial was the first randomized, single-blind, noninferiority trial to evaluate the utility of PFA in patients with AF. They assigned 305 patients with drug-refractory paroxysmal AF in a 1:1 ratio to undergo PFA or conventional radiofrequency or cryoballoon ablation. The primary efficacy end point was freedom from a composite of initial procedural failure, documented atrial tachyarrhythmia after a 3-month blanking period, antiarrhythmic drug use, cardioversion, or repeat ablation. The primary safety end point included acute and chronic device- and procedure-related serious adverse events. At 1 year, the primary efficacy end point was met (ie, no events occurred) in 204 patients (estimated probability, 73.3%) who underwent PFA and 194 patients (estimated probability, 71.3%) who underwent TA (between-group difference, 2.0 percentage points; 95% Bayesian credible interval, −5.2 to 9.2; posterior probability of noninferiority, >0.999). Primary safety end point events occurred in

six patients (estimated incidence, 2.1%) who underwent PFA and four patients (estimated incidence, 1.5%) who underwent TA (between-group difference, 0.6 percentage points; 95% Bayesian credible interval, −1.5 to 2.8; posterior probability of noninferiority, >0.999).

A recent meta-analysis analyzed data from 18 studies involving 4,998 patients (35.2% PFA). Overall, PFA was associated with a shorter procedure time (mean difference [MD] −21.68; 95% confidence interval [CI] −32.81 to −10.54) but longer fluoroscopy time (MD 4.53; 95% CI 2.18-6.88) than TA. Regarding safety, lower (peri-)esophageal injury rates (odds ratio [OR] 0.17; 95% CI 0.06-0.46) and higher tamponade rates (OR 2.98; 95% CI 1.27-7.00) were observed after PFA. In efficacy assessment, PFA was associated with a better first-pass isolation rate (OR 6.82; 95% CI 1.37-34.01) and a lower treatment failure rate (OR 0.83; 95% CI 0.70-0.98).

F. Surgical ablation to maintain sinus rhythm. The surgical maze procedure was first introduced in 1987 by Dr James Cox and tested the original hypothesis that reentry is the predominant mechanism for the development and maintenance of AF. Known as the Cox-Maze procedure, the original technique used biatrial "cut-and-sew" incisions in critical locations to create barriers to the propagating wavelets that are responsible for the initiation and maintenance of AF. The technique has undergone multiple revisions over the years, and the original "cut-and-sew" technique has mostly been replaced by the Cox-Maze IV, which utilizes radiofrequency and cryothermal devices to create the lines of ablation. The Cox-Maze procedure has not had widespread acceptance as a means of treatment for AF, except in patients undergoing open-heart surgery. Even in these patients, the additional intraoperative time and complexity of the procedure have limited its widespread surgical application.

G. Patient-reported outcomes (PRO). Patients' QoL metrics are a cornerstone in health care reform, especially in AF management. The Centers for Medicare & Medicaid Services assess health care institutions' performance by measures of adverse events, such as readmission rates, complications, and hospital-acquired conditions. Although such metrics remain important in health care delivery,

critical patient-centered outcomes, such as improvement in QoL, are not routinely collected. In current models, a poorly performed procedure for the treatment of a chronic condition, such as ablation of AF, can still score high on performance metrics in the absence of procedural complications while potentially not providing any true benefit to the QoL of the patient.

The importance of PRO is increasingly recognized as a paramount factor in the development of patient-centered care. AF ablation is most commonly performed for symptom relief, yet most outcomes in clinical research report arrhythmia recurrence and proposed registries only record acute outcomes mostly pertaining to complications. Most AF programs rarely have longitudinal arrhythmia follow-up, and to our knowledge, no program has any longitudinal QoL or symptom assessment after PFA. In 2015, our department has developed a PRO system to track QoL metrics following AF ablation. The PRO program is a mobile/email/web-based program that is user friendly and free for all Cleveland Clinic patients with AF. The program is an automated PRO data collection platform that allows collection of a large number of disease-specific variables related to symptoms, QoL, and health care utilization. The program is an automatic program that sends alerts as well as questionnaires at the time of ablation, 3, 6, and then every 6 months postablation. The use of the system has been validated in over 3,000 patients with a mean follow-up of 3 years.

V. SPECIFIC POPULATIONS

A. Postoperative cardiac and thoracic surgery. AF is common postoperatively. The incidence of postoperative AF varies with the type of surgery and is highest following cardiac surgery (between 20% and 50%). It usually occurs in the first 5 days after surgery and is a major determinant of the length of stay and hospital cost.

1. Therapy. Postoperative AF is usually self-limited, and DCCV is not always needed. Patients who develop AF should be treated with beta-blockers or nondihydropyridine calcium channel blockers to achieve adequate rate control. There are a variety of antiarrhythmic agents available for cardioversion in these patients.

AF carries an increased risk of stroke in the postsurgical patient; therefore, anticoagulation is recommended if AF persists for longer than 48 hours. The choice of antiarrhythmic agent, AV nodal blocker, and anticoagulant depends on the patient's comorbidities and type of surgery.

2. **Prevention.** There is evidence supporting the prophylactic administration of certain medications to prevent the development of AF in patients undergoing cardiac surgery. **Amiodarone**, when given prophylactically before or after cardiac surgery, has been found to significantly reduce the incidence of postoperative AF. **Sotalol** has also been studied, but there is conflicting evidence regarding its effectiveness. Administration of **colchicine** may also be considered in patients to reduce AF after surgery.

B. **Acute coronary syndromes.** The incidence of AF following acute coronary syndromes ranges between 10% and 20% at 30 days. AF is more commonly associated with acute myocardial infarction in older patients as well as those with significant left ventricular dysfunction. Patients with AF in this setting have a worse outcome at 30 days compared with those in sinus rhythm. Guidelines recommend **urgent DCCV in patients with acute myocardial infarction and AF with rapid ventricular rates and intractable ischemia**. IV beta-blockade is indicated for rate control to reduce myocardial oxygen consumption, and digoxin or amiodarone is an alternative for patients with significant left ventricular dysfunction and heart failure. Stroke rates are also increased in these patients, and anticoagulation is recommended for patients with a CHA_2DS_2-VASc score of at least 2.

C. **Preexcitation syndromes.** The most feared complication of AF in patients with ventricular preexcitation is the development of ventricular fibrillation because of a rapid conduction of AF down an accessory pathway. The incidence of sudden cardiac death in patients with preexcitation syndromes is around 0.6% per year. The risk factors for sudden death include a short refractory period of an antegrade accessory pathway (<250 ms), a short R-R interval during preexcited AF, and the presence of multiple accessory pathways. Immediate electrical cardioversion is recommended for

hemodynamically unstable patients. IV procainamide or ibutilide should be used in hemodynamically stable patients. **It is critical to avoid AV nodal blocking agents in patients with AF and evidence of ventricular preexcitation**.

D. Pregnancy. AF occurs infrequently during pregnancy and usually has an identifiable cause, such as mitral valve disease, thyroid disease, or pulmonary disease. The ventricular rate can be controlled with beta-blockers, nondihydropyridine calcium channel blockers, or digoxin. Currently available antiarrhythmic medications cross the placenta and are excreted in breast milk and should, therefore, be avoided if possible. However, amiodarone, sotalol, and flecainide have all been used successfully during pregnancy in selected instances. Quinidine has the longest safety record of any antiarrhythmic agent in pregnancy and remains the agent of choice for pharmacologic conversion of AF. In the hemodynamically unstable patient, electrical cardioversion can be performed without any concern for fetal damage. Anticoagulation should also be given high priority during pregnancy, given the risk of thromboembolic disease during pregnancy. Only those patients with a very low risk of thromboembolism do not require anticoagulation. Warfarin is generally avoided during the first trimester of pregnancy because of its teratogenic effects and during the last month of pregnancy because of bleeding concerns at the time of delivery. Administration of unfractionated heparin either by continuous IV infusion in a dose sufficient to increase the activated partial thromboplastin time (aPTT) to 1.5 to 2 times control or by intermittent subcutaneous injection of 10,000 to 20,000 units every 12 hours adjusted to prolong the mid-interval aPTT to 1.5 times control is appropriate. LMWH may also be considered during the first trimester and last month of pregnancy, although there are limited data about clinical outcomes.

E. Hypertrophic cardiomyopathy. Patients with AF and hypertrophic cardiomyopathy have a high risk of systemic thromboembolism. Therefore, **these patients should be anticoagulated, regardless of their CHA_2DS_2-VASc score**. Antiarrhythmic medications such as **amiodarone** and disopyramide can be used to maintain sinus rhythm

and should be used in combination with a beta-blocker or nondihydropyridine calcium channel blocker. Sotalol, dofetilide, and dronedarone may also be considered.

F. Pulmonary disease. AF commonly develops in patients with chronic obstructive pulmonary disease. General recommendations include the treatment of the underlying lung disease, correction of hypoxia, and correction of acid-base imbalances. Medications commonly used to treat bronchospastic airway disease such as theophylline and beta-adrenergic agonists can precipitate AF and decrease the ability of medications to control the ventricular response rate. Antiarrhythmic medications with beta-blocking properties such as sotalol, propafenone, and adenosine can worsen bronchospasm and are contraindicated in patients with severe bronchospastic airway disease. Ventricular rate control is usually achieved with nondihydropyridine calcium channel blockers, such as verapamil and diltiazem.

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SUGGESTED READINGS

RELEVANT GUIDELINES

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SECTION V

Vascular Disease

EDITOR: **G. Jay Bishop**

CHAPTER 26

Venous Thromboembolism and Hypercoagulable States

Todd J. Brophy and Leben Tefera

I. VENOUS THROMBOEMBOLISM AND HYPERCOAGULABLE STATES

A. Venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) represent different manifestations of the same clinical entity referred to as VTE. It is a common, lethal disease that affects hospitalized and nonhospitalized patients, recurs frequently, is often overlooked, and can result in long-term complications, including chronic thromboembolic pulmonary hypertension (CTEPH) and post-thrombotic syndrome (PTS). Usual sites of VTE include lower extremity DVT and PE, and unusual sites include cerebral sinus venous thrombosis, upper extremities, pelvic/gonadal, and splanchnic vein DVT.

1. **DVT.** The lower extremities are the most common sites for DVT, but other affected sites include the upper extremities and the mesenteric and pelvic veins. The main goal in the management of DVT is the prevention of PE and PTS. Proximal lower extremity DVTs (popliteal vein and above) have an estimated risk of PE of 50% if not treated. Approximately 6% to 8% of calf vein thrombi propagate (in the absence of treatment) to involve the popliteal vein or above.
2. **Pathogenesis and risk factors.** Virchow triad still forms the best framework for understanding the pathogenesis of VTE. **The triad includes stasis, hypercoagulability, and injury to the vessel wall**. There are both inherited and acquired risk factors for hypercoagulability. The most common **inherited** risk factors include **factor V Leiden** (FVL) and **prothrombin gene mutation (G20210A)**; deficiency of the natural **anticoagulant protein C (PC)**, **protein S (PS)**, and **antithrombin (AT)**; **hyperhomocysteinemia**; and **elevated factor VIII** levels. Acquired risk factors include **immobilization**, **surgery**, **trauma**, **pregnancy**, use of estrogen-containing oral **contraceptives** (OCPs) or **hormone replacement** therapy (HRT), **malignancy**, **antiphospholipid syndrome (APLS)** (lupus anticoagulant and/or anticardiolipin antibodies), **heparin-induced thrombocytopenia** (HIT), **myeloproliferative** disorders, **smoking**, **obesity** (body mass index [BMI] >30), **inflammatory bowel disease**, **central venous catheters** or **pacemakers, chronic kidney disease, and nephrotic syndrome**.
3. **Clinical manifestations.** Typical symptoms of DVT in the upper and lower extremities include pain and swelling. Signs of DVT on physical examination may include increased warmth, tenderness, edema, the presence of dilated veins (collaterals), erythema, and, in extreme situations, cyanosis or gangrene. A limb-threatening manifestation of DVT, **phlegmasia cerulea dolens**, occurs most often in the setting of malignancy, HIT, or other hypercoagulable conditions in which the thrombus completely occludes venous outflow, causing massive limb swelling, hypertension in the capillary bed, and, eventually, ischemia and necrosis. Phlegmasia cerulea dolens is a vascular emergency requiring leg elevation, anticoagulation, and, in select cases, thrombolysis or surgical or catheter-based thrombectomy. Fasciotomy may also be required to relieve associated compartmental syndromes.
4. **Diagnosis**
   a. **Clinical examination** is unreliable in the diagnosis of DVT, as symptoms and signs are often insensitive and nonspecific. Pretest probability scores improve the utility of further testing. For example, using the Wells score (**Table 26.1**), patients in the low pretest probability category have a 96% negative predictive value for DVT (99% if the D-dimer is negative as well), but the

positive predictive value in patients with a high pretest probability is <75%, supporting the need for further diagnostic testing to identify patients with thrombosis.

TABLE 26.1 Pretest Probability of Deep Vein Thrombosis (Wells Score)

Clinical Feature[a]	Score
Active cancer (treatment ongoing or within previous 6 mo of palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 d or major surgery, within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of DVT	−2
Score	
High	3 or greater
Moderate	1 or 2
Low	0 or less
Modified Score (Adds 1 Point If There Is a Previously Documented DVT)	
Likely	2 or more
Unlikely	1 or less

DVT, deep vein thrombosis.

[a]In patients with symptoms in both legs, the more symptomatic leg is used.

Reprinted from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet*. 1997;350(9094):1795-1798. (Copyright © 1997 Elsevier. All rights reserved.); Wells PS, Anderson DR, Rodger M, et al. Evaluation of D-dimer in the diagnosis of suspected deep-vein thrombosis. *N Engl J Med*. 2003;349(13):1227-1235. (Copyright © 2003 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.)

b. Venography has been the gold standard test for the diagnosis of DVT in the past.

However, because venography is invasive and requires the use of potentially harmful contrast agents, it has largely been replaced by noninvasive tests, such as duplex ultrasonography.

c. Duplex ultrasonography has a sensitivity and specificity of about 95% and 98%, respectively, for the detection of proximal DVT in symptomatic patients; however, it is operator dependent and is less sensitive in asymptomatic individuals and for thrombi located in the calf veins. **An inability to compress the vein with the ultrasound transducer is diagnostic for DVT**. Diagnosis of recurrent DVT is more challenging, given the high incidence of persistently noncompressible veins after an initial event. False positives may occur when pelvic masses result in isolated noncompressibility of the common femoral veins. Using echotexture and acoustic properties, venous duplex ultrasound can often be used to differentiate between acute thrombosis and the chronic vein wall sequelae of previous deep venous thrombotic event.

d. D-dimer. The sensitivity and negative predictive value of this test are high. The combination of a **low pretest probability and a negative D-dimer has an extremely high negative predictive value for VTE (approximately 99%)**. A positive D-dimer, however, is nonspecific, and other diagnostic testing should be performed.

e. Other diagnostic tests less frequently used to detect DVT include magnetic resonance venous imaging and computed tomography (CT) (computed tomography venography [CTV] with venous phase assay). These tests are mainly helpful in the diagnosis of DVT in the pelvic veins, inferior vena cava (IVC), or mesenteric veins.

5. Treatment

a. Anticoagulation. The main goals of treatment for DVT include relief of symptoms and prevention of PE, PTS, and recurrent VTE. Anticoagulation is helpful in facilitating the natural absorption of the thrombus within the vein wall. Once the diagnosis of DVT is confirmed, **anticoagulation should be started immediately unless there is a contraindication**. In patients with uncomplicated DVT, ambulatory treatment rather than hospital admission for anticoagulation is recommended. Indications for hospital admission include patients with significant risk for complications, such as limb-threatening DVT, elevated bleeding risk, severe pain requiring IV analgesic therapy, or other comorbidities. Initial therapy should include heparin, low-molecular-weight heparin (LMWH), fondaparinux, or a direct oral anticoagulant (DOAC).

TABLE 26.2 Overview of Phase III Clinical Trials With Non–vitamin K–dependent New Oral Anticoagulants for the Acute-Phase Treatment and Standard Duration of Anticoagulation After Venous Thromboembolism

Drug	Trial	Design	Treatments and Dosage	Duration	Patients	Efficacy Outcome (Results)	Safety Outcome (Results)
Dabigatran	RE-COVER	Double blind, double dummy	Enoxaparin/dabigatran (150 mg bid)[a] vs enoxaparin/warfarin	6 mo	2,539 patients with acute VTE	Recurrent VTE or fatal PE: 2.4% under dabigatran vs 2.1% under warfarin	Major bleeding: 1.6% under dabigatran vs 1.9% under warfarin
	RE-COVER IP	Double blind, double dummy	Enoxaparin/dabigatran (150 mg bid)[2] vs enoxaparin/warfarin	6 mo	2,589 patients with acute VTE	Recurrent VTE or fatal PE: 2.3% under dabigatran vs 2.2% under warfarin	Major bleeding: 15 patients under dabigatran vs 22 patients under warfarin
Rivaroxaban	EINSTEIN-DVT	Open label	Rivaroxaban (15 mg bid for 3 wk, then 20 mg od) vs enoxaparin/warfarin	3, 6, or 12 mo	3,449 patients with acute DVT	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs 3.0% under warfarin	Major or CRNM bleeding 8.1% under rivaroxaban vs 8.1% under warfarin
	EINSTEIN-PE	Open label	Rivaroxaban (15 mg bid for 3 wk, then 20 mg od) vs enoxaparin/warfarin	3, 6, or 12 mo	4,832 patients with acute PE	Recurrent VTE or fatal PE: 2.1% under rivaroxaban vs 1.8% under warfarin	Major or CRNM bleeding: 10.3% under rivaroxaban vs 11.4% under warfarin
Apixaban	AMPLIFY	Double blind,	Apixaban (10 mg bid for 7 d, then 5 mg	6 mo	5,395 patients	Recurrent VTE or	Major bleeding:

Drug	Trial	Design	Treatments and Dosage	Duration	Patients	Efficacy Outcome (Results)	Safety Outcome (Results)
		double dummy	bid) vs enoxaparin/warfarin		with acute DVT or PE	fatal PE: 2.3% under apixaban vs 2.7% under warfarin	0.6% under apixaban vs 1.8% under warfarin
Edoxaban	Hokusai-VTE	Double blind, double dummy	LMWH/edoxaban (60 mg od; 30 mg od if creatinine clearance 30-50 mL/min or body weight <60 kg) vs UFH or LMWH/warfarin	Variable, 3-12 mo	8,240 patients with acute DVT and/or PE	Recurrent VTE or fatal PE: 3.2% under edoxaban vs 3.5% under warfarin	Major or CRNM bleeding: 8.5% under edoxaban vs 10.3% under warfarin

bid, bis in die (twice daily); CRNM, clinically relevant nonmajor; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; od, omni die (once daily); PE, pulmonary embolism; UFH, unfractionated heparin; VTE, venous thromboembolism.

[a]Approved doses of dabigatran are 150 and 110 mg bid.
From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(43):3033-3073. Reproduced by permission of The European Society of Cardiology.

(1) Unfractionated heparin (UFH) utilizing weight-based dosing (80 U/kg bolus followed by 18 U/kg/h intravenous [IV] infusion) has been shown to achieve a therapeutic activated partial thromboplastin time (aPTT) more rapidly than fixed-dose regimens. The aPTT should not be followed in patients with an abnormal baseline aPTT (eg, in patients with lupus anticoagulant) and in patients who require unusually high doses of heparin, such as in AT deficiency. In these situations, **the anti–factor Xa assay** should be used.

(2) LMWH is administered as a weight-based subcutaneous injection. Enoxaparin is given as either a once-daily injection (1.5 mg/kg/d) or twice per day (bid) (1 mg/kg every 12 hours). No monitoring is required, except in patients who are obese, pediatric patients, pregnant patients, or patients with renal insufficiency. When necessary, the anti-Xa level using LMWH as a reference standard should be measured 4 hours after an injection. The therapeutic range is 0.5 to 1.0 IU/mL for the 12-hour regimen and ≥1.0 IU/mL for the daily dose.

(3) Once anticoagulation with UFH or LMWH is begun, if chosen, a **vitamin K anticoagulant (VKA)** may be initiated. The **overlap with a VKA should be continued for a minimum of 5 days** and until the international normalized ratio (INR) is within the target range of 2.0 to 3.0 for 2 consecutive days to permit adequate depletion of vitamin K–dependent coagulation factors.

(4) Fondaparinux, an indirect factor Xa inhibitor, is approved as the treatment for acute DVT and PE when used in combination with a VKA. Fondaparinux is administered as a once-daily subcutaneous injection of 5, 7.5, or 10 mg based on body weight (<50, 50-100, and >100 kg, respectively) for the treatment of DVT or PE. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min) and bacterial endocarditis.

(5) DOACs. Multiple new DOACs with different mechanisms of action have been evaluated in patients with VTE. These medications include rivaroxaban, apixaban, edoxaban (direct factor Xa inhibitors), and dabigatran (direct thrombin inhibitor [DTI]). The results of these trials are summarized in **Table 26.2**. **Overall, DOACs have proven noninferior to VKAs and are associated with fewer bleeding complications, including major bleeding and**

intracranial hemorrhage. Factor Xa inhibitors rivaroxaban and apixaban have a more rapid onset of action, which obviates the need for parenteral anticoagulation in the initial treatment of VTE. In addition, because these agents have stable pharmacodynamics (unlike warfarin), routine monitoring is not required. **Current guidelines recommend DOACs over VKAs for the treatment of VTE, and most recent guidelines have also extended a recommendation for DOACs over LMWH, even in patients with active cancer**.

(6) **Thrombolytic therapy** for DVT may be beneficial in select individuals and is preferably administered locally via a catheter-directed approach. Systemic lysis is also an option if a catheter-directed approach is not available. Both routes carry an increased risk of systemic hemorrhage compared with standard anticoagulation alone. Current guidelines recommend against routine thrombolytic use in patients with DVT, except for those patients (without contraindication) with an extensive acute proximal DVT (ileofemoral DVT) or individuals at risk for limb gangrene secondary to venous occlusion. The recently published ATTRACT trial demonstrated among patients with acute proximal DVT that catheter-directed thrombolysis did not lower the risk of PTS and resulted in a higher risk of major bleeding.

(7) Previous small trials suggested **graduated compression stockings** (GCS) may help prevent PTS; however, a large randomized trial reported no benefit. These trials have been criticized for methodologic flaws, but the routine use of GCS for the prevention of PTS has not been established but may have a benefit at limb reduction and symptomatic relief with the acute event. Early ambulation as tolerated after diagnosis is safe and should be encouraged.

(8) **Vena caval interruption.** Current guidelines recommend against the routine insertion of IVC filters for the treatment of DVT. **Indications for placement of IVC filters are as follows: an absolute contraindication to anticoagulation, a complication from anticoagulation, or recurrent and progressive VTE despite adequate anticoagulant therapy (failed anticoagulation). IVC filter alone is not an effective therapy** for DVT, and resumption of anticoagulation as soon as the risk of bleed is acceptable is recommended. To date, IVC filters have not shown a consistent benefit in preventing mortality with acute PE.

b. **Duration of treatment.** The duration of treatment following the diagnosis of DVT is **dependent on the risk of recurrence**. Risk factors for recurrence include an idiopathic DVT, underlying hypercoagulable states (listed in subsequent text), and malignancy. In addition, placement of a permanent IVC filter, elevated D-dimer levels, advanced age, male sex, and increased BMI also place individuals at a higher risk for recurrence. The risk of recurrence is low while patients are on anticoagulation; however, clinicians must weigh the risk of bleeding against the risk of new thrombosis. Current guidelines **recommend a minimum of 3 months of anticoagulation** for patients with a **first episode of DVT secondary to a transient cause**. Anticoagulation for at least **3 months** is recommended for patients with a **first episode of idiopathic DVT**, with consideration given to indefinite anticoagulation in patients with a first unprovoked proximal DVT who are at low or moderate bleeding risk. Long-term (indefinite) anticoagulation is also recommended in patients with malignancy for as long as the cancer remains active and in patients who have unexplained recurrent DVTs. Of note, recent trials have shown that **reduced-dose apixaban (2.5 mg bid) and rivaroxaban (10 mg bid) are effective for the prevention of recurrent VTE**, with no significant increase in major bleeding compared to placebo and aspirin, respectively. It should be noted that **aspirin** is much less effective than anticoagulation for VTE secondary prevention. Indefinite or extended indication requires a shared medical decision-making discussion with the patient, weighing various factors such as the risk of recurrence as well as the risk of bleeding.

c. **Calf vein/Distal DVT.** Current guidelines recommend anticoagulation for acute isolated distal DVT if there are **severe symptoms or high-risk features for extension to the proximal veins**. Risk factors for extension that favor anticoagulation over surveillance include positive D-dimer,

extensive thrombosis (>5 cm in length, multiple veins, >7 mm maximal diameter), close proximity to proximal veins, no provoking factor, active cancer, history of VTE, or inpatient status. In patients who are managed with surveillance (serial imaging once or twice weekly for 2-3 weeks), anticoagulation is recommended if the thrombus extends further into the distal veins or to the proximal veins. The decision for anticoagulation or surveillance should also consider bleeding risk and patient preference.

d. **Superficial venous thrombosis** frequently occurs as a complication of an IV line in an upper extremity but may occur spontaneously in the upper or lower extremities. Anticoagulation is not routinely administered but may be considered for those at higher risk for extension to the proximal veins (>5 cm length, <5 cm from the saphenofemoral or saphenopopliteal junction). **Patients with superficial venous thrombosis should undergo ultrasound to rule out DVT**.

e. **Upper extremity DVT.** Upper extremity DVT is most often related to central venous catheter placement and/or pacemaker devices. Other less common causes include thoracic outlet syndrome, Paget-von Schröetter syndrome (also referred to as effort thrombosis), and hypercoagulable conditions including malignancy. Patients may be asymptomatic but more frequently complain of arm swelling and pain. Anticoagulation is indicated if there are no contraindications. Thrombolysis should be considered in younger patients with effort thrombosis, who have a low risk of bleeding and symptoms of acute onset. Determination of the length of anticoagulation should be decided using the same processes described for acute lower extremity DVTs.

B. **PE.** It is difficult to approximate the true incidence of acute PE, but there are estimates that as many as 300,000 Americans have a fatal PE each year and as many as 34% of affected individuals present with sudden death. **The majority of patients die because of a failure in diagnosis rather than inadequate therapy**. In fact, the mortality rate for PE without treatment is approximately 30%, whereas it is only 2% to 8% with adequate treatment. PE remains the most common preventable cause of hospital death in the United States.

1. **Pathophysiology and symptoms.** Hemodynamic collapse related to PE results from the combination of vascular obstruction from thrombus and vasoconstriction caused by inflammatory mediators and hypoxia. Elevated pulmonary vascular resistance results in decreased right ventricular outflow, leading to a decrease in preload and cardiac output, resulting in hypotension. Elevated right ventricular wall tension can lead to decreased right coronary artery flow and ischemia. Cardiopulmonary collapse from PE is more common in patients with coexisting coronary artery disease (CAD) or underlying cardiopulmonary disease.

   PE may present as one of the following three syndromes: (a) **acute cor pulmonale**, (b) **pulmonary infarction**, or (c) **dyspnea**. Patients presenting with acute cor pulmonale, as manifested by the sudden development of dyspnea, cyanosis, shock, or syncope, usually have a massive PE, leading to cardiovascular collapse. Patients with pulmonary infarction usually present with pleuritic chest pain, dyspnea, and hemoptysis, and an audible friction rub may be heard. The majority of patients present with generalized symptoms of chest pain, dyspnea, and malaise.

2. **Diagnosis.** Several pretest probability scores have also been developed for the diagnosis of PE similar to those for the diagnosis of DVT. In a validation study of the Wells clinical decision rule, only 0.5% of patients who were unlikely to have PE and had a negative D-dimer had subsequent nonfatal VTE.

   a. **Troponin.** Cardiac troponins have been evaluated in the setting of acute PE, and elevated levels correlate with electrocardiographic and echocardiographic findings of right ventricular pressure overload. Troponin elevation can be seen in patients with and without CAD, but the overall mortality and in-hospital complications are higher in patients with acute PE and elevated cardiac troponin than in patients without elevated cardiac troponin.

   b. **Brain natriuretic peptide** elevation in the absence of renal dysfunction is also a marker of right ventricular dysfunction in patients with PE. Like elevated troponin levels, these elevated levels

have also been shown to be predictors of adverse outcome in patients with acute PE.

c. **Arterial blood gas.** PE can result in significant hypoxia, but in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 26% of patients with angiographically proven PE had Pao_2 >80 mm Hg. Similarly, a **normal alveolar-arterial gradient does not preclude the diagnosis of PE**. Therefore, a normal Pao_2 cannot rule out PE; however, hypoxia in the absence of cardiopulmonary disease should raise the suspicion for this diagnosis. In patients with cardiopulmonary collapse, a normal Pao_2 suggests that PE is an unlikely cause.

d. **Chest radiography** may be more helpful in establishing other diagnoses. When present, findings are nonspecific and include pleural effusion, atelectasis, and consolidation. The classic signs, including the Westermark sign (regional oligemia), Hampton hump (pleural-based, wedge-shaped shadow), and Palla sign (enlarged right inferior pulmonary artery), are uncommon.

e. **Electrocardiography (ECG).** Like chest radiography, the major utility of the ECG in the diagnosis of PE is to rule out other major diagnoses, such as acute myocardial infarction (MI). The most specific finding on an ECG is the classic $S_1Q_3T_3$ pattern, but the most common findings are nonspecific ST-segment and T-wave changes. Other commonly reported findings include sinus tachycardia, atrial fibrillation, and right bundle branch block.

f. **Echocardiography.** More than 50% of hemodynamically stable patients with PE will not have evidence of right ventricular dysfunction on transthoracic echocardiography (TTE). Patients with **hemodynamic collapse, however, will generally have severe right ventricle dysfunction**, and TTE can provide rapid bedside assessment in these critically ill patients. TTE findings include right ventricular dilation, right ventricular hypokinesis, tricuspid regurgitation, septal flattening, paradoxical septal motion, diastolic left ventricular impairment secondary to septal displacement, pulmonary artery hypertension, lack of inspiratory collapse of the IVC, and, rarely, direct visualization of the thrombus. In patients with large PE, it has been observed that despite moderate or severe right ventricular free wall hypokinesis, there is relative sparing of the apex. This finding is referred to as **McConnell sign** and has a specificity of 94% and a positive predictive value of 71% for PE. McConnell sign may be useful in discriminating right ventricular dysfunction because of PE versus other causes.

g. **Ventilation-perfusion (V·/Q·) scanning. V·/Q·** scanning is now considered a second-line imaging method for the diagnosis of PE. **V·/Q·** scans are helpful in patients who have normal chest radiography or who are unable to have CT scanning, such as those with renal insufficiency, contrast allergy, or pregnancy. The results of PIOPED suggest that **V·/Q·** scanning is helpful if the scan is normal or at high probability for PE (87% of patients with high probability scans had PE, but only 4% of patients with normal scans had PE). Intermediate or low probability scans are the most common finding, however, occurring in approximately 70% of patients in the PIOPED study. In addition, patients who had a high or intermediate clinical suspicion for PE but a low probability scan still had a 40% and 16% rate, respectively, of PE diagnosed by pulmonary angiography. Hence, it is currently advised that **patients with a high or intermediate clinical suspicion for PE but a low probability V·/Q· scan have additional tests to confirm or refute the diagnosis**.

h. **Computed tomography pulmonary angiography (CTPA).** Because of its wide availability and the ability to directly visualize thrombus, **CT imaging has become the standard imaging technique for the diagnosis of acute PE**. CTPA not only allows direct visualization of the thrombus but also has great value in excluding other diseases, including aortic dissection, pneumonia, or malignancy. It is especially useful in evaluating central PE (thrombus is seen as an intraluminal filling defect), and although the diagnostic yield for peripheral or subsegmental PE was low initially, the use of multidetector CTPA has greatly increased its sensitivity and specificity for the diagnosis of small peripheral or subsegmental PEs. The major disadvantages of CT are radiation exposure and the possibility of contrast-induced nephrotoxicity. A meta-

analysis of 23 studies including 4,657 patients who were suspected of having PE but had normal CT scans found that only 1.4% developed VTE and 0.51% developed fatal PE by 3 months. These rates are similar to those in other studies involving patients who had suspected PE but were found to have normal pulmonary angiograms.

i. **Pulmonary angiography** remains the gold standard diagnostic test for PE, but it is used infrequently because of the advent of CT scanning. In some situations where a lung scan shows perfusion abnormalities and is nondiagnostic for PE, selective angiography of the abnormal area may be considered so as to limit the amount of contrast needed. In experienced centers, associated morbidity and mortality are low.

j. **Magnetic resonance angiography** (MRA) may be an alternative to CT for the diagnosis of PE in patients who have contrast allergy or for whom avoidance of radiation exposure is desired. At the current time, an MRA should be considered only at those centers with experience with this modality and only for patients for whom standard tests are contraindicated.

3. **Treatment.** All patients with PE are treated with anticoagulation and supportive care. Risk stratification using a combination of hemodynamic stability, biomarkers, and echocardiographic criteria is utilized to determine the use of catheter-directed therapies and systemic thrombolysis. CTEPH is a rare but serious late complication of PE, and it presents a separate diagnostic challenge with distinct medical and surgical management options, as discussed in Chapter 14.

a. **Risk stratification and management algorithm.** The pulmonary embolism severity index (PESI) is a validated clinical tool to assess prognosis for patients presenting with acute PE (**Table 26.3**). In normotensive patients, this tool can reliably distinguish between intermediate and low risk and, therefore, identify patients who may require further evaluation. In addition, there is a growing body of evidence supporting early discharge or home therapy for patients at low risk. Current guidelines incorporate risk stratification utilizing the PESI score into an algorithm for managing patients with acute PE (**Figure 26.1**).

TABLE 26.3 Original and Simplified Pulmonary Embolism Severity Index

Parameter	Original Version	Simplified Version
Age	Age in years	1 point (if age >80 y)
Male sex	+10 points	–
Cancer	+30 points	1 point
Chronic heart failure	+10 points	1 point
Chronic pulmonary disease	+10 points	
Pulse rate ≥110 beats/min	+20 points	1 point
Systolic blood pressure <100 mm Hg	+30 points	1 point
Respiratory rate >30 breaths/min	+20 points	–
Temperature <36 °C	+20 points	–
Altered mental status	+60 points	–
Arterial oxyhemoglobin saturation <90%	+20 points	1 point
	Risk Strata[a]	
	Class I: ≤65 points Very low 30-d mortality risk (0%-1.6%) **Class II: 66-85 points** Low mortality risk (1.7%-3.5%)	**0 points** = 30-d mortality risk 1.0% (95% CI 0.0%-2.l%)
	Class III: 86-105 points Moderate mortality risk (3.2%-7.1%)	**≥point(s)** = 30-d mortality risk 10.9%

Parameter	Original Version	Simplified Version
	Class IV: 106-125 points High mortality risk (4.0%-11.4%) **Class V: >125 points** Very high mortality risk (10.0%-24.5%)	(95% CI 8.5%-13.2%)

[a]Based on the sum of points.

CI, confidence interval.

From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(43):3033-3073. Reproduced by permission of The European Society of Cardiology.

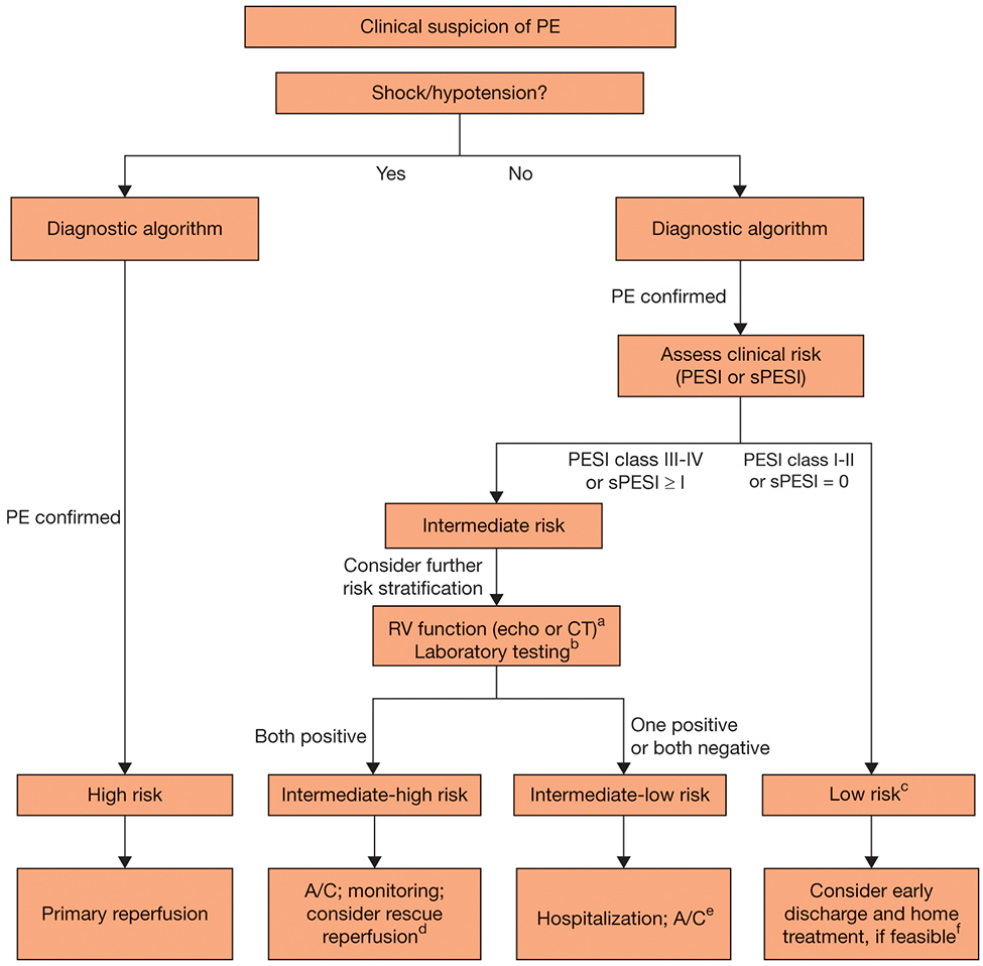

FIGURE 26.1 Risk-adjusted management strategies in acute pulmonary embolism (PE). A/C, anticoagulation; CT, computed tomography; PESI, pulmonary embolism severity index; RV, right ventricular; sPESI, simplified pulmonary embolism severity index. [a]If echocardiography has already been performed during diagnostic workup for PE, and RV dysfunction detected, or if the CT already performed for diagnostic workup has shown RV enlargement (RV/left ventricular [LV] ratio ≥0.9), a cardiac troponin test should be performed, except for cases in which primary reperfusion is not a therapeutic option (eg, because of severe comorbidity or limited life expectancy of the patient). [b]Markers of myocardial injury (eg, elevated cardiac troponin I or T concentrations in plasma) or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic workup (eg, in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be (re)assessed on CT. [c]Patients in the PESI class I-II, or sPESI of 0, and elevated cardiac

biomarkers or signs of RV dysfunction on imaging tests are also to be classified into the intermediate-low-risk category. This might apply to situations in which imaging or biomarker results become available for the calculation of the clinical severity index. These patients are probably not candidates for home treatment. [d]Thrombolysis, if (and as soon as) clinical signs of hemodynamic decompensation appear; surgical pulmonary embolectomy and percutaneous catheter–directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high. [e]Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT. [f]The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-armed (nonrandomized) management studies. (From Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism: the task force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(43):3033-3073. Reproduced by permission of The European Society of Cardiology.)

b. Anticoagulation and supportive care have remained the standard of care in the management of acute PE. **Current guidelines recommend initial treatment with anticoagulants for patients with a high clinical suspicion for PE while awaiting the results of diagnostic testing**. Traditionally, patients with acute nonmassive PE have been treated with parenteral anticoagulation (IV UFH, LMWH, fondaparinux) followed by the initiation of an oral agent. The advent of DOACs has revolutionized the management of VTE. Duration of treatment, including consideration of indefinite anticoagulation and low-dose DOAC regimens, mirrors the recommendations for the treatment of DVT as described earlier in this chapter.

c. DOACs, as discussed previously, are outlined in **Table 26.2**. As with DVT, current guidelines suggest DOACs over VKAs or LMWH for the treatment of acute PE in the general population.

d. Systemic thrombolysis for the treatment of acute PE is highly individualized, as there have been no clearly established short-term mortality effects. Because of favorable outcomes with prompt recognition and anticoagulation for PE, **thrombolysis should be reserved for hemodynamically unstable patients with acute massive PE and a low risk of bleeding**. The recent PEITHO trial investigated the role of systemic thrombolysis among patients with acute PE at intermediate risk, defined as hemodynamic stability but with positive cardiac troponin and evidence of right ventricular dysfunction by either CT or echocardiography. This double-blinded trial randomized >1,000 patients to receive IV tenecteplase single bolus (30-50 mg based on body weight) or placebo in addition to anticoagulation. Overall, mortality was <2% at 7 days with no significant difference between groups. The group receiving thrombolytics was less likely to develop hemodynamic decompensation; however, this was at the cost of significantly increased risk of intracranial and other major bleeding. Based on these results, **routine use of systemic thrombolysis is not recommended in normotensive patients at intermediate risk**.

e. Catheter-based therapies have gained interest in recent years, given the significant bleeding risk associated with systemic thrombolysis. These procedures include percutaneous catheter–delivered intrapulmonary thrombolysis, mechanical fragmentation, aspiration thrombectomy, rheolytic thrombectomy, and ultrasound-assisted thrombolysis. Data are limited to observational studies and small clinical trials with surrogate end points but suggest these therapies may be an effective option with acceptable safety profile. Currently, catheter-based therapies are only recommended at experienced centers for high-risk patients with contraindications to systemic thrombolysis or failed thrombolysis.

f. Surgical pulmonary embolectomy was the first definitive therapy to be performed for PE. The primary use of this procedure is in patients with shock and a contraindication to thrombolysis or failed thrombolysis.

g. Pulmonary embolism response teams (PERTs) were first described in 2013 and have since spread to numerous institutions worldwide. **The goal of a PERT is rapid multidisciplinary management of patients with high-risk PE, including consideration of advanced therapies such as systemic thrombolytics, catheter-based therapies, or surgical intervention**. Data thus far have been largely limited to cohort studies and case series, but a recent meta-analysis

suggests the PERT framework may increase the use of advanced therapies and trend toward lower mortality.

C. VTE primary prophylaxis. Although PE is the third most common cause of hospital-related death in the United States, less than half of all hospitalized patients at risk for VTE receive adequate prophylactic treatment. Most hospitalized patients have at least one or more risk factors for VTE, and **without prophylaxis, the incidence of hospital-acquired DVT is 10% to 20% among medical patients and even higher among surgical patients (15%-40%)**. The highest risk of postdischarge VTE in hospitalized medical patients is in the first 60 days.

There are two major forms of primary VTE prophylaxis, **mechanical and pharmacologic**. Those who cannot receive prophylactic anticoagulation should be prescribed mechanical modalities, such as intermittent pneumatic compression devices. Pharmacologic prophylaxis can be achieved by a number of agents, including UFH, LMWH, fondaparinux, VKA, and DOACs. Apixaban is approved for VTE prophylaxis following total hip arthroplasty (THA) or total knee arthroplasty (TKA), whereas rivaroxaban is approved for VTE prophylaxis in acutely ill medical patients in addition to THA or TKA. Recently, a large randomized clinical trial showed that low-dose rivaroxaban (10 mg daily) for 5 days followed by daily low-dose aspirin for 30 days was also successful in preventing VTE following THA and TKA. In high-risk populations such as those with hip or knee replacement, a combination of mechanical and pharmacologic therapies should be considered. In select surgical procedures, extended prophylaxis is recommended. For example, extended prophylaxis for up to 28 to 35 days is recommended for patients who have had a hip fracture or who undergo total hip replacement surgery.

II. HYPERCOAGULABLE CONDITIONS. Conditions that predispose persons to an increased risk of thrombosis are referred to as hypercoagulable states or thrombophilia. **These conditions are being identified more frequently and may be classified as inherited or acquired. Hypercoagulability testing should be considered in individuals with idiopathic VTE, family history of clotting, a first thrombotic event before the age of 50 years, thrombosis at unusual locations, resistance to anticoagulation, frequent miscarriages, stroke at a young age, and those with recurrent thromboses**.

A. FVL and prothrombin gene mutation. The FVL mutation is more prevalent in persons of European and Scandinavian ancestry. It is estimated that 5% to 8% of the Caucasian population has a single-copy mutation of FVL. The prothrombin gene mutation G20210A (PT G20210A) is also inherited as an autosomal dominant mutation and may lead to a higher plasma level of prothrombin. It is also more common in those of Caucasian ancestry and confers a 2.8-fold increased risk of VTE. The role of FVL and PT G20210A mutations in arterial thrombosis is unclear. There is only a modest association between inherited thrombophilias and major arterial thromboses, such as MI, stroke, or peripheral arterial disease. Therefore, routine screening for these mutations is not warranted in most patients with arterial thrombosis. FVL and PT G20210A are associated with VTE during pregnancy, OCP use, and HRT. There are no clear evidence-based guidelines for managing patients with thrombosis in the setting of these thrombophilias. In general, acute thrombosis should be managed in a standard manner, but the duration of therapy is less clear, and the benefits of long-term anticoagulation must be weighed against the risks of bleeding. Based on recent studies, heterozygosity for FVL is only associated with a modest risk for the first episode of VTE and most likely not associated with an increased risk of recurrence.

B. Defects in the natural anticoagulants (PC, PS, and AT). Deficiency of any of the three natural anticoagulants is associated with an increased risk of venous thrombosis. All are inherited as autosomal dominant defects and are further subclassified based on a reduction in their levels or defective quality of the protein. Levels of PS and PC are lower in conditions such as disseminated intravascular coagulation (DIC), inflammatory states, nephrotic syndrome, acute thrombosis, and liver disease. Pregnancy and OCP use can also decrease the levels of PS. Both PC and PS levels are lowered by warfarin therapy, and, therefore, these tests should not be assayed in patients who are receiving VKAs. Similarly, initiation of warfarin therapy without concomitant anticoagulation in the setting of acute VTE may lead to warfarin-induced skin necrosis (manifested as painful necrosis of the skin, primarily in fatty areas including the breast, buttocks, and thighs). There are two types of AT deficiencies: type I

(reduced synthesis) and type 2 (functional defect). Approximately 55% of patients with AT deficiency and UFH of VTE will develop a VTE by the age of 50. Most common sites include iliofemoral and mesenteric vein VTE. Acquired AT deficiency can be seen in several scenarios, including accelerated consumption (DIC, surgery), reduced synthesis (liver disease, cirrhosis), increased excretion (nephrotic syndrome), and drugs (heparin, estrogen, asparaginase chemotherapy).

C. Homocysteine. Hyperhomocysteinemia is a risk factor for venous and arterial thromboses. It may be inherited, and genetic defects causing a deficiency of cystathionine beta-synthase or a mutation in methylenetetrahydrofolate reductase has been reported. Acquired causes include deficiencies in vitamin B_{12}, B_6, or folate; smoking; and liver or renal failure. Treatment with folate in doses between 0.5 and 5 mg is usually effective in reducing the levels of homocysteine; however, this does not reduce the risk of major cardiovascular events, symptomatic venous thrombosis, or recurrent venous thrombosis.

D. HIT. HIT is a common, underrecognized but potentially devastating condition in patients who receive heparin or LMWH. The reported incidence is between 3% and 5% in patients exposed to UFH and lower (<1%) in patients exposed to LMWH. The pathogenesis of HIT involves the formation of antibodies (usually immunoglobulin G [IgG]) against a heparin-platelet factor 4 (PF4) complex. The **HIT antibodies then trigger procoagulant effects** through platelet and endothelial cell activation, as well as thrombin generation **leading to both microvascular and macrovascular thromboses**. The clinical spectrum of HIT ranges from isolated thrombocytopenia without thrombosis (referred to as isolated HIT) to HIT(T), which is associated with both arterial and venous thromboses. Other manifestations of HIT may include hypotension from adrenal hemorrhage secondary to adrenal vein thrombosis and ensuing infarction, skin necrosis at injection sites, or venous limb gangrene. **HIT should be suspected in any patient who develops thrombocytopenia while receiving heparin or LMWH**; any patient who develops a >50% decline in platelet count after the initiation of either anticoagulant; or any patient who develops new thrombosis or extension of an existing thrombosis while receiving either of these agents. In patients with HIT and de novo exposure to heparin, thrombocytopenia (platelet count <150,000 per mcL) usually occurs between days 5 and 14 (with the day of heparin exposure being day 0). In patients with a recent exposure to either agent (generally within the last 100 days), HIT may develop sooner and is referred to as rapid-onset HIT. This complication may also develop 9 to 40 days after heparin or LMWH has been discontinued and is known as delayed-onset HIT.

Laboratory tests to aid in the diagnosis of HIT include functional assays, such as heparin-induced platelet aggregation and serotonin release assays (SRAs), and antigen assays (immunoassays), which detect IgG, IgM, or IgA antibodies that bind UFH to PF4. The SRA has the highest sensitivity and specificity for the diagnosis of HIT.

The first step in the treatment of HIT is the prompt discontinuation of all sources of heparin or LMWH, including heparin flushes, heparin-coated catheters, any intermittent use of heparin during dialysis, and total parenteral nutrition or angiography. However, approximately 20% to 53% of patients with HIT will develop thrombosis (many within the first month) when heparin is discontinued or treated with LWMH alone. Therefore, the initiation of an alternative anticoagulant, unless contraindicated, is recommended. **DTIs**, including lepirudin and argatroban (both approved by the Food and Drug Administration), may be used initially. Once platelet counts are more than 100,000 to 150,000 mm^3, warfarin may be started at a low dose (2.5-5 mg preferred). Early introduction or higher doses of warfarin may lead to venous limb gangrene or warfarin-induced skin necrosis. Overlapping the DTI with the VKA should be continued for at least 5 days and not discontinued until the INR is therapeutic for 2 consecutive days. Argatroban falsely elevates the INR; therefore, it should not be discontinued until INR >4, as recommended by the manufacturer. After cessation of argatroban, the INR should be rechecked within a few hours to confirm that it is between 2 and 3. The duration of anticoagulation for patients with HIT is generally determined by the location and type of thrombosis. In patients without thrombosis (isolated HIT), the duration of anticoagulation is less clear, but given the high incidence of thrombosis within the first month, it is reasonable to continue anticoagulation for at least a month in the absence of contraindications.

E. Antiphospholipid antibodies are a heterogeneous group of autoantibodies that, if present in a patient with thrombosis, lead to the APLS. Antiphospholipid antibodies can be divided into three groups: (a) anticardiolipin antibodies, (b) lupus anticoagulants, and (c) beta$_2$-glycoproteins. They are often associated with other autoimmune conditions and can cause recurrent pregnancy loss, as well as arterial or venous thrombosis. Thrombocytopenia is also an occasional feature of this syndrome. Anticardiolipin antibodies are detected and quantified using an enzyme-linked immunosorbent assay and may be IgG, IgM, or IgA. IgG titers have been correlated more often with thrombosis. Lupus anticoagulants prolong phospholipid-dependent blood clotting times, and it has been reported that there is about a 5-fold increased risk of thrombosis in patients with this finding. Once a thrombotic event occurs, long-term therapy with warfarin must be considered. A higher target INR had been considered necessary in the past (approximately ≥3.0) but is no longer considered necessary as data have suggested that most patients can be maintained with a target INR of 2.0 to 3.0. In those individuals who are suspected of failing adequate therapy, one strategy is to correlate the INR to factor II and factor X levels (≤20%-30%) to ensure adequate anticoagulation. It should be noted that per societal guidelines, DOACs are not recommended for patients with APLS. VKAs are the preferred choice of anticoagulation.

F. Malignancy. Many malignancies induce a hypercoagulable state, and in patients with idiopathic VTE, a search for age- and gender-specific malignancies may be necessary.

G. Other conditions. Elevated factor VIII levels and dysfibrinogenemias have also been associated with thrombosis; however, the role of deficiencies of plasminogen, tissue plasminogen activator (of the fibrinolytic system), and factor XIII polymorphisms as emerging risk factors for hypercoagulability is less clear.

H. Disorders presenting as a thrombotic storm. Several disorders can present as a thrombotic storm predisposing the patient to extensive arterial and/or venous thrombosis. These include catastrophic antiphospholipid antibody syndrome, malignancy, HIT, and atypical microangiopathies, such as hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura (TTP), and DIC. These usually represent vascular emergencies and require an aggressive multidisciplinary approach to therapies.

I. Timing of thrombophilia testing and anticoagulant interference. Thrombophilia testing is expensive and judicious, and thoughtful use of these laboratory assays is recommended. This testing is often only useful when it assists in making treatment decisions that would influence the care of the patient or the family. Acute venous thrombosis is associated with decreases in PS, PC, and AT levels. As such, obtaining these labs at the time of index VTE event is often fraught with interpretation challenges. Anticoagulants can also interfere with thrombophilia assays; thus, timing of testing is an important consideration. Current guidelines discourage thrombophilia testing in the presence of an obvious provocative major transient or persistent risk factor.

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CHAPTER 27

Aortic Aneurysm and Dissection

Joshua Cohen and Vidyasagar Kalahasti

I. INTRODUCTION. This chapter reflects the 2022 guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) for the diagnosis and management of aortic disease. The italicized text represents guideline recommendations with associated class of recommendation (COR) and level of evidence (LOE).

A. Anatomy. The aorta is the **principal conductance vessel** in the body and is divided into the ascending, arch, descending thoracic, and abdominal components (**Figure 27.1**).

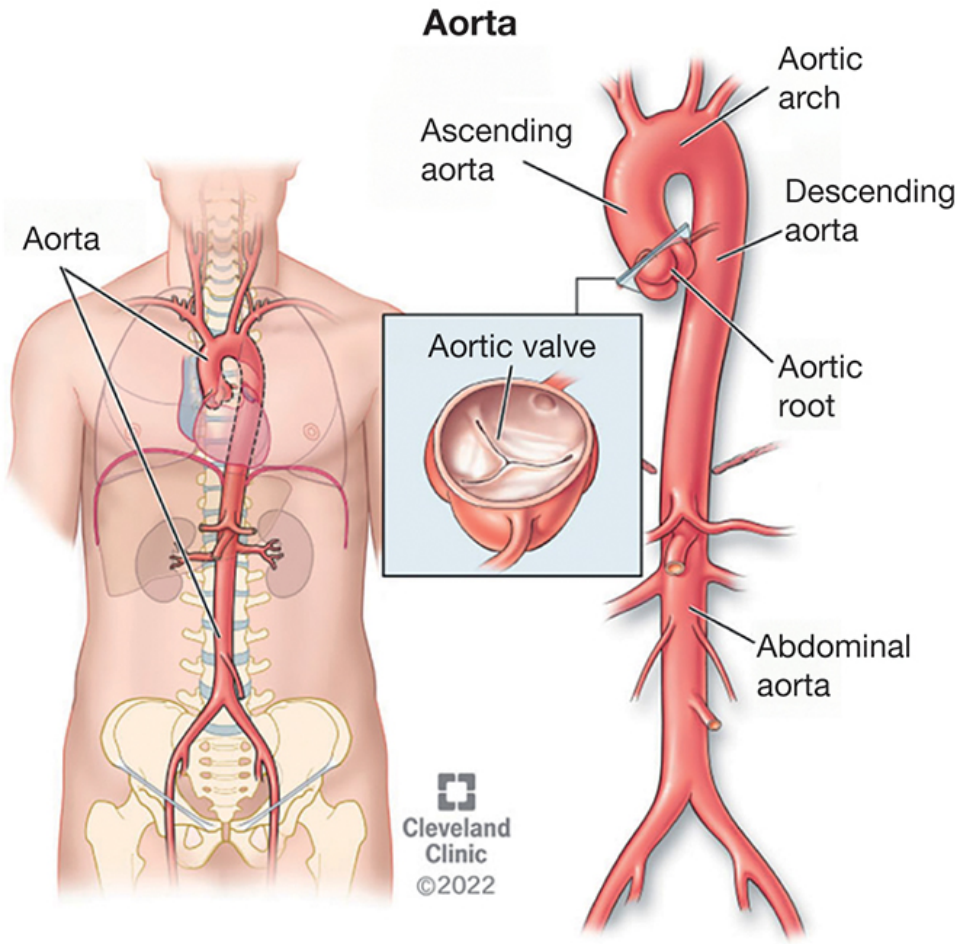


FIGURE 27.1 Aortic anatomy. (Copyright © Cleveland Clinic Foundation. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2011-2024. All Rights Reserved.)

1. The **ascending aorta** includes the aortic root, which contains the sinuses of Valsalva. The left and right coronary arteries arise from the left and right coronary sinuses, respectively. The **aortic arch** gives rise to the great vessels of the head and arms. These include the brachiocephalic (innominate), the left common carotid, and the left subclavian arteries.
2. The **descending aorta** begins distal to the left subclavian artery. The point at which the aortic arch joins the descending aorta is called the **isthmus**, marked by the ligamentum arteriosum. The aortic isthmus is often the site of origin of a dissection tear

because the aorta is relatively fixed to the thoracic cage in this region.

3. The **descending thoracic aorta** provides the intercostal vessels as it courses through the posterior mediastinum. These vessels provide arterial blood flow to a significant portion of the spinal cord.
4. The **abdominal aorta** begins just after the aorta crosses the diaphragm. It provides the splanchnic and renal arteries before bifurcating to become the common iliac arteries.

B. Histology. The aorta is composed of **three layers**: the intima, the media, and the adventitia.

1. The **intima** is the internal lining layer of the aorta and is easily damaged.
2. The **media** is the main structural layer of the aorta. It consists primarily of laminar layers of elastic tissue and smooth muscle in varying amounts. This structure allows for the high tensile strength and elasticity required to withstand the pressure changes of each heartbeat throughout the life of the individual.
3. The **adventitia** is the thin outer layer that anchors the aorta within the body, in addition to providing nourishment to the outer half of the wall through the vasa vasorum.

C. Physiology

1. The **elasticity of the aortic wall allows it to distend** under the pressure created during ventricular systole. In this way, the kinetic energy that was developed during ventricular systole is stored as potential energy in the distended aortic wall. Then, during ventricular diastole, the potential energy is converted back to kinetic energy by the elastic recoil of the wall. Therefore, forward blood flow is maintained throughout the cardiac cycle.
2. The aorta aids in the control of **systemic vascular resistance (SVR)**. Pressure receptors in the ascending aorta and aortic arch signal the vasomotor centers of the brain via the vagus nerve. When blood pressure (BP) is elevated, the reflex response is to

lower heart rate and decrease SVR. The converse is true when BP is decreased.

II. AORTIC DISSECTION

A. Etiology and pathology

1. Aortic dissection classically occurs when **a tear in the intima results in separation of the intima from the media**. This aortic tear then propagates anterograde or, less commonly, retrograde, creating a false lumen in the aortic wall. Less common acute aortic syndromes include intramural hematoma (IMH) and penetrating aortic ulcer (PAU). Acute aortic dissection results from a pathologic weakening of the aortic wall because of medial degeneration, atherosclerosis, or inflammation. **IMH** represents a focal hemorrhage of the aortic wall caused by rupture of the vasa vasorum within the aortic wall and may cause secondary dissection, whereas **PAU** is a focal defect in the endoluminal surface of the aortic wall produced by atherosclerotic erosion through the intima with ulceration into the media. The natural history of IMH is like that of classic aortic dissection. In fact, in 4% to 10% of dissections, an intimal tear is not found. Therefore, **it is reasonable to treat IMH similarly to de facto aortic dissection including emergency surgery if located in the ascending aorta (type A IMH) or aggressive medical therapy if uncomplicated and in the descending aorta (type B IMH)** (COR/LOE: 1 B-NR).
    a. Modifiable risk factors for thoracic aortic aneurysm (TAA)/dissection include hypertension, hypercholesterolemia, and smoking. Younger patients suffering aortic dissection are more likely to have syndromic or nonsyndromic heritable thoracic aortic disease (HTAD) or congenital conditions such as bicuspid aortic valve (BAV) or coarctation of the aorta versus sporadic aneurysms with no obvious heritable or syndromic cause. Other, more rare causes include infectious or inflammatory aortitis as well as traumatic aortic injury. Pregnant patient with aortic disease or risk factors for aortic

disease is another important consideration, though will not be covered in the current chapter. The following list includes the most common conditions associated with aortic aneurysm and dissection:

b. Increased age and uncontrolled hypertension are the two most common risk factors. Other modifiable risk factors include tobacco use, dyslipidemia, and cocaine use.

c. Syndromic and nonsyndromic HTAD. **These patients require comprehensive aortic imaging at diagnosis and heightened surveillance to follow aortic diameter due to the increased risk of complications related to aortic disease**. Genetic testing often in addition to aortic imaging is recommended for at-risk relatives of patients with HTAD (LOE: 1 B-NR). In patients with no family history of aortic disease and no disease-causing variant identified, screening of first-degree family members is still recommended (COR/LOE: 1 C-LD).

(1) Marfan syndrome. Autosomal dominant genetically mediated connective tissue disorder with high penetrance and variable expressivity. Marfan syndrome is associated with mutations of the *FBN1* gene, which encodes fibrillin-1, a large glycoprotein that contributes to the structure of the extracellular matrix and serves as a regulator of transforming growth factor-beta (TGF-β). The principal manifestations of Marfan syndrome are cardiovascular, ocular, and skeletal. These patients are at exceedingly high risk for aortic disease. In fact, nearly all patients with Marfan syndrome demonstrate some form of aortic disease during their lifetime.

(2) Loeys-Dietz syndrome. Autosomal dominant genetically mediated connective tissue disorder associated with mutations in TGFBR1, TGFBR2, TGFB2, TGFB3, or SMAD3. Patients with Loeys-Dietz classically have a triad of arterial tortuosity/aneurysm, hypertelorism, and bifid uvula. Aggressive arterial aneurysms are highly prevalent and portend a grim prognosis. Specific gene mutations

may correlate with earlier onset and severity of disease and, in turn, dictate the threshold to perform elective aortic repair.

(3) **Ehlers-Danlos syndrome, type IV (vascular type).** The vascular form of Ehlers-Danlos syndrome is characterized by an autosomal dominant inheritance of the *COL3A1* gene mutation that encodes type III procollagen. Clinical features include easy bruising, visceral organ rupture, and arterial dissection. Median survival is 50 years, with slightly lower survival for males as compared to females. Gravid women with this condition may have a poor prognosis due to the risk of arterial and uterine rupture associated with labor and delivery.

(4) **Nonsyndromic HTAD.** A significant number of patients presenting with aortic aneurysms and dissection have a family history of aortic disease in the absence of clinical features of Marfan or Loeys-Dietz syndrome. Multiple genetic mutations associated with TAA and dissection have been identified, the most common of which include ACTA2, MYH11, MYLK, and PRKG1. These disorders are typically inherited in an autosomal dominant manner.

d. Congenital conditions such as BAV and coarctation of the aorta are also established risk factors for aortic dissection. Turner syndrome is associated with BAV (15%-30%), aortic coarctation (7%-18%), and dilation of the ascending aorta (33%). Patients with Turner syndrome require screening for aortic disease and other associated congenital anomalies at diagnosis (COR/LOE: 1 B-NR). Risk factors for dissection and aortic size index (ASI) inform risk and dictate the frequency of surveillance. Patients with BAV should undergo transthoracic echocardiography (TTE) to assess valve morphology/function, aortic root and ascending aortic size, presence of coarctation, or other associated defects (LOE 1 B-NR). Screening of first-degree relatives of patients with BAV is reasonable to evaluate for BAV and/or aortic disease (LOE: 2a B-NR).

e. Less common conditions associated with TAD

(1) Vasculitides associated with large-vessel inflammation and aortitis contribute to medial degeneration of the aortic wall and may increase the risk of aortic dissection. Examples of these inflammatory disorders include giant cell arteritis, Takayasu arteritis, and Behçet disease. Syphilis represents a classic etiology of infectious aortitis.

(2) Aortic dissection exhibits a strong association with pregnancy in patients with predisposition or underlying aortopathy. Most dissections occur during the third trimester or in the early postpartum period. **Gravid women with HTAD and preexisting aortic root dilatation are at especially high risk for aortic complications**. Genetic mutation, aortic size, and risk factors for dissection dictate the threshold to undergo aortic surgery prior to pregnancy.

(3) Direct aortic trauma is associated with aortic dissection: Blunt chest trauma, such as that occurring in a motor vehicle accident, may cause aortic dissection, IMH, or aortic rupture. Iatrogenic injury during arterial catheterization, intra-aortic balloon pump insertion, aortic cannulation, cross-clamping, or graft insertion may also serve as a source of intimal damage and dissection.

(4) Multiple population-based studies have shown an association with **fluoroquinolone** use and aortic aneurysm and dissection, though no randomized data exist on this topic. As such, it may be reasonable to avoid these medications in patients with aortopathy or those with risk factors for aortic aneurysm or dissection.

B. Epidemiology. The incidence of aortic dissection has been estimated from 2 to 3.5 cases per 10,000 person-years, corresponding to 6,000 to 10,000 cases per year in the United States. The male-to-female ratio approaches 3:1, with the peak incidence in the sixth and seventh decades of life. The mortality for untreated acute aortic dissection is largely determined by the location of the dissection, but overall

mortality in type A dissection is approximately 1% per hour within the first 48 hours if surgery is not performed. Approximately 65% of dissections originate in the ascending aorta, 20% in the descending thoracic aorta, 10% in the aortic arch, and the remainder in the abdominal aorta.

C. Classification schemes

1. **Anatomic classification schemes** used to commonly describe aortic dissection include the DeBakey and Stanford systems. Anatomic classification refers to the portion(s) of the aorta involved. A newer classification schema published by the Society of Thoracic Surgeons (STS) and Society for Vascular Surgery (SVS) classifies dissections by site of intimal tear and the proximal and distal extent of the dissection (**Figures 27.2** and **27.3**). The Stanford classification is used throughout this chapter.

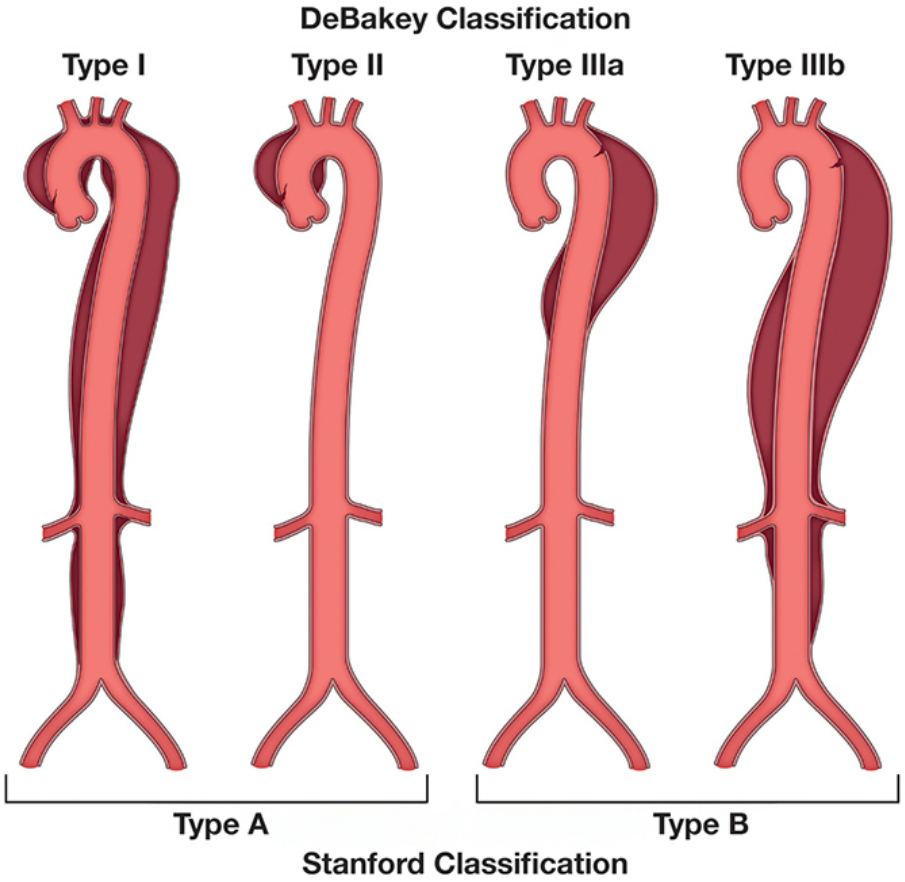
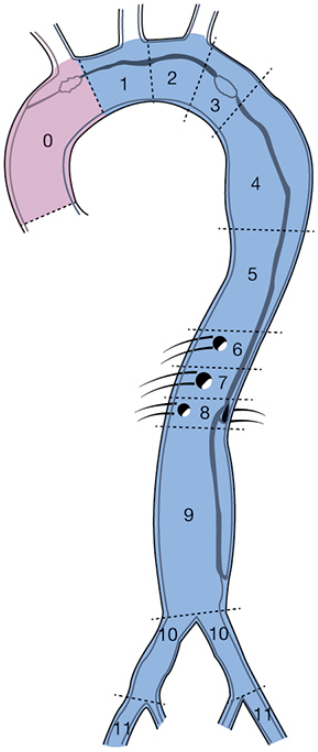


FIGURE 27.2 Stanford and DeBakey classification of aortic dissection. The DeBakey and Stanford classification systems are used most commonly. The DeBakey system offers greater anatomic detail, whereas the Stanford system is more simple, essentially distinguishing those dissections that involve the ascending thoracic aorta from those that do not. (Reprinted with permission from Isselbacher EM, Preventza O, Black JH, et al. ACC/AHA guidelines for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:e334-e482. Copyright © 2022 American Heart Association.)



Type	Proximal Extent	Distal Extent
A_D Entry tear: **Zone 0**	0	0
	1	1
	2	2
	3	3
B_{PD} Entry tear: **≥Zone 1**	4	4
	5	5
	6	6
	7	7
	8	8
I_D Unidentified entry tear involving **Zone 0**	9	9
	10	10
	11	11
	12	12

FIGURE 27.3 Anatomic reporting of aortic dissection based on the 2020 Society for Vascular Surgery/Society of Thoracic Surgeons reporting standards. (Reproduced from Lombardi JV, Hughes GC, Appoo JJ, et al. Society for Vascular Surgery (SVS) and Society of Thoracic Surgeons (STS) reporting standards for type B aortic dissections. *J Vasc Surg*. 2020;71:723-747.)

2. Dissections are further classified according to time from symptom onset: hyperacute (<24 hours), acute (1-14 days), subacute (15-90 days), and chronic (>90 days). Involvement and chronicity of

dissection influence the recommended treatment approach and influence prognosis.

D. Clinical presentation

1. Aortic dissection may present with a wide range of clinical manifestations. Type A dissections are most commonly characterized by a sudden onset of chest pain that is severe in intensity and described as ripping, tearing, stabbing, or sharp in quality. Pain may radiate to the interscapular region of the back or abdomen. Among descending aortic dissections, back pain, chest pain, and abdominal pain are most common. **Additional or atypical symptoms may suggest branch vessel involvement or malperfusion syndromes**.
2. Clinical findings often reflect malperfusion syndromes, and patients may present with the murmur of severe aortic regurgitation (AR), acute heart failure, cardiac tamponade, myocardial infarction (MI), cerebrovascular accident (CVA), paraplegia, oliguria, acute limb ischemia, mesenteric ischemia, or cardiac arrest. Potentially, catastrophic complications of aortic dissection are presented in **Figure 27.4**.

E. Diagnostic testing

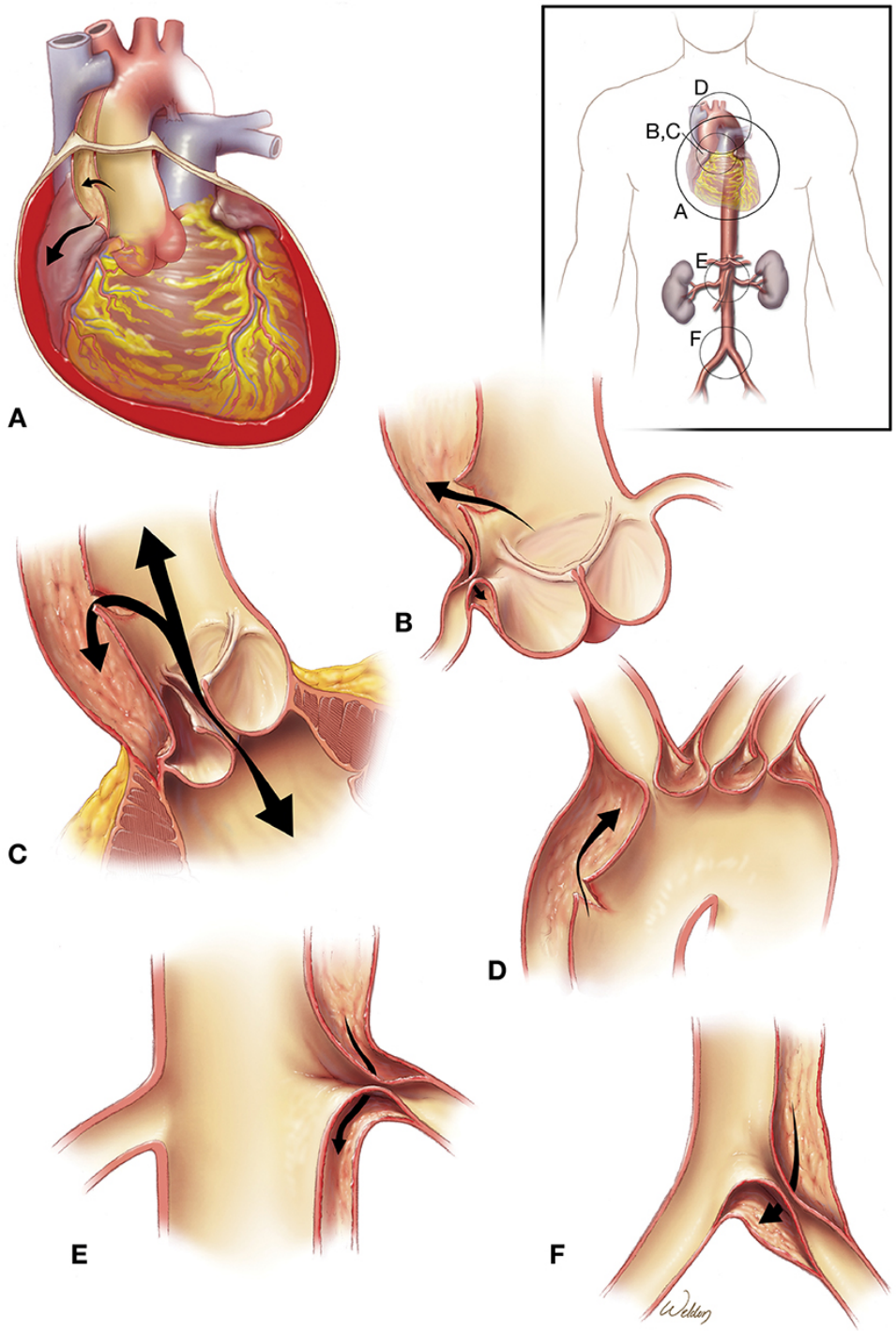


FIGURE 27.4 Potential catastrophic consequences of acute aortic dissection. **A.** Cardiac tamponade and rupture of the ascending aorta. **B.** Malperfusion of the coronary arteries. **C.** Acute aortic valve regurgitation. Compromised blood flow to the (**D**) brachiocephalic, (**E**) renal, and (**F**) iliac arteries. Inset: Malperfusion and other events may affect several anatomic regions. (Reprinted by permission from Springer, Le Huu A, Parikh UM, Coselli JS. Acute type A aortic

dissection. In: Raja S, eds. *Cardiac Surgery*. Springer; 2020:475-486. Used with permission of Baylor College of Medicine.)

1. **Evaluation.** In the setting of aortic dissection, the location and extent of the dissection and the presence or absence of malperfusion often dictate the type and rapidity of intervention. Computed tomography (CT) is the preferred imaging modality for diagnosis, though transesophageal echocardiography (TEE) and magnetic resonance imaging (MRI) are reasonable alternatives depending on availability, local expertise, and patient stability. Invasive aortography has largely been replaced by the aforementioned imaging modalities. The relative advantages and disadvantages of the four modalities are outlined in **Table 27.1**. **CT is recommended as the initial imaging modality for patients with suspected acute aortic syndromes (LOE: 1 C-LD). TEE and MRI are reasonable alternatives depending on patient stability and local availability and expertise (LOE: 2a C-LD)**.

TABLE 27.1 Diagnostic Performance of Aortic Imaging Modalities

Parameter	CT	MRI	TTE	TEE	US
Availability	+++	++	+++	++	+++
Portability	−	−	+++	+++	+++
Speed of acquisition	+++	+	++	++	++
Spatial resolution	+++	++	++	+++	++
Temporal resolution	+	++	+++	+++	+++
Three-dimensional data set	+++	++	+	+	+
Arch branch vessel evaluation	+++	+++	++	+	NA
Evaluation of valve and ventricular function	+	++	+++	+++	NA

CT, indicates computed tomography; MRI, magnetic resonance imaging; NA, not applicable; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; US, ultrasound; +++, excellent results; ++, good results; +, fair results; and −, not available.

Reprinted with permission from Isselbacher EM, Preventza O, Black JH, et al. ACC/AHA guidelines for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:e334-e482. Copyright © 2022 American Heart Association.

2. Chest radiography may occasionally detect findings suggestive of dissection, although it is neither sensitive nor specific to diagnose acute aortic dissection. A negative chest x-ray should not delay definitive aortic imaging in patients determined to be at high risk for aortic dissection by initial screening.

F. Selected imaging modalities for diagnosis of acute aortic dissection

1. **CT.** Contrast-enhanced, electrocardiogram (ECG)-gated multidetector CT angiography is a widely available and the most used imaging modality for the detection of aortic dissection, with excellent sensitivity and specificity approaching 100%. This modality has many advantages, including rapid scanning times, superior spatial resolution, and creation of a three-dimensional (3D) data set. Disadvantages include iodinated contrast and radiation exposure.
2. **MRI and magnetic resonance angiography (MRA).** Like CT, MRI provides multiplanar imaging of the thoracic aorta with high sensitivity and specificity that is very accurate for the diagnosis of acute aortic disease. MRA offers unique gadolinium-enhanced and black blood imaging techniques to evaluate aortic anatomy and morphology that prove particularly useful in assessing the aortic wall. MRI can also provide useful information on valvular and ventricular function while avoiding exposure to iodinated contrast or radiation. MRI is well suited for chronic follow-up of aortic syndromes because ionizing radiation is not necessary. The use of MRI is limited by availability, prolonged acquisition time, and artifacts created by implanted ferromagnetic devices. MRI is not an appropriate test for patients who are hemodynamically unstable.
3. **TTE and TEE.** TTE allows for a rapid noninvasive evaluation, primarily of the proximal aorta with overall limited sensitivity and

specificity. Visualization of the proximal aorta and other critical structures using TTE may be limited by factors that reduce image quality, such as emphysema, mechanical ventilation, and obesity. TEE overcomes many of the challenges with surface imaging, with improved sensitivity and specificity while offering a safe and rapid assessment of acute aortic disease. A major limitation of either TTE or TEE includes the appearance of ultrasound (US) artifacts that may mimic a dissection flap, such as that of reverberation artifact. In addition, TEE is often unable to reliably see the distal ascending aorta due to the overlying air-filled trachea.

4. **Invasive aortography.** Aortography offers accurate information about the location of dissection, providing visualization of the false lumen or intimal flap, branch vessel involvement, and communication between true and false lumens. Disadvantages of aortography include the invasive nature of the procedure, low sensitivity, need for iodinated contrast administration, and availability of experienced operators to perform the study. This has largely been replaced by the imaging modalities listed above, though becomes relevant when aortic dissection presents as acute coronary syndrome (ACS) and the patient has been triaged to the catheterization lab or during endovascular stent placement.
5. **Recommendations for aortic imaging techniques to determine the presence and progression of thoracic aortic disease (Figure 27.5)**

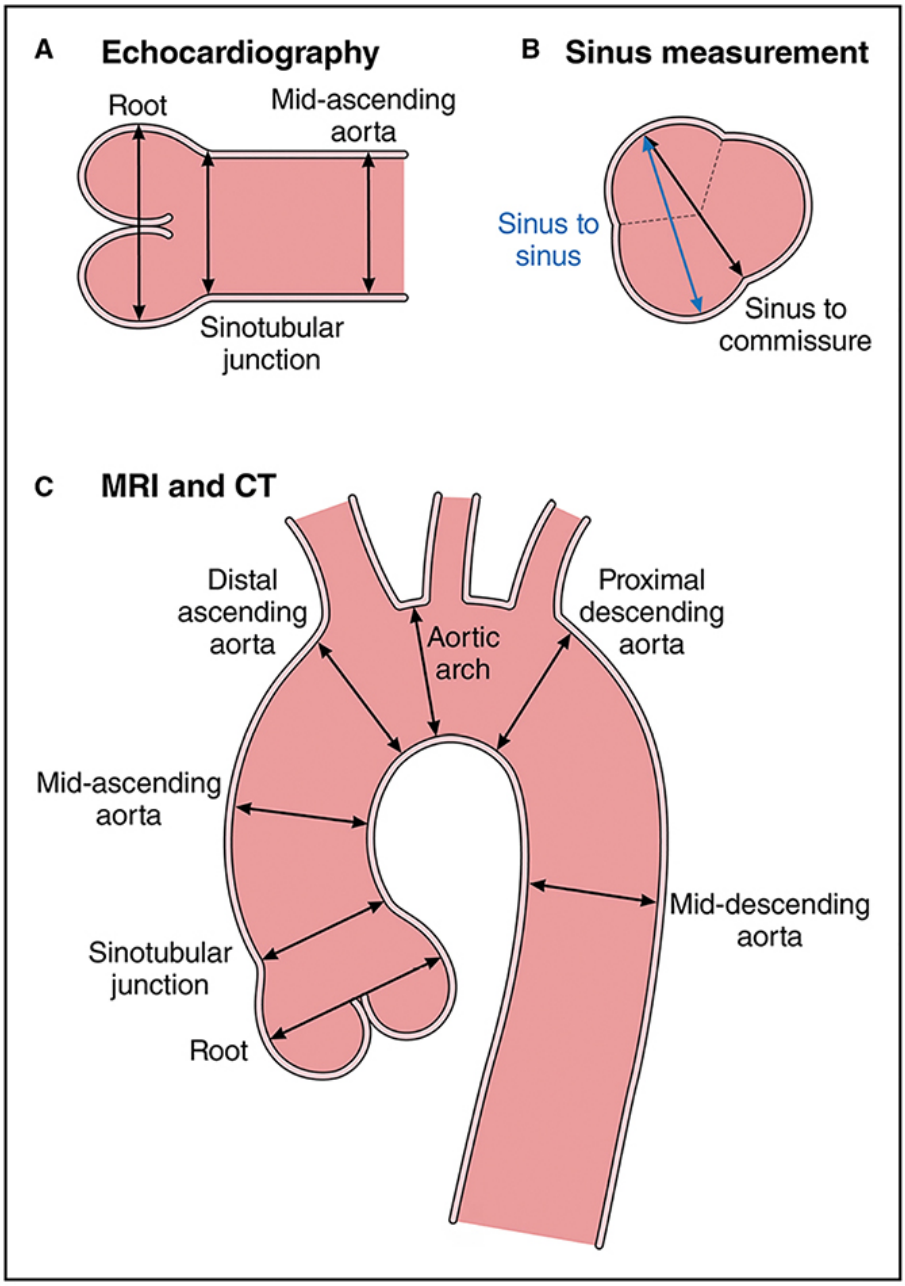


FIGURE 27.5 Aortic imaging techniques to determine the presence and progression of aortic disease. **A**. Leading-edge to leading-edge measurement technique used in echocardiography, from left to right: measurement of the aortic root (sinuses of Valsalva), sinotubular junction, and proximal tubular ascending aorta. **B**. Inner-wall to inner-wall measurements of the aortic root used in MRI and CT. The sinus-to-commissure and sinus-to-sinus measurements can both be used. **C**. Standard measurement locations for MRI and CT with the inner-wall to inner-wall technique. CT, computed tomography; MRI, magnetic resonance imaging. (Reprinted from Borger MA, Fedak

PWM, Stephens EH, et al. The American Association for thoracic surgery consensus guidelines on bicuspid aortic valve-related aortopathy: full online-only version. *J Thorac Cardiovasc Surg*. 2018;156:e41-e74, with permission from Elsevier.)

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a. Measurements of aortic diameter should be taken at reproducible anatomic landmarks, perpendicular to the axis of blood flow, and reported in a clear and consistent format (LOE: 1 B-NR).

b. For measurements taken by CT or MRI, the root and ascending aortic diameters should be measured from inner edge to inner edge using an ECG-synchronized technique. If aortic wall abnormalities are present, the outer edge to outer edge technique should be used. Aortic root diameter should be measured from sinus-sinus. In the presence of root asymmetry, multiple measurements should be reported (LOE: 1 C-EO).

c. In patients with known or suspected aortic disease, it is reasonable to index aortic measurements to patient height or body surface area (BSA) to aid in risk assessment (LOE: 2A C-LD).

d. In patients with known or suspected aortic disease, ionizing radiation doses should be kept as low as feasible while maintaining diagnostic quality (LOE: 1 C-LD).

e. For measurements taken by echocardiography, it is reasonable to measure the aorta from leading edge to leading edge, perpendicular to the axis of blood flow (LOE: 2A C-EO). Inner-edge to inner-edge measurements may be used if imaging in the short axis (LOE: 2B C-EO).

G. Therapy. Death in aortic dissection results from acute heart failure from acute aortic valve regurgitation, vascular compromise, cardiac tamponade, or aortic rupture. **Management of type A aortic dissection requires immediate surgical consultation and intervention (LOE: 1 B-NR)**. Surgery greatly improves outcomes and avoids the risks associated with progression of dissection. One- and 3-year survival after surgery for type A dissection is excellent,

with survival rates of 96.1% and 90.5%, respectively. Survival rates at 1 and 3 years are 88.6% and 68.7%, respectively, among those who do not receive surgery for type A dissection. **Patients with type B dissections should be managed medically as an initial strategy (LOE: 1 B-NR) unless complicated by aortic rupture, malperfusion, extension of dissection, aortic enlargement, intractable pain, or uncontrolled hypertension in which case intervention is recommended (LOE: 1 C-LD). Thoracic endovascular aortic repair (TEVAR)** is a technically feasible and effective option for nonsurgical treatment of type B aortic dissection that has decreased morbidity and mortality. **Figure 27.6** displays the course of treatment for various types of dissections if malperfusion is present.

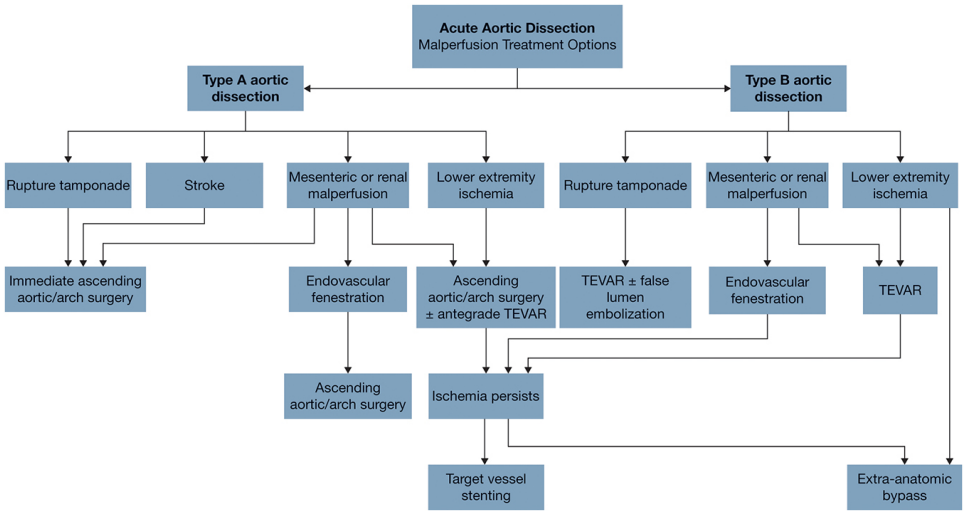

FIGURE 27.6 Acute aortic dissection: malperfusion treatment options. TEVAR, thoracic endovascular aortic repair. (Reprinted with permission from Isselbacher EM, Preventza O, Black JH, et al. ACC/AHA guidelines for the diagnosis and management of aortic disease: a report of the American Heart Association/American College of Cardiology Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;146:e334-e482. Copyright © 2022 American Heart Association.)

1. **Priority of therapy.** The initial management of patients with suspected aortic dissection is directed at **reducing aortic wall stress. Aortic wall stress is affected by the velocity of**

ventricular contraction (dP/dt), the rate of ventricular contraction, and BP. Medical stabilization of acute aortic dissection should target the reduction of heart rate followed by lowering of BP. Invasive hemodynamic monitoring and sufficient intravenous access for volume replacement should also be established simultaneously. An initial and aggressive treatment approach to reduce d*P*/d*t*, also known as impulse control, applies to all patients, regardless of the location of dissection or whether the eventual management strategy is medical or surgical. Caution should be exercised with aggressive rate control in the context of cardiac tamponade and acute AR. Impulse control is a critical management step because patients with aortic dissection often present and are diagnosed at smaller centers necessitating transfers to tertiary centers with expertise in aortic surgery.

2. **Medical therapy** (**Table 27.2**)

TABLE 27.2 Intravenous Dosing for Acute Medical Management of Acute Aortic Syndromes

Drugs	Loading Dose	Maintenance Dose
First-Line Agents		
Propranolol	1 mg IV q3-5 min (max 6.15 mg/kg)	2-6 mg IV q4-6h
Labetalol	10 mg IV over 2 min, then 20-80 mg q10-15 min (max 300 mg)	2 mg/min IV drip titrate to 5-20 mg/min
Esmolol	500 mcg/kg IV bolus	50-200 mcg/kg/min IV continuous
Metoprolol	5 mg IV q5 min to effect	5-10 mg IV q4-6h to effect
Second-Line Agents in Patients With Contraindications for Beta-Blockers		
Enalaprilat	0.625 mg IV	0.625 mg IV q4-6h
Diltiazem	0.25 mg/kg IV over 2 min; 0.35 mg/kg IV after 15 min if no effect	5 mg/h titrate by 2.5-5 mg/h increments; max 15 mg/h
Verapamil	0.075-0.1 mg/kg to 2.5-5 mg/kg over 2 min	5-15 mg/h IV drip

IV, intravenous; q, every.

a. **With suspicion of acute aortic dissection, anti-impulse therapy should be initiated, with invasive BP monitoring and in an intensive care unit (ICU) setting** (LOE: 1 B2-NR).

b. **Intravenous beta-blockers should be used as initial management (LOE: 1 C-LD) to target a heart rate of 60 to 80 beats/min and systolic BP of <120 mm Hg (COR/LOE: 1 B-NR).** In patients who are intolerant of beta-blockers, nondihydropyridine calcium channel blockers may serve as an acceptable alternative to control heart rate (see **Table 27.2**) (COR/LOE: 2a B-NR). In the setting of acute AR or cardiac tamponade, the use of rate-controlling agents, such as beta-blockers, should be used with caution because they block compensatory tachycardia.

c. If BP is not well controlled by intravenous beta-blockade, intravenous vasodilators should be used as an adjunctive therapy to achieve target BP (COR/LOE: 1 C-LD). In addition, pain should be promptly treated as this may assist with hemodynamic management (COR/LOE: 1 C-EO). Typical beta-blockers used in the management of acute aortic dissection include esmolol, metoprolol, and labetalol. Typical vasodilators include sodium nitroprusside, nicardipine, and clevidipine.

3. **Managing complications of acute aortic dissection**

a. **Aortic rupture, cardiac tamponade, and acute severe AR** may manifest as **hypotension and/or shock**. In the first two scenarios, **aggressive volume replacement should be initiated, and the patient taken to the operating room promptly**. Pericardiocentesis is generally not recommended. If pericardiocentesis becomes an absolute requirement to get the patient to the operating room, enough pericardial fluid should be removed to raise the BP to an acceptable level, but no more. **If vasopressors are required for hemodynamic stabilization, norepinephrine and phenylephrine are the drugs of choice,**

as neither has a demonstrable effect on dP/dt. Epinephrine and dopamine should be avoided. In the context of acute severe AR, balancing heart rate control and aggressive lowering of BP should be performed to maintain perfusion. In addition, respiratory support and diuretics may be required if acute pulmonary edema has developed. These therapies should be initiated en route to the operating room for definitive repair.

b. **Acute MI.** Coronary thromboembolism and retrograde progression of the aortic dissection flap into the coronary ostia are infrequent complications of type A dissection. In this setting, **thrombolysis is contraindicated**. Coronary angiography and percutaneous intervention are not recommended as these procedures **delay surgical repair of the dissection and do not address the underlying pathology**.

c. **Cerebral or visceral malperfusion.** Malperfusion can occur in essentially any branch vessel of the aorta. Malperfusion may present with focal neurologic symptoms (head vessel involvement), cold limbs with reduced pulses (upper or lower extremity vessel involvement), oliguria/anuria or acute kidney injury (AKI) (renal involvement), and abdominal pain or distension (mesenteric involvement). **In the presence of malperfusion syndromes, immediate operative repair of the ascending aorta in type A dissection (COR/LOE: 1 B-NR) and urgent or immediate TEVAR in type B dissection (COR/LOE: 1 C-LD) should be pursued**.

4. **Surgical/endovascular management of acute aortic dissection**

a. Patients with a type A aortic dissection should receive emergent surgery. A partially dissected aortic root with a normal aortic valve should be repaired with aortic valve resuspension over valve replacement (COR/LOE: 1 B-NR). In the presence of extensive root destruction, root aneurysm, or known genetic aortopathy, root replacement with a valve conduit is recommended (COR/LOE: 1 B-NR), though in select patients who are stable, valve-sparing root replacement (VSRR) may be a reasonable alternative if performed by an experienced

operator (COR/LOE: 2b C-LD). Placement of an open distal anastomosis is recommended to improve survival and increase false-lumen thrombosis (COR/LOE: 1 B-NR). Hemiarch repair is recommended over arch replacement in the absence of an intimal tear in the arch or significant arch aneurysm (COR/LOE: 1 B-NR). Extended aortic repair for patients with dissection extending through the arch and into the descending aorta with antegrade stenting of the proximal descending aorta may be considered to treat malperfusion and decrease late distal aortic complications (COR/LOE: 2b C-LD).

b. In patients with type B dissection who have evidence of rupture or other complications, intervention should be performed (COR/LOE: 1 C-LD). Assuming suitable anatomy, endovascular stenting rather than surgery is recommended for rupture (COR/LOE: 1 C-EO) and is reasonable in patients with complications other than rupture.

c. Perioperative risk. Compared with unstable patients with aortic dissection, those demonstrating preoperative stability have an improved prognosis. Surgical mortality associated with type A dissection is approximately 18%, though malperfusion, myocardial ischemia, tamponade, and shock significantly increase this figure. Even though age is an independent risk factor, data support that older patients still benefit from surgery as compared to medical therapy.

d. Postsurgical complications of open thoracic surgical repair include respiratory failure (5%-15%), stroke (2%-8%), bleeding requiring reoperation (1%-6%), infection (1%-5%), MI (1%-5%), heart failure (1%-5%), ventricular arrhythmias (1%-5%), acute postoperative renal failure, paraplegia (2%-10%), and mesenteric ischemia.

(1) Perfusion and cannulation strategies such as axillary cannulation over femoral when feasible and maintenance of cerebral perfusion when circulatory arrest is required are recommended to reduce the risk of stroke and improve neurologic outcomes (COR/LOE: 2a B-NR).

(2) Paraplegia is among the most feared complications of descending thoracic and thoracoabdominal aortic repairs, occurring in 2% to 4% and 3% to 10% of cases, respectively. Paraplegia results from the disruption of blood flow to the anterior spinal artery via the intercostal arteries. Cerebrospinal fluid drainage is recommended as a spinal-protective strategy in open and endovascular thoracic aortic repair for patients at high risk for spinal cord ischemic injury (COR/LOE: 1 A).

5. **TEVAR for type B aortic dissection.** TEVAR represents an effective option for nonsurgical treatment of type B aortic dissection, IMH, PAU, acute traumatic aortic injury, and pseudoaneurysm.

   a. **Potential advantages of TEVAR** over conventional surgery result from the fact that it is minimally invasive avoiding the need for thoracotomy, cardiopulmonary bypass, and aortic cross-clamping. Retrospective data would suggest lower morbidity and mortality associated with TEVAR, though surgery versus endovascular therapies have never been compared in randomized trials.

   b. **Comparing TEVAR with optimal medical management (OMM).** Although OMM remains the mainstay for acute treatment of uncomplicated type B dissection, long-term morbidity and mortality of chronic dissection remain substantial. The prospective INvestigation of STEnt grafts in patients with type B aortic dissection (INSTEAD and INSTEAD XL) trials provided the first randomized evaluation of elective stent graft placement in 140 patients with subacute or chronic uncomplicated type B aortic dissection. At 5 years, the TEVAR group had lower aorta-specific mortality and less disease progression. In addition, the ADSORB trial compared OMM to OMM plus TEVAR in type B dissection, with significant differences favoring TEVAR in the primary end points of false-lumen patency, aortic dilation, and rupture. The VIRTUE and RESTORE patient registries suggest benefit to

early intervention, though with high rates or reintervention. The optimal timing of intervention in uncomplicated type B dissection remains unclear.

6. Postoperative surveillance after thoracic aortic repair or monitoring of chronic descending aortic dissection

a. Following aortic dissection/IMH treated with open or endovascular aortic repair, if residual aortic disease remains, surveillance imaging utilizing CT (or MRI) is recommended at 1, 6, and 12 months, and annually thereafter if stable (COR/LOE: 1 B-NR).

b. If aortic dissection/IMH is treated medically, surveillance imaging with CT (or MRI) is recommended at 1, 3, 6, and 12 months after dissection, and annually thereafter (COR/LOE: 1 B-NR).

c. For patients with residual chronic dissection and an aortic diameter of ≥5.5 cm, thoracic aortic repair is recommended (COR/LOE: 1 B-NR). This recommendation may be modified in patients with an underlying genetic aortopathy.

d. Long-term, aggressive cardiovascular risk factor management is critical before and after thoracic aortic surgery and includes aggressive BP and cholesterol control as well as smoking cessation.

III. AORTIC ANEURYSM. An aortic aneurysm is a pathologic dilatation of the aorta to >1.5 times its normal diameter. Normal aortic diameter varies by age, sex, and imaging modality and increases with age and BSA. Aneurysms are classified based on the anatomic location and aortic segments. Most simply, there are abdominal aortic aneurysms (AAAs) and TAAs. The etiology, natural history, and treatments differ for aneurysms of each location.

A. Abdominal aortic diameter >3.0 cm

1. Etiology and pathology of aortic aneurysm

a. Aneurysms of the aorta are caused by degenerative disease within the aortic wall, leading to inflammation, weakening

of the aortic tissues, loss of elasticity, and dilatation of the aorta.

b. Risk factors for the development of AAA include current or past history of tobacco use, male gender, advanced age, family history of AAA, hypertension, hyperlipidemia, and atherosclerosis. Less common causes include infection (*Salmonella* and *Staphylococcus aureus*), *vasculitis*, and trauma.

2. Clinical presentation

a. Signs and symptoms. AAA develops gradually over years rarely causing any symptoms. Most AAAs are discovered incidentally on physical examination. Most patients are asymptomatic; therefore, the diagnosis of AAA should be considered in patients with an appropriate risk profile and family history.

(1) Rapid enlargement of the aneurysm may be associated with severe back or flank pain and herald impending rupture. Pain associated with an expanding AAA is described as sudden onset, constant, and not affected by movement or position. Occasionally, there is radiation to the legs, buttocks, groin, or testicles.

(2) Findings consistent with shock (hypotension, pallor, diaphoresis, oliguria, and obtundation) can develop rapidly with a ruptured aneurysm.

b. Physical findings

(1) Physical examination is unreliable for accurate sizing of AAAs.

(2) A palpable, pulsatile mass may be felt on abdominal examination in a minority of subjects.

(3) Associated vascular disease is common among those with AAA, and occasionally, abdominal or femoral bruits or decreased pulses in the extremities may be felt.

3. Diagnostic testing

a. **Abdominal US** is the most used screening tool for AAA. US has the capacity to obtain both longitudinal and transverse images of the aneurysm and has been validated to accurately measure size to within ±0.3 cm. **Major advantages of US include its wide availability, cost-effectiveness as a diagnostic and screening imaging technique, and avoidance of ionizing radiation**. If imaging is adequate, US is an effective option when monitoring aneurysm growth serially. Disadvantages of abdominal US include poor definition of branch vessels; therefore, US is insufficient for preoperative evaluation.

b. **CT angiography** allows for accurate evaluation of the aneurysm shape and size as well as branch vessel anatomy. CT measurements have been validated to within ±0.2 cm. CT offers the advantage of evaluating for extravasated blood in acute or subacute rupture. The major disadvantages of CT include the requirement for ionizing radiation and iodinated contrast.

c. **MRI** provides excellent definition of aneurysm size as well as suprarenal and iliofemoral extension. MRA allows for improved visualization of compromised flow to branch vessels, although it lacks sensitivity to absolutely define obstruction in the renal vessels. MRI is disadvantaged by cost and limited availability.

d. **Aortography** effectively defines both suprarenal and iliofemoral involvement as well as branch vessel impingement, although it tends to underestimate aortic size, especially when mural thrombus is present. Compared with other techniques, aortography is invasive and requires the use of intravenous contrast and ionizing radiation. Aortography is now generally reserved for planning endografting in some centers and is less useful as an initial diagnostic modality.

4. Therapy

a. Medical therapy and surveillance

(1) Aggressive risk factor modification with control of hypertension, hypercholesterolemia, and smoking cessation is **imperative to prevent adverse events from atherosclerotic disease in other vascular beds**.

(2) Statin use in patients with AAA and aortic atherosclerosis is recommended (COR/LOE: 1 B-NR), in addition to smoking cessation (COR/LOE: 1 C-LD). The use of low-dose aspirin can be considered (COR/LOE: 2b C-LD).

b. Multidisciplinary guidelines recommend surveillance every 6 months using US for aneurysms ≥5 cm in men and ≥4.5 cm in women to assess for change. Annual surveillance with US is recommended at 4.0 to 4.9 cm in men and 4.0 to 4.4 cm in women, while imaging every 3 years is recommended for both genders with an aortic diameter of 3.0 to 3.9 cm (COR/LOE: 1 B-NR). If US interrogation is not adequate, CT is recommended.

c. Aortic repair. The risk for aortic rupture or dissection increases with the size of the aneurysm. Aortic repair is **indicated for an aneurysm with diameter measuring ≥5.5 cm in men or ≥5.0 cm in women** (COR/LOE: 1 A). Symptomatic patients should also be referred for repair, irrespective of the size of the aneurysm (COR/LOE: 2b C-LD).

d. Aneurysm can be potentially repaired via open surgical or the less invasive endovascular approach.

e. Endovascular aneurysm repair (EVAR) is a less invasive option for the repair of AAA and is especially appealing for older patients or those with the highest perioperative risk.

(1) **The EVAR procedure.** Under fluoroscopic guidance, the proximal and distal ends of the stent graft are affixed to normal segments of the aorta above and below the aneurysmal portion, thereby sealing off the aneurysm. **Suitable anatomy is necessary for stent grafting**. Favorable characteristics for EVAR include normal aortic diameter proximal to the aneurysmal segment and distal to the renal arteries, minimal angulation, freedom from

severe obstructive lesions, and patency of side branch and distal iliac vessels. Operative mortality for elective EVAR is low (1%-2%). In the acute setting, EVAR should be performed over open repair (assuming suitable anatomy) for ruptured AAA (COR/LOE: 1 B-R).

(2) **Comparing EVAR with open surgical repair.** Multiple randomized controlled trials have compared endovascular repair with open surgical repair. The totality of data suggests that EVAR is associated with lower short-term mortality than open repair. However, individuals undergoing EVAR after approximately 8 years have higher rates of reintervention, aneurysm-related death, and rupture. In nonruptured AAA and high perioperative risk, EVAR is reasonable to reduce short-term morbidity and mortality (COR/LOE: 2a B-NR).

(3) **EVAR among unsuitable surgical candidates.** Compassionate use of EVAR among patients for whom open repair is deemed too high risk because of medical comorbidities was studied in the Endovascular Aneurysm Repair 2 (EVAR-2) trial. This study failed to show any early survival benefit with endovascular repair, though, at roughly 10 years follow-up, patients undergoing endovascular repair had lower aneurysm-related mortality.

(4) **Endoleak as a complication of EVAR.** One of the common complications of endovascular repair is endoleak. Endoleak represents a failure of the stent graft to completely exclude the aneurysm and results in persistent flow into the aneurysm, thereby increasing the risk of aneurysm expansion and rupture. Endoleaks occur in 10% to 20% of cases and are associated with more frequent reinterventions than open repair and require active surveillance (**Figure 27.7**).

(5) **Other complications related to EVAR** include endograft migration, prosthesis infection, vascular access site-related

infections, bleeding, thromboembolism, and spinal cord ischemia with paraplegia.

(6) In patients with AAA who have undergone EVAR, baseline postoperative CT is recommended at 1 month. In the absence of endoleak or aneurysm sac enlargement, duplex US should be performed at 1 year and annually thereafter (COR/LOE: 1 B-NR).

f. Surgical therapy. Surgical repair generally requires resection of the aneurysmal segment, with replacement using a tube graft inserted in place of the diseased aorta. The major branches are then reimplanted to the graft. Operative mortality for elective open repair varies from 1% to 4% depending on the degree of expertise. Given the strong association of coronary artery disease and its association with poor outcomes, preoperative cardiac risk assessment is recommended in patients referred for aortic repair. Current guidelines recommend that in the absence of ACS, severe valvular disease, uncontrolled arrhythmias, and decompensated heart failure, additional noninvasive testing is indicated only if it will change management.

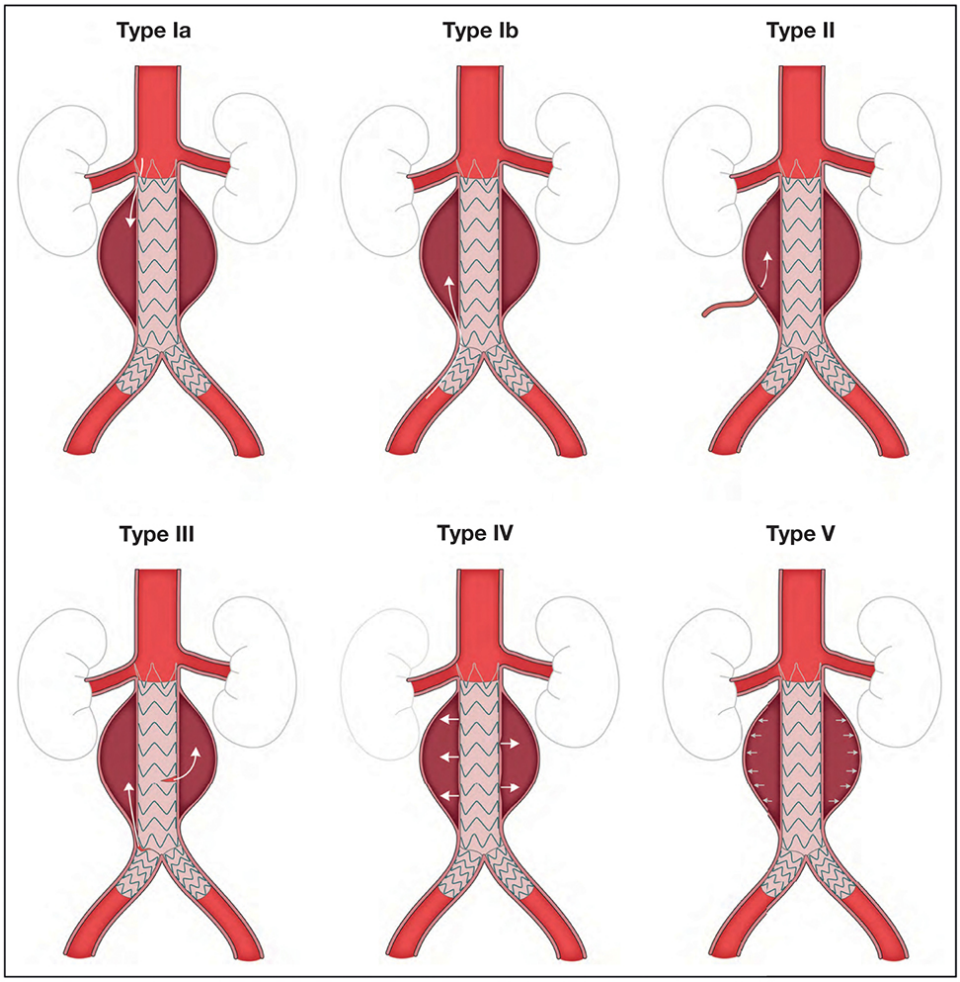

FIGURE 27.7 Endoleaks are classified into five types. Type Ia, proximal attachment site endoleak; type Ib, distal attachment site endoleak; type II, backfilling of the aneurysm sac through branch vessels of the aorta; type III, graft defect or component misalignment; type IV, leakage through the graft wall attributable to endograft porosity; and type V, caused by "endotension," possibly resulting from aortic pressure transmitted through the graft/thrombus to the aneurysm sac. (Adapted from Rokosh RS, Wu WW, Dalman RL, Chaikof EL. Society for Vascular Surgery implementation of clinical practice guidelines for patients with an abdominal aortic aneurysm: endoleak management. *J Vasc Surg*. 2021;74(6):1792-1794. Copyright 2021, with permission from Elsevier, Inc, and the Society for Vascular Surgery.)

B. TAA. TAAs include those that involve the aorta from the level of the aortic root to the diaphragmatic crura.

1. Etiology. The most common cause of TAA formation is medial degeneration, characterized by loss of elastic fibers and smooth

muscle within the aortic media with replacement of tissue with interstitial cysts of basophilic ground substance, leading to a cystic appearance. Various etiologies are similar to those described in the aortic dissection portion of this chapter.

2. **Clinical presentation.** Similar to AAA, most patients with thoracic aneurysms are asymptomatic at the time of diagnosis, and the condition is often discovered as an incidental finding on imaging that has been performed for other indications.

   a. **Signs and symptoms**

      (1) TAAs, although often asymptomatic, can present with **AR in the context of an aortic root aneurysm**. More rarely, compression of nearby structures such as the superior vena cava, esophagus, or trachea can lead to symptoms.

      (2) **Rupture** presents with sudden, severe, sharp chest or back pain. In order of decreasing frequency, TAAs rupture into the left pleural space, the pericardium (presenting as tamponade), and the esophagus (presenting as hematemesis) and are generally fatal.

      (3) **Aortic dissection.** See Section III.

   b. **Physical examination.** Specific physical findings directly attributable to TAA **are usually absent**.

      (1) **Cardiac.** Wide pulse pressure and the diastolic murmur of AR (classically left sternal border with the patient leaning forward at end expiration) may be noted in the setting of aortic root dilation and associated AR.

      (2) **Vascular.** Rarely, a pulsatile mass can be palpated in the suprasternal notch in the setting of ascending aortic or aortic arch aneurysm.

3. **Diagnostic testing.** Unique advantages and disadvantages of each radiographic technique are described in detail in the preceding sections. Imaging modalities for TAA are the same as those used in acute aortic syndromes with some caveats.

   a. **TTE and TEE.** TTE allows accurate measurement and visualization of the aortic root and ascending aorta. In addition,

any associated valvular heart disease may also be interrogated. TEE is not often used solely for aortic measurements, although it can visualize most of the thoracic aorta.

b. **CTA** is the most used modality owing to its excellent spatial resolution and the creation of a 3D data set to better characterize the entire thoracic aorta. ECG gating should be used if the pathology is in the root or ascending aorta. As discussed previously, radiation and iodinated contrast use are its major pitfalls.

c. **MRI and MRA** are also useful for detecting and defining the extent of aneurysmal involvement and allow for evaluation of the entire aorta, branch vessels, aortic valve, and pericardium. This modality is important when trying to limit or avoid radiation in serial follow-up of young or pregnant patients. In addition, valvular and ventricular assessment can be performed if there is concomitant aortic valve disease.

4. **Clinical course and recommendations for repair in asymptomatic TAA**

a. Onset of symptoms may herald a more rapid course and higher risk of rupture. Patients with symptomatic aortic root or ascending aortic aneurysm should undergo surgical repair (COR/LOE: 1 C-LD).

b. Elective surgery should be performed in asymptomatic patients with sporadic TAA **in whom the aortic root or ascending aorta is 5.5 cm or greater** (COR/LOE: 1 B-NR).

c. Interval change or **rapid growth** should also prompt surgical referral. Patients with aneurysm growth of ≥**0.5 cm in 1 year or ≥0.3 cm/y over 2 consecutive years should undergo surgery (COR/LOE: 1 C-LD)**.

d. Patients with sporadic TAA and aortic root or ascending aorta of ≥5.0 cm can be considered for surgery if performed by an **experienced surgeon at an experienced center (COR/LOE: 2a B-NR)**.

e. Patients with an ascending aortic dimension ≥4.5 cm who are undergoing aortic valve surgery (tricuspid aortic valve) replacement of the ascending aorta are reasonable (COR/LOE: 2a B-NR)

f. **For patients with BAV and associated aortopathy, surgery is recommended when the aortic root or ascending aortic diameter is ≥5.5 cm (COR/LOE: 1 B-NR). However, if performed in an experienced center by experienced surgery, surgery may be considered if cross-sectional area-to-height ratio is ≥10 cm_2/m, if the aortic dimension is 5.0 to 5.4 cm in the presence of additional risk factors for aortic dissection, or if the aortic dimension is ≥4.5 cm if the primary indication is for valve surgery (COR/LOE: 2a B-NR).**

g. **Patients with syndromic HTAD (Marfan syndrome, Loeys-Dietz syndrome, vascular Ehlers-Danlos syndrome) and nonsyndromic HTAD have lower thresholds for surgery to avoid dissection or rupture.** These thresholds range from ≥4.0 to 5.0 cm and are dependent upon the syndrome, the specific genetic mutation, and the presence or absence of high-risk features for aortic events.

5. Therapy

a. **Medical therapy.** Long-term data on medical management for TAA are lacking, although most data are extrapolated from trials in patients with Marfan syndrome. Beta-blockers and angiotensin receptor blockers are the mainstay of treatment to slow aneurysm growth for those with Marfan (COR/LOE: 1 A) and Loeys-Dietz syndromes (COR/LOE: 2a C-EO). For patients with nonsyndromic HTAD, beta-blockers are often used, although with little evidence in these populations. **For patients with TAA of any cause, it is reasonable to reduce BP with beta-blockers to target BP goals based on current guidelines (COR/LOE: 2a C-LD) with the addition of angiotensin receptor blockers as adjunct therapy if needed (COR/LOE: 2a C-EO)**.

b. Surgical therapy for TAA. The technical details of repair are beyond the scope of this text. However, the basic premise is for a tube graft to be inserted in place of the diseased aorta with the major branch arteries reimplanted into the graft. When the aortic valve is involved with aortic root dilatation, a modified **Bentall procedure** (composite aortic valve within the graft) or **David procedure** (VSRR) is performed. Aneurysms involving both the ascending and descending aorta can be treated by a two-stage approach, with a **frozen elephant trunk** procedure. With this, the ascending aorta and arch are replaced initially, and the distal portion of the graft is suspended into the proximal portion of the descending thoracic aorta for subsequent union with a descending aorta graft placed by either open surgical procedure or percutaneously.

(1) Patients undergoing aortic valve surgery with concomitant ascending aortic aneurysm should undergo separate aortic intervention and ascending aortic replacement (COR/LOE: 1 B-NR).

(2) In the presence an aortic root aneurysm and a valve unsuitable for sparing or repair, a valve conduit (mechanical or biologic) should be used (COR/LOE: 1 B-NR). VSRR is reasonable if performed at an experienced center (COR/LOE: 2a B-NR).

(3) For patients with sporadic descending TAAs exceeding 5.5 cm, TEVAR is recommended over open surgical repair (COR/LOE: 1 B-NR). However, in those patients with syndromic HTAD, open surgery (as compared to endovascular therapy) is reasonable. A threshold of ≥5.0 cm is reasonable to consider surgical repair in Marfan syndrome (COR/LOE: 2a C-EO).

(4) Patients with syndromic or nonsyndromic HTAD with dilation of the aortic root should undergo replacement of the aortic root and ascending aorta once size criteria and clinical risk profile are met (this threshold varies depending on syndrome and genetic mutation). Valved

conduit and VSRR are the most common surgical strategies employed. Evidence-based recommendations are primarily extrapolated from data involving patients with Marfan syndrome in which VSRR is a reasonable alternative to Bentall procedure in low-risk patients at an experienced center (COR/LOE: 2b C-LD).

(5) For patients with thoracoabdominal aneurysms ≥6.0 cm, repair is indicated. If degenerative in etiology with suitable anatomy, endovascular repair may be considered (COR/LOE: 2b B-NR); however, if in the context of syndromic HTAD, open repair is recommended (COR/LOE: 1 C-LD).

c. Complications after TAA repair. These include death (1%-5%), MI (7.2%), CVA (4.8%), acute renal failure (2.4%), perioperative hemorrhage (7.2%), and paraplegia (6.0%) because of perioperative ischemia of the anterior spinal cord. Revascularization of the left subclavian artery prior to TEVAR with expected subclavian coverage is recommended to prevent spinal cord injury (SCI) and reduce the risk of stroke (COR/LOE: 1 B-NR). In addition, it is recommended that patients undergoing open thoracoabdominal aortic repair at high risk for SCI should have cerebrospinal fluid drainage to reduce the risk of SCI (COR/LOE: 1 A).

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CHAPTER 28

Peripheral Arterial Disease and Carotid Artery Disease

Milad Matta and Pulkit Chaudhury

PERIPHERAL ARTERIAL DISEASE

I. INTRODUCTION. Peripheral arterial disease (PAD) describes a diverse set of conditions that may lead to obstruction or aneurysmal degeneration in the arterial bed other than the aorta or the coronary arteries (carotid, upper/lower extremities, renal, mesenteric arteries). Atherosclerosis is the most common etiology for PAD. Other rare causes of PAD include vasculitis, fibromuscular dysplasia, entrapment syndromes, trauma, cystic adventitial disease, and infectious processes. PAD affects approximately 8 to 12 million people in the United States and 230 million people worldwide. Despite its similar pathophysiologic basis to coronary artery disease (CAD), PAD is often underdiagnosed and undertreated, leading to excess morbidity and mortality. The goal of this chapter is to provide practicing clinicians with the latest evidence regarding clinical presentations, diagnostic modalities, and treatment strategies commonly employed. This chapter primarily focuses on atherosclerotic diseases of the extremities (both upper and lower), renal, and carotid arteries. Diseases of the aorta will be addressed elsewhere in this volume.

II. LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

A. Risk factors. Risk factors for PAD include ***age, hypertension, hyperlipidemia, diabetes mellitus, advanced chronic kidney disease (CKD), cigarette smoking, and genetic predisposition***. Smoking and diabetes have the highest magnitude of association, with the effect of smoking on PAD development lasting around two decades after

smoking cessation. ***Inflammation*** has also been associated with increased PAD prevalence. This is largely based on observational data, which have demonstrated an association between accelerated decline in ankle-brachial index (ABI), greater lower extremity functional impairment, and increased morbidity and mortality in patients with PAD with elevated markers of inflammation, such as C-reactive protein, tumor necrosis factor-alpha, interleukin-6, and soluble adhesion molecules.

B. Epidemiology. The prevalence of PAD increases significantly with age. PAD is relatively uncommon before the age of 50, with a prevalence of 2% to 3% in this age group. However, prevalence increases significantly, up to ***20% in people aged >80 years***. Also, the prevalence of PAD is nearly ***twice as high in the African American*** compared to the Caucasian population. It is also worth mentioning that up to ***60% of patients with PAD will also have concomitant CAD*** and/or cerebrovascular disease. Patients with PAD have a 2- to 4-fold increase in risk for cardiovascular (CV) and all-cause mortality. This increase in mortality is independent of the presence of symptoms as the majority of patients with PAD do not have classic intermittent claudication, due to the fact that those patients tend to slow down their pace and/or decrease the frequency of their walks to avoid symptoms. There is a graded association between ABI and total mortality as ABI decreases <1.00 and increases >1.40. Despite its association with coronary and cerebrovascular disease and the increased risk for CV and total mortality, patients with PAD often receive less aggressive treatment for comorbid CV conditions and are prescribed less antiplatelet agents when compared to their counterparts with CAD.

C. Clinical presentation

1. **Symptoms.** The most classic symptom of PAD is **intermittent claudication**, defined as fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and consistently relieved by rest (within 10 minutes). This phenomenon is due to a demand and supply mismatch. With exercise, vascular resistance in skeletal

muscle falls in order to augment blood flow. In the face of a critical stenosis, the distal vasculature is already maximally vasodilated and cannot compensate for this increased metabolic demand. Therefore, although rest perfusion may be adequate, exercise may precipitate supply-demand mismatch, leading to exercise-induced ischemia and **claudication**. The amount of exercise required to precipitate pain is related to the severity of the stenosis. Pain is usually manifested one segment below the area of severe stenosis (**Table 28.1**), and the most frequently involved artery in intermittent claudication is the superficial femoral artery. **Chronic limb-threatening ischemia** (CLTI) is an advanced presentation of PAD that can develop as disease burden progresses. It is characterized by chronic (≥2 weeks) ischemic rest pain, nonhealing wound/ulcers, or gangrene in one or both legs attributable to objectively proven arterial occlusive disease. CLTI is to be differentiated from **acute limb ischemia** (ALI), which occurs abruptly usually as a result of an embolic event or arterial thrombosis and is actually a surgical emergency. Classification of CLTI is presented in **Tables 28.2 and 28.3**.

TABLE 28.1 Localization of Peripheral Arterial Disease

Location of Pain	Likely Involved Segment
Buttock and thigh	Aortoiliac
Thigh	Aortoiliac, common and/or profunda femoral artery
Calf	Superficial femoral or popliteal artery[a]
Foot	Tibial or peroneal arteries

[a]Most commonly involved artery.

TABLE 28.2 Clinical Categories of Chronic Limb-Threatening Ischemia

Grade	Category	Clinical Description
	0	Asymptomatic
I	1	Mild claudication
	2	Moderate claudication

Grade	Category	Clinical Description
	3	Severe claudication
II	4	Ischemic rest pain
	5	Minor tissue loss—nonhealing ulcer, focal gangrene with diffuse pedal ischemia
III	6	Major tissue loss—extends above transmetatarsal level, functional foot no longer salvageable

Adapted from Rutherford RB, Baker JD, Ernst C, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. *J Vasc Surg*. 1997;26:517-538.

TABLE 28.3 Wound, Ischemia, and Foot Infection (WIFi) Clinical Classification of Chronic Limb-Threatening Ischemia

i. Estimated risk of amputation at 1 year

	Ischemia-0				Ischemia-1				Ischemia-2				Ischemia-3			
W-0	VL	VL	L	M	VL	L	M	H	L	L	M	H	L	M	M	H
W-1	VL	VL	L	M	VL	L	M	H	L	M	H	H	M	M	H	H
W-2	L	L	M	H	M	M	H	H	M	H	H	H	H	H	H	H
W-3	M	M	H	H	H	H	H	H	H	H	H	H	H	H	H	H
	FI-0	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**

ii. Estimated likelihood of benefit of revascularization

	Ischemia–0				Ischemia-1				Ischemia-2				Ischemia-3			
W-0	VL	VL	VL	VL	VL	L	L	M	L	L	M	M	M	H	H	H
W-1	VL	VL	VL	VL	L	M	M	M	M	H	H	H	H	H	H	H
W-2	VL	VL	VL	VL	M	M	H	H	H	H	H	H	H	H	H	H
W-3	VL	VL	VL	VL	M	M	M	H	H	H	H	H	H	H	H	H
	FI-0	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**	**FI-0**	**FI-1**	**FI-2**	**FI-3**

Ischemia grading—0: ABI >0.8; 1: Mild perfusion deficit ABI 0.6-0.79; 2: Moderate perfusion deficit ABI 0.4-0.59; 3:ABI <0.4
Wound grading—0: No wound; 1: Minor tissue loss; 2: Deep ulcer, exposed bone; 3: Extensive tissue loss, full-thickness ulcer requiring free flap/proximal amputation
Foot infection grading—0: Uninfected; 1: Without purulence/inflammation; 2: Two or markers of inflammation; 3: Systemic infection
Clinical stages: 1: Very low (VL), 2: Low (L), 3: Moderate (M); 4: High (H); 5: Unsalvageable
Adapted from Mills JL, Conte MS, Armstrong DG, et al. SVS lower extremity threatened limb classification system: risk stratification based on wound ischemia and foot infection (WIFi). *J Vasc Surg*. 2014;59:220-234.

2. **Physical examination.** People with suspected lower extremity PAD should have their ***blood pressure (BP) measured in both arms*** at least during the initial assessment to screen for upper extremity PAD. This is to be followed by a comprehensive lower extremity physical examination that includes a thorough characterization of peripheral pulses. Peripheral pulses' initial

description would be bounding/weak, regular/irregular, and equal/unequal bilaterally. Then the intensity of the pulse is subjectively graded on a scale of 0 to 3. Zero refers to a nonpalpable pulse, 1+ is diminished, 2+ is normal and should be easily palpable, and 3+ is "bounding" (eg, stronger than normal). The pulse examination is usually followed by **auscultation for bruits** in the abdomen and bilateral groins, and palpation for **aneurysms** in the abdomen and popliteal arteries with gentle pressing of the stethoscope against the vessel to not induce a false bruit with iatrogenic arterial compression. An assessment for skin changes to look for ulcers and gangrene is also necessary. Signs of lower extremity arterial insufficiency can include coolness, dry skin, scaling, dependent rubor, elevation pallor, and ulcerations. Rarely muscular atrophy can be seen.

D. Diagnostic evaluation

1. Functional assessment

a. ABI/toe-brachial index (TBI). The ABI is a measurement of lower extremity perfusion. To obtain this measurement, BP cuffs are placed on the upper arms and lower calves bilaterally and inflated above systolic pressure. As pressure is released, the onset of flow is detected by placement of a Doppler probe over the brachial and both pedal arteries (posterior tibial and dorsalis pedis). The ABI of each leg is calculated by dividing the higher of the two pedal arteries by the higher of the arm BP. **A cutoff of ABI <0.9 is used to make the diagnosis of PAD**. The ABI has a sensitivity of 68% to 84% and a specificity of 84% to 99% for the diagnosis of PAD. Recommendations for the interpretation of the ABI are listed in **Table 28.4**.

TABLE 28.4 Interpretation of the Ankle-Brachial Index

1.00-1.40	Normal
0.91-0.99	Borderline
≤0.90	Abnormal
>1.40	Noncompressible

Guidelines recommend obtaining a resting bilateral ABI in at-risk individuals (age >65, age 50-64 with risk factors for atherosclerosis, age <50 with diabetes + 1 more risk factor for atherosclerosis, patient with nonhealing wound and ulcers) and in patients with suspected PAD based on history and physical examination findings listed above. Following revascularization, a change in ABI of 0.15 is considered clinically significant, and in an observational study of 214 patients with CLTI, a postrevascularization change in ABI ≥0.23 was associated with improved wound healing. Guidelines give a **class I indication for periodic ABI assessment** to assess arterial patency **postintervention**.

It is worth noting that ABI measurements are inaccurate in patients with noncompressible vessels (ABI >1.4), in which case a TBI can be used to look for PAD. **A TBI <0.7 can be used to make the diagnosis of PAD**.

It is also worth mentioning that up to 30% of patients with CLTI may have normal or near-normal ABI, and thus if clinical suspicion is high, guidelines recommend utilization of alternate modalities (ie, TBI, skin perfusion pressure (SPP), or transcutaneous oxymetry ($TCPO_2$) to help establish a diagnosis.

b. **Exercise ABI.** Patients with PAD are often asymptomatic at rest and only develop claudication symptoms with exertion. In such individuals, it is possible for resting ABI measurements to be normal. As a result, when the suspicion for PAD is high and resting measurements are normal, it is recommended to obtain an exercise ABI. Protocols usually involve fixed treadmill settings of 2 miles/h at a 2% grade for a maximum of 5 minutes. Pre- and postexercise ABI can be obtained, with an abnormal result being **defined as a decrease in the postexercise result by >20%.** This modality is often helpful to unmask proximal aorta iliac inflow disease.

c. **Pulse volume recordings (PVRs).** PVR refers to the graphic representation of the change in volume of the pulse contour in a specific segment of the extremity during the cardiac cycle.

They are typically obtained by using BP cuffs placed at the high thigh, low thigh, calf, ankle, midfoot, and toe and may be used in conjunction with segmental pressure (**Figure 28.1**). PVRs are usually paired with the ABI as a single test at multiple institutions as **PVR can help localize anatomic segments of the disease** (in contrast to the ABI that cannot). PVRs also have the advantage in patients with noncompressible vessels as they can still yield diagnostic information through a review of the pulse volume contours and amplitude. However, despite their ability to localize disease, PVR measurements do not yield any information about lesion characteristics (ie, length, chronic total occlusion [CTO]) and have decreased sensitivity for distal disease when inflow disease is present.

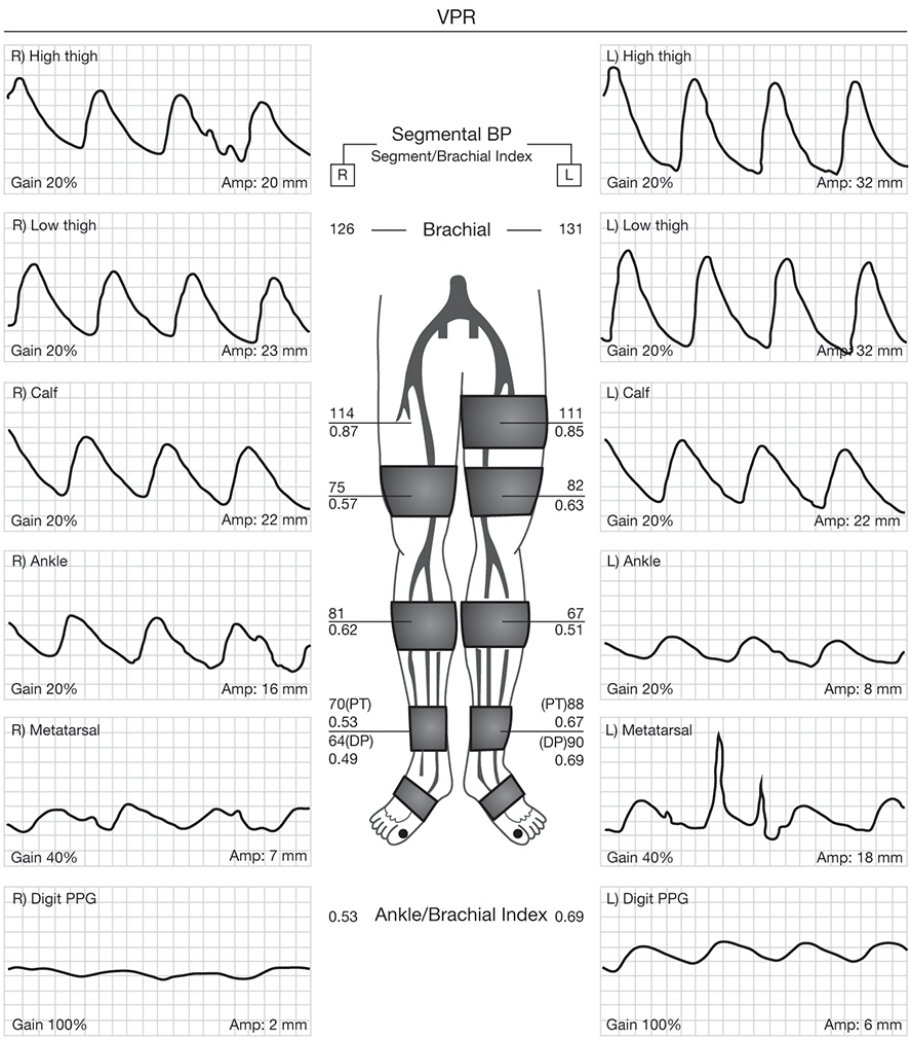

FIGURE 28.1 Pulse volume recording (PVR) of the lower extremities. This PVR was obtained from a 74-year-old man with a history of diabetes mellitus who presented with persistent Rutherford class 3 claudication in the left leg despite guideline-directed medical therapy and supervised exercise therapy. It demonstrates bilateral aortoiliac and superficial femoral artery disease. He was found to have flow-limiting lesions in his left common iliac artery and external iliac artery, which were stented in addition to a long superficial femoral artery chronic total occlusion, which was treated with drug-coated balloon therapy. BP, blood pressure.

2. Anatomic assessment

Anatomic assessment is usually reserved for patients who are highly symptomatic and are being considered for revascularization.

a. **Duplex ultrasound (DUS).** Arterial duplex can be used for an anatomic assessment of the arterial system using a combination of B-mode US imaging and spectral Doppler analysis. Doppler complements the standard qualitative US imaging by allowing waveform analysis and assessment of peak systolic velocities (PSVs). Using the concept that the velocity of blood flow increases as it flows through a stenotic lesion, PSV and end-diastolic velocities (EDVs) are measured and used to estimate the severity of stenosis. This modality is useful for anatomic visualization of lesions and for surveillance after stenting or bypass grafting. A class IIa recommendation is given for routine surveillance using DUS following infrainguinal revascularization, with a goal of early identification of high-grade stenosis (PSV >300 cm/s) and impending graft failure (PSV <40 cm/s).

b. **Magnetic resonance angiography (MRA).** The MRA signal is a reflection of the velocity and flow patterns of protons within the artery. The noninvasive nature of MRA and its ability to generate three-dimensional (3D) reconstructions are the main advantages of MRA over conventional angiography. Its limitations include a tendency to overestimate lesion severity secondary to flow turbulence, imaging artifact with metal clips or stents, and its association with nephrogenic systemic fibrosis in patients with a glomerular filtration rate (GFR) <30 mL/min who are exposed to gadolinium contrast agents. Noncontrast options are also available. Despite these limitations, MRA still has a class I indication to diagnose the anatomic location and severity of stenosis in patients with PAD.

c. **Computed tomographic angiography (CTA).** CTA uses an intravenous (IV) contrast agent and a multidetector scanner to obtain images that are of similar quality to those of conventional angiography. CTA has the advantage of being capable of reconstructing 3D images in virtually any oblique projection to help evaluate eccentric stenoses. Other advantages of CTA include better visualization of collaterals,

anatomic assessment of inflow disease, as well as identification of aneurysms and extraluminal structures (cystic adventitial disease), which may not be detected by conventional angiography. CTA also has several disadvantages when compared with catheter-based angiography: CTA has lower spatial resolution than digital subtraction; venous opacification can interfere with visualization of arterial filling; asymmetric leg filling may miss the arterial phase in some vessels. Several recent studies have shown high accuracy of CTA for the diagnosis of stenoses >50%, and CTA is quickly becoming an important imaging modality for the diagnosis of PAD. Currently, the American College of Cardiology/American Heart Association (ACC/AHA) PAD guidelines give a class I indication for CTA in the diagnosis of the anatomic location and severity of stenosis in patients with PAD.

d. Catheter-based angiography. Long considered the gold standard for the diagnosis of arterial disease, this invasive procedure requires intra-arterial vascular access and contrast (often nonionic dye, although gadolinium or carbon dioxide can be used). It is recommended for the evaluation of patients for whom revascularization procedures are planned (those with lifestyle-limiting claudication, rest pain, ischemic ulceration, or gangrene) or for whom noninvasive techniques are inconclusive. Because contrast angiography demonstrates only the arterial lumen, it can underestimate lesion severity. Current guidelines give contrast angiography with digital subtraction a class I indication for patients with PAD when revascularization is considered.

E. Treatment. The three main goals of therapy for patients with PAD are **to improve survival from related cardiovascular diseases (CVDs), relieve symptoms, and preserve limb integrity**. Aggressive risk factor modification is the cornerstone for the prevention of CV events. In select individuals, this is complemented by surgical or percutaneous revascularization, with mostly a goal of relieving symptoms and sometimes limb salvage.

1. **Antiplatelet therapy.** Current guidelines advocate the use of antiplatelet therapy to reduce the risk of myocardial infarction (MI), stroke, and CV mortality in patients with PAD.

   Aspirin (ASA), with a dose range of 75 to 325 mg daily, is recommended in the absence of a clear contraindication in patients with **symptomatic PAD (class I) and asymptomatic PAD with ABI ≤0.9 (class IIa)**.

   a. The **CAPRIE** trial compared the efficacy of ASA (325 mg) versus clopidogrel (75 mg) in reducing the risk of a composite outcome of ischemic stroke, MI, or vascular death, showing that clopidogrel is more effective. A subset analysis of 6,452 patients with symptomatic PAD from the CAPRIE trial showed a **23.8% reduction in the primary outcome in patients treated with monotherapy using clopidogrel rather than ASA** (compared to 7.3% in the ischemic stroke group and −3.7% in the MI group, showing the greatest benefit in patients with PAD compared to other groups of patients included in the trial).

   b. The **EUCLID** trial **failed to demonstrate a benefit in terms of the efficacy of ticagrelor compared to clopidogrel** in patients with symptomatic PAD.

   c. Dual-antiplatelet therapy (DAPT) is not routinely used in the management of PAD. In a post hoc analysis of 3,096 patients with symptomatic and asymptomatic PAD from the **CHARISMA** study, treatment with DAPT did not yield a significant additive reduction in the composite end point of CV death, MI, or stroke. There was a **reduction in the incidence of MI and hospitalization for ischemic events, although this occurred at the expense of increased risk of minor bleeding**. With the above data in mind, the **guidelines do not advocate for routine use of DAPT in patients with PAD** but indicate that it may be potentially appropriate in those who are perceived to be at high CV risk, presuming that they do not have comorbid conditions that place them at increased bleeding risk.

d. Vorapaxar, an antagonist of protease-activated receptor-1, was studied in patients with PAD to be added to existing antiplatelet therapy in the **TRA2P-TIMI 50 trial**. It showed a **decreased risk of major adverse cardiac event (MACE) and decreased risk of ALI and peripheral revascularization at the cost of increasing bleeding**, leading to an unclear overall benefit in the PAD population.

2. **Anticoagulation.** A class III recommendation (Harm) is given to the use of full-dose anticoagulation therapy as a means of reducing CV ischemic events in patients with PAD. The above recommendations were largely based on patients treated with warfarin (WAVE trial). With the advent of direct oral anticoagulants (DOACs), several newer studies deserve consideration.

   a. **COMPASS trial** randomized 27,395 patients with CAD or PAD in 1:1:1 ratio to ASA 100 mg daily, rivaroxaban 5 mg twice daily (bid), or ASA 100 mg daily + rivaroxaban 2.5 mg bid. In a subgroup analysis of the study cohort, 7,470 patients with lower extremity PAD and carotid disease were evaluated for several PAD end points. In addition to a decrease in the primary end point of MI, cerebrovascular accident (CVA), and CV death, patients treated with ASA + rivaroxaban experienced a statistically significant reduction in major adverse limb events (composite of ALI, CLTI, or major amputation). Although this came at the expense of an increased incidence of major bleeding (utilizing the modified International Society on Thrombosis and Haemostasis [ISTH] criteria) in the ASA + rivaroxaban group, there was no significant increase in fatal or critical organ bleeding.

   b. **Voyager PAD** randomized patients with infrainguinal (endovascular and surgical) revascularization procedures to ASA 100 mg daily + rivaroxaban 2.5 mg bid and ASA 100 mg daily + placebo. The primary efficacy outcome was a composite of MI, ischemic CVA, CV death, ALI, and major amputation. The primary safety outcome was Thrombolysis in

Myocardial Infarction (TIMI) major bleeding, and the secondary safety outcome was ISTH major bleeding. The study showed a significant decrease in the incidence of the primary outcome, without a significant increase in the incidence of TIMI major bleeding but a higher incidence of ISTH major bleeding events.

c. **ePAD trial.** In this study, 203 patients who underwent femoropopliteal endovascular revascularization were randomized to 3 months of therapy with ASA + edoxaban or ASA + clopidogrel. After 6 months of observation, there was a lower numerical but nonstatistically significant incidence of restenosis/reocclusion in the edoxaban group without an increase in major or life-threatening bleeding events.

The current iteration of the PAD guidelines gives a class IIb recommendation to the use of oral anticoagulation to improve patency following autogenous vein or prosthetic bypass. This is largely based on conflicting results with regard to graft patency balanced against increased rates of bleeding complications.

3. **Risk factor modification.** PAD is a coronary risk equivalent, and as such, aggressive risk factor modification is warranted.

a. **Tobacco.** Cigarette **smoking** has been associated with progression of atherosclerosis. Physician counseling is essential and is recommended to be done at every visit, as **tobacco cessation can reduce the 5-year amputation and mortality rate by 50%**. The importance of this intervention cannot be underestimated. Whenever possible, extensive counseling and referral to formal smoking cessation programs should be offered (class I). In addition, several pharmacologic therapies are available (nicotine replacement, bupropion, and varenicline) and should be prescribed when indicated.

b. **Hypertension.** Initially, concerns were raised regarding antihypertensive medication leading to decreased limb perfusion. However, multiple studies have demonstrated that treatment of high BP does not worsen claudications or impair functional status. The most recent ACC/AHA guidelines give a

class IIa recommendation for the use of angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB) to be used as antihypertensive patients with PAD and is thought to be effective in reducing the risk of CV ischemic events in this patient population. It is also worth mentioning that the use of beta-blockers as antihypertensive agents in patients with PAD is **not contraindicated**.

c. **Hyperlipidemia.** Based on the current PAD guidelines, ***aggressive treatment with statin therapy*** is indicated for all patients with PAD (class I) as it has been shown to improve both CV and limb outcomes. Statin therapy has been associated with plaque stabilization and perhaps plaque regression. In addition to statin therapy, newer generation proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors have been shown to reduce the risk of CV events in patients who do not adequately respond to statin therapy. The FOURIER trial showed that in patients who fail to achieve a low-density lipoprotein level of 70 mg per deciliter or less despite statin therapy, the use of PCSK-9 inhibitors resulted in a 15% decrease in the primary end point primarily driven by MI, stroke, and coronary revascularization.

d. **Diabetes mellitus.** The management of **diabetes** in patients with PAD is important, given their increased risk of amputation (overall 20%) and increased mortality (estimated to be 50% at 5 years). Current guidelines advocate that the management of diabetes mellitus in patients with PAD be coordinated with members of the patient's health care team (class I), reflecting the importance of multidisciplinary care in this subset of patients. The PAD guidelines also acknowledge that improved glycemic control can be beneficial in patients with CLTI as a means of improving limb-related outcomes (class IIa), though do not advocate for a specific target. Lastly, it is worth mentioning that aggressive risk factor modification is a critical component of management for patients with diabetes with PAD, and these patients should be treated with antiplatelet

therapy, lipid-lowering agents, and ACEi in the absence of contraindication. The emerging use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in diabetes is based not only on glycemic control but also improved CV outcomes. Close consistent monitoring by both the patient and health care providers for the development of lower extremity wounds is also critical, given the preponderance of neuropathy and distal infrapopliteal disease seen in these patients.

4. Medical therapy

a. Exercise. Exercise is an inexpensive, low-risk option in comparison with invasive therapies and pharmacotherapies for intermittent claudication. Potential mechanisms by which exercise improves symptoms include augmentation of collateral flow, decreased reliance on anaerobic metabolism, and greater oxygen extraction. **Supervised exercise programs have been shown to improve pain-free walking distance by up to 180% from resting values**. It consists of intermittent walking exercise for 30 to 45 min/session with 3 sessions/week for a minimum of 12 weeks done under the supervision of a qualified health care provider. In the CLEVER trial, 111 patients with aortoiliac disease were randomized to optimal medical therapy (with or without stenting) or to supervised exercise and followed for 18 months. When compared to individuals treated with optimal medical therapy alone, those treated with either stenting or supervised exercise experienced increase in peak walking time as well as claudication onset time. For patients with claudication, current guidelines recommend a supervised exercise program with the goal of improving functional status, quality of life (QoL), and leg symptoms (class I). It is also suggested that this be discussed as a treatment option for claudication prior to possible revascularization (class I).

For patients who do not have access to a supervised exercise program, it is reasonable to employ a structured, home-based program (class IIa), though careful attention must be given to

providing detailed instructions and ensuring compliance given that unstructured community- or home-based walking programs that consist of walking more are not efficacious

b. **Cilostazol** is a type 3 phosphodiesterase inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator via its effect on cyclic adenosine monophosphate (AMP). Randomized controlled trials (RCTs) of patients with moderate-to-severe claudication have demonstrated 40% to 60% increases in maximal walking distances after 12 to 24 weeks of therapy with cilostazol 100 mg bid. In a meta-analysis, cilostazol also demonstrated benefits in terms of restenosis, freedom from target lesion revascularization (TLR), limb salvage, and amputation-free survival. **A trial of cilostazol 100 mg bid is recommended in all patients with PAD and intermittent claudication to relieve symptoms and improve walking distance (class I)**. Cilostazol is contraindicated in patients with congestive heart failure (CHF), owing to an increased risk of sudden death associated with related phosphodiesterase inhibitors. Common side effects associated with cilostazol include diarrhea, palpitations, and headaches.

c. **Pentoxifylline.** Oral pentoxifylline is no longer recommended for the treatment of claudication (class III).

5. **Revascularization.** Historically, surgical bypass was seen as the preferred modality of revascularization, with endovascular approaches being reserved for select cases with relatively straightforward anatomy. This was predominantly due to limited procedural success and worse patency rates with endovascular as compared to surgical intervention. However, with improved operator experience, various technical advances, and institution of modern pharmacologic treatment regimens, better outcomes were seen in patients treated via an endovascular approach. This, in addition to a relative high morbidity associated with surgery, led to increased adoption of an “endovascular-first” strategy.

a. Percutaneous therapy. Currently, endovascular revascularization is advocated for patients with lifestyle-limiting claudication despite optimal medical therapy, patients with CLTI, and patients with PAD in whom revascularization is necessary to allow for another indicated percutaneous procedure (ie, coronary stenting, hemodynamic support device insertion, transcatheter aortic valve replacement [TAVR]). It is important to emphasis that in patients who present for revascularization in the setting of claudication the primary goal of intervention is symptom relief whereas in the setting of CLTI the goal is limb salvage.

(1) Aortoiliac disease or inflow disease. Current guidelines support the importance of addressing inflow disease, especially in the presence of CLTI. Options for percutaneous revascularization include angioplasty with or without stenting. In a meta-analysis conducted by Bosch et al which included 14 studies comprising 2,116 patients undergoing iliac stenting or angioplasty, there was a 39% reduction in long-term failure in the stent group as compared to the angioplasty group with >90% procedural success and similar complication rates in these patients. This has caused many to adopt a primary stent strategy in patients with aortoiliac disease

(2) Femoropopliteal disease. This is the most common segment of the lower extremity involved in patients with PAD. Given the high degree of collateralization in the superficial femoral artery (SFA), patients often present late with advanced disease, including long segments of severe stenosis and/or occlusion often with high degrees of calcification. There are fortunately several tools available to address such disease, including atherectomy devices, various specialized balloons (including cutting, chocolate, drug-coated, and lithotripsy), and various stents (nitinol, wire-interwoven nitinol, drug-eluting, and covered). Given the high degree of mechanical stress that the superficial

femoral artery is exposed to, many practicing physicians have been concerned about the potential for accelerated rates of in-stent restenosis (ISR) as well as stent complications such as kinking, compression, and fracture in patients who undergo stent implantation. This concern and a lack of consensus for the optimal treatment strategy have led to several clinical trials designed to address various approaches. In an RCT including 104 patients with severe PAD, ***vessel patency and functional status were improved with self-expanding stent placement as compared to angioplasty alone***, with a stent fracture rate of 2% in the stent group. Subsequent well-conducted studies in patients treated with a wire-interwoven stent (SUPERA) as well as a drug-eluting stent (ZILVER PTX) demonstrated excellent results with regard to patency rates, need for TLR, and rates of stent fractures. There have also been two more recent randomized trials comparing angioplasty to drug-coated balloon treatment in patients with PAD, which have similarly demonstrated excellent outcomes in terms of patency extended out to 2 years. As of now, there is not a clear consensus as to the optimal treatment strategy in patients with femoropopliteal disease, and as such, clinicians must individualize treatment by carefully weighing patient, lesion, and device-specific characteristics.

(3) **Infrapopliteal disease.** Because of the often complex nature of infrapopliteal disease with potential for serious complications such as perforation with compartment syndrome and distal embolization, attempts at endovascular intervention should be done by physicians who specialize in invasive management of patients with PAD. Several devices including atherectomy devices, standard peripheral balloons, a variety of specialized balloons, and coronary drug-eluting stents may be used depending on the specific clinical scenario. In a recent

meta-analysis that compared angioplasty to femoral tibial bypass surgery, there was no difference in rates of limb salvage between treatment groups, further supporting the feasibility of endovascular approaches in this disease subset.

b. Surgery. Surgical revascularization also has a class IIa indication for individuals with lifestyle-limiting claudication, acceptable perioperative risk, inadequate response to guideline-directed medical therapy, and technical aspects that favor a surgical over endovascular approach. Surgery is used to bypass long segments of diffuse disease (particularly involving the femoropopliteal segment) or when endovascular therapy fails. Various conduits, such as reversed or in situ saphenous vein grafts, Dacron grafts, and polytetrafluoroethylene (PTFE) grafts, can be used. The best outcomes are achieved with single segments of saphenous vein grafts with less optimal results with PTFE grafts. This is reflected in the class I recommendation for the use of autogenous vein bypass to the popliteal artery over prosthetic grafts. The **BEST-CLI** study randomized 1,830 patients with CLTI in whom both surgical and endovascular interventions were feasible to either strategy. Results revealed that surgical revascularization with a great saphenous venous (GSV) conduit was superior to an endovascular approach (reduced above-ankle amputation, major intervention). When a GSV conduit was not available, there was no difference in outcomes in the surgical and endovascular group.

III. LOWER EXTREMITY ANEURYSMS. Aneurysms of the peripheral arteries, as in the aorta, are most commonly due to atherosclerotic disruption of the arterial media. Up to ***70% of lower extremity aneurysms involve the popliteal*** arteries. The incidence of bilateral involvement in lower extremity aneurysm is high (45%-68%). The majority of patients (62%) with popliteal aneurysms have been reported to have concomitant abdominal aortic aneurysms (AAAs), and this co-prevalence increases to 85% in patients with femoral artery aneurysms. Accordingly, patients

diagnosed with peripheral arterial aneurysms, especially femoral or popliteal, should be screened with US for AAA and for the presence of contralateral lower extremity disease (class I). The greatest concern with lower extremity aneurysms is ***thrombosis and thromboembolism***. Lower extremity aneurysms infrequently rupture (7%-12%), but up to 60% will have an ischemic complication. Therefore, ALI is the most common presenting symptom. As an aneurysm increases in size, it can compress adjacent venous and lymphatic structures, causing lower extremity edema. Given the risk of thrombosis, it is recommended that ***popliteal aneurysms >2.0 cm (class I) and femoral artery aneurysms >3.0 cm be repaired***. Unless symptomatic, aneurysms of smaller caliber should be followed by annual arterial DUS examinations (class IIa).

IV. UPPER EXTREMITY ARTERIAL DISEASE. Upper extremity PAD is rare and underestimated. However, it should have the same medical attention allocated to it as lower extremity PAD. Causes are much more heterogeneous compared to the lower extremity disease, with ***atherosclerosis*** still being the most common cause. Other pathologic states can result in stenosis of the upper extremity arteries: ***inflammatory vascular diseases (particularly Takayasu and giant cell arteritis), noninflammatory vascular diseases (fibromuscular dysplasia), thoracic outlet syndrome, ionizing radiation, and repetitive injury***. Associated clinical symptoms include claudications, digital ulceration, and neurologic symptoms caused by vertebral-subclavian steal syndrome (VSCSS). VSCSS occurs in the presence of a flow-limiting lesion in the subclavian artery proximal to the origin of the vertebral artery, leading to a decreased distal perfusion of the ipsilateral vertebral artery, and the axillary artery, leading to the blood flow in the ipsilateral vertebral artery. Rarely, VSCSS can lead to coronary subclavian steal syndrome (CSSS) in coronary artery bypass grafting (CABG) patients with left internal mammary artery (LIMA) to left anterior descending artery (LAD) graft. CSSS manifests itself as angina due to hypoperfusion of the myocardium secondary to retrograde blood flow through the patent LIMA graft to restore perfusion in the left subclavian artery. The diagnostic modalities are similar to those in lower extremity arterial disease. The simple clinical maneuver of checking BP measurements in

both arms is an excellent screening test for significant upper extremity PAD. ***Brachial BP gradients greater than 15 mm Hg are considered clinically significant***. Bruits may be audible in the supraclavicular fossa as well. Risk factor modification for atherosclerotic lesions and revascularization (for symptomatic patients) are the mainstays of therapy. Upper extremity PAD should be treated medically the same way as lower extremity PAD.

V. RENAL ARTERY DISEASE

A. Clinical manifestations. Renal artery stenosis (RAS) is commonly associated with multiple clinical syndromes: resistant hypertension (the leading cause of secondary hypertension), ischemic nephropathy (leading to a decline in renal function), and cardiac destabilization syndrome (pulmonary edema, recurrent heart failure, or acute coronary syndrome [ACS]). Clues to the presence of RAS include the following: **abrupt onset of hypertension** (before age 30 years, often because of fibromuscular dysplasia (FMD), or after age 55 years, often because of atherosclerotic disease); **previously well-controlled chronic hypertension that becomes resistant to medical therapy** (three antihypertensive medication including a diuretic); **worsening kidney function with ACEi and ARB use**; and **recurrent flash pulmonary edema**, often with normal left ventricular function (because of renin-angiotensin–mediated volume overload and peripheral vasoconstriction). Physical examination in RAS may reveal hypertension, epigastric bruits, and evidence of atherosclerosis in other vascular beds (eg, carotid or femoral bruits and diminished pedal pulses). Renal imaging can reveal an atrophic kidney or a size discrepancy between the two kidneys.

B. Etiology and natural history. The most common causes of RAS are ***atherosclerosis and FMD***. ***Atherosclerosis accounts for 90% of RAS*** and usually involves the ostium and proximal third of the main renal artery compared to FMD, which usually causes a "string-of-beads" appearance that usually occurs in the mid- and distal portions of the artery (accounts for <10% of RAS). The prevalence of atherosclerotic RAS increases with age, with diabetes, PAD, CAD, or hypertension.

Studies have suggested that the prevalence of RAS in patients with PAD may be as high as 59%. Rarer causes of RAS include vasculitis, neurofibromatosis, congenital bands, extrinsic compression, and ionizing radiation. RAS is an independent risk factor of mortality in patients with other vascular diseases. Moreover, end-stage renal disease because of RAS is associated with the highest mortality (median survival of 2.7 years) among all dialysis-dependent patients.

C. Diagnostic evaluation

1. Noninvasive assessment

a. DUS. Renal DUS imaging is an excellent initial choice for the diagnosis of renal artery disease. Arterial duplex uses a combination of B-mode US imaging and Doppler spectral analysis. Three criteria can be looked at in DUS for evaluation: PSV, the renal-to-aortic ratio (RAR), and the presence of color and spectral turbulence. A PSV >200 is associated with 95% sensitivity and 90% specificity for >50% stenosis. A renal artery PSV to aorta PSA >3.5 had a 92% sensitivity for >60 stenosis. In addition, DUS allows for the calculation of the renal resistive index (renal parenchymal PSV minus EDV divided by the PSV), which is a potential marker of renal parenchymal disease. Some data suggest that patients with an elevated resistive index may not improve after revascularization. DUS is inexpensive, widely available, and highly sensitive and specific for RAS when compared with angiography. It is also highly useful for surveillance of renal arteries after stenting, as flow through a stent can be easily detected, in contrast to MRA, which is limited by metal artifact. DUS for RAS must be performed in experienced centers. The test may be limited by difficulty in obtaining measurements because of excess bowel gas or obesity. It also has lower sensitivity (64%) for identifying accessory renal arteries, narrowing of which could also lead to the signs of RAS. If unable to obtain decent imaging with DUS, then the next step would be to get cross-sectional imaging with CTA or MRA.

b. **Renal scintigraphy.** Renal scintigraphy plasma renin measurements before and after ACEi provocation is no longer considered for the diagnosis of RAD and has largely fallen out of favor.

c. **CTA.** CTA has the capability of producing excellent 3D images of the renal arteries as well as the aorta and other visceral vessels. CTA has a sensitivity and specificity for detecting significant RAS ranging from 90% to 100% and 97%, respectively. Contrast administration (100-150 mL) and radiation dose remain limitations of CTA. Unlike MRA, CTA does not have significant imaging artifact with metal clips or stents and, therefore, can be used to detect ISR. However, calcified arteries remain a challenge for CTA.

d. **MRA.** MRA now has a class I indication as a test for the diagnosis of RAS, with reported sensitivity and specificity from 90% to 100% and 76% to 94%, respectively. MRA is noninvasive and has the ability to generate 3D reconstructions. Its limitations include expense, limited availability, lack of resolution in the setting of high-grade stenosis (often appearing as an occlusion or loss of signal), a tendency to overestimate lesion severity, and difficulty with poststent imaging because of artifact. It is also less sensitive for the detection of FMD, given that the typical arterial beading may be subtle and resolution of MRA is still limited, particularly of the distal renal vasculature. In addition, in patients with advanced renal insufficiency or renal failure, gadolinium-containing contrast agents have been linked to nephrogenic systemic fibrosis. This has complicated the use of contrast-enhanced MRI in patients with RAS and advanced kidney disease.

2. **Invasive assessment**

a. **Renal arteriography.** This is the gold standard for the diagnosis of RAS. It allows for excellent visualization of the main renal and accessory renal arteries and their branches. By expert consensus, an angiographic stenosis of >70% is significant, and stenosis of 50% to 70% are moderately severe

with uncertain hemodynamic significance. For stenosis with uncertain hemodynamic significance, confirmation of severity is required if an intervention is being planned, leading to arteriography often being used in conjunction with intravascular US (IVUS) and fractional flow reserve (FFR) in order to obtain a more complete anatomic and physiologic assessment of the renal vasculature. A renal FFR <0.8, peak pressure gradient >20 mm Hg, or mean pressure gradient >10 mm Hg will confirm a hemodynamically significant stenosis. Disadvantages include the requirement for intra-arterial access, radiation exposure, and the use of nephrotoxic radiocontrast. CO_2 angiography can be used as a safer option; however, bowel gas and motion artifact can affect image quality.

D. Treatment. Despite antihypertensive therapy, RAS tends to progress and may be associated with renal ischemia and loss of renal function. Atherosclerotic nephropathy is complex and not simply related to stenosis of the renal artery. Examination of renal histology in patients with atherosclerotic nephropathy reveals other potential mechanisms for loss of function, including small-vessel occlusion from atheroemboli, intrarenal arterial stenoses, and preexisting hypertensive nephrosclerosis. Importantly, as with other peripheral vascular disease processes, a high index of suspicion for concurrent CVD and cerebrovascular disease should be maintained.

1. **Medical therapy.** Aggressive antihypertensive therapy using multiple agents remains the cornerstone of RAS treatment and is often the control arm of randomized trials of interventional approaches to RAS. ACEi, ARBs, diuretics, beta-blockers, calcium channel blockers, and various other antihypertensive agents have been shown to be effective in treating hypertension associated with RAS. ACEi and ARBs should not be used in patients with bilateral RAS or a solitary kidney with RAS. However, these agents can be highly effective in the management of hypertension in patients with unilateral RAS (class I). Patients with RAS should be treated to achieve BP targets consistent with the most recent iteration of the guidelines. Aggressive

atherosclerotic disease risk factor modification should be part of a comprehensive treatment plan.

2. **Percutaneous revascularization.** The principle behind revascularization is that early restoration of renal artery patency in patients with atherosclerotic RAS may improve hypertension management and minimize progressive renal dysfunction. Although there is a paucity of data from controlled clinical trials to show that revascularization for RAS improves hypertension or delays renal dysfunction, the application of current studies to real-world clinical practice has been affected by several important limitations.
   a. **STAR (2009).** This trial randomized 140 patients with RAS (defined as ostial RAS of >50% on CTA, MRA, or digital subtraction angiography [DSA]) and CKD (defined at creatinine clearance [CrCl] <80 mL/min/1.73 m^2) to medical therapy with or without renal stenting. The primary outcome of worsening renal function >20% did not differ between groups at 2-year follow-up. It is noteworthy that of the 64 patients randomized to stenting, 30% did not undergo revascularization, predominately because of the fact that the lesion was not deemed to be severe at the time of angiography. Overall, only a small proportion of patients in both arms reached the primary end point, which resulted in the study being underpowered and thereby limiting its applicability to clinical practice. The criticism of this trial was being a small underpowered cohort that included renal artery disease with 50% or more stenosis with knowledge of the fact that RAS does not affect kidney flow unless it causes 70% to 80% narrowing of the lumen.
   b. **ASTRAL (2009).** This study randomized 806 patients with atherosclerotic renovascular disease to medical therapy with or without revascularization (much larger than the STAR trial). The primary outcome of progression of renal dysfunction and key secondary outcomes including major CV and renal events were similar between groups after a mean follow-up of 34 months. Despite this result, it is worth noting that patients with

a clear indication for revascularization as well as those with a high likelihood of needing revascularization within 6 months were excluded from the trial—both important factors that limit the generalizability of the results to the patients the procedure is actually intended to benefit. In addition, of the 403 patients randomized to revascularization, 40% had lesions <70% in severity and 25% had normal estimated GFR. ASTRAL trial was criticized for not including enough high-risk patients who benefit from revascularization.

c. **CORAL (2014).** This is the largest and most recent trial addressing the utility of renal stenting. In this study, 947 patients with RAS and either systolic hypertension (>155 mm Hg on two or more antihypertensives) or CKD (eGFR <60 mL/min/1.72 m^2) were similarly randomized to medical therapy with or without stenting. At a mean follow-up time of 43 months, there was no difference in the incidence of the primary outcome of CV or renal death, MI, stroke, CHF hospitalization, progressive renal dysfunction, or need for renal replacement therapy (RRT). The biggest criticism of this study was the fact that the hemodynamic severity of moderate lesions (50%-70% diameter stenosis) was not hemodynamically confirmed, so it is very likely that patients with nonobstructive RAS were enrolled in this study.

Based on those three randomized trials, there was no significant evidence of benefit in revascularization with stenting in those with RAS. However, all three trials have been criticized for not including enough high-risk patients.

The ACC/AHA guidelines recommend that patients most likely to benefit from renal artery stenting are patients with hemodynamically significant RAS (>70% stenosis or 50% to 70% stenosis with invasive hemodynamic measures confirming severity as detailed above) along with recurrent CHF, flash pulmonary edema (class I), refractory ACS (class IIa), refractory hypertension who failed or are intolerant of

guideline-directed medical therapy (GDMT) (class IIa), and patients with progressive CKD because of RAS (class IIa).

Renal angioplasty without stenting is the mainstay for FMD RAS, with stenting being a bailout strategy in case of failure.

Predictors of poor outcomes with RAS interventions include significant proteinuria (>1 g/d), renal atrophy, parenchymal renal disease, and diffuse renal arterial disease. In patients undergoing renal stenting, baseline azotemia is the strongest predictor of long-term mortality (70% 5-year mortality with serum creatinine >2.5 mg/dL).

d. Surgical revascularization. Surgical approaches to RAS include surgical bypass (aortorenal, celiac-renal, or mesenteric-renal) and endarterectomy. Perioperative mortality rates range from 1% to 5%. The comparable procedural success with percutaneous approaches and fewer major complications have led to a decline in the number of vascular surgeries for RAS. In the setting of RAS and aortic disease (either aneurysmal or occlusive), surgical revascularization with renal artery bypass grafting is the preferred approach (class I). Surgical revascularization is also recommended for patients with significant atherosclerotic RAS and clinical indications for intervention with multiple renal arteries or early branching main renal artery (class I). In patients with FMD, surgical revascularization is recommended for RAS associated with macroaneurysms or complex disease involving segmental renal arteries (class I).

CAROTID ARTERY DISEASE

I. EPIDEMIOLOGY AND ETIOLOGY OF STROKE

A. There are nearly 800,000 strokes annually in the United States, with 1 stroke occurring every 40 seconds. Stroke is the **third leading cause of death** in Western societies, with one death occurring every three and half minutes due to stroke. It is also the leading cause of long-

term disability. This disease burden is not exclusive to the United States, with 15 million strokes occurring yearly worldwide.

B. About ***87% of all strokes are ischemic strokes***. Of these, 60% are embolic in nature, whereas 40% are due to atherothrombotic disease divided into small-vessel (25%) ***versus large-vessel disease (15%) including carotid disease***.

II. RISK FACTORS FOR CAROTID ATHEROSCLEROSIS. Carotid atherosclerosis shares the same risk factors as atherosclerosis in any other vascular bed. However, some nuances are to be taken into consideration as below.

A. Smoking (25%-50% increase in related risk of stroke) and age are the two most important risk factors for developing carotid atherosclerosis. The others, in order of importance, are **hypertension, diabetes, gender** (men more than women if younger than 75 years; women more than men if older than 75 years), **and hyperlipidemia**.

B. Between 30% and 60% of patients with PAD have carotid disease, and approximately 40% of patients with carotid disease had CAD. However, only 10% of patients with CAD have severe carotid disease. Vascular disease in two or more vascular beds is termed "polyvascular disease," and data from the REACH registry indicates that vascular thrombotic events (CV death, MI, stroke) are increased proportionally to the number of vascular beds involved.

III. DEFINITION AND PATHOPHYSIOLOGY. Carotid artery stenosis refers to >50% stenosis of the extracranial internal carotid artery (ICA), with stenosis estimated using the North American symptomatic carotid endarterectomy trial (NASCET). A clear separation between symptomatic and asymptomatic carotid stenosis is critical. "Symptomatic" carotid stenosis is defined as associated with symptoms of stroke and transient ischemic attack (TIA) in the preceding 6 months. A carotid stenosis is defined as "asymptomatic" if no prior symptoms can be identified or when symptoms have occurred >6 months ago.

A. As with coronary disease, atherosclerotic carotid disease usually develops at branch points, especially at the bifurcation of the common carotid artery along with the origin of the ICA.

B. The reasons that carotid stenoses become symptomatic are not completely understood, but there is a linear increase in the ***risk of stroke as the stenosis increases to >70%***. Two hypotheses explain how carotid disease can cause stroke.

1. **Carotid plaque is highly vascularized.** Rupture of this vasculature or rupture of the plaque can result in plaque hemorrhage or ulceration, with subsequent in situ thrombus formation. This can lead to complete vessel obstruction or distal atherothromboembolism. This mechanism accounts for most cerebrovascular events caused by carotid disease.
2. Larger plaques can result in high-grade carotid stenosis or obstruction, with subsequent ischemic stroke because of a reduction in cerebral flow; in the setting of inadequate or absent collateral circulation, this usually affects watershed areas in the brain.

IV. DIAGNOSIS

A. History and physical examination

1. Careful history can aid in the localization of neurologic symptoms. Hemispheric symptoms include unilateral weakness, numbness, difficulty with speech, and visual field defects, whereas vertebrobasilar symptoms can include cerebellar disturbances such as ataxia or brainstem symptoms including syncope, dysphagia, dysarthria, or diplopia. Amaurosis fugax is transient, unilateral vision loss (often described as a shade being pulled down over the eye) ipsilateral to a carotid lesion.
2. **An assessment for the presence of a cervical bruit is an important part of the physical examination but should not be relied on as the sole marker for the presence of carotid disease.** In the NASCET trial, the presence of a cervical bruit had an approximately 60% sensitivity and specificity for high-grade carotid stenosis. In the Framingham study, the presence of a carotid bruit in asymptomatic patients doubled the risk of stroke, but most of these strokes occurred in vascular beds different from those of the carotid bruit. This observation leads to the thought

that the presence of a bruit may be a general marker for patients at higher risk for cerebrovascular and CV events.

3. In addition to auscultation for carotid bruits, a complete evaluation of a patient with symptoms includes a focused neurologic examination to correlate symptoms with neurologic territory, a fundoscopic examination to detect retinal embolization. Even if the stroke was thought to be attributed to carotid disease, cardiac examination to rule out potential cardioembolic sources for symptoms should be pursued.
4. All patients should have an evaluation of the carotid arteries after a stroke or a TIA. The risk of a second stroke is elevated for several years after the first stroke or TIA.

   For symptomatic carotid stenosis, in the NASCET trial, the **annual stroke rate** under uncontrolled medical treatment was **13%** for >70% stenosis.

   For asymptomatic carotid stenosis, a retrospective cohort study including 3,737 participants with asymptomatic severe carotid stenosis per the NASCET criteria (between 70% and 99%) with no surgical intervention had a risk of stroke of **4.7% over 5 years**.

   Carotid occlusion was found to be associated with a low risk of stroke of 2.1%/year for ipsilateral stroke.

B. Imaging

1. DUS

Although carotid angiography is the gold standard, DUS is the most widely used method for the detection and quantification of carotid artery disease. It has a sensitivity of 89% and specificity of >84% among patients with 70% to 90% stenoses and a sensitivity and specificity of >95% among patients with complete carotid occlusion. Because of its high sensitivity and specificity in severe carotid disease as well as its noninvasive nature, DUS should be the first study performed to assess for carotid disease.

The US diagnosis of carotid stenosis is based largely on PSV and EDV in the ICA. DUS criteria for carotid stenosis can vary widely between institutions, and each vascular laboratory must assess the accuracy of its criteria for stenosis in a quality

assurance program. Compared with angiography, DUS is noninvasive, is less expensive, and can be done at the bedside. It is important to mention the multiple limitations of this imaging modality. Patient body habitus, atypical anatomic variants, and tortuous vessel course might make imaging acquisition and velocity interpretation more challenging. Another important limitation is the limited ability of DUS to differentiate between occlusive and subocclusive carotid stenoses. DUS also lacks the ability to visualize collateral flow. It is also worth mentioning that velocities contralateral to an occlusive carotid stenosis need to be interpreted with caution, given that PSV is often increased in the vessel contralateral to the occlusion, leading to overestimation of a stenosis. DUS is also limited to the evaluation of the posterior circulation.

2. CTA

CTA offers high sensitivity and specificity for the identification of severe (>70%) CAD (sensitivity 77%, specificity 94%). However, CTA sensitivity and specificity drop with the decreased stenosis severity, with 67% sensitivity and 79% specificity for 50% to 69% stenosis. CTA allows for visualization of the carotid artery lumen as well as adjacent bony and soft tissue structures. Advantages include high sensitivity (particularly for carotid artery occlusion and high degree of stenosis), reproducibility (operator independent), and the ability to visualize the entire carotid artery, including the extracranial and intracranial portions. Disadvantages include radiation exposure and the need for contrast injection, which may be unsuitable for patients with CKD.

3. MRA

Contrast-enhanced magnetic resonance angiography (CEMRA) is rapidly gaining acceptance as a sensitive (94%) and specific (93%) test for severe carotid disease. CEMRA has several of the DUS advantages, including higher sensitivity, reproducibility, and the ability to visualize the entire carotid artery, including the extracranial and intracranial portions. Disadvantages include high cost, limited availability compared to other imaging modalities,

and the inability to study critically ill patients, claustrophobic patients, or patients with non–MRI-safe intracardiac devices.

The combination of either CEMRA or CTA with Doppler US results in a lower number of misclassifications and higher sensitivity and specificity for the diagnosis of severe ICA stenosis. When there is concern regarding the accuracy of one study, it is justifiable to evaluate the stenosis using two imaging modalities.

As a matter of fact, a class I indication is given by European Society of Cardiology (ESC) guidelines for CTA or MRA to follow DUS in case of carotid artery stenosis for evaluation of aortic arch as well as extra- and intracranial circulation along with corroboration of the degree of stenosis estimated.

4. Contrast angiography

Contrast angiography with DSA is the gold standard for assessment of carotid atherosclerosis. It allows the simultaneous assessment of the aortic arch, subclavian arteries, vertebral arteries, and intracranial circulation. Angiography enables the accurate assessment of collateral circulation. This is important because the presence of collateral circulation in medically treated patients with high-grade stenosis reduces the risk of ipsilateral stroke.

Two criteria are used to quantify carotid stenosis angiographically: the NASCET criteria and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria (**Figure 28.2**). The NASCET criteria compare stenosis to the distal normal poststenotic ICA diameter. The ECST criteria compare stenosis to an estimate of the normal diameter of the carotid bulb. The same lesion will be estimated to a have a higher degree of stenosis using the NASCET criteria compared to the ECST criteria. **In addition, the NASCET criteria are difficult to apply in subtotal occlusions with collapse of the distal ICA because of underfilling**. However, the NASCET criteria inherently have less variability and are now recommended as the standard for reporting of angiographic carotid stenosis.

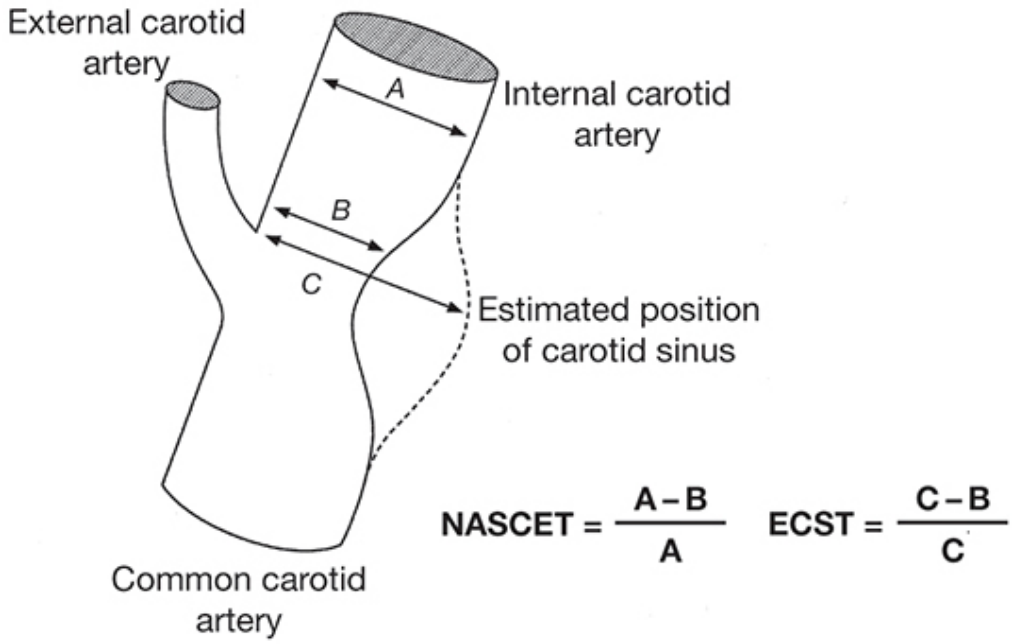

FIGURE 28.2 The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria for determining the degree of carotid stenosis.

V. MANAGEMENT OF CAROTID DISEASE

A. Medical management

1. **Risk factor modification.** Aggressive CV risk factor modification is recommended to reduce the risk of stroke and prevent the progression of existing disease, regardless of whether revascularization is indicated. This includes careful attention to smoking cessation and optimal control of various CV comorbidities according to established guidelines.

2. **Antiplatelet therapy**

   Antiplatelet therapy is indicated in all patient with carotid artery stenosis, irrespective of clinical symptoms and revascularization.

   a. **ASA** is the most extensively studied antiplatelet drug for the prevention of stroke and should be initiated in all patients with evidence of carotid atherosclerosis. Current guidelines advocate initiation of ASA 75 to 325 mg daily in all patients with extracranial carotid or vertebral atherosclerosis to reduce

the risk of MI and other ischemic CV events as those patients are at twice the risk of MI compared to the general population.

b. Clopidogrel 75 mg daily may be used in primary prevention settings when there is a contraindication to ASA therapy. Following a stroke, it is reasonable to use clopidogrel as an alternative to ASA in select clinical situations depending on the risk factor profile of the patient.

c. DAPT is **not** routinely used in patients with carotid atherosclerosis in the absence of an endovascular intervention or alternate indication (ie, coronary stenting). This is mostly based on the results of the CHARISMA trial, where 15,603 patients with evidence CVD were enrolled (7% of patients enrolled with carotid artery disease) showing that ASA plus clopidogrel was not significantly more effective than ASA alone in reducing MACE but had an increased risk of bleeding.

d. Low-dose ASA (**25 mg bid**) plus dipyridamole (**200 mg bid**) has been found to be more beneficial than ASA alone or dipyridamole alone for the secondary prevention of stroke in the ESPS-2 study. Similarly, in the European/Australian Stroke Prevention in Reversible Ischemia Trial, extended-release dipyridamole administered with ASA was superior to ASA alone in the prevention of MI, stroke, or vascular death.

e. The PROFESS trial, which enrolled over 20,000 patients with noncardioembolic ischemic stroke, showed that clopidogrel monotherapy and ASA plus extended-release dipyridamole have similar risks and benefits for secondary stroke prevention. There was no difference between treatment with ASA plus extended-release dipyridamole or clopidogrel for the primary outcome of recurrent stroke or the composite secondary outcome of stroke, MI, or vascular death. However, despite the nearly identical event rates, the trial failed to meet the prespecified noninferiority criteria for treatment with ASA and extended-release dipyridamole.

f. According to the AHA/American Stroke Association (ASA) Guidelines for the Prevention of Stroke in Patients with

Ischemic Stroke or TIA, the accepted treatment strategies for the secondary prevention of noncardioembolic stroke include one of the following:

(1) ASA (75-325 mg daily)

(2) ASA (25 mg) and extended-release dipyridamole (200 mg) bid

(3) Clopidogrel (75 mg daily), especially for patients with ASA allergy or resistance

g. Lipid-lowering agents

Epidemiologic data have shown higher stroke rates among patients with high low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol levels. Several studies have consistently shown carotid plaque regression in patients treated with statins. Lipid-lowering therapy with ***statins reduces the risk of stroke in patients with carotid artery disease***. In the SPARCL trial, atorvastatin (80 mg) was associated with a decreased risk of stroke and reduced major CV events compared to placebo in patients with TIA or ischemic stroke. As noted above, the FOURIER trial enrolled patients with ischemic stroke and demonstrated that the use of PCSK-9 inhibitors decreased the risk of CV events in patients with suboptimally controlled LDL on oral statin medications.

h. Antihypertensive agents

a. Hypertension is the single most modifiable risk factor in the prevention of stroke, and epidemiologic data suggest that approximately 60% of all strokes are attributable to hypertension. Several RCTs have shown benefit of a variety of antihypertensive agents—ACEi (HOPE, PROGRESS), ARBs (LIFE), and diuretics (ALLHAT) in particular.

b. Current updated guidelines recommend treatment of **hypertension** in patients with clinical CVD or 10-year atherosclerotic CVD risk >10% and BP ≥130/80 mm Hg.

i. Anticoagulation

a. Current guidelines ***recommend antiplatelet agents rather than anticoagulants*** in patients with extracranial carotid or vertebral atherosclerosis whether they have ischemic symptoms, unless there is an alternate indication for anticoagulation (ie, mechanical heart valve, atrial fibrillation). However, the antithrombotic landscape in this patient population is rapidly changing. The recent COMPASS trial revealed a 25% relative risk reduction with the use of low-dose rivaroxaban (2.5 mg bid) along with ASA 81 mg compared to ASA 81 mg alone in patients with stable atherosclerotic disease, including carotid artery stenosis. Patients with polyvascular atherosclerotic disease derived the most benefit.

B. Carotid revascularization

1. Indications for carotid revascularization

The decision to pursue surgical management for carotid artery disease is majorly dependent on the surgical risk, percentage of stenosis, and symptomatic versus asymptomatic status. Generally speaking, ***carotid revascularization is not recommended when the percentage of stenosis is <50%***. Strong evidence exists showing the significant benefit of carotid revascularization over maximal medical therapy in patient with symptomatic carotid artery stenosis. In contrast to symptomatic carotid patients, the benefit of revascularization is still debatable in patients with asymptomatic carotid stenosis, which is currently being looked at in two large RCTs: ECST-2 and CREST-2. The 5-year data from the SPACE-2 trial suggest that for asymptomatic carotid stenosis greater than 70%, carotid endarterectomy + best medical treatment (CEA+BMT) or carotid artery stenting (CAS)+BMT was not superior to BMT alone, but sample size was small.

- In ***asymptomatic, low-risk patients (<3%) with >70% stenosis, CEA is recommended*** over maximal medical therapy (grade IB).
- In ***symptomatic, low- and standard-risk patient (<6%) with >50% stenosis, CEA is recommended (grade IA)***. For patients

with recent stroke and >50% stenosis, carotid revascularization is recommended if patient neurologically stable after 48 hours but definitely before 14 days after the onset of symptoms (grade IB).

2. CEA

CEA is the standard of care for the reduction of stroke or TIA in patients with high-grade symptomatic or asymptomatic carotid stenosis. Several trials have firmly established the utility of CEA in preventing stroke in the presence of severe carotid stenosis as compared with medical therapy. It is important to keep in mind that high-risk patients were not enrolled in these trials. Because the risk of surgery among such patients probably would be higher than reported in these trials, extrapolation of these data to high-risk patients must be done with caution.

a. Major trials

See **Tables 28.5 and 28.6**.

TABLE 28.5 Trials of Carotid Endarterectomy in Asymptomatic Patients

Study Name	Study Type and Inclusion Criteria	Measured Outcomes and Follow-Up	Results
VA (1993)	Multicenter, prospective trial with 444 **male patients (only)** with asymptomatic >50% stenosis (by angiogram) randomized to medical management vs CEA	Composite of TIA and stroke Follow-up 4 y	**Ipsilateral neurologic event**: 8% for surgical patients vs 20% for medically treated ($P <$ .001)
ACAS (1995)	Multicenter, prospective trial with 1,662 patients with asymptomatic >60% stenosis (by angiogram)	Composite of ipsilateral stroke, perioperative stroke, death Follow-up 2.7 y	**5-year estimate** was 5.1% for surgical patients vs 11% for patients

Study Name	Study Type and Inclusion Criteria	Measured Outcomes and Follow-Up	Results
	randomized to medical management vs CEA		medically treated.
ACST (2004)	Multicenter, prospective trial with 3,120 patients with asymptomatic >60% stenosis (DUS) randomized to medical management vs CEA	Composite of perioperative MI, CVA, or death and nonperioperative stroke Follow-up 3.4 y	**5-year estimate** was 6.4% for surgical patients vs 11.8% for patients medically treated.

CEA, carotid endarterectomy; CVA, cerebrovascular accident; DUS, duplex ultrasonography; MI, myocardial infarction; TIA, transient ischemic attack.

TABLE 28.6 Trials of Carotid Endarterectomy in Symptomatic Patients

Study Name	Study Type and Inclusion Criteria	Measured Outcomes and Follow-Up	Results
NASCET (1991)	Multicenter, prospective trial with 659 patients with TIA/stroke <120 d and 70%-99% stenosis (on angiogram) randomized to medical management vs CEA	Cumulative risk of any ipsilateral stroke Composite of any stroke and death Follow-up 1.5 y	**Cumulative risk of ipsilateral stroke**: 9% for surgical vs 26% for medically treated ($P <$ .001) **Risk of any stroke or death:** 15.8% for surgical vs 32.3% for medically treated ($P <$ .001)
ESCT (1998)	Multicenter, prospective trial with 3,024 patients with TIA/stroke <6 mo with any stenosis (on	Composite outcome of major	**3 y estimate in patient with >80% stenosis** was 14.9% for

Study Name	Study Type and Inclusion Criteria	Measured Outcomes and Follow-Up	Results
	angiogram) randomized to medical management vs CEA	stroke and death Follow-up 6.1 y	surgical vs 26.5% for medically treated.

CEA, carotid endarterectomy; TIA, transient ischemic attack.

b. Complications of CEA

Major complications of CEA include MI, stroke, and death. Other complications include bleeding and wound hematoma, cranial nerve injury, wound infection, bradycardia, hyper- or hypotension, and, rarely, seizures and intracerebral hemorrhage. CEA should only be performed at institutions where the perioperative stroke and death rate is at the most <3% in asymptomatic patients and <6% in symptomatic patients.

3. CAS

Since the first description of carotid angioplasty in 1980, a number of registry studies and trials have been published, reporting high rates of procedural success. However, percutaneous carotid angioplasty was rarely performed as a stand-alone procedure because of unacceptably high rates of recoil, restenosis, and adverse procedural outcomes. Major advances have been made since with the development of enhanced embolic protection devices and dual-layered stents that lead to further improvement in outcomes. As with any other intervention, there are data showing a positive relationship between higher operator or institutional volume and experience for CAS outcomes.

a. Major trials

See **Tables 28.7** to **28.9**

TABLE 28.7 Contemporary Trials Comparing CAS and CEA That Included Only Asymptomatic Patients

Study Name	Study Type and Inclusion Criteria	30-Day Stroke/Death/MI
ACT-1 (2016)	Multicenter prospective trial with 1,453 asymptomatic patients with >70% (on DUS or angiography) randomized to CAS vs CEA	CAS = 2.9% vs CEA = 1.7% (*p* = NS)
SPACE-2 (2020)	Multicenter prospective trial with 513 asymptomatic patients (unable to enroll the initially planned 3,550 due to low recruitment) with >50%-70% (on DUS) randomized to CAS vs CEA vs medical treatment	CAS = 2.5% vs CEA = 2.5% (*p* = NS)
ACST-2 (2021)	Multicenter, prospective trial with 3,625 asymptomatic patients with >60% stenosis (on DUS) randomized to CAS vs CEA	CAS = 3.9% vs CEA = 3.2% (*p* = NS)

CAS, carotid artery stenting; CEA, carotid endarterectomy; DUS, duplex ultrasonography; MI, myocardial infarction; MRA, magnetic resonance angiography; NS, not significant.

TABLE 28.8 Trials Comparing CAS and CEA That Included Only Symptomatic Patients

Study Name	Study Type and Inclusion Criteria	Results	Notes
EVA-3S (2006)	Multicenter prospective trial with 527 patients with >60% symptomatic stenosis (confirmed by angiography or DUS+MRA) randomized to CAS vs CEA	• 30 d incidence of any stroke or death 3.9% after CEA vs 9.6% after CAS • 30 d incidence of disabling stroke or death 1.5% after CEA vs 3.4% after CAS • 6 mo incidence of any stroke or death 1.5% after CEA vs 3.4% after CAS **All three with statistically**	Stopped early for both safety and futility Initially designed as a noninferiority trial

Study Name	Study Type and Inclusion Criteria	Results	Notes
		significant differences	
SPACE (2006)	Multicenter prospective trial with 1,183 patients with >70% symptomatic stenosis (on DUS) randomized to CAS vs CEA	• 30 d incidence of death or stroke 6.34% after CEA vs 6.84% after CAS (*P* = .09)	Designed as a noninferiority trial
ICSS (2010, 2014)	Multicenter prospective trial with 1,713 patients with >50% symptomatic stenosis (on invasive or noninvasive imaging) to CAS vs CEA	• 120 d incidence of disabling stroke or death 3.2% after CEA vs 4% after CAS (*P* = .006) • 4 y follow-up 5 y risk of any stroke 9.4% after CEA vs 15.2% after CAS (*P* = .04), **however, mainly nondisabling strokes**	

CAS, carotid artery stenting; CEA, carotid endarterectomy; DUS, duplex ultrasonography; MRA, magnetic resonance angiography.

TABLE 28.9 Trials Comparing CAS and CEA That Included Both Symptomatic and Asymptomatic Patients

Study Name	Study Type and Inclusion Criteria	Results
SAPPHIRE (2008)	Multicenter prospective trial with 260 **high-risk** patients (>50% **symptomatic** stenosis, >80% **asymptomatic** stenosis) to CAS vs CEA	• 30 d composite of death, stroke, MI + ipsilateral stroke or death from neurologic cause between 31 and 1 y: 20.1% after CEA vs 12.2% after CAS (noninferiority *P* = .004) • 1 y composite as above 16.5% after CEA vs 16.8%

Study Name	Study Type and Inclusion Criteria	Results
		after CAS (*P* = .95)
CREST (2010, 2016)	Multicenter prospective trial with 2,502 patient with symptomatic or asymptomatic patients (50% on angiography, 70% or more on DUS, CTA, MRA)	• 4 y composite of death, stroke, MI, ipsilateral stroke: 6.8% after CEA vs 7.2% after CAS (*P* = .51) • 10 y composite of death, stroke, MI, ipsilateral stroke: 9.8% after CEA vs 13.4% after CAS (*P* = .4)

CAS, carotid artery stenting; CEA, carotid endarterectomy; DUS, duplex ultrasonography; CTA, computed tomography angiography; MRA, magnetic resonance angiography.

b. Complications of CAS

(1) Minor complications

(a) Carotid artery spasm. Spasm of the ICA following distal deployment of a filter usually resolves after removal of the filter wire. A flow-limiting spasm could be a potential hazard in the presence of occlusion of the contralateral ICA or in case of incomplete circle of Willis formation.

(b) Transient bradycardia. Transient sinus bradycardia is a relatively common physiologic response to balloon dilatation of the carotid bifurcation lesions, usually leading to hypotension. It can be avoid usually by small pretreatment with IV atropine.

(c) Sustained hypotension. Occurs in 4% to 11% of carotid stenting procedures and is usually not associated with clinical adverse events. Mostly due to carotid sinus reflex leading to improper activation of baroreceptors and subsequent development of sustained hypotension. Usual treatment is IV hydration and small dose of vasopressors.

(2) Major complications

(a) **Distal embolization.** Caused by release of material from the site of intervention. Usual risk factors are poor proper pretreatment with DAPT, insufficient heparin during the procedure, and aggressive procedure technique. The extensive use of embolic protection devices has been shown to reduce the incidence of this complication.

(b) **Intracranial hemorrhage.** Cerebral hemorrhage is a life-threatening and usually fatal complication due to excessive anticoagulation and poorly controlled hypertension, in the presence of a vulnerable aneurysm.

(c) **Hyperperfusion syndrome.** After revascularization, the increased perfusion overwhelms the ability of the dilated arterioles to constrict in the setting of long-standing hypoperfusion with impaired autoregulation of the microcirculation. Clinical manifestations are various with ipsilateral headache, markedly elevated BP, altered mental status, and seizures. Current management of the hyperperfusion syndrome consists of early recognition, careful monitoring, and aggressive BP control.

(d) **Carotid artery dissection.** When there is suspicion of a carotid dissection, it is essential to maintain the guidewire position until the final angiographic assessment has been completed and the presence or absence of dissections has been ascertained. Usual treatment is additional stenting.

(e) **Carotid artery perforation**. Extremely rare complication, usually linked to aggressive balloon dilatation

(f) **Acute stent thrombosis.** The use of appropriate doses of adjunctive DAPT has lowered the rates of this remarkably rare complication.

(g) **Contrast agent encephalopathy.** Causing transient neurologic syndrome related to the use of large volume of contrast. Patient typically completely recovers within 24 hours.

c. Postprocedural antiplatelet management. Patients undergoing carotid stenting should be preloaded with ASA and clopidogrel at least 2 days prior to the procedure if possible. After the procedure, **lifelong ASA therapy should be instituted**, and **clopidogrel (75 mg daily) should be continued for at least 6 weeks**. For patients with recurrent symptoms or a history of neck irradiation, clopidogrel should be continued indefinitely. The incidence of restenosis after carotid stenting is lower than after coronary stenting and ranges between 1% and 6% per year. Patients should be followed in the outpatient setting with routine clinical assessment as well as DUS monitoring after carotid stent implantation.

C. Patient selection for CAS versus CEA. There is an abundance of RCT data demonstrating similar safety and efficacy of both carotid stenting and CEA for the treatment of severe carotid artery stenosis. Whichever approach is chosen, it is important to recognize the importance of proper patient selection as well as adherence to guideline-recommended medical therapy. Furthermore, given the potential for devastating complications with either procedure, both should be performed only by experienced operators. The choice between CEA and CAS should be driven by specific patient comorbidities and features of their vascular anatomy.

Some anatomic features might make ***CAS a better option*** compared to CEA: surgically inaccessible lesions (above C2 and below the clavicle), ipsilateral neck irradiation, spinal immobility, and contralateral carotid artery occlusion. Other clinical comorbidities such as heart failure with reduced ejection fraction (HFrEF), unstable angina, advanced CAD, and severe pulmonary disease might also push the clinician toward the less invasive option for revascularization of CAS over CEA.

Some anatomic features might make ***CEA a better option*** compared to CAS: high-grade aortic arch atheroma, type II/III aortic arch, tandem lesions, two or more acute (90°) bends, and circumferential lesion calcification.

Despite the well-established efficacy of both carotid stenting and CEA, the importance of aggressive medical management cannot be understated. Many of the aforementioned studies were conducted prior to the advent of the most current established medical regimens, leading many to question the impact this may have on the role of carotid revascularization. Indeed, despite increasingly complex patients with carotid disease, stroke rates have continued to decline in patients with severe asymptomatic carotid disease who are being medically managed.

D. Combined CEA and CABG

Patients with severe coronary disease may have severe carotid disease, and surgery in this population is a high-risk procedure. The optimal treatment strategy remains controversial. In this setting, options include simultaneous CABG and carotid intervention, staged procedures, or CABG without carotid intervention.

In a single-center study conducted at our institution, 350 patients who underwent carotid revascularization within 90 days prior to open-heart surgery (OHS) were analyzed with respect to rates of a composite of all-cause death, stroke, or MI. The population included 45 staged CEA-OHS procedures, 195 combined CEA-OHS procedures, and 110 staged CAS-OHS procedures. All patients who underwent carotid stenting were required to complete a 3- to 4-week course of DAPT prior to OHS. In this cohort, patients who underwent staged CEA-OHS experienced the highest rates of the primary outcome in the short term, primarily driven by the occurrence of MI. The early event rates ***were similar between the combined CEA-OHS and staged CAS-OHS groups. However, after 1 year, the patients in the CAS-OHS group experienced fewer events than both the staged and combined CEA-CABG groups***. Thus, provided that concomitant carotid revascularization is required and OHS can be delayed 3 to 4

weeks to allow for a course of DAPT to be completed, CAS followed by OHS may be the most attractive strategy.

Although, in ideal circumstances, OHS would be delayed when carotid stenting is performed, this is not always feasible. In a small, single-center study comprising 20 patients who underwent CAS prior to CABG, CABG could be performed safely at a mean of 6.4 days poststent implantation. Despite the use of DAPT, there were no significant bleeding complications, and no strokes or deaths were seen at a mean follow-up of 486 days. Although perhaps not generalizable to all patients, this study does suggest that in carefully selected patients in whom carotid revascularization is needed and CEA is significantly high risk, early CABG following carotid stenting could be an option.

It is important to note that not all patients with severe carotid stenoses who are scheduled for OHS require carotid revascularization. Patients who are at low risk from a neurologic perspective can have their carotid disease medically managed and undergo their OHS without concomitant carotid intervention. High-risk patients, including symptomatic individuals and those with significant contralateral disease, may benefit from either staged CAS-OHS or combined CEA-OHS, depending on the specific patient and procedural characteristics.

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SECTION VI

Adult Congenital Heart Disease

EDITORS: Joanna Ghobrial and Margaret Fuchs

CHAPTER 29

Atrial Septal Defect and Patent Foramen Ovale

Simrat Kaur and Margaret Fuchs

I. INTRODUCTION

A. Atrial septal defects (ASDs) constitute approximately 5% to 10% of congenital heart disease. Excluding bicuspid aortic valve, ASD is the most common form of congenital heart defect found among adults and is the most common acyanotic shunt lesion.

B. Often, an atrial communication may go unrecognized into adulthood because the clinical symptoms and physical manifestations may be subtle.

C. Although survival into adulthood is the rule, overall life expectancy is decreased in patients with an unrepaired ASD. Long-term exposure to chronic right heart volume overload can have deleterious effects, such as atrial arrhythmias, pulmonary vascular disease, and right heart failure. These clinical findings are directly related to patient age, with almost all patients becoming symptomatic by the fifth or sixth decade. The presence of an atrial communication is also a potential source of paradoxical embolus.

D. A patent foramen ovale (PFO) is a specific form of interatrial communication caused by incomplete closure of the foramen ovale after birth. PFOs are present in 25% to 30% of the general population. The prevalence of PFO in patients with cryptogenic stroke is approximately 40% to 50%.

E. Atrial septal aneurysms are congenital outpouchings of the atrial septum near the fossa ovalis. They can be detected in up to 10% of the general population and in up to 30% of patients with cryptogenic stroke, frequently with a concomitant PFO.

II. ANATOMY AND EMBRYOLOGY. In the fourth week of embryonic life, the primitive atrium is first partitioned into right (RA) and left atria (LA) by the growth of the septum primum—a thin, crescent-shaped membrane that grows from the roof of the primitive atrium toward the endocardial cushions located between the atria and the ventricles. An atrial communication initially persists as the ostium primum that is composed of the free edge of the septum primum and the endocardial cushions. Before the closure of the ostium primum, fenestrations due to tissue reabsorption occur in the superior portion of the septum primum that coalesce to form the ostium secundum in the fifth to sixth weeks of embryonic life. As the septum primum fuses with the endocardial cushions, the ostium secundum maintains an RA-to-LA flow that is important in the fetal circulation. The septum secundum then develops from the anterosuperior in-folding of the atrial roof to the right of the septum primum, and the inferior limb of the septum secundum fuses with inferior atrial septum, joining the endocardial cushion. The superior limb of the septum secundum lies over the ostium secundum and leaves open the PFO during fetal life. The septum secundum forms an incomplete partition of the atria, leaving a foramen ovale (ie, fossa ovalis). Septum secundum forms the superior margin of the fossa ovalis, referred to as the annulus ovalis, while the septum primum forms the flap valve, or the valve of fossa ovalis, and allows for the continued right-to-left shunting in the fetal circulation. At birth, when LA pressure increases, the septum primum and the septum secundum fuse, thus closing the PFO. A "true ASD" results from a deficiency in septal development or the resorption of atrial tissue, whereas a **PFO results from failure of this septum primum flap to adequately seal the fossa ovalis**. At autopsy, a "probe-patent" PFO remains in 25% to 30% of patients.

During development, the septum becomes very mobile if there is overabundant or weakened septal tissue. This can be visualized during echocardiography, and the degree of excursion can be measured. If the maximal right-left excursion of the interatrial septum is **15 mm or more or** the excursion of the aneurysm beyond the plane of the residual atrial septum into the LA or RA is at least 10 mm, this abnormality is called an

atrial septal aneurysm. If the atrium septum is mobile but does not meet these criteria, it is referred to as a redundant atrial septum.

ATRIAL SEPTAL DEFECTS

I. ATRIAL SEPTAL DEFECT TYPES (FIGURE 29.1)

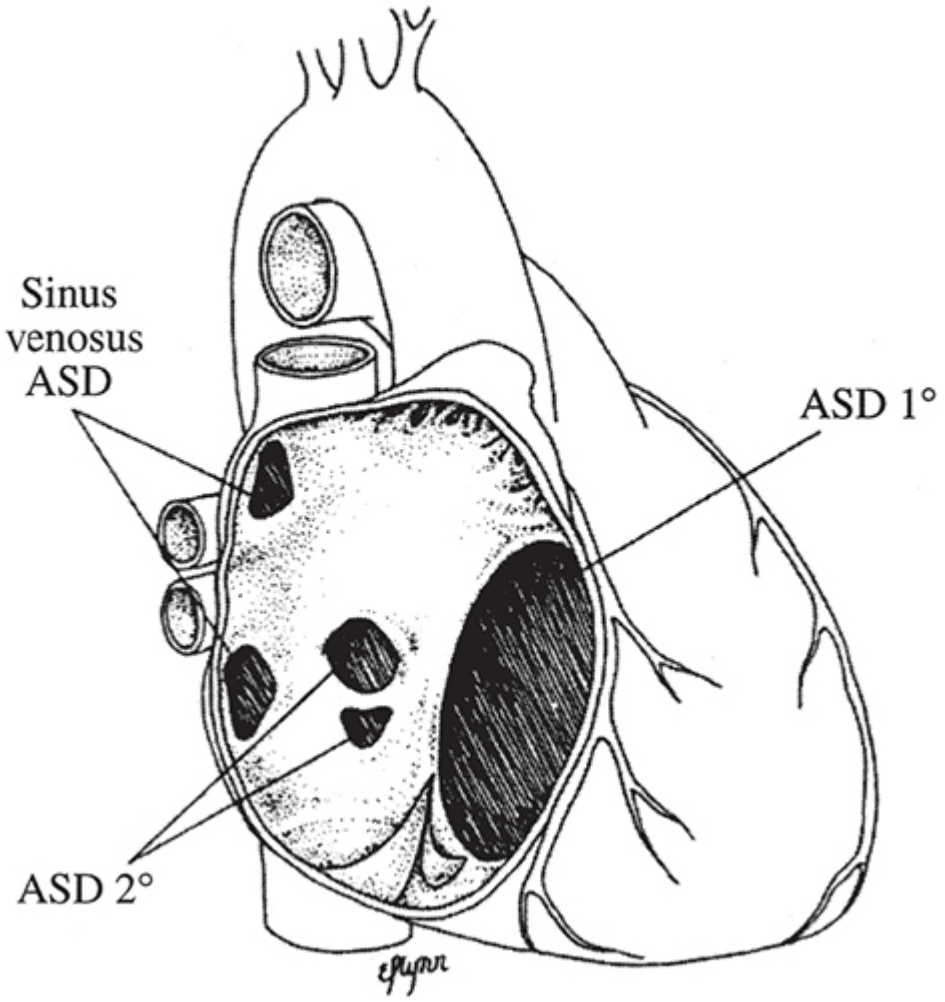

FIGURE 29.1 Diagrammatic representation of common atrial septal defects (ASDs). 1°, primum; 2°, secundum. (Reprinted from Fyler DC, ed. *Nadas Pediatric Cardiology*. Hanley & Belfus; 1992. Copyright © 1992 Elsevier. With permission.)

A. **Secundum ASDs** constitute the most common type, accounting for 70% to 75% of ASDs. This defect, a true defect of the atrial septum, is located in the midportion of the atrial septum, within or including the fossa ovalis. It occurs due to failure of resorption of the septum primum or inadequate growth of the septum secundum. Defects result from a deficient septum primum or an abnormally large ostium secundum. This type of ASD is 2 times more common in female patients. Isolated secundum ASD has been associated with mitral valve prolapse and other forms of congenital heart disease.

B. **Primum ASDs** account for 15% to 20% of ASDs and are part of the spectrum of atrioventricular (AV) septal defects (previously known as AV canal defects or endocardial cushion defects). A complete defect occurs due to the lack of fusion between superior and inferior endocardial cushions, thus forming separate anterior and posterior leaflets along the ventricular septum and resulting in primum ASD. This also results in the downward displacement of the anterior mitral leaflet to the same level of septal tricuspid leaflet. This is also associated with a deficiency of the ventricular component of the AV septum that, in turn, leads to anterior displacement of the left ventricular (LV) outflow tract, resulting in elongation and producing a "gooseneck" deformity. These defects occur in the inferior-anterior portion of the atrial septum and are frequently associated with a cleft in the anterior leaflet of the mitral valve, leading to varying degrees of mitral regurgitation. In their complete form, they include a ventricular septal defect and a common AV valve. Depending on the severity of dysfunction of the mitral valve, these patients may become symptomatic at a young age. Complete AV septal defects are commonly associated with trisomy 21, as are other forms of congenital heart disease.

C. **Sinus venosus** defects constitute 5% to 10% of ASDs. Distinct from the "true" ASDs described previously, these lesions involve the portion of the atrial wall derived from the sinus venosus (ie, there is no direct communication between the RA and the LA). **Sinus venosus defects** are typically at the orifice of the superior vena cava (SVC) at the junction of the RA or, less frequently, in the region of

the inferior vena cava (IVC). These sinus venosus defects are commonly associated with partial anomalous pulmonary venous connection of the right pulmonary veins and require a high index of suspicion for diagnosis because they are generally not visualized by standard transthoracic echocardiography (TTE). Other imaging modalities, including transesophageal echocardiography (TEE), magnetic resonance imaging (MRI), or computed tomography, are generally required for definitive diagnosis and allow for confirmation of the pulmonary venous anatomy. These defects should be considered in any patient with unexplained RA or right ventricular (RV) dilation.

D. **Unroofed coronary** sinus (CS) (or CS ASD) accounts for <1% of atrial shunting lesions. In this defect, there is partial "unroofing" of the CS, such that it communicates with the LA and, therefore, allows for flow from the LA through the CS into the right heart. These defects are commonly associated with other forms of congenital heart disease, such as complete AV septal defect, or can be associated with an absence of CS and a left SVC that drains into the LA.

II. **PATHOPHYSIOLOGY.** The magnitude and direction of the shunt through the ASD depend on the size of the defect as well as relative pressures in the RA and LA. Any condition that causes reduced LV compliance, such as LV hypertrophy or LV scar, or increased LA pressure, such as mitral stenosis, will increase the degree of left-to-right shunting. Conversely, conditions that cause reduced RV compliance, such as pulmonary hypertension or pulmonary stenosis, or increased RA pressure, such as tricuspid stenosis, will reduce the degree of left-to-right shunting and, in some instances, even lead to shunt reversal. In general, the ASD is expected to be at least 10 mm in its greatest dimension to cause a significant shunt, although this can be hard to measure as most ASDs are not circular. **A left-to-right shunt is considered significant when the ratio of pulmonary-to-systemic blood flow, or shunt fraction (Q_p/Q_s), is >1.5:1.0 or when right heart chamber dilation is present.**

III. **CLINICAL MANIFESTATIONS.** The clinical presentation of a patient with an ASD results from the effects of long-term left-to-right shunting and

subsequent volume loading of the right heart. The age at which the symptoms occur is variable and does not always correlate with the size of the defect.

A. Exercise intolerance with **fatigue** and **dyspnea** may occur, though it is sometimes insidious in onset such that the patient does not appreciate their deficit until after the defect has been closed. Late findings include **supraventricular arrhythmias**, such as atrial fibrillation or flutter, severe irreversible **pulmonary vascular disease**, and, eventually, **right heart failure**. Occasionally, a **paradoxical embolus** causing a stroke or transient ischemic attack (TIA) is the first clue to an ASD.

B. The physical findings may include a parasternal lift, the characteristic **wide or fixed split-second heart sound**, and a **soft systolic murmur at the second left intercostal space** because of increased flow across the pulmonary valve. If the shunt is more than a shunt fraction (Q_p/Q_s) of 2.5:1, there may be a diastolic murmur secondary to increased flow across the tricuspid valve. A loud P_2 component of the second heart sound indicates the presence of pulmonary hypertension, which can affect up to 20% of patients; if cyanosis is present, this generally suggests advanced pulmonary hypertension with reversal of shunt flow (**Eisenmenger syndrome**). An important clue to the presence of Eisenmenger syndrome is an oxygen saturation that does not significantly improve with supplemental oxygen. Another physical examination finding that may be encountered is a holosystolic murmur characteristic of mitral regurgitation, which should cause the listener to suspect a cleft mitral valve and diagnosis of AV septal defect.

IV. LABORATORY EXAMINATION

A. Electrocardiogram (ECG). The ECG can provide clues to the possibility of an ASD. The rhythm may be sinus, but it may also be atrial fibrillation or atrial flutter. Inverted P waves in the inferior leads suggest an absent or nonfunctional sinus node, as may be seen with a sinus venosus defect.

1. Secundum ASD

a. RSR′ pattern in lead V_1

b. QRS duration <0.11 seconds (incomplete right bundle branch block)

c. Right-axis deviation

d. RV hypertrophy

e. First-degree AV block (20%) RA enlargement (about 50%) with a prominent P wave in lead II

f. Notched R wave of the QRS complex in inferior limb leads —"crochetage" pattern

2. **Primum ASD**

a. RSR′ pattern in lead V_1

b. Superior left-axis deviation

c. First-degree AV block, classically seen with right bundle branch block and left anterior fascicular block

B. Chest roentgenogram may reveal cardiomegaly because of right heart enlargement. With large left-to-right shunts, the central pulmonary arteries and vascular markings may appear prominent. In the setting of advanced pulmonary vascular disease, however, the pulmonary arteries may appear large but have oligemic peripheral lung fields, the so-called vascular pruning.

V. DIAGNOSTIC STUDIES

A. Echocardiography is the primary means by which an ASD is diagnosed. TTE can document the size of the defect as well as the direction of the shunt flow and occasionally the location of the pulmonary veins in the younger patient. Transesophageal studies are generally required for a full anatomic assessment in the adult. An ASD should be suspected when right-sided chamber enlargement is noted on echocardiography and no other cause is identified.

1. Typical transthoracic views for imaging an ASD include the parasternal short-axis view, the apical four-chamber view, and the subcostal coronal and sagittal views. Findings include RA and RV enlargement, which indicates a functionally important defect. An

estimate of RV pressure should be made via the jet of tricuspid insufficiency (or via the jet of pulmonary regurgitation if tricuspid regurgitation [TR] is insufficient), and evidence for RV pressure and volume overload should be noted via observation of ventricular septal motion in systole and diastole, respectively. Evidence of left-to-right (or right-to-left) shunting across the defect should be demonstrated using color Doppler techniques. Evidence of RA and RV enlargement in the absence of an obvious cause on echocardiography, such as TR or an ASD, should prompt a search for a sinus venosus defect and/or partial anomalous pulmonary venous drainage. Intravenous contrast (ie, agitated saline) and TTE can identify a shunt, but TEE is usually required to demonstrate a sinus venosus defect. Of note, in isolated partial anomalous pulmonary venous return, the intravenous contrast study will be negative.

2. TEE is usually required in adult patients for further anatomic definition and to determine whether the defect is amenable to percutaneous closure. Contrast studies with agitated saline are helpful in confirming the presence and location of atrial shunting. The mid-esophageal four-chamber and bicaval views are preferred, with an injection of agitated saline through an upper extremity vein. **Injection into the left arm** may be particularly helpful to establish the presence of a persistent left SVC that drains into the CS or directly into the LA. In the diagnosis of a sinus venosus defect, care must be taken to evaluate the location of the pulmonary veins for evidence of anomalous drainage.

B. **Cardiac catheterization** is typically not required for diagnostic purposes, except to assess pulmonary pressures and resistance, to assess for coronary artery disease before planned surgical closure in the adult patient, or as part of a planned transcatheter device closure. Right heart catheterization can be performed in most cases using a standard end-hole catheter. The lateral camera is helpful in directing the catheter posterior before advancing across the ASD. Our standard is to perform a complete right heart catheterization, including oximetry measurements and hemodynamic assessment.

1. Oximetry samples obtained during catheterization demonstrate a step-up within the RA because of shunting across the defect. Careful interrogation of innominate vein saturation and SVC saturation is important to exclude a step-up at the SVC level that would support the existence of associated partial anomalous pulmonary venous drainage. Desaturation in the LA systemically confirms right-to-left shunting and should prompt further investigation of RV and pulmonary artery pressures. Other diagnoses producing a similar picture include large ventricular septal defects with TR, partial or complete AV canal defects, or systemic arteriovenous fistulas.

   The degree of shunting can be assessed by calculating the **shunt fraction (Q_p/Q_s)**, which is the ratio of pulmonary blood flow (Q_p) to systemic blood flow (Q_s). Oximetry values, obtained during right heart catheterization and used previously to determine if a step-up is present, can be helpful for shunt calculation as follows:

$$Q_p / Q_s = \frac{\text{aortic saturation} - \text{mixed venous saturation}}{\text{pulmonary vein saturation} - \text{pulmonary artery saturation}}$$

   The mixed venous saturation is obtained in the setting of an ASD by multiplying the SVC saturation by 3, adding the IVC saturation, and then dividing the sum by 4. If the pulmonary vein saturation is not directly measured, it can be assumed in the absence of considerable lung disease to be 95%.

2. Hemodynamic assessment may reveal modest elevations in RV and pulmonary artery pressures. A critical assessment is the comparison of pulmonary artery pressure with systemic pressure and the measurement of pulmonary vascular resistance. If pulmonary pressures are elevated, the response to oxygen or other vasodilators should be assessed. Alternatively, the ASD can be balloon occluded with assessment of hemodynamics to ensure that closure is safe. Examples of the usual catheterization findings with and without pulmonary vascular disease are illustrated in **Figure 29.2**.

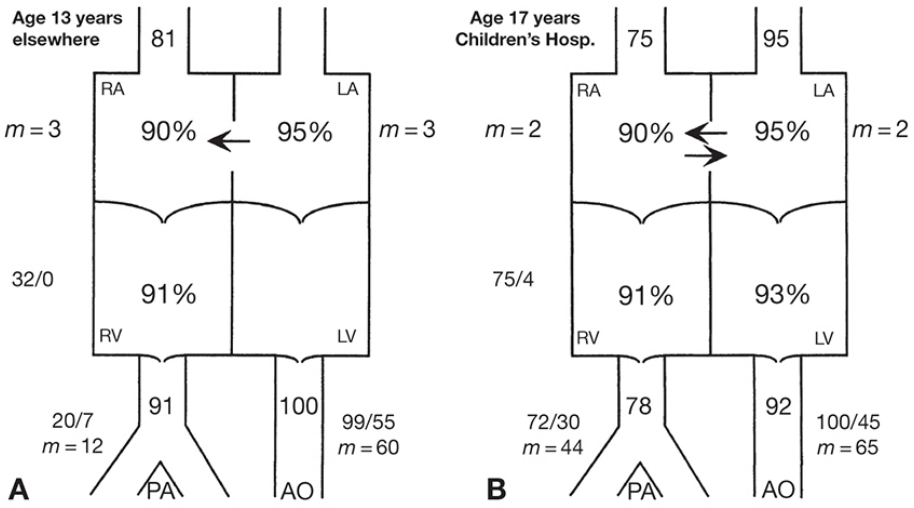

FIGURE 29.2 Catheterization data derived from two studies of the same female patient. **A.** The data obtained at age 13 were interpreted as compatible with a small atrial septal defect of insufficient size to require closure. **B.** Some years later, she had developed pulmonary vascular obstructive disease and was no longer shunting enough to recommend surgery. Death occurred 5 years later. AO, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; numeric values within the schematic, oxygen saturation (%); numeric values outside the schematic, pressure (mm Hg). (Adapted from Fyler DC, ed. *Nadas Pediatric Cardiology*. Hanley & Belfus; 1992. Copyright © 1992 Elsevier. With permission.)

Using a derivative of Ohm's law, $P = Q \times R$, an ASD will increase the flow (Q) to the lungs and, therefore, increase the pulmonary pressure (P) without a significant change in resistance (R). According to 2018 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of adults with congenital heart disease, findings that may preclude eventual ASD closure include one or more of the following: pulmonary systolic pressure is more than two-thirds of the systemic vascular resistance or an indexed pulmonary vascular resistance of more than two-thirds of systemic pressure. Encouragingly, however, many of these patients have excellent response to pulmonary vasodilator therapy and can become ASD

closure candidates after treatment of their pulmonary hypertension.

3. Angiography is typically not necessary for diagnostic purposes. Some transcatheter closure device protocols include angiography, typically performed in the right pulmonary vein, or levophase from a main pulmonary artery injection in the left anterior oblique and cranial projections. This may be an important way to confirm the absence of additional defects, such as partial anomalous pulmonary venous drainage, before proceeding with transcatheter device closure.

C. Cardiac MRI can be helpful, as it can provide additional information beyond echocardiography. MRI provides an excellent assessment of RV size and function, especially if views obtained with echocardiography are not diagnostic. MRI is also excellent at determining the location of the pulmonary veins as well as calculating ventricular volumes and shunt fraction. In patients who are not considered immediate candidates for ASD closure, serial MRI over time can be used to trend RV size and function; progressive RV enlargement or the onset of RV dysfunction should trigger the provider to refer for closure.

VI. TREATMENT

Medical intervention is typically not required preoperatively because many patients are asymptomatic. Congestive symptoms may be improved with standard diuretic therapy. Rhythm disturbances such as atrial fibrillation require attention with respect to rate control and anticoagulation. Endocarditis antibiotic prophylaxis during dental procedures is not required in the setting of an isolated ASD before surgery, but it is warranted for 6 months after surgical or device closure (AHA/ACC class IIa).

A. Surgical or transcatheter therapy. The mainstay of therapy is closure of the defect by surgical or transcatheter techniques. Because of the reduced life expectancy associated with an unrepaired ASD, closure is recommended at diagnosis if there is evidence of a hemodynamically significant shunt ($Q_p/Q_s \geq 1.5:1$), evidence of right heart dilation, symptoms attributed to the shunt lesion, or certainly if

a paradoxical embolism has occurred. In the setting of pulmonary hypertension, pulmonary reactivity to vasodilators should be documented and a net left-to-right shunt demonstrated during catheterization before consideration for closure. In older patients with secundum ASD, LA hypertension or diastolic dysfunction should be assessed before abrupt closure of a secundum ASD to avoid pulmonary edema, pulmonary venous hypertension, or exacerbation of atrial arrhythmias.

Situations in which ASD closure should not be pursued are listed in **Table 29.1** and include advanced, irreversible pulmonary hypertension (Eisenmenger syndrome) and severe LV dysfunction with elevated LA pressure.

TABLE 29.1 Conditions for Which ASD Closure Is Not Favored

Defect is too small to be hemodynamically significant.
Pulmonary hypertension is too advanced.
Severe LV dysfunction, where ASD is acting as a "pop-off" valve for the LV
In most cases where ASD is diagnosed in pregnancy, closure can be postponed until 6 mo after delivery.

ASD, atrial septal defect; LV, left ventricular.

B. Primary surgical closure has been the standard approach for many years. Generally, surgical closure is the treatment of choice for primum, sinus venosus, and CS defects. Patients with secundum ASDs and anatomy that is not amenable to percutaneous closure (ASD diameter >35 mm; inadequate septal rims to permit device deployment; or close proximity to AV valves, CS, or venae cavae) are also candidates for open surgical closure. Depending on the defect size and location, the secundum ASD can be closed by primary suture or, if needed, using an autologous pericardial or synthetic patch. Primum defects require patch closure as well as repair of the likely cleft mitral valve (if not undertaken during childhood). Repair of sinus venosus defects is technically more challenging, as the pulmonary veins often have anomalous drainage and require rerouting. Important preoperative risk factors include older age at

operation, the presence of atrial fibrillation, and elevated pulmonary pressure and resistance. Postoperatively, patients are at risk for heart block, which is a significant complication in these cases. They are also at risk for postpericardiotomy syndrome, more so than after other surgery for congenital defects. Atrial arrhythmias may persist in short- and long-term follow-ups because the RA and RV sizes may take time to return to normal, so anticoagulation is often recommended for several months after surgery, depending on the patient's postoperative rhythm. In some centers, prophylactic beta-adrenergic blockade is advocated empirically for 3 to 6 months after surgery.

C. **Transcatheter closure** of a secundum ASD is now considered the treatment of choice as an alternative to surgical closure. Any patient with an isolated secundum ASD may be suitable for transcatheter closure, which is generally assisted with TEE or intracardiac echocardiography in addition to fluoroscopy. Catheter closure decreases hospital length of stay, avoids median sternotomies and their possible complications, and significantly speeds up postprocedural recovery. With the devices available today, defects with a resting "stop-flow" diameter of <38 mm may be considered. In general, the gently stretched "stretch" diameter of the defect is approximately 2 to 8 mm greater than the "stop-flow" diameter. The defect must be located centrally with adequate rims for the device to be positioned, without interference from nearby intracardiac structures, such as the AV valves, CS, or pulmonary veins. The currently U.S. Food & Drug Administration (FDA) approved devices for the closure of secundum ASDs are the Amplatzer Septal Occluder (Abbott Medical, Abbott Park, IL), approved in December 2001, and the Cardioform Septal Occluder (WL Gore & Associates, Flagstaff, AZ) approved in May 2018. Studies have proved the safety and efficacy of catheter-based closure of a secundum ASD compared with surgical closure. The Amplatzer device consists of two disks made of nitinol wire mesh filled with polyester fabric and separated by a narrower waist, which is appropriately fitted by balloon sizing. It is inserted percutaneously through a 6F to 12F sheath, depending on the

device size required. The Cardioform device is also disk like and consists of expanded polytetrafluoroethylene patch material supported by a nitinol wire frame. Intraprocedural or short-term complications such as device embolization pulmonary vein injury or stroke are quite rare at less than 1%, whereas long-term possible complications such as device erosion described with the Amplatzer septal occlude device are even rarer at an estimated 0.04% to 0.3%. Successful closure of the defect is achieved in up to 95% of all patients. After closure, antiplatelet therapy, frequently aspirin or with the addition of clopidogrel, is prescribed for a period of 6 months, after which time the device is generally believed to be endothelialized. In patients with sinus venosus ASD who are deemed high risk for surgery, covered stent correction using Cheatham-platinum stent (NuMED Inc) is suggested as a possible therapy. A covered stent of adequate length is expanded in the SVC to the SVC-RA junction, occluding the superior sinus venosus defect while maintaining drainage of anomalous pulmonary veins behind the covered stents into the LA.

II. PROGNOSIS. Hemodynamically significant ASDs are associated with increased morbidity and mortality. Long-term outcomes can be improved by closing these defects, especially if performed early in life. Atrial arrhythmias are common, especially in older patients, and are the result of long-standing atrial enlargement. Arrhythmias, particularly atrial flutter and atrial fibrillation, contribute to a significant portion of the morbidity and mortality of older patients, particularly the risk of systemic embolization and the resultant stroke. It has been demonstrated that age at the time of surgical repair is inversely related to the risk of subsequent atrial fibrillation or flutter after repair and argues for earlier closure. Some have advocated for consideration of a concomitant ablation procedure in high-risk patients, but the available data do not generally support this.

The functional capacity of patients frequently improves after closure of the ASD, and often, they do not realize how severely their functional capacity had been affected until after the defect is closed. In addition, improvements in LV filling and systemic cardiac output are seen rapidly

after defect closure. Reduced RA and RV volumes can be seen within 24 hours and continue to improve over the course of the first year following closure.

PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM

I. PATHOPHYSIOLOGY. Flow across a PFO is typically very small and generally left to right. Right-to-left shunting can occur when RA pressure exceeds LA pressure, such as during coughing or straining. These defects generally do not cause significant hemodynamic derangements and should not result in right heart enlargement unless the defect has been stretched by atrial enlargement related to other structural heart diseases. The clinical importance of an atrial septal aneurysm or a PFO is its impact on the risk of stroke. PFO features that increase the risk of a paradoxical embolus include large tunnel lengths (≥4 mm), high mobility of the valve of the foramen ovale, a well-formed eustachian valve, and a resting right-to-left shunt. A higher percentage of atrial septal aneurysm is reported in cryptogenic stroke; however, it has been difficult to establish a direct relationship between atrial septal aneurysm and stroke due to its frequent association with other cardiac abnormalities, such as PFO, ASD, and mitral valve prolapse. However, in patients with PFO-associated strokes, atrial septal aneurysm is an important predictor for recurrent stroke.

II. CLINICAL MANIFESTATIONS. Generally, these defects are asymptomatic, most often coming to attention in patients with cryptogenic (unexplained) stroke. PFO is more common in patients with cryptogenic stroke than in the general population, but PFO alone has not been shown to be an independent risk factor for cryptogenic stroke. There are now accumulating data to suggest that an isolated PFO is not associated with an increased risk of recurrent ischemic stroke. The data in patients with both a PFO and an ASD are conflicting but suggest an increased risk of recurrent stroke when both lesions are present. PFO should be suspected in young patients who sustain a stroke, as more than one-half of patients with stroke younger than 45 years have a PFO. Other less common clinical associations with PFO include migraine headaches, platypnea-

orthodeoxia syndrome, and decompression illness in divers and those who work in high altitudes.

III. DIAGNOSTIC STUDIES. Echocardiography can easily differentiate between an ASD and a PFO if the interatrial septum is well visualized. If this is not possible via a transthoracic approach, a TEE may be necessary. A simple way to determine if a shunt is present is the "**bubble study**," which is the injection of agitated saline via an upper extremity vein. If shunting is not present at rest, the patient can perform a Valsalva maneuver, which augments the right-to-left shunt. If bubbles can be seen in the LA or the LV within **three** cardiac cycles on TTE, the diagnosis of an interatrial right-to-left shunt is established. Generally, administration of agitated saline in patients with suspected right-to-left shunts is considered safe, but there have been rare case reports of cerebral ischemic events from the passage of bubbles into the systemic circulation.

TEE will likely be required in most adults for better visualization of the interatrial septum. TEE helps to differentiate between a PFO and a secundum ASD, both of which can have positive bubble studies. TEE also allows assessment of other potential sources of emboli, such as atheroma in the aortic arch, thrombus in the LA appendage, left-sided valve masses, or cardiac tumors.

IV. TREATMENT. A multidisciplinary guideline panel from Society of Cardiovascular Angiography And Interventions (SCAI) published guidelines for the management of PFO. In general, atrial septal abnormalities are not treated in patients without a PFO-associated stroke. For patients with concerns for PFO-related stroke, PFO-associated stroke causal likelihood (PASCAL) classification and risk of paradoxical embolization (RoPE) score should be utilized. In general, PFO closure is recommended in individuals aged ≤60 years, embolic stroke without alternative etiology, possible or higher likelihood of PFO-associated stroke according to PASCAL classification, and no current indications for anticoagulation. The decisions about PFO closures in patients >60 years old are more individualized since these patients were excluded from major trials. It is also recommended that, in patients who have

embolic appearing stroke (ie, atrial fibrillation or arterial thromboembolism), routine use of PFO closure is not beneficial.

A meta-analysis of four landmark trials—RESPECT with extended follow-up, REDUCE, PC, and CLOSE—included a total of 2,531 patients and found that PFO closure significantly reduced the risk of recurrent strokes compared to medical therapy (absolute risk reduction 3.3%) with a number needed to treat of approximately 30. This was further validated by individual patient data meta-analysis from the SCOPE (systemic, collaborative, PFO closure evaluation) consortium analyzing data from RESPECT, CLOSURE-1, and PC trials. This study demonstrated the benefit of using RoPE score to identify patients who would benefit from device closure. The RoPE score constitutes three vascular risk factors (diabetes, hypertension, and smoking) and a history of stroke or TIA, with the absence of each adding 1 point. The presence of cortical stroke on imaging adds another point to the score. Five points are given for age 18 to 29 years, 4 points for 30 to 39, 3 points for 40 to 49, 2 points for 50 to 59, 1 point for 60 to 69, and 0 points for >70 years. This constitutes a maximum score of 10; however, a score of 7 or more may identify patients likely to benefit from PFO closure. Patient selection for device closure is critical, as is excluding other potential sources of stroke. The devices used to percutaneously close PFO are similar in design to those used in ASD closure (Gore Cardioform Septal Occluder and Abbott Amplatzer PFO Occluder devices). Contraindications to percutaneous closure are noted in **Table 29.2**.

TABLE 29.2 Contraindications to Percutaneous PFO Closure

Presence of an alternative source of emboli
Severe pulmonary hypertension
Recent gastrointestinal bleeding
Presence of congenital heart defect that needs surgical repair
Documented hypercoagulable state
Hypersensitivity or contraindication to antiplatelet or anticoagulant therapy
Unexplained fever or infection

PFO, patent foramen ovale.

Primary surgical closure of PFO is generally not pursued unless the patient needs concomitant surgery for other conditions.

There is a dearth of data to support PFO closure in patients with migraine headaches. The Migraine Intervention with STARFlex Technology trial randomized 147 participants with severe migraine headaches and right-to-left shunt consistent with PFO to either percutaneous closure or sham procedure. After 6 months, there was no statistically significant difference in the primary end point of complete cessation of migraine headache or in a host of secondary endpoints, including change in severity, quality, and frequency of headache as well as the quality of life. As such, SCAI guidelines suggest against routine use of PFO closure devices for the treatment of migraines.

Patients with platypnea-orthodeoxia syndrome (acute arterial desaturation with a change in position from supine to upright) should be considered for closure because oxygen saturation generally improves with the successful elimination of the right-to-left shunt.

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CHAPTER 30

Ventricular Septal Defect

Simrat Kaur and Margaret Fuchs

I. INTRODUCTION. Ventricular septal defect (VSD) is one of the most common congenital heart defects, accounting for up to 40% of all cardiac anomalies. The prevalence in neonates is difficult to ascertain as many small muscular septal defects close spontaneously within the first year. Unlike many other congenital abnormalities, males and females appear to be affected equally. Membranous VSDs are most common, followed by muscular, outlet, and inlet VSDs. VSDs are often isolated lesions but can also frequently be associated with other congenital defects, particularly conotruncal defects (eg, transposition of great arteries, tetralogy of Fallot).

II. ANATOMY

A. Embryology. Partitioning of the ventricular mass begins as a muscular ridge in the floor of the ventricle near the apex. This ridge later undergoes active growth, which forms the muscular ventricular septum. Concomitantly, the conotruncal and atrioventricular (AV) endocardial cushions fuse, and the two regions meet, completing the closure of the interventricular foramen. **Figure 30.1** shows the anatomic localization of VSDs.

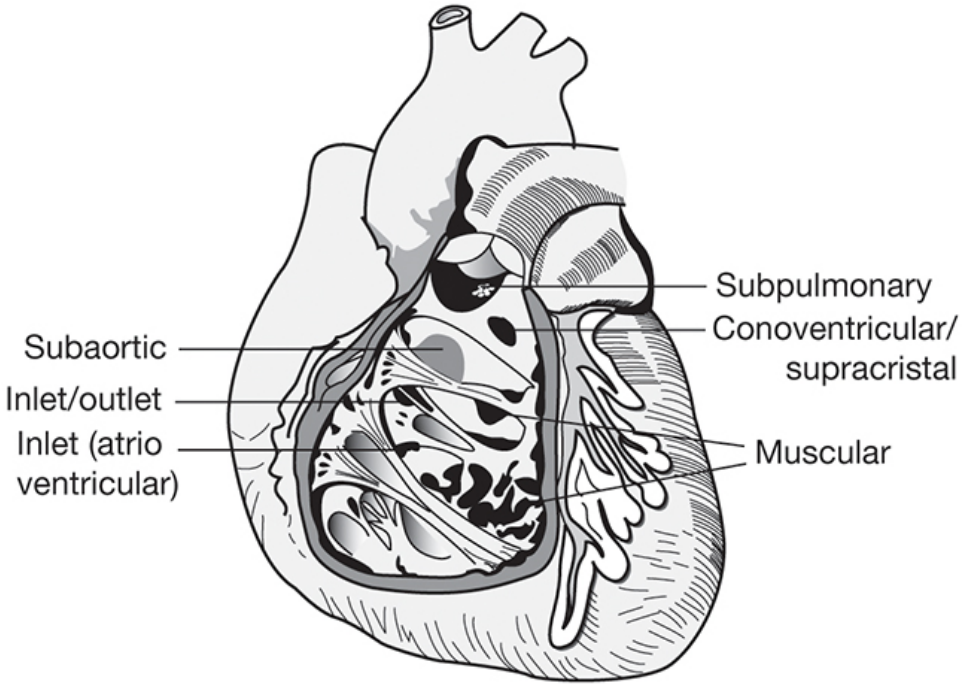

FIGURE 30.1 Anatomic localization of ventricular septal defects.

B. Defect size. The consequences of a VSD depend on the size of the defect and the pulmonary and systemic vascular resistances. Smaller defects provide higher resistance to flow and will result in lower shunt volume. **A VSD is** described as **small** when the defect size is **less than one-third of the size of the aortic root, moderate** when the defect size is **less than one-half of the size of the aortic root,** and **large** when the defect size is equal to or **larger than the size of the aortic root**. VSD size is often classified based on its hemodynamic consequences:

1. **Restrictive** VSDs result in a significant pressure gradient between the left (LV) and right ventricles (RV) (eg, pulmonary/aortic systolic pressure ratio <0.3) and are associated with a small shunt ($Q_p/Q_{sn} \leq 1.4{:}1$).
2. **Moderately restrictive** VSDs produce an intermediate interventricular gradient, resulting in a moderate shunt (Q_p/Q_s = 1.4 to 2.2:1).
3. **Nonrestrictive** VSDs are usually larger than 1 cm^2. They are associated with a large shunt ($Q_p/Q_s > 2.2{:}1$). The pressures in the

LV and RV will eventually approach equalization, and the amount of flow across the defect will be determined by the ratio of pulmonary-to-systemic vascular resistance.

C. Anatomic classification

1. **Membranous** defects are the most common type, accounting for approximately **70% to 80% of VSDs**. The membranous septum is the area under the aortic valve on the left side and next to the septal leaflet of the tricuspid valve on the right side. **Membranous defects** are less likely to be associated with additional intracardiac defects and **have a high rate of spontaneous closure**.
2. **Muscular** defects account for approximately 5% to 20% of VSDs and can be single or multiple (ie, Swiss cheese septum). These defects, when single, also have a high spontaneous closure rate.
3. **Inlet or AV canal–type** defects account for approximately 5% to 8% of cases. These defects rarely close spontaneously, are usually large, and are often associated with abnormalities of the AV valves on the spectrum of AV septal defects. These abnormalities range from cleft mitral and tricuspid valves to the common AV valve, as seen in complete AV septal defect. Complete AV septal defects have an increased incidence in patients with trisomy 21.
4. **Outlet defects (also termed supracristal, subaortic, and doubly committed VSDs)** account for approximately 5% to 7% of cases in non-Asian populations but constitute up to 33% of cases in Asians. These are located in the conal septum immediately beneath the pulmonary and aortic valves. The defect commonly occurs in the muscular infundibulum that supports the pulmonary valve, which can lead to continuity between the aortic and pulmonary valves. These defects vary in size but are often small. Because of their **proximity to the aortic valve, aortic leaflet tissue can prolapse through the defect, resulting in aortic regurgitation**.

D. Associated lesions. Approximately 20% of VSDs are associated with other forms of congenital heart disease, including aortic coarctation, bicuspid aortic valve, and patent ductus arteriosus. Of patients who present with a VSD, 5% to 10% will develop aortic regurgitation

because of poor support of the right coronary cusp and the Venturi effect caused by the VSD jet, resulting in prolapse of one of the aortic valve leaflets. Discrete, fibrous subaortic stenosis and RV outflow tract (RVOT) obstruction are less common associations. Less than 10% develop subvalvular pulmonary stenosis or an obstructive muscle bundle referred to as a double-chamber RV. Double-chambered RV can lead to midcavity obstruction due to the creation of proximal high pressure and distal high pressure within the RV cavity. VSDs are also commonly found in conotruncal defects, such as tetralogy of Fallot and truncus arteriosus.

III. NATURAL HISTORY AND FACTORS IN PREVALENCE AND PROGNOSIS

A. Natural history. Spontaneous closure occurs most commonly with smaller, restrictive VSDs, usually before the age of 2 years. Nearly 35% of perimembranous defects close spontaneously, and 75% to 80% of small muscular VSDs close spontaneously by 10 years of age. These higher rates of spontaneous closure in more recent series reflect the ability of contemporary echocardiographic modalities to diagnose much smaller defects. Large and nonrestrictive defects have significantly lower spontaneous closure rates (approximately 10%-15%); inlet and outlet defects also rarely close spontaneously. Defects close by two mechanisms: (1) muscular septum growth and (2) “aneurysmal tissue” from the septal leaflet of the tricuspid valve in the case of perimembranous defects. For VSDs that persist, a restrictive nature, for example, small defect with high-velocity flow, can protect the patient from pulmonary vascular injury, given the flow-limiting nature of these defects.

B. Complications

1. **Endocarditis** is a risk because of the presence of a high-velocity, turbulent jet into the RV and is a concern in both large and small restrictive VSDs. Endocarditis most frequently involves the septal leaflet of the tricuspid valve apparatus at the point of jet impact. The incidence of endocarditis varies widely in the literature but ranges from 1% to 15%. Muscular VSDs have a lower incidence of endocarditis, as the jet is attenuated prior to reaching the

tricuspid valve. Risk factors for endocarditis include age >20, male sex, and those with unrepaired VSDs (when there is an indication for repair). In addition, patients who develop significant right-to-left shunting are at increased risk of brain abscess from endocarditis. Although there is an increased risk of endocarditis in the presence of a VSD, the American College of Cardiology and the American Heart Association (AHA) do not recommend antibiotic prophylaxis in the acyanotic patient with an uncomplicated VSD and no prior history of endocarditis.

2. A large VSD during childhood is typically associated with significant **left-to-right shunt** and eventual development of **congestive heart failure**. Children with very large defects usually present during infancy or early childhood with signs and symptoms of heart failure and pulmonary hypertension. Patients with moderate-sized VSDs can survive to adulthood before detection. Given the gradual development of symptoms in these patients, they may not be perceived until late in the disease course. The excess right-sided flow may lead to pulmonary vascular remodeling, increasing pulmonary vascular resistance, and eventually irreversible pulmonary vascular disease and obligate right-to-left shunting, termed **Eisenmenger syndrome**. As pulmonary vascular resistance increases, the left-to-right shunt volume decreases and eventually reverses. The VSD murmur disappears during this transition and is often replaced by the murmur of tricuspid and pulmonic (Graham-Steele murmur) regurgitation. After Eisenmenger physiology has developed, patient survival beyond the fourth decade becomes highly variable, but with close medical follow-up and attention to special risks (ie, general anesthesia, pregnancy), patients may live much longer and into their seventh decade. Complications in patients with Eisenmenger syndrome include pulmonary hemorrhage, endocarditis, cerebral abscess, arrhythmias, thromboembolism, renal insufficiency, and the complications associated with secondary erythrocytosis.

C. Prognosis. Poor prognostic factors in this population include syncope, congestive failure, and hemoptysis. Risk factors for decreased survival include cardiomegaly seen on the chest radiograph; elevated pulmonary artery systolic pressure (>50 mm Hg and/or more than one-half of the systemic pressure); cardiovascular symptoms such as shortness of breath, fatigue, or dyspnea on exertion; and progressive aortic insufficiency. Good prognostic factors include normal LV size and function, small left-to-right shunt, normal pulmonary pressures or resistance, an intact vasodilator response in the pulmonary vasculature, and lack of symptoms.

D. Genetic factors play a role in this disease, as in other forms of congenital heart disease. Having an affected father increases the risk of VSD in the offspring to 2%; moreover, an affected mother appears to confer an even higher risk of recurrence in offspring—as high as 6% to 10%. Generally, VSDs arise because of a combination of polygenic, multifactorial abnormalities. However, several monogenetic abnormalities leading to VSDs, such as mutations in the transcription factors TBX5 and GATA4, have been described, and approximately 5% of patients have chromosomal abnormalities, including trisomies 21, 18, and 13.

IV. CLINICAL PRESENTATION. Adult presentation occurs most frequently in small, restrictive VSDs and occasionally occurs in patients with moderate lesions and associated pulmonary hypertension or with Eisenmenger syndrome in large, unoperated lesions.

A. Symptoms. The most common symptoms in adult patients with hemodynamically significant VSD are dyspnea on exertion and exercise intolerance. The symptoms are related to the degree and chronicity of left-to-right shunt and the resultant increase in pulmonary pressure and resistance.

B. Physical findings. The auscultatory findings classically include a holosystolic murmur of varying intensity. The pitch of the murmur can be a clue to the size and hemodynamic consequences of the defect. Smaller and more restrictive defects produce higher pitched and louder murmurs. Another important feature is the intensity of the

pulmonary component of S_2, which, if increased, suggests increased pulmonary pressure. A diastolic flow rumble at the apex may be heard in large left-to-right shunts because of increased flow across an otherwise normal mitral valve. Depending on associated lesions, other findings may be present, such as a diastolic murmur of aortic insufficiency that may occur with outlet defects. A prominent systolic ejection murmur at the left upper sternal border suggests subvalvular pulmonic stenosis or double-chamber RV. As pulmonary hypertension and right-to-left shunting develop, other signs, including cyanosis, elevated jugular venous pressure, enlarged and pulsatile liver, clubbing, and a decrease in murmur intensity, may occur. A systolic murmur in this setting often reflects concomitant tricuspid insufficiency. Notably, the murmur of a large VSD is often less harsh and more blowing in nature than that of a small VSD (or often there is no murmur at all) because of the absence of a significant pressure gradient across the larger defect, which results in less turbulent flow.

V. LABORATORY TESTS

A. The **electrocardiogram (ECG)** can be one of the first tests to help discern the extent of hemodynamic impairment resulting from VSD. ECG is usually unremarkable with small defects; however, it can reveal left atrial and LV enlargement in patients with larger defects. Right-axis deviation, with right atrial and RV enlargement, suggests elevated RV and pulmonary artery pressure. After surgical repair, right bundle branch block may occur. An inlet or AV canal defect can be diagnosed from the ECG based on the presence of marked left-axis deviation.

B. A **chest radiograph** is often helpful in determining the degree of left-to-right shunt. A small- or normal-sized heart with normal pulmonary vascular markings on the chest radiograph suggests a hemodynamically insignificant lesion, whereas cardiomegaly and left atrial and LV enlargement are seen with large left-to-right shunts. A large defect associated with a small heart, oligemic lung fields, and enlargement of proximal pulmonary arteries with peripheral tapering should raise the suspicion of pulmonary vascular disease.

VI. DIAGNOSTIC TESTING

A. Echocardiography is the diagnostic modality of choice for VSDs and associated lesions. Transthoracic echocardiographic (TTE) imaging is almost always sufficient to make the diagnosis in the hands of an experienced sonographer. Defect size and location should be defined using two-dimensional and color Doppler techniques. Complete scans of the ventricular septum from multiple acoustic windows should be performed to rule out additional defects. Optimal images are usually obtained from the parasternal long-axis, short-axis, and apical four-chamber views. Other views may fail to visualize the VSD jet owing to the perpendicular alignment of the echocardiographic probe and the jet. In some patients, subcostal coronal and sagittal views may also be helpful. Measurements of left atrial and LV size are key to determining the amount of volume load and magnitude of the left-to-right shunt. Large VSDs leading to augmented pulmonary venous return can result in eccentric LV hypertrophy, which can be observed on echo. Echocardiographic features of pulmonary hypertension are helpful in confirming the impending reversal of shunt. Quantification of shunt velocity provides an estimate of the restrictive nature of the defect. Higher velocities suggest a more restrictive defect, reducing the likelihood that the patient has experienced pulmonary vascular insult. The RV systolic pressure can be calculated using the patient's systemic blood pressure and the peak VSD velocity. This pressure can also be estimated if tricuspid insufficiency exists. A **membranous VSD** can be associated with a **ventricular septal aneurysm formed by the septal leaflet of the tricuspid valve bowing into the defect**. Similarly, outlet VSDs are associated with aortic insufficiency caused by prolapse of the right or left coronary cusps into the VSD. TTEs can be used to estimate Q_p/Q_s; however, given the often incomplete visualization of the RVOT in adults, this assessment can be of limited value. A complete study is always indicated to exclude other associated findings, such as aortic coarctation, atrial septal defect, patent ductus arteriosus, and RVOT or LV outflow tract obstruction.

B. Catheterization is seldom needed in the management of isolated VSD in the infant or child. Surgical correction, when indicated, proceeds in most cases based on echocardiographic evaluation. In adults, catheterization should be considered if anatomic questions remain despite TTE and transesophageal echocardiography (TEE) or if pulmonary hypertension is suspected based on these studies. Hemodynamic assessment should include an assessment of the cardiac output, as well as the careful oximetric definition of the shunt level and calculation of the Q_p/Q_s, which is the ratio of total pulmonary blood flow to total systemic flow. It is calculated by measuring the difference between systemic oxygen saturation and mixed venous saturation divided by the difference between pulmonary venous oxygen saturation and pulmonary arterial oxygen saturation. Closure of a VSD is generally considered when Q_p/Q_s is ≥1.5. A step-up in saturation measured at the pulmonary artery level confirms persistent left-to-right shunt across the defect and should correlate with acceptable pulmonary artery pressures and resistance. Evidence of low pulmonary artery saturation is expected with elevations in pulmonary resistance. Simultaneous comparison of RV pressure with systemic pressure is mandatory in these cases, along with the documentation of changes in response to oxygen or nitric oxide administration. Left ventriculography performed with **left anterior-oblique and cranial angulation** demonstrates the defect in most cases. If an inlet-type defect is present, the hepatoclavicular view (about 40° left anterior-oblique and 40° cranial) is usually adequate. Right ventriculography does not adequately opacify the LV unless there is suprasystemic RV pressure. Coronary angiography should be performed when patients are felt to be at risk for coronary artery disease and likely to require concomitant coronary artery bypass grafting. Aortography can be helpful in eliminating the possibility of an associated ductus arteriosus or coarctation of the aorta. Catheterization is also undertaken to close an uncomplicated malformation via a transcutaneous approach.

C. Magnetic resonance imaging (MRI), using spin-echo and velocity-encoded cine sequences, can be obtained to delineate VSD location

and shunt fraction. MRI is particularly helpful in patients with associated complex lesions and those with inadequate echocardiographic images. MRI can also be used to assess RV and LV stroke volumes and pulmonary artery pressure and evaluate extracardiac defects, such as coarctation of the aorta.

III. THERAPY

A. Indications for VSD closure (surgical or transcatheter) in adults include evidence of LV volume overload or significant right-to-left shunt (Q_p/Q_s >1.5:1), provided pulmonary artery systolic pressures are less than half of the systemic pressure and pulmonary vascular resistance is less than one-third systemic. Closure is also reasonable in adults with worsening aortic regurgitation (IIa) caused by perimembranous or outlet VSD.

B. Surgical closure continues to be the primary means of defect repair. Factors supporting intervention include cardiomegaly on the chest radiograph, significant left-to-right shunt (pulmonary-to-systemic flow ratios >1.5:1), elevated but responsive pulmonary vascular resistance, symptoms of congestive failure or associated lesions such as aortic insufficiency, RVOT or LV outflow tract obstruction, and recurrent endocarditis. Patch closure or suture closure can be performed via transatrial, RV, aortic, or pulmonary artery approach. Outcomes after VSD closure are good in children, with low mortality rates of 2% to 3%. Repair of VSDs in patients with evidence of increased pulmonary artery pressure is generally performed before the age of 2 years and, in many centers, in the first year of life. Surgical closure in the symptomatic adult appears to be well tolerated, with acceptable mortality and improved functional status. Irreversible pulmonary vascular disease with Eisenmenger physiology, however, is a general contraindication for surgical closure because right heart failure will often develop thereafter. Pulmonary artery banding (performed to limit pulmonary blood flow) was more frequently done in the past and is now reserved for the few patients who are very small, who have lung disease, or who have complex, multiple VSDs. Postoperative sequelae include residual patch leaks,

as well as supraventricular and ventricular arrhythmias. Studies have shown the presence of a residual shunt following surgical closure in 5% to 31% of patients depending on the type of VSD that was repaired. Data also suggest that postsurgical residual VSDs <2 mm close spontaneously within 1 year in the majority (83%) of patients.

C. **Transcatheter device closure** of VSD using the Amplatzer Muscular VSD Occluder (Abbott Medical, Abbott Park, IL) is mostly reserved for muscular or membranous defects. The Amplatzer Ductal Occluder (ADO I and ADO II) and Amplatzer Vascular Occluder have also been used successfully. Perimembranous defects pose particular problems for transcatheter closure, given their close proximity to the conduction system and the AV and semilunar valves, which can be assessed intraprocedurally by TEE. Usually, a rim of ~2 to 4 mm below the aortic valve is sufficient to avoid interaction with the aortic valve. The septal leaflet of the tricuspid valve can, at times, be involved, and transesophageal evaluation after device placement but before release is warranted. Importantly, there is a 1% to 4% risk of complete AV block either noted immediately on placement of the device across the defect or can develop later at a rate similar to that seen in surgical membranous VSD closure. Recent data from these devices have shown overall improved outcomes, with a decrease in the rate of heart block. Oversizing increases this risk, while undersizing can increase the risk of residual shunting and subsequent hemolysis or embolization. Studies show that the rate of complete closure for the Amplatzer muscular device at 6 months is 100% at 3 to 96 months follow-up. The most common technique utilized is the antegrade approach via the creation of an arteriovenous wire loop, and the device advanced over the wire from the vein across the defect into the ascending aorta. This technique prevents damage to the aortic valve as the sheath is withdrawn into the LV and avoids entanglement with the trabecular RV surface or tricuspid valve chordae. Complications with these devices, as previously described, include early- or late-onset complete heart block, arrhythmia, and tricuspid valve damage resulting in stenosis or regurgitation, and mechanical device failure during deployment. Long-term follow-up is required in

patients whose VSDs were repaired later in life because the majority of patients already have some degree of pulmonary hypertension, LV dysfunction, or both. Patients with residual shunt after repair, arrhythmias, or conduction blocks also require continued follow-up.

D. Patients who do not undergo surgical or percutaneous closure of VSDs and who are asymptomatic are recommended to **establish care with a cardiologist trained in adult congenital heart disease and need outpatient visits every 3 years accompanied by ECG and echocardiography**. Further assessment can be obtained by pulse oximetry and exercise testing. Patients who are symptomatic due to their VSDs need more frequent follow-up and testing with the abovementioned tests. Additional tests based on clinical circumstances include a 6-minute walk test or cardiopulmonary exercise testing.

E. Eisenmenger syndrome is usually referred to in the context of **irreversible pulmonary hypertension from long-standing exposure of the pulmonary vasculature to left-to-right shunting** across a VSD. Diagnosis of pulmonary arterial hypertension is made using invasive hemodynamic assessment via right heart catheterization. As a result of the elevated pulmonary pressures, the direction of shunting is reversed across the defect, producing systemic cyanosis and associated complications. Newer agents aimed at decreasing resistance in the pulmonary vasculature may benefit these patients. Selective pulmonary vasodilators may improve hemodynamics and exercise tolerance, including phosphodiesterase-5 inhibitors, prostacyclin analogs, and endothelin receptor antagonists. Situations leading to dehydration (excessive exercise) and hypoxia (high altitudes) should be avoided. **Pregnancy is poorly tolerated in the presence of Eisenmenger syndrome and is associated with considerable maternal and fetal morbidity and mortality**. Endocarditis is a well-recognized complication of VSD. In the patient with culture-proven endocarditis, 4 to 6 weeks of antibiotics should be administered parenterally before consideration of intervention. This must be tailored to the individual patient's clinical status, the infective organism's identification and sensitivity, and the presence of

concomitant valvular lesions and prosthetic material. According to the AHA guidelines, **antibiotic prophylaxis** is recommended in three situations in relation to congenital heart disease: (1) unrepaired cyanotic defect (ie, VSD with right-to-left shunt), (2) repaired defect (ie, VSD) with prosthetic material/device for the first 6 months, and (3) repaired defect (ie, VSD) with residual defect at the site of a prosthetic patch/device. In addition, excellent oral hygiene and regular dental examinations are important in reducing the risk of developing infective endocarditis.

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CHAPTER 31

Patent Ductus Arteriosus and Coarctation of the Aorta

Kara Denby and Joanna Ghobrial

PATENT DUCTUS ARTERIOSUS

I. INTRODUCTION

A. The ductus arteriosus is fully developed by 6 weeks of gestation and connects the main pulmonary trunk with the descending aorta at approximately 5 to 10 mm distal to the origin of the left subclavian artery. The purpose of the patent ductus arteriosus (PDA) is to efficiently carry partially oxygenated blood from the right ventricle to the descending aorta and eventually back to the placenta for oxygenation. This process diverts blood flow away from the lungs, which would constitute wasted circulation and thus reduces the total workload of the fetal ventricles. A PDA occurs when the ductus arteriosus fails to close and regress after birth to form the ligamentum arteriosum. It occurs in 1:2,000 live births, but it is relatively uncommon among the adult population. In infants, it accounts for 10% to 12% of all congenital heart disease.

B. Natural history. The natural history depends on the size of the PDA, the direction of the shunt, and the development of any associated complications. At birth, 95% of patients with isolated PDA have left-to-right shunts and normal, or near-normal, pulmonary pressures. Patients with normal pulmonary artery (PA) pressures and no evidence of chronic left ventricular (LV) volume overload have a better prognosis. With a PDA, congestive heart failure (CHF) can occur because of chronic left heart volume overload and because of excess dumping of arterial circulation back into the pulmonary circuit and subsequently the left chambers of the heart. Pulmonary vascular

disease can also develop with associated pulmonary hypertension. Development of right-to-left shunting is an ominous sign because it reflects the development of advanced pulmonary vascular disease and associated elevation in right-sided cardiac pressures, related to Eisenmenger syndrome. In patients with death related to PDA, CHF is the most common cause.

C. Risk factors. Factors that increase the risk for PDA include ***maternal rubella infection, birth at high altitude, premature birth, female sex, and genetic factors***. In infants born at <28 weeks of gestation, there is a 60% incidence of PDA, and PDAs are twice as common in females as they are in males. Most cases of PDA are seemingly sporadic, but it is likely a multifactorial inheritance with the requirement of genetic predisposition and an environmental trigger that is induced during a vulnerable period. In a family in which one child has a PDA, there is approximately a 3% risk of having a PDA in subsequent offspring.

II. ANATOMY AND PATHOPHYSIOLOGY

A. Embryology. The ductus arteriosus is a normal and essential component of cardiovascular development that originates from the distal sixth left aortic arch. A PDA is most commonly funnel shaped with the larger aortic end (ampulla) distal to the left subclavian artery, then narrowing toward the pulmonary end, with insertion at the junction of the main and left PAs (**Figure 31.1**).

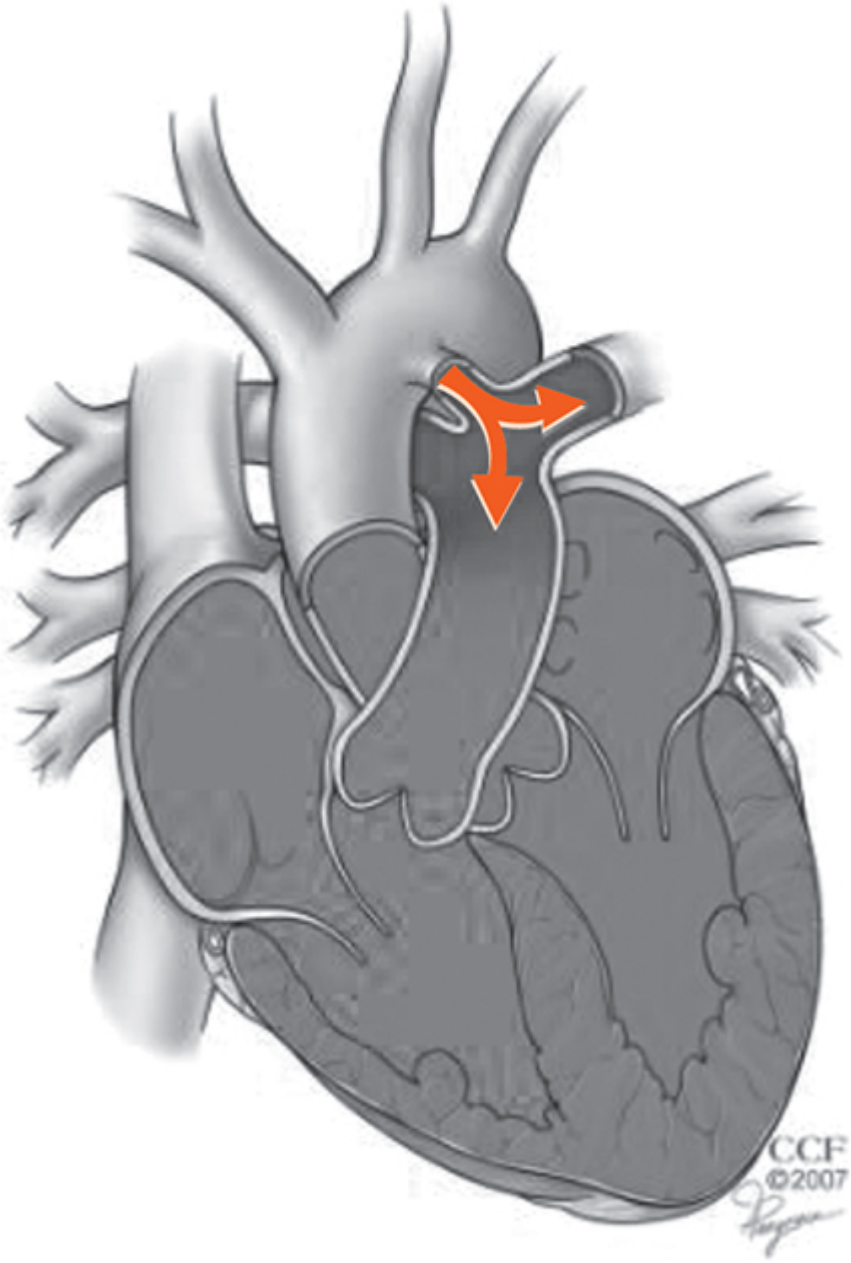

FIGURE 31.1 Patent ductus arteriosus. (From CCF Medical Arts—Courtesy of Joe Pangrace. Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2007-2018. All Rights Reserved.)

B. Fetal circulation. The presence of the ductus arteriosus in the fetal circulation is essential to allow right-to-left shunting of nutrient-rich, oxygenated blood from the placenta to the fetal systemic circulation,

thereby bypassing the fetal pulmonary circuit. In the normal fetal circulation, oxygenated blood travels from the mother through the placenta to the fetus. The oxygen-rich blood traverses the fetal inferior vena cava, right atrium, right ventricle, and main PA. The fetal PAs are constricted and have high pulmonary vascular resistance (PVR). Oxygenated blood bypasses the fetal pulmonary circulation and enters through the ductus arteriosus to the lower resistance systemic circulation. Oxygenated blood then enters the fetal aorta distal to the left subclavian artery, perfuses the fetal systemic circulation, becomes deoxygenated, and returns to the maternal circulation. The ductus arteriosus is kept open by low arterial oxygen content and prostaglandin E2 (PGE2). The fetus has high circulating concentrations of prostaglandins, particularly PGE2, owing to low fetal pulmonary blood flow and decreased prostaglandin catabolism in the lungs, as well as due to the fact that the placenta produces prostaglandins.

C. Birth. Several changes occur at birth to initiate the normal functional closure of the ductus arteriosus within the first 15 to 18 hours of life. Spontaneous respirations result in increased blood oxygen content and decreased PVR, resulting in increased blood flow to the lungs. Prostaglandin levels decrease because of placental ligation and increased metabolism of prostaglandins within the pulmonary circulation by prostaglandin dehydrogenase. The combination of increased oxygen content and lowered circulating prostaglandin levels usually results in closure of the ductus arteriosus. Generally, the ductus arteriosus is hemodynamically insignificant within 15 hours and completely closed by 2 to 3 weeks. The fibrotic remnant of this structure persists in the adult as the ligamentum arteriosum. Spontaneous closure of a PDA is unlikely in term infants after 3 months and in preterm infants after 12 months.

III. CLINICAL PRESENTATION

A. Symptoms. The severity of symptoms depends on the degree of left-to-right shunting, which, in turn, is determined by three interrelated factors: (1) the size of the PDA, (2) the pressure difference between

the aorta and the PA, and (3) the systemic vascular resistance and PVR. PDA size is categorized by the degree of left-to-right shunting determined by the pulmonary-to-systemic flow ratio: Q_p:Q_s (**Table 31.1**). Between 25% and 40% of patients with PDA are asymptomatic, especially those with a small PDA. They are often diagnosed by auscultation of a continuous murmur on examination or incidentally during diagnostic testing. With moderate-sized to larger PDAs, symptoms may develop. **The most common symptom is exercise intolerance followed by dyspnea, peripheral edema, and palpitations**. Increased volume shunted left to right through the PDA increases LV output. By Frank-Starling law, the resultant increase in preload will lead to a greater stroke volume. The LV must compensate by eccentric hypertrophy and eventual dilation, leading to overt left heart failure. Given the excess volume load in the left atrial (LA) and LV, functional mitral regurgitation and/or pulmonary edema may occur. This can occur anywhere from early infancy to late adulthood.

TABLE 31.1 PDA Size by Q_p:Q_s

Q_p:Q_s	Size
<1.5	Small
1.5-2.2	Moderate
>2.2	Large

PDA, patent ductus arteriosus.

B. Physical examination. Patients with PDAs may present with a wide range of physical findings. Pulse pressure may be wide because of diastolic runoff into the PDA, and peripheral pulses may be bounding. The jugular venous pressure is often normal with a small PDA, whereas with a large PDA, prominent *a* and *v* waves may be present. Precordial palpation often reveals a normal precordial impulse with a small PDA and a prominent LV impulse with a large PDA. A **harsh, continuous murmur may be heard at the left first or second intercostal space**. The murmur envelops the second heart

sound (S_2) and decreases in intensity during diastole. A small PDA has a soft, high-frequency, continuous murmur, whereas a large PDA classically has a machinery-like, loud murmur. With a large PDA, a mid-diastolic apical murmur may occur because of increased diastolic flow across the mitral valve. If pulmonary hypertension is present, a right ventricular lift may be present and the pulmonic component of S_2 will have increased intensity. The duration of the diastolic murmur reflects PA pressures; elevated PA pressures lead to a decreased gradient for left-to-right flow through the PDA during diastole, which results in a shorter diastolic murmur. As pulmonary pressure increases, the systolic component of the murmur shortens. Right-to-left flow may not generate a systolic murmur. For patients with a right-to-left shunt, a pathognomonic physical finding is differential cyanosis of the lower extremities and may include the left hand.

C. **Complications.** The most common complications of PDA include **CHF, infective endocarditis, PDA aneurysm, and pulmonary hypertension**. CHF occurs through volume overload of the left side of the heart and may be accompanied by atrial fibrillation. Vegetations generally develop on the pulmonary side of the PDA, and septic lung emboli may occur. Spontaneously occurring aneurysms of the ductus arteriosus have been reported, although they are typically seen in association with endocarditis or among very young or very old patients. Pulmonary hypertension develops as a result of increased pulmonary vascular flow from a large PDA with significant left-to-right flow. Elevation in right-sided pressures may eventually result in Eisenmenger physiology, right-to-left flow, isolated cyanosis, and clubbing of lower extremities (occurring in 5% of patients with unrepaired PDA) with signs of pulmonary hypertension.

D. **Differential diagnosis.** The differential diagnosis of PDA includes ventricular septal defect associated with aortic insufficiency, aortopulmonary window, pulmonary atresia with systemic collateral vessels, innocent venous hum, and arteriovenous communications, such as pulmonary arteriovenous fistula, coronary artery fistula, systemic arteriovenous fistula, and ruptured sinus of Valsalva aneurysm.

IV. LABORATORY TESTING

A. Hematology. Blood laboratory results are generally unremarkable, although compensatory erythrocytosis may be present in the setting of long-standing cyanosis resulting from a right-to-left shunt.

B. Electrocardiogram (ECG). ECG is neither sensitive nor specific for PDA. The ECG for a patient with a small PDA is often normal. Depending on the duration and hemodynamic significance of the PDA, electrocardiographic criteria for LA enlargement or LV hypertrophy may be present. If pulmonary hypertension exists, the ECG may demonstrate right ventricular hypertrophy or right atrial enlargement.

C. Chest radiography (CXR). CXR is neither sensitive nor specific for PDA. A normal chest radiograph implies a small, hemodynamically insignificant PDA. With a large PDA, LA and LV enlargement may be present, as well as increased pulmonary vascularity. With right-to-left shunting from pulmonary hypertension, the main PA is frequently enlarged. The PDA occasionally appears as a separate convexity between the aortic knob and the pulmonary trunk. Calcification of the PDA may be visualized in older individuals.

V. DIAGNOSTIC TESTING.

Standard two-dimensional transthoracic echocardiography (TTE) combined with Doppler is the preferred initial diagnostic modality because of its low cost and noninvasive nature. Transesophageal echocardiography (TEE) may be required in subjects with suboptimal echocardiographic windows. Computed tomography (CT) and magnetic resonance imaging (MRI) provide more anatomic and hemodynamic details than TTE. Cardiac catheterization is definitive but is typically reserved for therapeutic intervention.

A. TTE has a 42% sensitivity and 100% specificity for the diagnosis of PDA. The suprasternal notch view is usually best for demonstrating the PDA, particularly its aortic origin. The complete course of a PDA may be difficult to follow in some patients because of its tortuosity. Color Doppler imaging can often reveal flow between the descending aorta distal to the left subclavian artery and the pulmonary trunk. It is imperative to demonstrate color Doppler flow within the PA,

typically on a high parasternal short-axis view. Color Doppler and continuous wave Doppler help determine the direction of flow in the PDA. The timing of flow (systolic or diastolic) depends on pressure gradients between the systemic and pulmonary circulation. Quantitative assessment of shunt velocity is valuable to estimate the degree of restriction across the PDA. This measurement becomes important when planning transcatheter intervention. Diastolic aortic flow reversal is seen in the descending aorta if the shunt is significant. Associated LA and LV enlargement also suggests a hemodynamically significant lesion.

B. **TEE** may be required if TTE windows are suboptimal or nondiagnostic. TEE is nearly 100% specific for the diagnosis of PDA and is 97% sensitive.

C. **MRI and CT** are superior in defining the anatomy in patients, especially in those with unusual PDA geometry and in patients with associated abnormalities of the aortic arch. They aid in choosing the appropriately sized device when catheter-based intervention of PDA closure is contemplated. MRI may also provide shunt fraction data, LV volumetric assessment, and presence of valvular regurgitation.

D. **Cardiac catheterization** is definitive if there are inconclusive imaging data, but is rarely necessary for diagnostic purposes. In the most recent American College of Cardiology/American Heart Association (ACC/AHA) 2018 guidelines, there is a class IIa recommendation for cardiac catheterization in patients with PDA and suspected pulmonary hypertension. A PDA is best demonstrated by a **descending aortogram** performed in the **lateral projection** with a standard angiographic catheter positioned just below the ductal ampulla. If biplanar imaging is used, the right anterior-oblique cranial projection is sometimes helpful. A PDA can be crossed from the main PA or from the descending aorta, with the latter being easier and best guided by the lateral projection. Oximetric sampling typically demonstrates an increase in saturation in the main PA compared with the right ventricle. PA and right ventricular pressures may be slightly elevated but typically remain below systemic levels. The presence of

systemic pulmonary pressures generally indicates severe and advanced pulmonary vascular disease.

VI. THERAPY. Treatment differs depending on whether the individual is a preterm infant. Given the sensitivity of the PDA to prostaglandins in the premature infant, indomethacin (a prostaglandin synthesis inhibitor) can be administered to close the PDA. The use of oral, or preferably, intravenous indomethacin to constrict the PDA has led to successful nonsurgical closure in a large proportion of treated infants, with the best results administered before 10 days of age in preterm infants. This medication is not effective in term infants or older individuals.

In the event that medical treatment is unsuccessful or not possible, surgical or catheter closure can be performed. The ACC/AHA 2018 guidelines for adults with congenital heart disease recommend closure of PDA (catheter or surgical) if there is LA or LV enlargement and PA systolic pressure is <50% systemic vascular resistance and PVR are less than 1/3 systemic (class I). Closure may be considered in the presence of a net left-to-right shunt if PA systolic pressure is ≥50% systemic and/or if PVR is 1/3 system (class IIb). PDA closure is contraindicated in patients with net right-to-left shunt and PA systolic pressure >2/3 systemic or PVR >2/3 systemic (class III). Successful closure of PDA generally results in a good prognosis and may prevent adverse LV remodeling resulting from volume overload. In those with elevated PA pressures, but not with Eisenmenger physiology, there has been occasional success in the initiation of pulmonary vasodilators first, until the PA pressure is <50%, followed by PDA closure.

The shape and size of a PDA determine the mode of therapy. Small- or moderate-caliber PDAs are generally closed percutaneously with coils. Moderate or large PDAs may require the Amplatzer duct occluder (ADO I or ADO II) or at times the Amplatzer ventricular septal defect closure device. In large PDAs not amenable to percutaneous closure, surgery is indicated, especially in infants. In adults, surgery is rarely indicated as most are often amenable to transcatheter closure. Heavily calcified PDAs represent a relative contraindication to surgical closure because of an increased risk of bleeding and incomplete closure with surgery. Cardiopulmonary bypass may be required for heavily calcified PDAs.

PDAs with significant right-to-left shunts and Eisenmenger physiology should generally not be closed. In patients with PVR >8 U/m^2, lung biopsy has been recommended to determine candidacy for closure. However, even histologically severe pulmonary vascular disease may resolve after closure of the PDA. Reactivity of the pulmonary vascular bed to pulmonary vasodilating agents or significant reduction in PA pressure during test occlusion may signal reversibility of pulmonary hypertension, but the absence of these findings does not rule out the possibility of reversibility in the long term, and natural history may be significantly altered by treating with pulmonary vasoactive medications.

A. Since the early 1990s, transcatheter techniques have become the first-line therapy for most PDAs. Many centers use single or multiple stainless steel coils to achieve complete closure. These procedures can often be performed on an outpatient basis, and complete closure rates at follow-up generally exceed 90% to 95% in most studies. The mortality rate is typically <1% at experienced centers

1. **Percutaneous coil occlusion.** Percutaneous coils were developed in 1992 and are the preferred treatment for older children and adults with PDAs <3.5 mm in diameter. Embolization coils have thrombogenic strands spanning the coils and are placed across the PDA to occlude flow. Advantages include low cost, small-caliber venous access, and easy implantation. Selected coil sizes are 2 to 2.5 times the narrowest diameter of the PDA. With moderate- or large-sized PDAs, multiple coils may be used. However, as PDA size becomes larger (>3.5-4.0 mm), percutaneous, 0.038-in coils become a less desired closure option, and alternative therapies become preferred.
2. The **ADO**, a cone-shaped plug occluder made of thrombogenic wire mesh delivered with a 5F to 7F venous system, is the preferred device for percutaneous closure of moderate to large PDAs. Once the ADO is positioned in the PDA, blood flows through the device, which is lined with thrombogenic wire mesh and leads to thrombotic occlusion of the PDA. Advantages include simple implantation, ability to retract the ADO into the sheath and redeploy if needed, and high success rates. There is an 89%

occlusion rate on postprocedure day 1 and 97% to 100% complete occlusion after 1 month.

3. The **ADO II** is a newer generation device. It has a lower profile made of two nitinol discs with a connecting waist, but without fabric. It was designed for ease of delivery to treat small- to moderate-sized PDAs in smaller children and preterm infants.
4. **Complications** of transcatheter closure are rare. The most common complication is embolization of the coil or device. Embolized coils can usually be retrieved using a snare technique; but even when this is impossible, adverse consequences are rare. Other potential complications include flow disturbance in the PA or aorta from device protrusion, hemolysis from high-velocity residual shunting, vascular access complications, and infection.

B. Surgical closure is the most effective method in children for complete closure and is usually performed without cardiopulmonary bypass by double ligation and division of the PDA. In addition, it has been shown to be the most cost-effective over time with fewer complications compared with transcatheter occlusion methods in children. Ligation may be performed without division, but there is a risk of recanalization of the PDA in up to 20% of cases. With continued advances in percutaneous closure devices, surgery has become second-line therapy for most adults with PDAs. If surgery is necessary, the procedure is >95% successful and has a low complication rate. The operative mortality rate is <1%.

C. Antibiotic prophylaxis. The most recent guidelines from the AHA recommend antibiotic prophylaxis for endocarditis only for 6 months following transcutaneous closure of the PDA. Prophylaxis is not recommended for those with repaired PDA without residual shunt.

D. Follow-up. If immediate duct closure is demonstrated after the procedure, a 6-month follow-up with TTE should suffice to assess for residual flow through the PDA. If a residual shunt exists after the procedure, TTE should be performed every 2 to 3 months and early repeat attempt of complete closure considered, depending on the size of the residual shunt or the presence of hemolysis. For long-term follow-up, annual TTEs are adequate.

COARCTATION OF THE AORTA

I. INTRODUCTION. Coarctation of the aorta (CoA) has been found at autopsy in approximately 1 in every 1,550 individuals. It accounts for 5% to 10% of congenital heart disease and occurs more frequently in Whites (7:1) and males (2:1). The disorder is typically diagnosed in childhood but may go undetected well into adulthood. Most patients develop **persistent systemic hypertension**, often as children, and are at risk for premature coronary artery disease. Cases usually occur sporadically, but an autosomal dominant inheritance pattern has been observed. It is frequently associated with **bicuspid aortic valve**, and coarctation should be excluded in patients with bicuspid aortic valve and hypertension. Coarctation also occurs in 15% to 35% of patients with **Turner syndrome**. Potential catastrophic complications include **aortic rupture or dissection and cerebral berry aneurysm rupture**.

II. ANATOMY. CoA usually consists of a narrowing in the region of the ligamentum arteriosum, the remnant of the ductus arteriosus, just distal to the origin of the left subclavian artery. Most coarctations, therefore, are juxtaductal. The exact anatomy, however, varies, and the coarctation may include a long segment, the transverse arch, or the abdominal aorta. Rarely, tortuosity of the arch is identified. The main anatomic substrate is a prominent posterior shelf of the aorta, composed predominantly of thickened media.

A. Embryology. The exact embryonic origin remains uncertain, but two main theories exist. The first suggests that the narrowing is caused by aberrant ductal tissue that constricts the aorta at the time of ductal closure. The second proposes that aortic hypoplasia develops as a consequence of reduced blood flow in utero.

B. Associated cardiac defects include bicuspid aortic valve in 50% to 85% of cases, valvular and subvalvular aortic stenoses, ventricular septal defects, PDA, and congenital malformations of the mitral valve (ie, smaller orifice, supravalvular ring, and parachute mitral valve resulting from a single papillary muscle). Multiple left-sided heart lesions may be associated with CoA and are often referred to as the ***Shone*** complex.

C. Associated extracardiac defects include intracranial aneurysms, especially within the circle of Willis (3%-5% of cases), hemangiomas, hypospadias, and ocular defects.

III. CLINICAL PRESENTATION

A. Symptoms. For patients with CoA who survive to adulthood, symptoms are often nonspecific. Patients may complain of headaches, nosebleeds, cool extremities, leg weakness, or claudication with exertion. More serious manifestations include angina and heart failure.

B. Physical examination

1. A thorough cardiovascular examination may identify a systolic ejection murmur at the left upper sternal border that radiates to the intrascapular area located immediately anterior or posterior to the CoA. The murmur may be longer in systole and even continue into diastole, depending on the degree of obstruction. Increased **flow through the collateral intercostal arteries can produce a continuous murmur** appreciated diffusely over the precordium.
2. Upper extremity hypertension is often present, usually in conjunction with **diminished and delayed femoral pulsations**. CoA should always be considered in the differential diagnosis of refractory hypertension, especially in younger patients. Blood pressures should be obtained from all four extremities in any patient in which CoA is suspected. In addition, patients with important CoA will usually exhibit "radiofemoral delay," wherein the femoral artery pulsation occurs after, rather than simultaneous with, the radial artery pulse.
3. Funduscopic examination may demonstrate a "corkscrew" tortuosity of the retinal arterioles.

IV. DIAGNOSTIC TESTING

A. ECG findings are frequently normal but may demonstrate manifestations of long-standing hypertension, such as LV hypertrophy and LA enlargement.

B. CXR. Cardiomegaly, dilated ascending aorta, and prominent pulmonary vasculature are common. Rib notching usually develops by 4 to 12 years of age and is caused by enlarged intercostal collaterals. The classic "3" or inverted-E sign is pathognomonic for CoA and is created by a dilated left subclavian artery above the CoA and poststenotic dilation of the aorta below the CoA.

C. Echocardiography is most useful in infants and children. In adults, the suprasternal notch view is most helpful; color Doppler can be used to localize the site of turbulence. Continuous wave Doppler can assess the pressure gradient. If severe narrowing is present, **persistence of flow in diastole** (widening of the flow profile from systole into diastole) is seen by continuous wave Doppler in the aorta below the coarctation, such as in the abdominal aorta. This is a useful method to ascertain the presence of significant coarctation, even if imaging the direct site of the obstruction is impossible. A complete study should measure LV size and ascending aortic size, determine aortic valve anatomy and function, and identify any potential associated congenital anomalies. TEE can also better define the anatomy if TTE proves inadequate.

D. MRI provides excellent anatomic and hemodynamic information (**Figure 31.2**). MRI is increasingly utilized before catheterization, particularly in adults. This enables the precise anatomy to be delineated and helps in decision-making regarding surgery or catheterization as treatment options. Serial MRI scans may be used to follow the results of therapeutic procedures. It is also useful in evaluating the intracranial vessels for ***associated berry aneurysms***.

FIGURE 31.2 Magnetic resonance imaging of aorta showing coarctation in typical position in descending thoracic aorta.

E. CT provides superior spatial definition and anatomic delineation and is especially helpful in preplanning before intervention or surgery.

F. Cardiac catheterization provides excellent image data and pressure information and is often more reliable than echocardiography in

adults. An aortic angiogram in left anterior-oblique or caudal and direct lateral projections usually best defines the lesion. Pressures should be obtained in the LV and the ascending aorta, and the gradient across the lesion should be measured. A pullback pressure of >**20 mm Hg** signifies hemodynamic significance and warrants intervention. The presence of collateral vessels or concomitant aortic stenosis may falsely diminish the gradient.

G. Other testing may be performed after the diagnosis of CoA is established and includes screening for intracranial aneurysms with magnetic resonance angiography or CT angiography (class IIb) and exercise testing to assess for exercise-induced hypertension in adults (class IIb).

V. THERAPY. Several factors need to be considered when deciding on optimal therapy for CoA, including the age of the patient, the anatomy of the coarctation, any prior CoA operations, and the local surgical expertise. Whatever mode of treatment is chosen, the presence of postprocedural upper extremity hypertension influences survival.

A. In general, **medical therapy** for CoA has very limited utility, but it may be useful in a supportive role along with mechanical treatment. Hypertension should be medically treated, with the goal of controlling blood pressure and preventing end-organ damage. When pursuing medical therapy, drugs in the beta-blocker, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) classes are most beneficial.

B. Percutaneous management

1. **Percutaneous balloon angioplasty** is generally **less effective than surgery for the treatment of primary coarctation**. Neonates and infants treated with angioplasty experience high rates of recurrent CoA (about 50%-60%) and aneurysm formations (5%-20%); therefore, surgical repair is preferred in this patient population. Likewise, balloon angioplasty of the unoperated coarctation in adults is not recommended due to data suggesting higher rates of restenosis and aneurysm formation compared with surgical repair.

2. **Percutaneous stent implantation.** Catheter-based **stenting for repair of coarctation** is a class I recommendation for adults with hypertension and significant native or recurrent CoA. Stenting has a good safety and efficacy profile as well as lower rates of restenosis, and with covered stenting availability, there is also a lower rate of aneurysm formation compared with balloon angioplasty or uncovered stenting. For **recurrent coarctation, stenting is the preferred first-line therapy**. Balloon angioplasty may be utilized if stent placement is not feasible and surgical intervention is not an option (class IIb).

C. **Surgery** remains the therapy of choice in neonates and infants. Four types of surgical repair have been used for correction of CoA: resection of the stenosed segment with end-to-end anastomosis, use of a subclavian flap, patch aortoplasty, and ascending-to-descending bypass conduit. The approach with the best long-term outcome and sustained resolution of obstruction has been resection of the stenosed segment with end-to-end anastomosis. This approach carries with it the lowest risk of recurrent CoA (3%) and late aneurysm formation (rare). Major surgical complications include paraplegia caused by perioperative spinal cord ischemia (0.4%-1%), residual coarctation, aneurysm formation at the site of repair, and, rarely, death. Survival rates of >90% at 10 years and 84% at 20 years have been reported. Late deaths after surgical repair are related primarily to coronary artery disease, CHF, and aneurysm rupture. Young age favorably influences outcomes after surgery.

VI. **FOLLOW-UP.** Lifelong follow-up is indicated after the diagnosis of CoA is established, especially after any type of mechanical repair. Key issues to be cognizant of include:

- Progression of hypertension either at rest or with exercise
- Development of CoA recurrence
- Aneurysm formation
- LV dysfunction
- Associated aortic valve dysfunction and aortopathy when bicuspid valve is present

In patients repaired at older ages, **hypertension commonly persists** despite treatment by percutaneous intervention or surgery. Serial echocardiography is an important component of follow-up. Advanced imaging modalities such as CT or MRI are used increasingly postrepair to screen for aortic wall complications, with a preference for MRI given the radiation and contrast issues. Therefore, these patients should be considered "treated" and not "cured" despite repair.

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CHAPTER 32

Complex Congenital Heart Disease

Thomas M. Das and Joanna Ghobrial

I. TETRALOGY OF FALLOT.

Tetralogy of Fallot (TOF) is the most common form of cyanotic heart disease. It occurs in approximately 1 in 3,000 live births and accounts for 10% of congenital heart disease in infants. It is also the most common congenital heart disease condition requiring surgical correction in the first year of life. The earliest description of TOF dates back to the 17th century; however, Fallot is credited with describing the classic features of the disease in 1888. Surgical treatment for TOF did not become available until well into the 20th century, and it dramatically improved life expectancy. The **current reparative approach has shifted from palliative shunt procedures to primary surgical repair**, most recently with valve-sparing techniques and usually performed in infancy. Without surgical intervention, only about 10% of patients survive beyond the age of 20 years. Adults with TOF usually have undergone surgical repair or palliation. A wide and complex spectrum of TOF exists, including association with pulmonary atresia, absent pulmonary valve, and atrioventricular (AV) canal defects. Classic "simple" TOF is discussed here.

A. Anatomy

1. Anterocephalad deviation of the outlet septum results in four defining features:
   - **a. Right ventricular (RV) outflow tract (RVOT) obstruction**
   - **b. Nonrestrictive ventricular septal defect (VSD)**
   - **c. Aortic override of the ventricular septum (>50% over the RV)**
   - **d. Right ventricular hypertrophy (RVH)**

2. **Associated defects.** Anomalous origin of the left anterior descending coronary artery from the right coronary artery (5%) or a prominent conal branch from the right coronary artery can occur. These vessels cross the RVOT. This anatomic feature is important to surgeons because infundibular resection or future conduit placement may be needed in this location and can lead to inadvertent arterial damage. Right aortic arch occurs in 25% of cases. A secundum atrial septal defect (ASD) occurs in 15% of cases, completing the pentalogy of Fallot. Persistent left superior vena cava (SVC) occurs in 5% of cases. Among adult patients, aortic insufficiency can occur naturally from long-term dilation of the aortic root, after endocarditis, or as a postoperative sequela. Rare complications include pulmonary hypertension, supravalvular mitral stenosis, and subaortic stenosis. There is an association with deletion in the chromosome 22q11 region, which is also present in DiGeorge syndrome and/or velocardiofacial syndrome.

B. Clinical presentation

1. **Patients who have not undergone surgical repair** have variable clinical features, depending on the amount of RVOT obstruction, degree of aortic override, and, to a lesser extent, systemic vascular resistance, all of which dictate the amount and direction of shunting across the VSD.
   a. With severe RVOT obstruction, patients have **central cyanosis** and **clubbing** by 6 months of age. Hypoxic "spells" may be seen and are characterized by tachypnea, dyspnea, cyanosis, or even loss of consciousness or death. If the obstruction is mild, however, the shunt through the VSD may be left to right, resulting in "pink tet" with minimal symptoms.
   b. On physical examination, the patient is usually cyanotic and clubbed. A prominent RV impulse may be appreciated because of equalization of RV and left ventricular (LV) pressures. A lift may be palpated under the right sternoclavicular junction in patients with a right-sided arch. The first heart sound (S_1) is usually normal, but the second heart sound (S_2) is often single

because of an inaudible P_2. Auscultation is notable for a **prominent systolic ejection murmur at the left upper sternal border**, possibly with an associated thrill. The shorter the murmur, the more severe the infundibular pulmonary stenosis (PS). The murmur of aortic insufficiency may be audible along with an aortic click resulting from a dilated overriding aorta. Continuous murmurs may be heard because of aortopulmonary collateral vessels. The presence of these vessels is more likely in the setting of pulmonary atresia, but they can also be acquired if RVOT stenosis develops gradually.

2. Most adult congenital patients will have undergone surgical repair with or without a prior palliative procedure. The term "**palliation**" (as opposed to "repair") in these patients refers to a surgical procedure that consists of a **systemic-to-pulmonary artery (PA) shunt** (modified Blalock-Taussig-Thomas [BTT] shunt, classic BTT shunt, Potts shunt, or Waterston shunt; **Table 32.1**). These procedures are initially performed to supplement the deficiency of antegrade pulmonary blood flow and are taken down at the time of complete repair. The latter two procedures are less commonly performed in modern practice because of associated uncontrolled pulmonary blood flow and the subsequent development of pulmonary hypertension.

TABLE 32.1 Index of Postoperative Anatomy Among Adult Patients With Congenital Heart Disease

Underlying Pathology	Procedure	Notes
Single ventricle Hypoplastic left heart Tricuspid atresia	**1. Norwood**	Incorporation of native aorta and PA (one of which may be hypoplastic or atretic) to produce a "**neo-aorta**" for the single ventricle
Pulmonary atresia with intact ventricular septum Unbalanced complete AV canal defect		Main PA is transected from the heart. Pulmonary flow is maintained with placement of a **Blalock-Taussig-Thomas shunt**

Underlying Pathology	Procedure	Notes
		(connecting the subclavian artery to the PA) or a **Sano shunt** (connecting the RV to PA). **Atrial septectomy** is often performed to allow complete mixing at the atrial level.
	2. Bidirectional Glenn	Usually performed at 4-6 mo if PA anatomy, pressures, and resistances are adequate Anastomosis of the **superior vena cava to the PA**, usually with takedown of a previously placed systemic-to-PA shunt and repair of PA branch stenosis if necessary Term *bidirectional* is used in descriptions of this procedure because both right and left PAs usually remain in continuity.
	3. Fontan	Usually performed at 1-5 y depending on growth of vasculature and cyanosis Anastomosis of **inferior vena cava to the PA** by intra-atrial lateral tunnel or extracardiac conduit Pulmonary blood flow is achieved passively, without the assistance of a ventricular pumping chamber.
dTGA (ventriculoarterial discordance)	**Rashkind**	**Atrial balloon septostomy** to create mixing of systemic and pulmonary circulation
	Blalock-Hanlon	Surgical atrial septectomy
	Mustard or Senning (atrial switch)	Baffle material (Mustard) or native atrial tissue (Senning) used to direct pulmonary venous blood → right ventricle → aorta; systemic venous blood → left ventricle → PA

Underlying Pathology	Procedure	Notes
	Jatene (arterial switch)	Great arteries are transected and reanastomosed to the appropriate ventricle. Coronary arteries are removed with a button of surrounding tissue and reimplanted to the appropriate sinuses.
	Rastelli	For dTGA with VSD and pulmonary outflow tract obstruction VSD patch closure that directs left ventricular blood across the VSD to the aorta Pulmonary valve is oversewn. Valved conduit from the RV to the PA to create RV outflow
Deficient PA or RV outflow tract Pulmonary atresia, tetralogy of Fallot with hypoplastic PAs	**Classic Blalock-Taussig-Thomas** **Modified Blalock-Taussig-Thomas** **Waterston shunt** **Potts shunt**	Native subclavian artery anastomosed to the right or left PAs Expanded polytetrafluoroethylene (Gore-Tex) material connecting the subclavian or innominate artery to the PA Anastomosis between the ascending aorta and right PA Anastomosis between the descending aorta and left PA

AV, atrioventricular; PA, pulmonary artery; RV, right ventricular; TGA, transposition of the great arteries; VSD, ventricular septal defect.

a. Patients who have undergone palliative repair alone have variable clinical findings, depending on the type of palliation performed. In those who have undergone a classic BTT shunt, the brachial pulse on that side may be diminished or absent. If patent, shunts can produce a continuous murmur. Continuous murmurs can also result from aortopulmonary collaterals. Branch PA stenosis at prior shunt insertion sites can produce unilateral systolic or continuous murmurs. Systolic ejection

murmurs may be audible depending on the degree of antegrade flow across the outflow tract.

3. **Complete (or total) repair** consists of patch closure of the VSD and variable degrees of RVOT resection and reconstruction. It may involve pulmonary valvotomy, RVOT patch augmentation, transannular patch enlargement, or placement of an RV-to-PA conduit (ie, bioprosthetic or homograft). Distal branch PA stenosis may have been repaired, or residual lesions may be present. These patients typically have first undergone a palliative shunt procedure, but the current surgical approach has shifted to primary complete repair in infancy.
   a. Patients are often asymptomatic. However, residual RVOT stenosis, branch PA stenosis, residual ASD or VSD, tricuspid regurgitation (TR), RV dilation and dysfunction, aortic dilation, aortic regurgitation (AR), and LV dysfunction are some of the anatomic and functional abnormalities encountered in patients with repaired TOF. These patients may present with late symptoms, such as dyspnea, exercise intolerance, palpitations, signs of right heart failure (HF), or syncope.
   b. The jugular venous pressure is usually normal unless there is RV dysfunction, in which case elevated jugular venous pressure with a prominent *a* wave is seen. The brisk pulse of aortic insufficiency may also be appreciated. On palpation, there may be an RV lift or a lift under the right sternoclavicular junction when the arch is right sided. Some degree of turbulence almost always remains across the RVOT and produces a variable systolic ejection murmur at the left upper sternal border, with radiation to the back and peripheral lung fields. Of importance is the presence of associated pulmonary insufficiency. This, even if severe, may occasionally be inaudible due to low-pressure hemodynamics. It is generally appreciated at the left upper sternal border, sometimes producing a to-and-fro murmur together with the outflow tract murmur. A high-frequency systolic murmur at the left lower sternal border suggests the presence of a residual VSD (often due to a small

leak in the VSD patch). Continuous murmurs from collateral formation or prior shunts may be appreciated. The diastolic murmur of aortic insufficiency may also be heard.

C. Diagnostic testing

1. **Chest radiographic** findings depend on the surgical history. The presence of a right aortic arch may be confirmed. A concave deficiency of the left heart border reflects various degrees of PA hypoplasia. Upturning of the apex from RVH causes the classic finding of a "boot-shaped" heart. Pulmonary vascular markings may vary throughout the lung fields, depending on associated branch PA stenosis and relative blood flow. Calcification or aneurysmal dilation of surgical conduits or RVOT repair may be visible on plain radiographs.
2. An **electrocardiogram** usually demonstrates sinus rhythm and may reveal RVH. Both atrial and ventricular rhythm disturbances can be present. The QRS axis is usually normal or rightward. If left-axis deviation is present, an associated AV canal defect should be suspected. A patient who has undergone surgical repair typically has right bundle branch block. **A QRS duration of >180 ms is a predictor of sustained ventricular tachycardia (VT) and sudden cardiac death**.
3. **Echocardiography**
   a. For a child or young adult, transthoracic echocardiography may be the only modality necessary for diagnosis. For adults or patients who have undergone surgical intervention, catheterization or magnetic resonance imaging (MRI) may be necessary to identify the presence and location of residual lesions, as well as to quantify RV volume.
      (1) It is clinically useful to identify a residual VSD or the presence of aortic insufficiency. Palliative shunts are often best visualized in the suprasternal notch view, where the subclavian arteries course distally.
      Continuous flow is typically demonstrated with color Doppler techniques. Less common shunts may be difficult to image in adult patients. Aortopulmonary collateral

vessels are extremely difficult to visualize but may be seen in suprasternal notch views of the descending aorta.

(2) **Transesophageal echocardiography (TEE)** may allow improved imaging of the intracardiac anatomic structures in adults, but limitations often remain with regard to the distal PAs, and additional testing is frequently necessary.

(3) **Intracardiac echocardiography** is perhaps the best method to visualize the pulmonary valve and RVOT; however, it is an invasive modality and requires venous access.

b. **Computed tomography (CT) imaging** can play a role in the assessment of anatomy and associated defects in unrepaired, palliated, and repaired TOF patients. CT also has utility in identifying complications of prior repairs (including residual RVOT obstruction, stenotic or occluded shunt segments, and conduit stenosis) and can assist in planning surgical and transcatheter procedures. CT has also become the mainstay test for preplanning of transcatheter pulmonary valve replacement (TPVR), given its excellent spatial definition.

c. **Cardiac magnetic resonance (CMR) imaging** is considered the gold standard for evaluating the RV and quantitating pulmonary insufficiency in these patients. It can demonstrate the presence of scar, distal PA anatomy, and RV aneurysms, as well as other associated defects. It can also provide hemodynamic information about residual lesions and provide flow quantification in each branch main branch PA. Previously placed shunts and possibly aortopulmonary collateral vessels can be identified as well. The anatomic information may be sufficient to proceed with surgical treatment or to guide the interventional cardiologist in planning a transcatheter procedure, though at times is supplemented by CT.

d. **Cardiopulmonary testing** should be performed as a baseline study and with progression of symptoms. It is useful in determining the timing for reintervention in the setting of RV volume overload secondary to free pulmonary insufficiency.

e. **Quantitative pulmonary flow scans** are useful to determine discrepancies in pulmonary flow that may be caused by branch PA stenosis. These scans also provide objective baseline clinical information when obtained after surgical or transcatheter intervention.

f. The role of **cardiac catheterization** is vital despite the advent of other imaging modalities as it can provide definitive hemodynamic data when assessing residual shunts, branch PS, and pulmonary hypertension.

   a. **Right heart catheterization.** Residual shunts are actively sought at the atrial and ventricular levels. The PAs and pulmonary branches are evaluated extensively in search of peripheral PS. Findings of right heart catheterization and their clinical significance are as follows:

      (1) RV pressure is generally systemic in a patient who has not undergone surgical repair.

      (2) After surgical repair, elevated RV pressure suggests the presence of residual obstructive lesions, the levels of which are to be documented.

      (3) Careful pullback recordings are performed from the branch PAs to the RV because stenosis at each level is possible.

      (4) The presence of stenosis at a prior shunt site is expected.

      (5) RV end-diastolic pressure (RVEDP) may be elevated in the setting of pulmonary insufficiency and would be equal to the PA diastolic pressure in the setting of free PR.

   b. **Left heart catheterization** is performed if noninvasive studies suggest residual VSD.

      (1) **Angiography** includes a cranialized right ventriculography and, possibly, selective PA injections if hemodynamic findings suggest stenosis.

(2) **Left ventriculography** better demonstrates residual VSD in the presence of subsystemic RV pressures.

(3) **Aortic root injection** demonstrates the presence of aortic insufficiency, confirms the presence of grossly abnormal coronary artery origins or branching patterns, and reveals prior surgical shunts or aortopulmonary collateral vessels. If present, shunts and collateral vessels are best visualized in the posteroanterior and lateral projections after selective injection by hand.

(4) **Selective coronary angiography** is recommended in the care of adult patients to exclude acquired coronary artery disease and to identify the path of any anomalous coronaries before surgical intervention. **The anomaly that is not to be missed is the left anterior descending artery originating from the right coronary artery**—it crosses the RVOT anteriorly and can be damaged during surgery.

D. Therapy and follow-up care

1. Medical treatment

a. If an adult has **not been surgically treated or has undergone palliative treatment**, a relatively well-balanced situation must exist. However, the following problems are to be expected.

(1) Long-term effects of RVOT obstruction

(2) Progressive infundibular PS

(3) Exposure of the pulmonary circulation to systemic shunt flow

(4) Development of distal PA stenosis, typically at shunt sites

(5) Erythrocytosis

(6) Chronic hypoxemia

(7) Pulmonary hypertension

(8) Paradoxical emboli

(9) Atrial and ventricular arrhythmias

(10) Increased risk of aortic insufficiency over time

(11) Endocarditis

b. Follow-up care increasingly involves **patients who have undergone surgical repair** and management of residual postoperative lesions.

(1) These patients are at increased risk for **sudden cardiac death**. Atrial and ventricular rhythm disturbances are common in the postoperative patient. Frequent Holter monitoring is warranted for this reason. Atrial tachyarrhythmias are found in up to one-third of patients and are predictive of morbidity and mortality. If patients are found to have nonsustained VT, an electrophysiologic study and, possibly, an implantable cardioverter-defibrillator implantation can be considered. Atrial and ventricular arrhythmias may be the presenting problem for postrepair patients when a component of the repair is failing. There are no data to support prophylactic antiarrhythmic therapy to lower the risk of sudden death in this patient population. An increased incidence of ventricular rhythm abnormalities has been associated with RV volume overload from pulmonary insufficiency, LV systolic or diastolic dysfunction, and with QRS prolongation >180 ms (QRS duration correlates with degree of RV dilation).

(2) **Pulmonary regurgitation (PR)** is the most common hemodynamic sequela of TOF repair. The goal of TOF repair is to relieve the outflow tract obstruction while maintaining the competency of a preferably native pulmonary valve with closure of the VSD. Some younger patients need extensive reconstruction of the RVOT with early placement of a bioprosthetic valved conduit or homograft. In time, these usually become restrictive to flow and/or are insufficient. The result is progressive right heart hypertrophy, fibrosis, and failure if revision is not performed.

(3) The ideal timing for pulmonary valve replacement (PVR) remains controversial. Cardiac MRI may be helpful in determining optimal timing, and there is evidence to support pursuing pulmonic valve replacement when RV end-diastolic volume index is 150 to 170 mL/m^2, RV end-systolic volume index is 80 to 90 mL/m^2, or RV end-diastolic volume is twice that of LV end-diastolic volume.

(4) **TPVR** is increasingly used to treat patients if the anatomy is amenable. TPVR has emerged as a viable alternative to surgical PVR, especially in patients with multiple prior sternotomies or in patients expected to need multiple revisions in their lifetime. Options include the Melody or Harmony valves (Medtronic; Minneapolis, MN), as well as the Sapien valve with or without the Alterra PreStent (Edwards Lifesciences, Irvine, CA). For the most part, transcatheter therapies for adults with TOF are limited to patients who have undergone prior surgical treatment, with attention to residual obstructive lesions in the main PA, RV-to-PA conduit, or distal PAs. Prior shunt sites may become stenotic with time and necessitate balloon angioplasty and, possibly, stent placement. Residual VSD and ASD may be closed percutaneously in select situations.

(5) Other indications for **reintervention** include the replacement or revision of conduits/homografts in the presence of symptoms, residual VSD with reasonable shunt (approximately 1.5:1), RV pressures greater than two-thirds of systemic pressures because of residual obstructive lesions, progressive aneurysmal dilation of RVOT patch, residual systemic-pulmonary shunts with LV volume overload, clinically significant arrhythmias, symptomatic or progressive aortic insufficiency, and significant progressive aortopathy (>5.0 cm).

(6) Recent **infective endocarditis guidelines** have departed considerably from prior iterations in that antibiotic

prophylaxis is recommended only for those who are at the highest risk for adverse outcomes from endocarditis. Specifically, prophylaxis is still appropriate for patients with TOF who are unrepaired, including those who have undergone a palliative procedure. For patients with TOF who have undergone total repair, antibiotic prophylaxis is now recommended only for 6 months following the placement of prosthetic material or device, if there is a residual defect at, or adjacent to, the site of prosthetic material (VSD patch leak, for example), or if there is a prior history of endocarditis. If the pulmonary valve has been replaced or repaired with prosthetic material, antibiotic prophylaxis is appropriate as well.

II. COMPLETE TRANSPOSITION OF THE GREAT ARTERIES.

This is a relatively common congenital anomaly that occurs with a prevalence of 20 to 30 in 100,000 live births and is found more often in males (2:1). It is not associated with other syndromes and does not tend to cluster in families. Although it represents **5% to 8% of all congenital heart disease**, it accounts for **25% of deaths in the first year of life**. Adult patients almost invariably have undergone prior surgery and carry with them important morbidities that require ongoing surveillance and care.

A. Anatomy

1. The defining feature of this anomaly is **ventriculoarterial (VA) discordance**, in which there is an abnormal alignment between the ventricles and the great arteries. Hence, the aorta arises from the RV, and the PA arises from the LV, creating two parallel circuits instead of one in series. Deoxygenated blood flows from the right atrium (RA) across a tricuspid valve (TV) → RV → aorta, whereas oxygenated blood flows from the left atrium across the mitral valve → LV → PA. Unless there is bidirectional shunting at the atrial (ASD), ventricular (VSD), or great artery level (patent ductus arteriosus) to allow mixing of blood, this anatomy is incompatible with life (**Figure 32.1**).

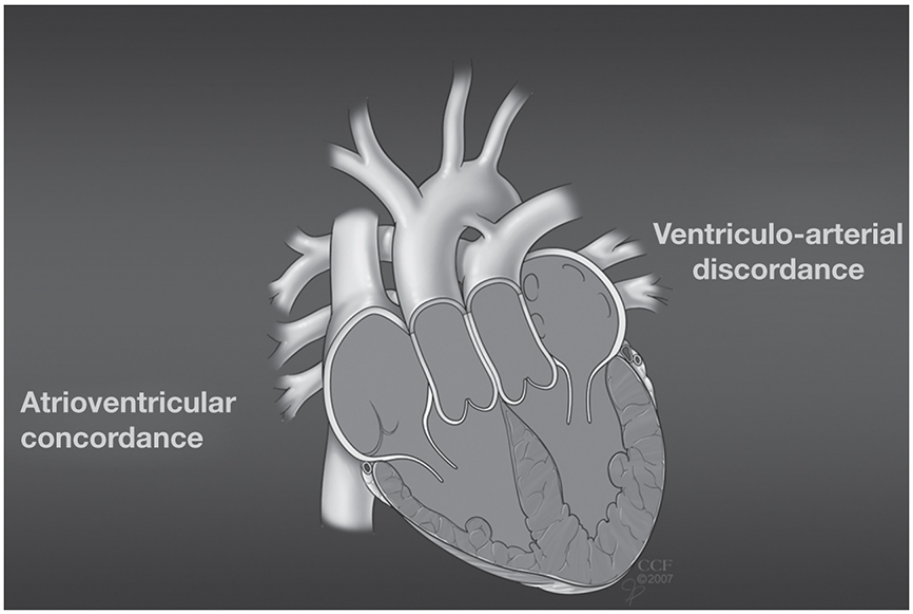

FIGURE 32.1 Complete (d) transposition of the great arteries.

2. There is an abnormal spatial relationship between the great arteries such that instead of the normal spiral configuration, the great arteries run parallel to one another. The **aorta is rightward and anteriorly displaced**, whereas **the PA occupies a position more leftward and posterior**. This is the most common pattern, but other configurations can also be seen, such as side-by-side great arteries with the aorta to the right or an aorta directly anterior to the PA.
3. Associated cardiac anomalies include **VSD in 40%** to 45% of cases (usually perimembranous but can involve any portion of the interventricular septum), **LV (or subpulmonary) outflow tract obstruction in 25%**, aortic coarctation in 5%, patent foramen ovale (PFO), and patent ductus arteriosus. (Patients with these associated cardiac anomalies are considered to have **complex** transposition, whereas patients without these associated anomalies are considered to have simple transposition.)
4. This lesion is also referred to as "D-Transposition of the Great Arteries" (dTGA), in which the "d" refers to the dextroposition of the bulboventricular loop, which is characterized by a right-sided RV.

5. The coronary anatomy in dTGA is variable. The aortic sinuses are described according to their relationship to the PA, such that the "facing sinuses" are closest to the PA. The most frequent coronary arrangement is when the "left-facing" sinus gives rise to the left main coronary artery, whereas the "right-facing" sinus gives rise to the right coronary artery.

B. Natural history and surgical repair

1. Without surgical intervention, survival beyond infancy is dismal, with 89% mortality by the first year of life and worse outcomes for those without an associated lesion to allow for adequate mixing of blood. At birth, infants are treated with intravenous (IV) prostaglandin E to keep the ductus arteriosus open, and some may undergo a **Rashkind balloon atrial septostomy** (**Table 32.1**) to improve oxygenation until definitive surgery can be performed.
2. Adults invariably have undergone some type of cardiac surgery, although, in rare cases, they may present with Eisenmenger physiology (see subsequent text) if a "balanced" situation exists with a concomitant large VSD and pulmonary vascular disease. Surgical repairs include the atrial switch procedure **(Senning or Mustard operation)**, the arterial switch procedure **(Jatene surgery +/− the LeCompte maneuver)** (**Figure 32.2**), or the **Rastelli operation** (**Table 32.1**).

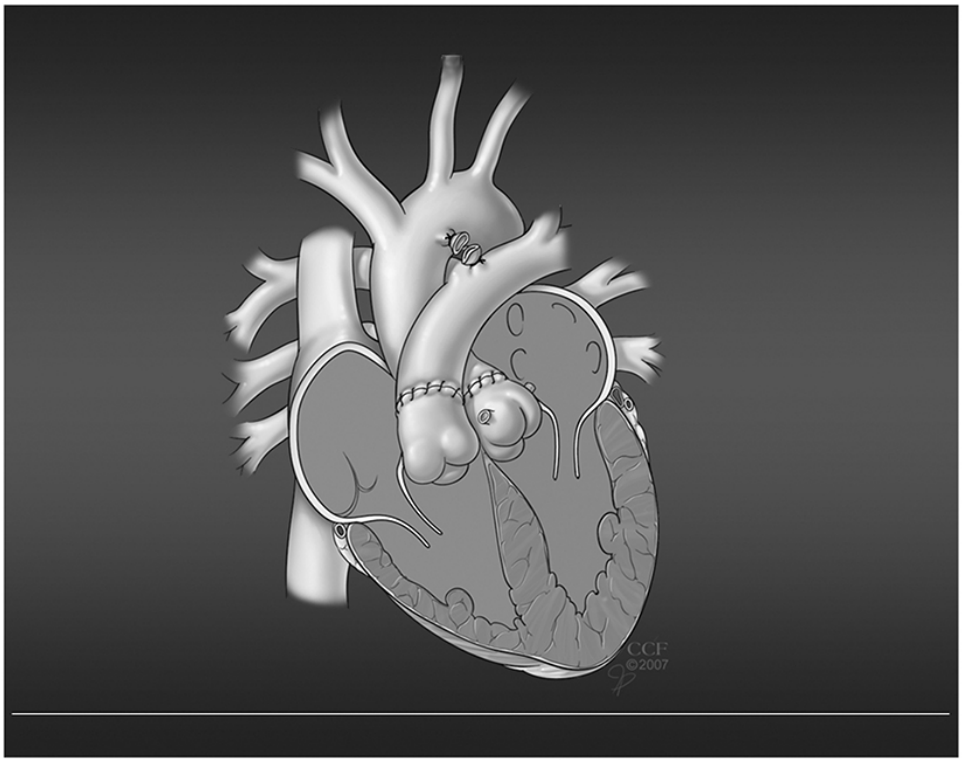

FIGURE 32.2 Arterial switch operation.

C. Clinical presentation

1. The clinical presentation of the surgically repaired patient with dTGA depends on the type of previous surgery. Although no longer cyanotic, these patients have a host of mid- to late-term morbidities that require lifelong surveillance. Patients who have undergone an arterial switch procedure are approaching adulthood only now and presenting in adult congenital cardiology clinics.

2. **Atrial switch (Mustard or Senning)**

   a. Patients who have undergone an atrial switch operation often report New York Heart Association (NYHA) functional class I-II symptoms but, on exercise testing, may have significant exercise intolerance. They have a **systemic RV**, which, over time, can develop systolic dysfunction and progressive TR. These patients may present with signs and symptoms of congestive HF—the most common cause of death. Arrhythmias are common, and patients may present with palpitations, presyncope, or syncope. Venous baffle obstruction can lead to

peripheral edema, hepatomegaly, ascites, and fatigue because of low cardiac output. The obstruction of the superior limb can produce an SVC syndrome. Pulmonary venous baffle obstruction can lead to fatigue, exertional dyspnea, and chronic cough. Baffle leaks are often asymptomatic, but large leaks can lead to intracardiac shunting and cyanosis.

b. On physical examination, focus should be on signs of AV regurgitation and HF. There may be an RV heave at the left sternal border on palpation. S_2 is loud at the second left intercostal space from an anterior aorta. Audible splitting of the S_2 may indicate the development of pulmonary hypertension.

3. Arterial switch (Jatene procedure)

a. This has become the standard corrective surgery for those born without significant LV outflow obstruction. The majority of these patients are asymptomatic with NYHA functional class I symptoms, though can present with worsening HF due to branch PA stenosis or neoaortic valve (native pulmonary valve) regurgitation. Arrhythmias are not a significant problem with this subset.

b. While coronary obstruction is a concern following arterial switch procedures, presentations may be atypical due to the heart being denervated during surgery. Few will present with chest pain, and in these patients, ischemia must be ruled out. As arterial switch procedures did not come into common practice until the late 1980s, the longer term natural history of the coronary arteries after the arterial switch remains to be seen.

c. The physical examination is sometimes notable for turbulence across the RVOT, which may be palpated as a thrill. The diastolic murmur of aortic insufficiency should also be sought.

4. Rastelli operation

a. Both atrial and ventricular arrhythmias are mid- to late-term complications, and patients with these conditions may present with palpitations or syncope. Conduit obstruction may manifest as insidious exercise intolerance, dyspnea, or new-onset

arrhythmias. On physical examination, the character of the pulmonic ejection murmur should be carefully noted to evaluate for conduit obstruction.

D. Diagnostic testing

1. The **chest radiograph** of patients with dTGA displays a narrow mediastinum because of the parallel orientation of the great arteries. The cardiothoracic silhouette is normal. The pulmonary vasculature is normal in patients without pulmonary hypertension. The RV-to-PA conduit in patients who have undergone a Rastelli procedure may be visualized on plain radiograph because of calcification.
2. In patients who have undergone an atrial switch operation, the **electrocardiogram** may display an ectopic atrial or junctional rhythm because of loss of sinus node function. There is usually right-axis deviation and RVH as a result of the systemic position of the RV. In patients who have undergone arterial switch, RVH is distinctly abnormal and suggests pulmonary outflow tract obstruction. After a Rastelli operation, the electrocardiogram is notable for a right bundle branch block, and patients may develop complete heart block.
3. **Transthoracic echocardiography** in atrial switch patients can assess the degree of systemic TR and estimate systemic RV function. Color Doppler is helpful in detecting baffle leaks or obstruction, although more detailed analysis may require TEE. For those who have undergone an arterial switch, transthoracic echocardiography can assess LV function and help exclude supravalvular and PA stenosis. Two-dimensional Doppler can be used to look for conduit stenosis after the Rastelli operation and estimate RV systolic pressures. It can also exclude any residual VSDs in these patients.
4. **CT** may aid in defining anatomy in patients with dTGA, including the evaluation of great vessel and conduit patency and stenosis with its superior spatial definition.
5. As in the TOF population, **CMR** imaging has emerged as an invaluable imaging modality for patients with repaired dTGA. For

post–atrial switch patients, CMR imaging is used to quantify the size and function of the RV, assess TR, and evaluate the systemic and pulmonary venous limbs of the atrial baffle for potential obstruction or leaks. In patients who have undergone arterial repair, RV and LV function can be quantitated, and both the right and left outflow tracts examined. Focus is placed on the great arteries to look for the presence of supravalvular and branch PA stenosis as well as dilation of the neo-aorta. Conduit stenosis and gradients as well as RV size and function can be determined in those who have had a Rastelli operation.

6. **Cardiopulmonary testing** is very useful in detecting subtle clinical changes and a decrease in functional capacity. As mentioned previously, there is often a discrepancy between self-reported symptoms and performance on metabolic exercise testing. Patients who have undergone atrial switch often have chronotropic incompetence and may benefit from pacemaker implantation. Stress testing may be useful in patients after arterial switch to detect coronary artery stenosis and resultant ischemia.
7. **Quantitative pulmonary flow scans** are an important part of the diagnostic workup for suspected PA or branch PA stenosis in those who have undergone arterial switch repair. It is useful to obtain these scans before and after potential intervention to assess for functional improvement.
8. **Cardiac catheterization** is the definitive modality in the diagnosis and treatment of baffle obstruction and leaks, pulmonary hypertension, PA stenosis, coronary artery stenosis, conduit obstruction, and residual VSD.

E. Therapy and follow-up

1. Follow-up should focus on potential late complications after repair and depends on the type of surgery the patient has undergone.

a. Atrial switch

(1) Arrhythmias including sinus node dysfunction and intra-atrial reentry tachycardia (frequent Holter monitoring is recommended)

(2) RV dysfunction
(3) TR
(4) Sudden cardiac death
(5) Baffle obstruction or leak
(6) Pulmonary hypertension
(7) Endocarditis

b. Arterial switch

(1) Supravalvular or peripheral PA stenosis
(2) Pulmonary outflow tract obstruction
(3) Neoaortic regurgitation and aortic root dilation
(4) Coronary artery stenosis (either from anastomotic stenosis or abnormal flow at the suture line leading to plaque formation) causing ischemia and sudden death
(5) LV dysfunction
(6) Endocarditis

c. Rastelli operation

(1) Atrial and ventricular arrhythmias (particularly scar-based VT)
(2) Complete heart block
(3) Sudden cardiac death
(4) LV dysfunction
(5) Conduit stenosis
(6) VSD patch leaks/dehiscence
(7) Endocarditis

2. Medical management

a. In the treatment of systemic RV dysfunction, there are limited data to suggest any long-term benefits from applying the evidence-based drugs utilized for LV dysfunction. Renin-angiotensin-aldosterone system (RAAS) inhibition has not been shown to have a treatment effect. Beta-blockers should be used with caution in patients after atrial switch repairs, because

this could precipitate heart block (due to sinus node and AV conduction abnormalities).

b. As mentioned previously, the latest **infective endocarditis** guidelines have changed such that in the absence of valve replacement or prosthetic material used to repair a valve, implantation of prosthetic material within the last 6 months, or prosthetic material accompanied by residual leaks, it is no longer officially recommended that patients with dTGA postrepair receive antibiotic prophylaxis.

3. Late intervention options include both surgical and transcatheter procedures and, again, depend on the type of repair. Systemic ventricular failure may ultimately require workup for orthotopic heart transplantation.

a. Atrial switch

(1) The procedure of choice in patients with baffle obstruction is transcatheter stent implantation, with best results in the systemic venous baffle. Although technically more challenging, transcatheter dilation of the pulmonary venous baffle can be performed but may require surgical revision. Clinically significant baffle leaks can be treated with catheter-based techniques as well as with septal occluder devices.

(2) In view of the high prevalence of atrial arrhythmias and sinus node dysfunction, these patients are referred for radiofrequency ablation procedures and pacemaker implantation.

(3) Conversion to an arterial switch for systemic RV dysfunction or LV "training" by PA banding has not been reliably successful in the adult population and has been largely supplanted by cardiac transplantation in many centers.

b. Arterial switch

(1) Percutaneous balloon angioplasty with or without stent placement is an excellent option for those with PA and

supravalvular or branch PA stenosis with suitable anatomy. As balloon angioplasty is a safe procedure, there is an approximately 15% restenosis rate, with lower risk after stent implantation. The greatest success lies with branch PA stenosis.

(2) Coronary artery stenosis can be treated with both stenting and coronary bypass surgery.

(3) Severe neoaortic regurgitation is treated surgically with either valve repair or replacement.

c. Rastelli operation

(1) All RV-to-PA conduits inevitably fail and require replacement. There is a role for percutaneous stenting of conduit obstruction in some patients, because this can delay the need for surgery. Concurrent coronary angiogram performed at the time of conduit intervention can help define spatial relationships between the conduit and coronary arteries and can inform whether intervention in the conduit can be safely performed without coronary compression.

(2) Residual VSD leaks may be amenable to closure by percutaneous means but often require surgical revision. Clinically significant residual LV outflow tract obstruction is also managed surgically.

III. CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES.

Ventricular inversion or congenitally corrected transposition of the great arteries (ccTGA) is a rare congenital anomaly that occurs in <1% of children with congenital cardiovascular defects. The natural history of isolated ccTGA depends largely on the function of the systemic RV, the function of the systemic TV, and the presence of arrhythmias; these patients may progress to congestive HF in time. The vast majority of patients with ccTGA have associated structural abnormalities, most commonly VSDs, pulmonary valve stenosis, and TV abnormalities (sometimes described as an “Ebstenoid” TV). The presence of associated defects and conduction abnormalities contributes to a further decrease in

life expectancy without intervention. Surgical approaches are either "anatomically corrective" wherein the LV is established as the systemic arterial pump, or "physiologic," wherein the RV remains the systemic ventricle.

A. Anatomy

1. The defining feature of this congenital abnormality of cardiac looping is **AV and VA discordance**. Blood flows from the RA across a mitral valve → right-sided, morphologic LV → PA → lungs → left atrium across a TV → left-sided, morphologic RV → aorta (**Figure 32.3**).

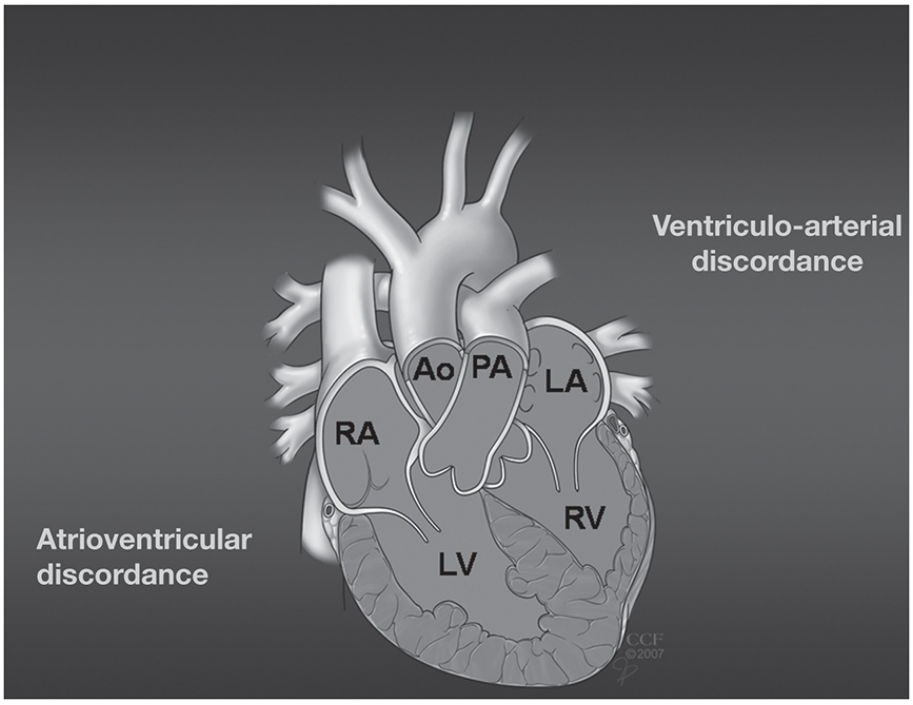

FIGURE 32.3 Congenitally corrected (l) transposition of the great arteries. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

2. The great arteries are not in their normal configuration and often run parallel to one another instead of crossing. The PA is more posterior and rightward than usual, and the aorta is more anterior and leftward.

3. 3. The anatomic coronary arteries, like the AV valves, follow their respective ventricles. The left-sided coronary artery resembles the anatomic right coronary artery as it courses in the AV groove and gives rise to infundibular and marginal branches. The right-sided coronary artery resembles the morphologic left coronary artery, which branches into the anterior descending and circumflex arteries (**Figure 32.4**).

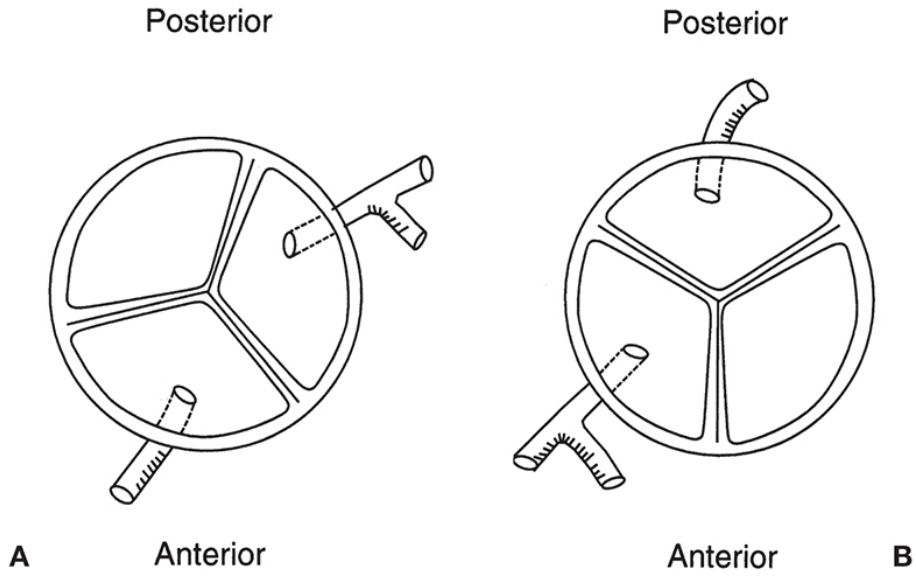

FIGURE 32.4 Schematic representation of coronary artery origins and branching in the normal heart (**A**) and in a congenitally corrected transposition (**B**).

4. The conduction system likewise follows the respective ventricle, as the right-sided, morphologic LV depolarizes first. Accessory AV nodal tissue is located anteriorly with respect to normal, and the His bundle must traverse anterior to the PA and along the superior margin of a VSD if present. There is increased risk of acquired **complete heart block** in this lesion because of the abnormally placed AV node and its extended course. Approximately 30% of adolescents and adults develop complete heart block, the incidence of which is 2% per year without surgical intervention, with the site of block being within or above the His bundle.

Accessory pathways have been described and are typically left sided in the presence of an Ebstein anomaly–like malformation of the left-sided (tricuspid) AV valve.

5. Isolated ccTGA is the exception. **Associated lesions** are common and are considered in the diagnostic evaluation. They include VSD (70%), pulmonary outflow obstruction (~40% and usually subvalvular), or abnormalities of the left-sided, systemic TV. Up to 90% of patients have an abnormality of the TV in some form (ie, dysplastic or Ebstein-like TVs).

B. Clinical presentation

1. Because physiologic blood flow is preserved, patients may have no symptoms through adulthood in the absence of other structural lesions or associated complications. This scenario is rare, however, because associated lesions commonly dictate the clinical features.
2. Without associated structural abnormalities, **failure of the systemic morphologic RV** with various degrees of systemic AV valve (tricuspid) insufficiency is the norm. In this setting, the patient has nonspecific descriptions of fatigue, shortness of breath, and exercise intolerance or congestive failure. Patients may have **syncope or presyncope** caused by conduction abnormalities or complete heart block.
3. On physical examination, there is a loud A_2 caused by an anterior and leftward aorta. The murmurs of a VSD or PS may also be appreciated. Tricuspid insufficiency can be heard with systemic ventricular failure.

C. Diagnostic evaluation

1. In the usual anatomic configuration of ccTGA, the aorta is anterior and to the left, which produces a **chest radiograph** with a straight left heart border. The left PA is not well defined, and the ascending aorta is not visible on the right. The chest radiograph may appear normal or reflect the presence of associated lesions, such as increased pulmonary flow from a VSD or decreased pulmonary flow in the setting of PS. Dextrocardia occurs in approximately

20% of these patients, and the diagnosis should be suspected if seen with abdominal situs solitus.

2. The typical **electrocardiogram** shows a left-axis deviation. Among pediatric patients, there is a loss of the usual Q waves in the precordial leads, with deep Q waves in leads II and aVF reflecting reverse septal activation. A variety of AV node conduction abnormalities may manifest with time and progress to complete heart block.
3. In most instances, the diagnosis can be made with **echocardiography**. The essential findings of AV and VA discordance must be demonstrated. Imaging may be difficult in the presence of dextrocardia or mesocardia. Close attention must be paid to the morphologic details of each chamber.
    a. The morphologic **RV** is identified by its **triangular** shape, the presence of **trabeculations and moderator band**, an inferiorly positioned AV valve, and the presence of AV valve attachments to the interventricular septum.
    b. The morphologic **LV** is identified based on its bullet shape, smooth wall, and more superiorly positioned AV valve and absence of AV valve attachments to the interventricular septum. In the case of ccTGA, these relationships are preserved but reversed.
    c. Apical four-chamber and subcostal images are particularly helpful. The suprasternal notch view is essential in evaluating the great vessels that lie parallel to each other.
    d. The **aortic arch** typically lies to the left of midline in the sagittal plane and can often be visualized from the high left parasternal position. Because variations in great vessel position occur, the spatial orientation must be clarified.
    e. **Associated defects** (eg, systemic AV valve insufficiency, VSD, and outflow tract obstruction) with ccTGA must be excluded or defined.
4. **CMR** can be used to quantify systemic RV size and function as well as valvar regurgitation and shunts. Abnormal late gadolinium

enhancement may also identify RV fibrosis, which has been associated with RV dysfunction, arrhythmia, poor exercise tolerance, and worsened clinical outcomes.

5. **CT** may also be used to define anatomy, particularly in cases where CMR is contraindicated. Coronary computed tomographic angiogram (CTA) may be particularly useful in defining coronary artery anatomy and course.
6. **Catheterization** is unnecessary for the diagnosis of ccTGA but may be helpful in preoperative planning regarding the hemodynamic significance of associated lesions. In rare instances, ccTGA is diagnosed by catheterization and was not recognized during routine echocardiography. An unusual arterial catheter course is caused by the anterior and leftward position of the aorta in most instances. The left-sided coronary artery typically arises from the posterior sinus and assumes a right coronary branching distribution, whereas the right-sided coronary artery arises from the anterior and rightward sinus and assumes a typical left coronary branching distribution (**Figure 32.4**). Because the ventricular septum often lies in the sagittal plane, ventriculography is usually best performed in the straight posteroanterior and lateral projections.

D. Therapy

1. **Medical management** is dictated primarily by the associated malformations.
   a. In the case of isolated ccTGA, the risk of development of conduction abnormalities is cumulative over time; therefore, periodic Holter monitoring is warranted. Permanent pacemaker placement is often needed.
   b. The systemic AV valve and ventricle may show signs of failure that necessitate initiation of HF measures in the form of diuretics and afterload reduction, although data are lacking on the use of agents such as angiotensin-converting enzyme (ACE) inhibitors or beta-blockers in systemic RVs.

c. Associated lesions such as PS or pulmonary atresia, severe systemic AV valve regurgitation, or VSD may likewise contribute to the medical treatment of these patients but often also necessitate surgical intervention.

d. The American Heart Association (AHA) guidelines do not recommend routine antibiotic prophylaxis for these patients unless they have had recent placement of prosthetic material within the preceding 6 months or have a leak at, or adjacent to, the site of a previous prosthesis.

2. Surgery

a. Infants and children who are brought to medical attention early often need surgical intervention in the form of relief of pulmonary outflow tract obstruction or placement of palliative shunts, depending on the associated lesions.

b. An **"anatomically corrective"** or "**double-switch"** approach establishes the LV as the systemic ventricle. Venous return in the atrial portion of the heart is redirected to the left atrium using a Mustard or Senning Baffle. Blood is then redirected again at the great artery level through an arterial switch procedure (see section "Complete Transposition of the Great Arteries") or at the ventricular level using a Rastelli repair if an amenable VSD is present. Other alternatives for establishing the LV as the systemic ventricle include a hemi-Mustard or bidirectional Glenn with an arterial switch.

c. LV deconditioning (due to a low-pressure load from the pulmonary circulation) over time may prohibit pursuing this repair, as the LV must be able to generate enough pressure to overcome the systemic arterial circulation. If a VSD, PS, or subpulmonic stenosis is present to pressure load the LV, a double-switch repair can be deferred outside the neonatal period without risking LV deconditioning. In the setting of isolated ccTGA without pulmonary outflow obstruction or VSD, PA banding may be used to "train" the LV prior to double-switch repair. However, this is not commonly pursued in adults or adolescents, as in older patients, the myocardial

response to afterload is primarily hypertrophic and fibrotic rather than hyperplastic.

d. In an "**anatomically passive**" approach, the RV remains the systemic ventricle, and AV regurgitation, pulmonary outflow obstruction, and VSD are only surgically corrected if clinically indicated. Atrial baffling and/or arterial switch procedures are not pursued at the time of surgery.

e. While this approach avoids more complex surgical intervention and associated complications, leaving the RV as the systemic ventricle frequently results in systemic RV dysfunction and TV insufficiency over time. PA banding may be pursued to increase LV afterload to the point where the ventricular septum shifts toward the RV, leading to less tricuspid insufficiency and improved RV performance.

IV. EBSTEIN ANOMALY. This anomaly of the TV represents 0.5% of congenital heart defects. The natural history of this lesion varies from early death to nearly normal expected survival, depending on the degree of TV involvement and the presence and type of arrhythmias. An increased risk of **sudden death** irrespective of functional class, presumably caused by arrhythmia, has been observed. **Predictors of poor outcome** include earlier **age** at presentation, **cardiomegaly**, severe **RV outflow abnormalities**, and **disproportionate dilation of the RA** relative to the other chambers. There is an association with maternal lithium administration, but most cases are sporadic.

A. Anatomy

1. The **TV** is morphologically and functionally abnormal. The basic features include adherence of the septal and posterior leaflet to the myocardium due to failure of delamination, which lowers the functional annulus toward the RV apex. This results in the classic **atrialization** of the RV (**Figure 32.5**) and dilation of the true tricuspid annulus. The anterior leaflet is usually not displaced but is redundant and may be fenestrated and tethered. The TV can be not only apically displaced but also abnormally located in or near the RVOT.

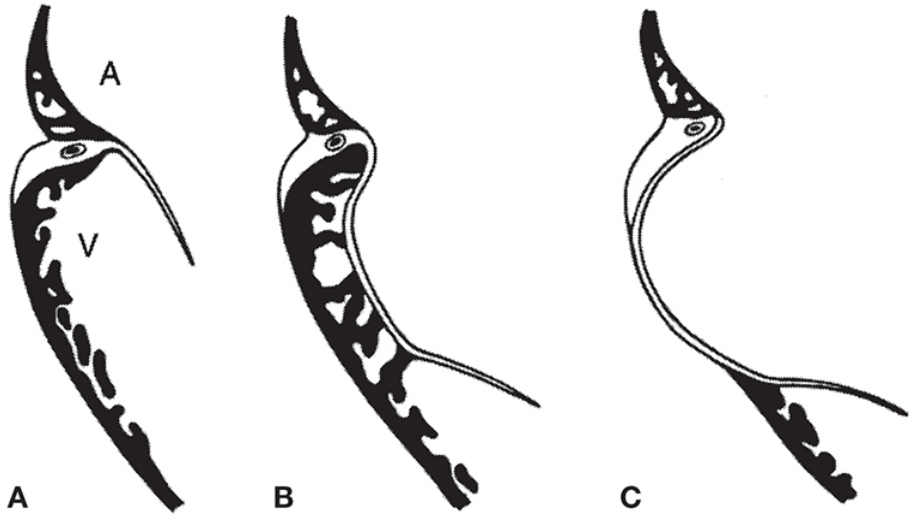

FIGURE 32.5 Section through the right atrioventricular junction. **A.** Normal heart showing the right atrium (**A**) and right ventricle (V). **B.** Mild degree of Ebstein anomaly. **C.** Severe Ebstein anomaly. In (**B**) and (**C**), there is apparent displacement of the tricuspid valve. (From Adams FH, Emmanouilides GC, Riemenschneider TA, eds. *Moss' Heart Disease in Infants, Children, and Adolescents*. 4th ed. Williams & Wilkins; 1989, with permission.)

2. **Associated structural anomalies** include **a PFO or ASD** (found in ≥80%), **VSD, mitral valve prolapse, PS, and LV noncompaction**. ccTGA is associated with Ebstein-like anomaly of the tricuspid (systemic) valve.

B. Clinical presentation

1. **Signs and symptoms** are variable.

   a. The presence of a severely insufficient valve can be apparent at birth because of right-to-left shunting across a stretched PFO or ASD, resulting in cyanosis. PVR is high in the neonate and worsens cyanosis, but as PVR falls, cyanosis may resolve. In adulthood, as TR becomes long standing with associated decreased RV compliance, cyanosis can reappear. In subtle cases, the anomaly may not be evident until adulthood and then results in nonspecific fatigue, shortness of breath, palpitations, near syncope, or syncope. In the presence of an interatrial communication, patients may present with paradoxical embolization or brain abscess. Because the spectrum of

involvement varies greatly, a high index of suspicion must be maintained.

b. The downward displaced septal leaflet creates a substrate for **accessory pathways**, and clinical Wolff-Parkinson-White syndrome is found in 10% to 25% of patients. Arrhythmias include supraventricular tachycardia mediated by an accessory pathway or caused by atrial arrhythmias from progressive atrial dilation. The combination of atrial fibrillation or flutter conducted rapidly across an accessory pathway is often poorly tolerated.

2. **Physical examination**

a. General inspection usually reveals normal jugular venous pulsations despite severe TR, which is masked by a large compliant RA. Cyanosis may be present because of the right-to-left shunting at the atrial level. Digital clubbing will vary depending on the amount of cyanosis.

b. The most common auscultatory findings are the regurgitant murmur of tricuspid insufficiency, gallop rhythms, multiple systolic ejection sounds, and a widely split S_2.

C. Diagnostic evaluation

1. **Chest radiography** may reveal cardiomegaly, caused by RA enlargement from tricuspid insufficiency. Typically, it is described as a globe-shaped heart with a narrow waist.

2. The **electrocardiogram** can demonstrate PR prolongation, RA enlargement ("Himalayan" P waves), and superior axis with or without right bundle branch block (**Figure 32.6**). The QRS amplitude is characteristically low over the right precordial leads because of a diminutive RV. The preexcitation pattern, if present, is almost always type B (ie, left bundle branch pattern). Deep Q waves may be seen in leads II, III, and aVF from fibrotic thinning of the RV free wall and/or septal fibrosis.

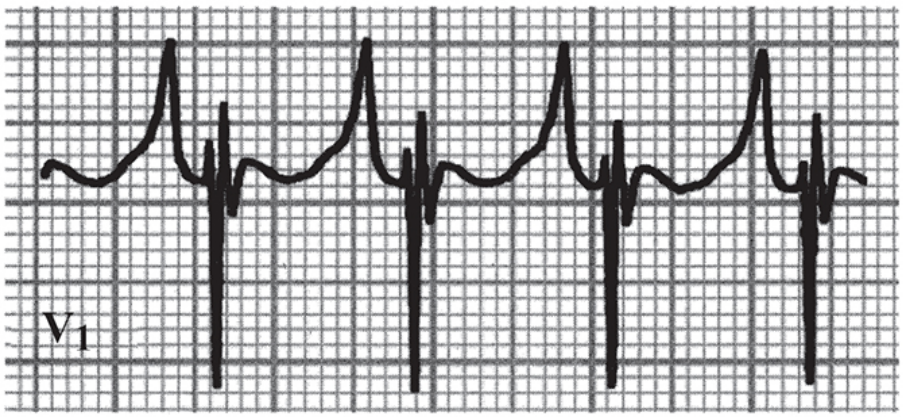

FIGURE 32.6 Lead V_1 of an electrocardiogram from a newborn infant with Ebstein anomaly demonstrates marked right atrial enlargement and an rSR′ pattern.

3. The diagnosis can be confirmed with transthoracic **echocardiography** or TEE, with the TV readily visualized in the parasternal long- and short-axis, apical four-chamber, and subcostal views.
   a. **Apical displacement of the septal leaflet** from the insertion of the anterior mitral valve leaflet by at least 8 mm/m^2 body surface area is considered diagnostic. In less obvious cases, only tethering of the septal leaflet may be found, defined as at least three accessory attachments of the leaflet to the ventricular wall causing restricted motion. An imperforate valve may rarely occur, causing stenosis rather than the typical regurgitation.
   b. The **anterior leaflet** may produce functional obstruction of the pulmonary outflow tract. The leaflet in this circumstance is often called "sail like." The pulmonary outflow is carefully studied to discern functional obstruction from such a leaflet rather than true anatomic atresia of pulmonary outflow.
   c. Views of the **atrial septum** are included in all studies to assess the size of the ASD and degree of shunting, if present. New patients should have agitated saline study to exclude atrial shunting.

d. The size of the **RV** and true tricuspid annulus is assessed because size guides the feasibility of surgical intervention.

e. The size and function of the **LV** are assessed. The shape of the LV may be unusual because of extreme leftward bowing of the ventricular septum. LV function can be affected, and abnormalities may affect long-term outcome.

f. **Associated lesions** must be excluded, such as ASD, RVOT obstruction, patent ductus arteriosus, and, in rare instances, mitral valve abnormalities with associated insufficiency.

4. **Cardiac catheterization** is unnecessary for the diagnostic evaluation of Ebstein anomaly, except to exclude coronary artery disease in adult patients with risk factors for whom surgical intervention is planned. A diagnostic right heart study may be indicated in the presence of associated hemodynamic abnormalities as part of preoperative planning. RV and PA pressures are usually normal in patients with Ebstein anomaly, although RVEDP may be increased. RA pressure may be normal even in the presence of severe TR due to the compliance of the markedly dilated RA.

5. Formal **electrophysiologic study** may be considered for patients with arrhythmias or for those being considered for surgical treatment with symptomatic palpitations. Radiofrequency ablation of accessory pathways is performed.

D. Therapy

1. Many adult patients may undergo **medical treatment**, which includes standard HF medications, including diuretics and digoxin. There are no good data to support ACE inhibitors in right HF due to Ebstein anomaly. Particular attention must be focused on the management of atrial dysrhythmias, which become more common with age. Permanent pacemaker therapy is required in 3.7% of patients, mostly for AV block and rarely for sinus node dysfunction. Endocarditis prophylaxis is no longer recommended for these patients unless they are cyanotic and unrepaired, have undergone placement of prosthetic material within the preceding 6 months (ie, ASD occluder device), have a leak adjacent to or at the

site of prosthetic material, or have had tricuspid valve replacement (TVR).

2. **Surgical correction** is recommended for adults with Ebstein anomaly and significant TR when one or more of the following are present: HF symptoms, objective evidence of worsening exercise capacity, or progressive RV dilation and systolic dysfunction by echo or CMR.
    a. The **cone repair** is generally seen as the optimal strategy for TV repair. The anterior and posterior leaflets are surgically delaminated and detached from their position in the RV, rotated clockwise, and sutured to the septal margin of the anterior leaflet, creating a cone. If a septal leaflet is present, it is delaminated and incorporated into the cone. Annuloplasty banding and vertical plication of the RV are performed, and the interatrial connection is closed. In situations where the RV systolic function may be inadequate, a Glenn shunt can be pursued to offload the RV.
    b. In situations where the TV cannot be repaired, surgical TVR may be pursued. Bioprosthetic TVR is associated with improved mortality when compared to mechanical TVR in these patients, which is rarely if ever used given the higher risk of mechanical valve thrombosis in this position. Favorable results have been achieved at centers experienced in the care of adult patients, and functional class has improved after therapy.
3. **Transcatheter closure** of an interatrial shunt can be considered in select patients with cyanosis at rest (oxygen saturation <90%). Patient selection must be carefully evaluated, as closure of an ASD or PFO may lead to worsening RV dysfunction because of increased right-sided heart pressures. In the case of paradoxical embolic events (ie, stroke), ASD/PFO closure is indicated.

V. **EISENMENGER SYNDROME.** Eisenmenger syndrome is the clinical phenotype of an **extreme form of PA hypertension caused by congenital heart disease with a shunt lesion**. Eisenmenger syndrome is characterized by **cyanosis and chronic hypoxemia**, with associated

secondary erythrocytosis, bleeding diathesis, high burden of arrhythmia, and progressive HF. Over the past few decades, rapid advances in the modalities of diagnosis and treatment of congenital heart disease have resulted in the ability to repair defects at a much younger age, and pulmonary vascular injury is prevented in many of these children. However, Eisenmenger syndrome is still seen in older patients and occasionally in younger patients, particularly in those from developing countries where access to care may be limited. The natural history of Eisenmenger syndrome is variable; and although a cause of significant morbidity, many patients with Eisenmenger survive 30 years or more after the onset of the syndrome.

A. Physiology. Patients with a systemic-to-pulmonary circulation connection will initially have left-to-right shunting of blood because of the lower PVR compared with systemic vascular resistance. Over time, because of excessive flow to the pulmonary vasculature, resulting in increased shear and circumferential stress, PVR increases. Eventually, the shunt reverses, creating right-to-left flow. Although the classic form of the disease was initially used to describe the long-term consequences of a VSD, it can occur with any congenital defect with an initial left-to-right shunt, including ASD, AV canal defect, patent ductus arteriosus, aortopulmonary window, and surgically created systemic-to-PA shunts. It is important to note, however, that the **physiology and clinical presentation differ depending on the *level* of shunt**. In contrast to patients with nonrestrictive shunts at the ventricular or arterial level, most patients with ASDs do not develop Eisenmenger syndrome, and if they do, they present much later in life. In this case, atrial-level shunting is determined by the compliance of the ventricles and is not due to systemic or suprasystemic PA pressures.

B. Clinical presentation of Eisenmenger syndrome has multiorgan involvement

1. **Symptoms.** Pulmonary congestion (from the left-to-right shunt) in early childhood may be evident from the history but improves as the shunt reverses with ensuing cyanosis. Exercise intolerance is very common. **Hypoxemia** can lead to **erythrocytosis** and

symptoms of **hyperviscosity** (eg, headache, dizziness, fatigue, and cerebrovascular accidents). These patients can have a bleeding diathesis due to thrombocytopenia and inadequate clotting factors. This can complicate the management of intrapulmonary thrombosis, which occurs in up to one-third of patients. **Hemoptysis** is a common symptom—alone or caused by pulmonary infarction. Infectious complications include bacterial endocarditis and **septic cerebral emboli**. Atrial arrhythmias and symptoms of congestive HF are usually late signs and are associated with an increased risk of sudden cardiac death. Patients may also present with volume overload or hepatic dysfunction due to right HF.

2. **Physical examination.** The initial murmur of the associated lesion goes away with reversal of the shunt and equalization of right- and left-sided pressures. **Cyanosis and digital clubbing** are present, and arterial pulses may be diminished. Classically, patients with Eisenmenger syndrome due to a PDA have differential clubbing (where the toes exhibit clubbing, but the hands do not). The cardiac examination reveals signs of elevated right heart pressure, such as jugular venous distention with a prominent *v* wave, a right parasternal heave, a loud pulmonary component of S_2 (sometimes palpable), a right-sided S_4, a holosystolic murmur of TR, and a diastolic decrescendo murmur of PR. Signs of congestive HF such as peripheral edema, ascites, and hepatosplenomegaly are seen later in the disease course.

C. Diagnostic evaluation

1. **Chest radiography** is variable. It may show dilated, even calcified, central pulmonary arteries. Reduced peripheral lung markings are not commonly seen. Patients with ASDs tend to have cardiomegaly due to RV enlargement.
2. The **electrocardiogram** shows evidence of RA enlargement and RVH. The presence of atrial arrhythmias should be investigated, particularly in the presence of palpitations.

3. **Echocardiography.** Two-dimensional echocardiography helps in the detailed assessment of the level of the defect, associated lesions, and ventricular function. Doppler measurements can demonstrate and assess the size of the shunt as well as RV pressure and volume overload.
4. **Cardiac catheterization.** Cardiac catheterization is often necessary in these patients to assess the PVR. Demonstration of pulmonary vasoreactivity to oxygen, nitric oxide, or other pulmonary vasodilators is prognostic for these patients and can help identify which patients will most benefit from advanced therapies for PA hypertension.

D. Therapy

1. Medical management

a. Chronic nocturnal oxygen therapy has not been shown to be beneficial, although it may improve symptoms in some patients.

b. Hyperviscosity can be managed in **symptomatic** patients by performing phlebotomy with isovolumic replenishment, but **routine phlebotomy is contraindicated** due to deleterious effects on iron stores, oxygen-carrying capacity, and increased risk of stroke. Monitoring of iron levels and iron replacement, therefore, is paramount.

c. The management of right-sided HF is problematic, and the use of digoxin in these patients is controversial. Diuretics should be used cautiously because aggressive diuresis predisposes to hyperviscosity and decreases preload.

d. Endocarditis prophylaxis is warranted.

e. Arrhythmia may lead to hemodynamic collapse, and prompt restoration of sinus rhythm is recommended when possible. Anticoagulation is nuanced in this population due to the concomitant bleeding diathesis and risk of hemoptysis and is not routinely recommended. Regarding device therapy, transvenous systems are not preferred due to the risk of systemic thromboembolism. Subcutaneous, epicardial, and

leadless systems can be considered in certain patients at specialized centers.

f. Over the past few years, the treatment of pulmonary hypertension in Eisenmenger syndrome has undergone a paradigm shift. While traditional therapy focused on preventive and palliative measures, there is accruing evidence to suggest that the **disease is in fact modifiable and that selective pulmonary vasodilators are not only safe but likely beneficial** in this population. These agents include **endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors (PDE5i)**. Small randomized controlled trials (RCTs) have shown benefits with both endothelin antagonists and PDE5i. Limited data exists on the use of prostacyclin analogs in Eisenmenger syndrome as a third-line therapy; inhaled and subcutaneous preparations are seen as safer than IV treatments due to the risk of paradoxical embolism and increased infectious risk with indwelling lines, though no comparative studies exist. Approach to treatment (such as the timing for initiation of therapy, monotherapy vs dual therapy, and choice of agent) is a matter of expert opinion and differs among centers.

2. Surgical and transcatheter management

a. **Once the shunt has reversed, it should not be closed**. Closure of a right-to-left shunt in the presence of Eisenmenger physiology will lead to right HF and hemodynamic collapse. Rarely, if the pulmonary hypertension is medically managed, and the shunt is reversed to left-to-right flow, there may be a role for shunt closure that warrants careful hemodynamic evaluation with transient shunt occlusion to demonstrate safety.

b. Catheterization can be therapeutic in the patient who presents with hemoptysis in identifying and occluding whether via plug or coil the aortopulmonary collateral that may be responsible for this potentially life-threatening bleeding.

c. Selected patients may be candidates for **combined heart-lung transplantation or lung transplantation with concomitant**

repair of the intracardiac defect, if feasible. Timing of these interventions may be difficult because of the relatively long-term survival of these patients after the onset of the disease process and the recent availability of selective pulmonary vasoactive therapy.

d. Anesthesia should be performed by specialized teams, and indications for noncardiac surgery should be closely considered, given the risk for hemodynamic complications. Volume status, coagulation factors, and iron stores should all be optimized prior to surgery.

E. Eisenmenger syndrome in special situations

1. **Travel** to areas of **high altitude** should be avoided because it may result in acute right HF. Air travel, however, is not contraindicated, as cabin pressures during commercial flights are generally well tolerated.
2. **Pregnancy** in these patients is at high risk to the fetus and the mother (>50% maternal mortality) and is **generally contraindicated**. Given the high risk of maternal and fetal mortality, contraceptive methods (preferably without the use of estrogen) are critical. Elective termination should be discussed with pregnant patients with Eisenmenger.
3. **Air filters** should be placed on peripheral IV to avoid paradoxical emboli from right-to-left shunting.

VI. TRUNCUS ARTERIOSUS.

Truncus arteriosus is a rare cyanotic defect associated with **22q11 deletion**, representing ~3% of all congenital heart disease. It is characterized by **a VSD, a single truncal valve, and a common arterial trunk that supplies systemic, pulmonary, and coronary circulation**. While mortality is nearly 100% in the first year of life without surgery, in modern practice, it is commonly diagnosed in the prenatal period and surgically corrected. Long-term morbidity and mortality are related to dysfunction of the common truncal valve, dysfunction of an RV-PA conduit, and arrhythmia.

A. Anatomy

1. Truncus arteriosus results from failure to form a trunco-septal wall during embryogenesis, leading to a lack of division between the aorta and pulmonary outflow tracks, as well as a single truncal valve. Systemic venous blood and pulmonary venous blood are mixed at the ventricular level (due to the VSD) before being pumped through the truncal valve into the truncal artery.
2. The common truncal valve may have 1 to 4 cusps, though a tricuspid valve is most common.
3. PA anatomy arising from the common trunk is variable and can include hypoplasia of the PAs.
4. **Associated defects** include structural abnormalities of the truncal valve, coronary artery anomalies, interrupted aortic arch, right aortic arch, left SVC, PDA, and ASDs. Rarer associations include complete atrioventricular septal defect (AVSD), double aortic arch, and univentricular anatomies.

B. Clinical presentation

1. If unrepaired, truncus arteriosus anatomy leads to cyanosis and high pulmonary blood flow.
   a. Cyanosis arises due to mixing at the ventricular level of oxygenated and deoxygenated blood due to the VSD.
   b. High pulmonary blood flow results from low PVR (compared to systemic vascular resistance), the common outflow track, and nonrestrictive PAs. Over time, pulmonary overcirculation will lead to pulmonary vascular remodeling, pulmonary hypertension, HF, and potential right-to-left shunting.
   c. Insufficiency of the truncal valve leads to earlier presentation.
   d. While the location of the sinus and AV node is usually normal, the AV bundle course is abnormal and varies depending on the location of the VSD.

2. Surgical repair

   a. Early surgical repair consisted of palliative banding of the PAs in the neonatal to mitigate pulmonary overcirculation. These patients can present with pulmonary vascular disease and branch PA stenosis in adulthood.

b. Modern standard is complete surgical repair in the neonatal period, consisting of closure of the VSD, committing the common arterial trunk to the LV, reconstruction of the RVOT-to-PA connection (usually using a conduit), and repair or replacement of the truncal valve if dysfunctional. In all, 10% to 20% of patients require intervention on the truncal valve at the time of initial surgery, and need for truncal valve intervention is associated with worse outcomes.

3. Patients who undergo complete surgical repair can present in adulthood with dysfunction of the RV-PA conduit, residual VSD leak, stenosis of the branch PAs, pulmonary hypertension, arrhythmias, and truncal valve dysfunction. Redo truncal valve procedures are historically associated with poor outcomes.

C. Diagnostic testing

1. Serial **transthoracic echocardiography** should be performed after repair to assess for truncal valve dysfunction, RV-PA conduit stenosis, residual atrial- or ventricular-level shunting, and ventricular function.
2. **CMR** is the most reproducible method for assessing ventricular size and function and can also evaluate branch PA and conduit patency.
3. **Cardiopulmonary testing** is very useful in detecting exercise intolerance in patients following surgical repair, especially if it is unclear whether symptoms are cardiac in nature.
4. **Quantitative pulmonary flow scans** are an important part of the diagnostic workup for suspected branch PA stenosis.

VII. SINGLE VENTRICLE PHYSIOLOGY AND FONTAN PALLIATION. Many underlying defects can be classified as single ventricle anatomies, including

- hypoplastic left heart syndrome
- double inlet LV
- tricuspid atresia
- pulmonary atresia with intact ventricular septum

- unbalanced AV canal defects

In each of these defects, **a single ventricle must pump blood for both the high resistance systemic circulation and low resistance pulmonary circulation**. Spontaneously balanced circulation is rare in these defects, and most patients require **palliation with the Fontan procedure** to survive into adulthood. The general principle of Fontan circulation is that in lieu of a subpulmonary ventricular pump, **systemic venous return, pulmonary blood flow, and preload to the single ventricle can be passively driven by a moderately elevated central venous pressure through a series of surgically created connections**. While bypassing the subpulmonic ventricle successfully separates pulmonary and systemic circulation, Fontan physiology **inherently involves elevated systemic venous pressures and decreased cardiac output and inevitably leads to complications over time**.

A. Anatomy

1. A detailed discussion of the underlying congenital univentricular anatomies is beyond the scope of this chapter. A common theme among these anatomies is a single functional ventricle supplies both systemic and pulmonary circulation at birth.
2. Fontan palliation involves multiple preceding surgeries prior to the ultimate Fontan procedure. The initial surgery often involves augmentation of pulmonary blood flow and is usually performed in the first week of life.
    a. In situations of excessive pulmonary blood flow (such as tricuspid atresia with a VSD), PA banding is pursued to avoid pulmonary overcirculation and pulmonary vasculature remodeling.
    b. In situations of inadequate pulmonary blood flow, a systemic-to-pulmonary shunt is created. Examples include the **BTT shunt** (connecting the right subclavian artery to the right PA), the **Waterston shunt** (connecting the ascending aorta to the right PA), the **Potts shunt** (connecting the descending aorta to the left PA), and the **Sano shunt** (connecting the systemic ventricle directly to the PA). While these surgeries reestablish pulmonary blood flow, the systemic vascular flow in the low resistance pulmonary circulation will lead to pulmonary vascular remodeling over time.

3. Patients with **hypoplastic left heart syndrome** may have a three-stage **Norwood procedure** performed, wherein the first stage includes the creation of a neo-aorta for the single ventricle using main PA, the hypoplastic native aorta, and homograft material. Pulmonary blood flow is established through either a BTT shunt or Sano shunt. Atrial septectomy is also performed to allow complete mixing at the pulmonary level.
4. Between 4 and 6 months of age, a **cavopulmonary shunt (or Glenn shunt)** is created and the initial shunt is revised or removed.
    a. In the **classic Glenn** procedure, the SVC is transected and directly anastomosed to the right PA, and the right and left PAs are discontinuous. Alternatively, in a **hemi-Fontan,** the continuity of the SVC and RA is maintained and the SVC is connected to the right PA, but a dam of homograft tissue is sewn in the superior cavoatrial junction, preventing blood flow into the RA from the SVC. This approach with discontinuous PAs has been generally abandoned, given the high frequency of pulmonary arteriovenous malformations that form in the right lung without hepatic blood flow.
    b. In the **bidirectional Glenn** procedure, the left and right PAs remain in continuity, and the SVC is anastomosed to the PA.
5. Between 1 and 5 years of age, the **Fontan procedure** is performed to complete the palliation by rerouting systemic venous return from the inferior vena cava (IVC) into the pulmonary circulation.
    a. While the **classic Fontan and atriopulmonary Fontan** are no longer commonly performed, many patients have survived into adulthood with this anatomy. In this anatomy, the RA appendage is directly anastomosed to the main PA. While this was initially theorized to preserve pulsatility in the pulmonary circulation, instead patients experienced progressive atrial dilation, atrial arrhythmias, and thrombosis; the presence of these complications should prompt conversion to a lateral tunnel Fontan or extracardiac Fontan.
    b. In the **lateral tunnel Fontan**, the RA is baffled with an intra-atrial patch, forming a channel that routes blood from the IVC, through

the RA, and into the right PA. A fenestration may be created in this tunnel, creating a controlled right-to-left shunt that augments ventricular preload and partially offloads systemic venous hypertension.

c. In the **extracardiac Fontan**, the RA is bypassed completely using an entirely extracardiac conduit that connects the IVC to the right PA. This approach avoids suture lines within the atrium, potentially decreasing the risk of atrial arrhythmia.

B. Clinical presentation

1. Symptoms

a. Due to relatively low cardiac output and inability to increase stroke volume with exercise (primarily due to preload restriction), patients with Fontan circulation often have exercise limitations at baseline. Worsening from this baseline may suggest impairment of the Fontan circuit.

b. Both ventricular dysfunction and systemic venous hypertension can present with fluid retention, ascites, and exercise limitation.

c. Atrial tachycardias are common in adult patients with Fontan circulation (with higher prevalence in atriopulmonary Fontan due to atrial surgical scars). Arrhythmias are poorly tolerated, and sinus rhythm should be promptly restored.

d. **Protein-losing enteropathy (PLE)** is characterized by abnormal protein loss in the intestinal lumen and occurs in 5% to 12% of patients with Fontan circulation. PLE can present insidiously with disorders in somatic growth, tissue edema, coagulopathy, wound healing, gastrointestinal (GI) bleeding, diarrhea, and immune abnormalities.

e. **Plastic bronchitis** is characterized by the production of thick proteinaceous casts within the airway lumen and occurs in <5% of patients after Fontan palliation. While symptoms of cough are common, in severe cases, airway obstruction, hypoxia, asphyxiation, and death can occur.

f. **Fontan-associated liver disease (FALD)** can present with hepatomegaly and sequela of hepatic congestion. Regular

screening for hepatocellular carcinoma should be pursued in patients with known liver dysfunction. Decompensated cirrhosis from FALD is rare.

2. **Physical examination**
   a. Mild nonpulsatile jugular venous distension is common after cavopulmonary Fontan operations. In atriopulmonary Fontan patients, prominent A waves can be appreciated.
   b. Patients with prior BTT shunts may have low or absent upper extremity blood pressure on the side of the shunt.
   c. Baseline oxygen saturations rarely reach higher than 95% and more commonly are between 90% and 95%. Patients with Fontan fenestration or extensive venovenous collaterals may have saturations less than 90%.
   d. Ascites and lower extremity edema should raise concern for cardiac dysfunction, Fontan obstruction, liver dysfunction, or PLE.

C. Diagnostic testing

1. Screening **electrocardiogram** should be performed on a regular basis to assess for occult arrhythmia. An event monitoring can be pursued to further quantify arrhythmic burden.
2. **Transthoracic echocardiogram** can evaluate ventricular function and AV valve function. Note that symptoms of HF may exist in the setting of reasonable ventricular function if systemic venous hypertension and subsequent end-organ dysfunction are present. Either echocardiography or **CMR** should be performed annually.
3. **CMR** is vital in assessing single ventricular volume and function, single AV valvular function, and the patency of the Fontan conduit. It can also quantify the burden of shunt from venovenous collaterals.
4. **CT** can be a useful tool in assessing the anatomy of the Fontan conduit and presence of thrombus and venovenous collaterals.
5. **TEE** can be used to rule out thrombus in the RA or Fontan itself. TEE can also assess gradients across a Fontan fenestration. TEE should be performed prior to cardioversion in patients with Fontan circulation, regardless of anticoagulation status.

6. **Cardiac catheterization** is the gold standard for hemodynamic assessment in patients with Fontan circulation and should be performed at least every 10 years after Fontan palliation, and more frequently as these patients age and are at higher risk of Fontan failure. In addition to invasive pressure measurements, angiography can be used to rule out Fontan circuit obstruction and assess for venovenous collaterals. Liver biopsy can also be considered at the time of catheterization.
7. Biochemical and hematologic testing can be pursued on an annual basis to assess for hepatic and renal dysfunction, including a cystatin-c, which is a better assessment of renal function, given the low muscle mass and creatinine in most patients with Fontan palliation.
8. **Regular abdominal imaging** is imperative in those patients with known FALD, given the also increased risk of hepatocellular carcinoma.

D. Therapy and follow-up care

1. Anticoagulation with a vitamin K antagonist is recommended for adults with known or suspected thrombus, thromboembolic events, or prior atrial arrhythmia. The role of direct oral anticoagulants in Fontan patients is emerging given its ease of use but is yet undefined given the lack of sufficient data.
2. In patients with atriopulmonary Fontan complicated by incessant atrial arrhythmia, revision to a cavopulmonary Fontan with concurrent arrhythmia surgery can be considered.
3. PDE5i can be considered to reduce PVR and improve cardiac output.
4. Catheter-based treatment of baffle obstruction should be performed, even in the setting of low-pressure gradient.
5. Timing and listing considerations for heart transplantation vary between centers. The most common diagnoses among Fontan patients listed for transplant are PLE (40%), ventricular dysfunction (50%), and other diagnoses such as plastic bronchitis and arrhythmias (10%). The potential need for renal transplantation and liver transplantation should also be considered, given the potential risk for end-organ

dysfunction from chronic systemic venous hypertension and low cardiac output.

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SECTION VII

Clinical Cardiology

EDITOR: **Neha Quatromoni**

CHAPTER 33

Syncope

Eunice S. Dugan and Kenneth Mayuga

I. INTRODUCTION. Syncope is a common medical problem that accounts for approximately 2% to 3% of emergency department (ED) visits and 6% of medical admissions. It is defined as a **sudden and transient loss of consciousness accompanied by loss of postural tone with subsequent rapid complete recovery**. It has a trimodal presentation with peak incidence at ages 20, 60, and 80 years. The recurrence rate and prognosis of syncope is mainly dictated by the underlying causative mechanism, but a general recurrence rate of 20% has been reported.

II. ETIOLOGY AND PATHOPHYSIOLOGY. Syncope is ultimately caused by **a transient interruption or reduction of cerebral blood flow**. Cessation of brain blood flow for at least 6 to 8 seconds is enough to cause syncope, and reduction in systolic blood pressure (SBP) to less than 60 mm Hg is also associated with syncope. Presyncope or syncopal prodrome is the symptoms that occur before syncope, including lightheadedness, visual sensations (tunnel vision, graying, etc), and variable degrees of consciousness without complete loss. Presyncope can progress to syncope or abort without progression. **Prompt identification of the specific cause behind the episode can help minimize expensive evaluations and guide therapy to prevent recurrences and decrease morbidity**. Based on the underlying pathophysiology, syncope is classified into **reflex-mediated syncope, orthostatic hypotension (OH), and cardiac syncope** (**Table 33.1**).

TABLE 33.1 Cardiovascular Causes of Syncope

Neurally mediated (vasovagal)

Situational
Micturition
Defecation
Postprandial
Swallowing
Coughing
Sneezing
Glossopharyngeal neuralgia
Orthostatic syncope
Carotid sinus syncope
Cardioinhibitory
Vasodepressor
Mixed
Mechanical
Aortic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Mitral stenosis
Pulmonic stenosis
Pulmonary hypertension or embolism
Myocardial infarction
Cardiac tamponade
Electrical
Second- and third-degree AV block
SSS
SVT
VT
Torsade de pointes
Pacemaker malfunction

AV, atrioventricular; SSS, sick sinus syndrome; SVT, supraventricular tachycardia; VT, ventricular tachycardia.

A. **Reflex-mediated syncope** (previously termed *neurally mediated syncope*) results from an exaggerated or inappropriate reflex, which causes unopposed parasympathetic tone, leading to inappropriate vasodilation (vasodepressive effect) and/or bradycardia (cardioinhibitory effect). This group can be subclassified into the following:

B. **Vasovagal syncope ("common faint")** is the **most common cause of syncope, irrespective of age, gender, or comorbidities**. It is usually triggered by prolonged sitting or standing, emotional stress, or hot environments and has a characteristic prodrome of warmth,

pallor, and so on. Orthostatic stress is thought to be central in the development of vasovagal syncope, causing a decrease in preload. A ventricular contraction on a less than full left ventricle leads to the activation of ventricular mechanoreceptors, which results in an increased parasympathetic tone, ultimately causing syncope via sudden bradycardia and/or hypotension. Other potential mechanisms include release of endogenous opioids or nitric oxide and primary central nervous system activation.

C. **Situational syncope** is usually associated with distension of hollow viscera (micturition, defecation, cough, postexercise, and trumpet playing), which triggers a vagally mediated reflex that causes syncope via vasodilation and bradycardia.

D. **Carotid sinus syncope** causes less than **1% of syncope**; yet, it accounts for **25% to 50% of unexplained syncope events in patients over 50 years**. Hypersensitivity of carotid baroreceptors is important in this situation because their activation, with or without obvious triggers (shaving, swimming, turning head, or wearing a tight collar), leads to syncope via bradycardia (70% of cases) or pauses ≥3 seconds, hypotension or decrease in SBP ≥50 mm Hg (10%), or a mixed response in the rest of cases.

E. **OH** accounts for **9% of all syncope episodes** but is the **most common cause of syncope in the older patients**. It is characterized by an impaired sympathetic tone leading to **insufficient peripheral vasoconstriction during gravitational stress**, especially during position changes. Inappropriate drop in blood pressure with orthostatic stress defines OH. The following are the most common forms of OH:

1. **Initial OH** is characterized by a brief (<15 seconds) but exaggerated drop in blood pressure of more than 40 mm Hg with syncope or presyncope and rapid normalization afterward.
2. **Classic OH** is defined by a sustained decrease in SBP exceeding 20 mm Hg and diastolic blood pressure (DBP) drops of at least 10 mm Hg within 3 minutes of standing.
3. **Delayed OH**, common in the older patients, presents as a slow progressive decline in blood pressure with prolonged standing,

often more than 3 minutes. The lack of bradycardia sets orthostatic episodes apart from reflex-mediated hypotension.

Common causes of OH include **dysautonomic syndromes**, **volume depletion, medications, diabetes mellitus, alcohol abuse, infection, and varicose veins**.

4. **Dysautonomic syndromes** are divided into two categories. **Primary autonomic failure** includes pure autonomic failure (ie, Bradbury-Eggleston syndrome) and multisystem atrophy (ie, Shy-Drager syndrome). **Secondary causes** include amyloidosis, Parkinson disease, Lewy body dementia, tabes dorsalis, diabetes, and multiple sclerosis.

F. Cardiac syncope is the **second most common cause of syncope** responsible for 9% to 20% of all syncope episodes. It carries a **high rate of recurrence and a poor prognosis**.

1. **Arrhythmia induced** is the most common form of cardiac syncope and the main **cause of syncope in patients with known cardiac disease**. The arrhythmic heart rate is the main factor leading to syncope in close interplay with the type of arrhythmia, cardiac preload, left ventricular function, and vascular adaptation. Commonly identified rhythms include **sick sinus syndrome, atrioventricular block (AV block), and ventricular tachycardia (VT), and less common** but important potential causes include supraventricular tachycardia (SVT) and torsade de pointes. Specific syndromes with known electrophysiologic abnormalities may be involved and should be sought in the appropriate circumstances, such as Wolff-Parkinson-White syndrome, arrhythmogenic right ventricular dysplasia, long QT syndrome, and Brugada syndrome.
2. **Mechanical cardiac syncope** frequently occurs with exertion and arises from left ventricular outflow obstruction, as seen in aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM). **Right ventricular outflow obstruction such as pulmonic stenosis** may also result in syncope. Typically, exertion leads to a drop in peripheral vascular resistance, and hypotension develops, given the inability to increase flow because of fixed cardiac output

in the setting of mechanical obstruction. Arrhythmias and altered baroreceptors response also play a role in syncope in patients with an obvious mechanical cause. **Myocardial ischemia, pulmonary embolism, and cardiac tamponade** should be kept in mind as potential causes of syncope. Up to 7% of patients older than 65 years with myocardial ischemia may present with syncope.

G. Unexplained etiology. Up to half of patients with syncope have no identifiable cause after initial presentation. **Asystole** has been identified as an underlying mechanism in **50% of patients over 40 years of age with no structural heart disease and normal electrocardiogram (ECG) presenting with recurrent syncope**. A new classification has been proposed for unexplained and/or recurrent syncope using precipitating mechanism (bradycardia or asystole, tachycardia or none to minimal rhythm variation) rather than the underlying etiology. Recent evidence revealed higher diagnostic yields when identifying mechanism of syncope via ECG monitoring compared with conventional assessment. This classification aims to promote an early use of ECG monitoring during workup of unexplained syncope to allow prompt use of ECG-tailored therapy in selected cases to ultimately improve treatment efficacy.

III. CLINICAL PRESENTATION. A thorough history and physical examination can provide a clue to the diagnosis in up to 50% of cases. **The most important** aspects of history-taking during syncope evaluation are as follows (**Table 33.2**):

TABLE 33.2 Clinical Features Suggesting Specific Causes

Symptoms or Finding	Diagnostic Consideration
After sudden unexpected pain, unpleasant sight, sound, or smell	Vasovagal syncope
During or immediately after micturition, cough, swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Bradycardia or vasodepressor
Upon standing	Orthostatic hypotension

Symptoms or Finding	Diagnostic Consideration
Taking hypotensive medication	Drug-induced syncope
Symptoms within 1 h after meals	Postprandial hypotension
Prolonged standing at attention	Vasovagal
Well-trained athlete after exertion	Vasovagal
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Aortic stenosis, pulmonary hypertension, mitral stenosis, hypertrophic obstructive cardiomyopathy, coronary artery disease
With head rotation, pressure on carotid sinus associated with vertigo, dysarthria, diplopia with arm exercise	Carotid sinus syncope, transient ischemic attack , stroke, subclavian steal syndrome

Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med*. 1994;97(1):78-88. Copyright © 1994 Elsevier. With permission.

A. Pertinent medical history. The initial approach should focus on the following:

1. **Patient age** as **young patients** are more likely to have **reflex-mediated syncope, whereas the older patients** commonly present with cardiac syncope, **carotid hypersensitivity**, or **OH**.
2. **Comorbidities with special attention to history of heart disease**, such as valvular stenosis, hypertrophic myocardium, cardiomyopathy, infiltrative/inflammatory diseases or myocardial infarction. The presence of any of these may suggest more malignant causes such as VT or other causes of cardiac syncope.
3. **Family history** looking for syncope and/or sudden cardiac death in family members. These are more often associated with cardiac causes of syncope.
4. **Medications review** for their potential causative role or interaction with other medications
5. **Circumstances before syncope**; whether there is association with any particular activity, exertion, or change in position; and the

frequency of occurrence

a. Syncope **during exercise or in a supine position suggests cardiac etiology**. Similarly, **noise and strong emotion** are known triggers of long **QT-related syncope**.

b. An event **after exertion** in young athletes or syncope triggered by **pain, prolonged standing, and hot or crowded environments** is indicative of **vasovagal syncope**.

c. **Situational syncope** presents during **urination, defecation, cough, postexercise, and trumpet playing**.

d. **Carotid syncope** is triggered by **shaving, swimming, head turning, or neck extension**.

6. **Prodrome** with diaphoresis, warmth, nausea, abdominal discomfort, or ear ringing is common in vasovagal syncope (except in older patients), whereas none or short prodrome with palpitations suggests cardiac syncope. Seizures are typically preceded by an aura.

7. **The syncopal event** provides useful information to differentiate syncope from other causes of loss of consciousness, so an effort must be made to contact witnesses.

   a. Syncope is a transient loss of consciousness (<30 seconds). Vasovagal syncope might present with generalized pallor, whereas cardiac syncope could reveal cyanosis.

   b. Occasionally, syncope is accompanied by **mild muscular jerking** (convulsive syncope) as a result of cerebral anoxia. The evaluating physician must make every effort to distinguish this from seizure and pseudoseizure.

8. **Recovery postsyncope** with persistent somnolence, fatigue, and nausea from minutes to hours is suggestive of vasovagal syncope, whereas fast recovery is seen after tachycardia or bradycardia. Seizures commonly present with prolonged (hours) confusion and transient focal neurologic deficits.

B. **Physical findings**. The **physical examination is important, especially when the patient is unable to describe the event** and no witnesses are available, because certain findings on examination can

direct the physician in the diagnostic evaluation. A **comprehensive examination** includes:

1. Blood pressure measurement in both arms
2. **Orthostatic vital signs** should be serially checked immediately upon standing and after 3 and 5 minutes of orthostatic stress. **SBP drop of over 20 mm Hg or to less than 90 mm Hg and DBP decreases over 10 mm Hg** are **diagnostic for OH**.
3. Evaluation for the presence of carotid bruit and assessment of the carotid upstroke
4. **Carotid sinus massage testing** should be considered in **patients over 40 years of age with syncope of unknown etiology** after initial assessment. Massage is performed on one side followed by contralateral side for 5 to 10 seconds under continuous ECG and beat-to-beat blood pressure monitoring. A **diagnosis of carotid sinus hypersensitivity** is made when massage elicits an asystolic **sinus pause >3 seconds or drop in SBP over 50 mm Hg. Carotid sinus syndrome** is made only when **symptoms accompanies carotid hypersensitivity**. Contraindications include carotid bruits, significant carotid stenosis, or myocardial infarction or stroke within 3 months.
5. Cardiac examination **evaluating heart rhythm, heart rate, extra heart sounds** (such as S_3, S_4, or tumor plop), and murmurs
6. **Peripheral pulses** for evidence of peripheral vascular disease and entities such as subclavian steal; and dermatologic clues that may suggest collagen vascular disease or vasculitis
7. Neurologic examination for focal neurologic deficits

IV. MANAGEMENT. The initial management of syncope includes a thorough history, physical examination, and an ECG. The following systematic stepwise assessment is recommended (**Figure 33.1**):

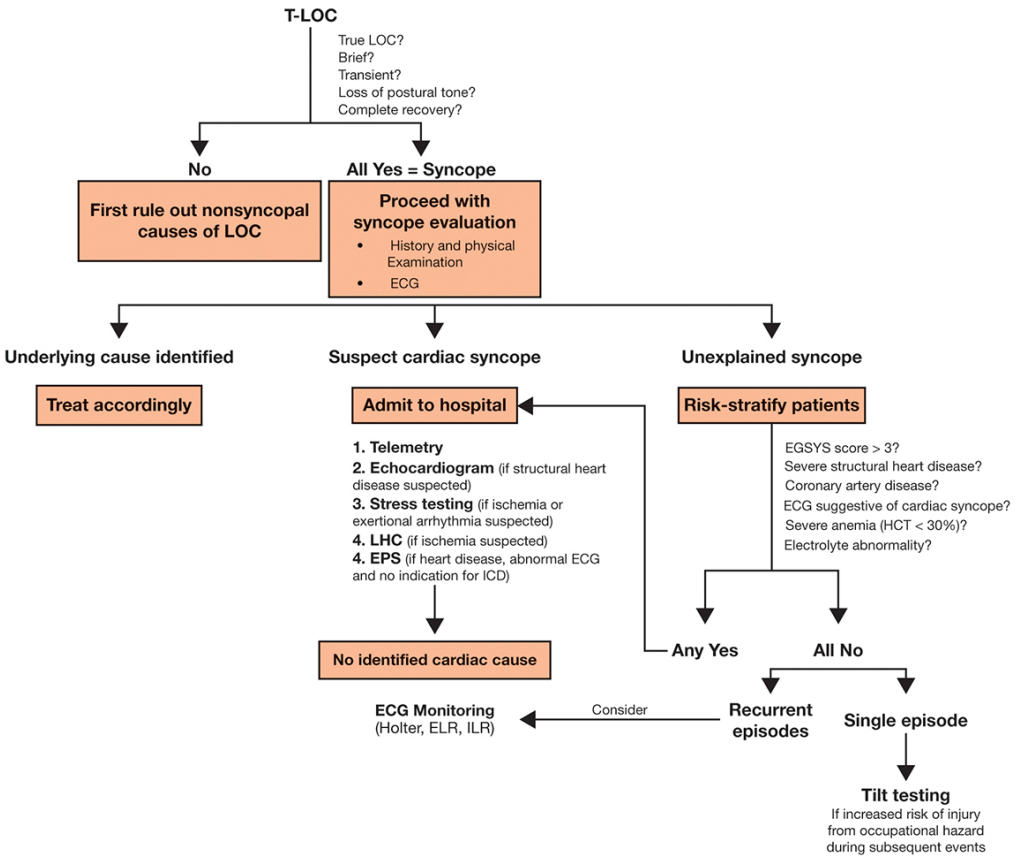

FIGURE 33.1 Schematic algorithm for the evaluation of patients presenting with syncope. ECG, electrocardiogram; EGSYS, Evaluation of Guidelines in Syncope Study; ELR, external loop recorder; EPS, electrophysiologic study; HCT, hematocrit; ICD, implantable cardiac defibrillator; ILR, implantable loop recorder; LHC, left heart catheterization; T-LOC, transient loss of consciousness.

A. Determine likelihood of syncope versus nonsyncopal event (stroke, transient ischemic attacks, normal pressure hydrocephalus, seizures, metabolic causes, and psychogenic). Syncope is highly likely when there is **complete loss of consciousness** of **rapid onset** and **short duration** accompanied by **loss of postural tone** followed by **complete recovery**. If one or more of these criteria are absent, nonsyncopal causes must be ruled out before proceeding with syncopal assessment.

B. Identify specific cause of syncope (**Table 33.3**). The most important goal during this step is to rule out structural heart disease. A **single**

ECG offers the possible **diagnosis in approximately 5%** of cases. The following **ECG findings are suggestive of heart-related** syncope:

TABLE 33.3 **Causes of Syncope in the Evaluation of Guidelines in Syncope Study 2 Trial**

Neurally Mediated	Orthostatic Hypotension	Cardiac Arrhythmia	Structural Cardiopulmonary	Nonsyncopal
Vasovagal	Drug induced	Bradycardia	AMI	Metabolic
Carotid sinus	ANS failure	Sick sinus	Aortic stenosis	Epilepsy
Situational	Primary	AV block	HOCM	Intoxications
Cough	Secondary	Tachycardia	Pulmonary HTN	Drop attacks
Micturition	Volume	VT	Others	Psychogenic
Defecation	depletion	SVT		TIA
Swallow		Inherited		Falls
Others:66%	10%	11%	5%	6%

Unknown cause: 2%.

AMI, acute myocardial infarction; ANS, autonomic nervous system; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; SVT, supraventricular tachycardia; TIA, transient ischemic attack; VT, ventricular tachycardia.

Adapted from Brignole M. Diagnosis and treatment of syncope. *Heart*. 2007;93(1):130-136. With permission from BMJ Publishing Group Ltd.

1. Persistent sinus bradycardia <40 beats/min or sinus pauses >3 seconds
2. Mobitz II second or complete heart block
3. Bifascicular block or alternating left and right bundle branch block (RBBB)
4. Preexcited or wide QRS complexes
5. Rapid paroxysmal SVT
6. VT or nonsustained polymorphic VT with abnormal QT interval
7. RBBB with ST elevation in leads V1 to V3 (Brugada syndrome)
8. Inverted T waves in precordial leads with epsilon waves and ventricular late potentials (arrhythmogenic right ventricular dysplasia)

9. Ischemia signs with or without myocardial infarction

C. **Risk-stratify syncope events of unknown etiology.** The main goal is to identify those with unexplained syncope at higher risk of cardiovascular event or cardiac sudden death. A number of validated risk scoring systems exist, including San Francisco Syncope Rule (SFSR), Evaluation of Guidelines in Syncope Study (EGSYS) score, Syncope Risk Boston Syncope Rule, and Osservatorio Epidemiologico sulla Sincope nel Lazio (OESIL) score. The following are the main high-risk features:

1. **Severe structural or coronary artery disease** (eg, heart failure, low ejection fraction [EF], or previous myocardial infarction) is the major predictor of VT and death.
2. **ECG findings suggestive of cardiac syncope** as described before
3. **Severe anemia** (hematocrit <30%) **and electrolyte abnormality**
4. **Older males**

D. **Assess need for hospital admission.** It is recommended to admit only cases of syncope with **suspicion for cardiac etiology** or syncope of **uncertain etiology** at an increased risk of major cardiovascular events or death.

A genuine effort must be made to accurately follow this stepwise assessment and to pursue hospital admission and/or further testing only in appropriately selected patients. Besides standardization of assessment, the use of EGSYS-2 online interactive decision-making software and utilization of syncope units are the only interventions known to further improve the diagnostic yield and rate of hospitalization and/or testing.

E. **Need for further testing.** Additional testing is generally not needed when an underlying cause for syncope has been identified by initial assessment. Further workup is recommended when there is a suggestion of cardiac cause or uncertain etiology. Investigations should be individualized to be cost-effective (**Figure 33.1**).

1. **Echocardiography** is recommended when **structural cardiac disease is suspected**. It is useful in diagnosing valve pathology and myocardial processes that may contribute to syncope (eg,

aortic stenosis, malignant mitral valve prolapse, and cardiac tumors). It has a low diagnostic yield in the absence of clinical, physical, or ECG findings, suggesting a cardiac abnormality.

2. **Stress testing** is recommended in patients with exertional syncope or with presentation suggestive of coronary artery disease. In addition to ischemia assessment, stress test helps in the detection of exertional arrhythmias (eg, catecholaminergic polymorphic ventricular tachycardia).
3. **Cardiac computed tomography (CT) or magnetic resonance imaging (MRI)** use in evaluating syncope is increasing. It is recommended when other means are inadequate or inconclusive. Superior spatial resolution is especially useful in structural, infiltrative, or congenital disease.
4. **Patients with pacemakers** should undergo **pacemaker interrogation** for possible malfunction (battery depletion, lead malfunction, lead dislodgement, or R-on-T phenomenon).
5. **Tilt-table testing** works via orthostatic stress induced by upright position with or without chemical stimulation, which provokes a reflex-mediated syncope. Isoproterenol is needed in >50% of cases to trigger the reflex but at the expense of a higher false-positive rate. The following are **indications for tilt testing**:
   a. **Single unexplained syncope** at increased risk of traumatic injury or with occupational hazard during subsequent events (eg, driver, pilot)
   b. **Unexplained recurrent syncope in patients with no heart disease or in those with heart disease after ruling out a cardiac cause**
   c. Also used to **differentiate vasovagal syncope from OH**

      A positive test is defined by hypotension and/or relative or absolute bradycardia. **Bradycardia** (cardioinhibitory response) translates into a **higher risk of subsequent asystolic syncope**. Tilt-table testing has a sensitivity of 70% and specificity of 35% to 92% with isoproterenol. **The sensitivity increases with higher angle of tilt and longer duration**. It appears that **tilt-**

table testing, when used in the appropriate setting, is beneficial in diagnosing previously unexplained syncope.

d. It can help establish a diagnosis of psychogenic pseudosyncope, which is not a true loss of consciousness.

6. **ECG monitoring** encompasses a variety of ECG-monitoring techniques with different recording times. It is indicated when there is **suspicion for arrhythmia-induced syncope.** Guidelines also recognize the **early use of implantable loop recorders (ILRs)** in the workup of **unexplained and recurrent syncope with low risk for cardiovascular events. High-risk patients** can be considered for ECG monitoring **only after a complete comprehensive workup fails to reveal a cardiac cause** because a delay in diagnosis could pose harm to the patient. The main goal of this monitoring strategy is to detect a correlation between **symptoms and the arrhythmia**. Yet, certain rhythms are considered **diagnostic even if asymptomatic**:

   a. **Asystole** >3 seconds

   b. **SVT** with rate higher than 160 beats/min for 32 or more beats

   c. **VT**

   d. **Second-degree AV block (type II) or complete AV block, and runs of nonsustained ventricular tachycardia (NSVT)** should be taken seriously. Even a normal cardiac rhythm during a syncopal episode helps exclude an arrhythmia-induced event, suggesting a good prognosis. The main disadvantages of monitoring strategies include **delayed diagnosis and variable diagnostic yield based on event frequency**. Therefore, the selection of recording device is based on risk of cardiovascular event and frequency of symptoms.

   e. **In-hospital telemetry** is the ECG monitoring of choice in patient with **high risk for major cardiovascular events or sudden death requiring admission**.

   f. **Holter monitor** offers generally 24- to 48-hour monitoring with a diagnostic yield for arrhythmia of 24% and correlation

of a cardiac arrhythmia with a syncopal spell of 4%. It can be considered **when symptoms occur on a daily basis**.

g. **External loop recorders** are capable of monitoring the heart's electrical activity for up to 4 weeks; thus, they are **only indicated if symptoms frequency is greater than monthly**. They continuously record and delete electrical activity in a loop until it is activated by the patient to record activity during symptoms. When activated by the patient, loop recorders permanently record the previous 5 to 15 minutes of rhythm data. The recorder can capture arrhythmias during a syncopal episode, even if the patient activates it after regaining consciousness. Reported diagnostic yield is better than Holter monitoring (50% at 2 weeks and 90% at 4 weeks) but is significantly reduced by operator error.

h. **ILRs** offer a long recording time with battery life up to 3 years. They are **implanted subcutaneously** via a minor surgical procedure. They can be manually or automatically activated with wireless transmission. **Early use of ILR enhances diagnostic yield and time to diagnosis** in an unselected population with **recurrent and unexplained syncopal events** compared with conventional management. Pooled analysis from available studies revealed a **diagnostic yield of 32% at 18 months**. Reports suggest that diagnostic yield **can increase up to 80% with extended monitoring for 2 years**. Early ILR use also **decreases the number of hospitalizations and testing** without impact on mortality. **ILR** allows earlier initiation of ECG-targeted therapy with associated **reduction of syncopal recurrences in selected cases** (eg, documented asystolic pauses). Nonetheless, no evidence exists to support the use of ILR as a first-line diagnostic tool in all patients with syncope. ILR is recommended during the following scenarios:

   (1) Recurrent unexplained syncope at low risk for cardiovascular event or sudden death. **In high-risk patients, it may be used only after prompt cardiac evaluation failed to reveal the cause of the event**.

(2) Patients with **recurrent reflex-mediated syncope** despite appropriate medical management **when identification of underlying mechanism might change management** (eg, identification of asystolic pauses).

(3) Other suggestions include **differentiation of seizure from syncope** when anticonvulsive therapy failed to control episodes.

i. **Mobile cardiac outpatient telemetry (MCOT)** provides continuous ambulatory ECG monitoring with continuous recording or 24-hour loop memory. MCOT offers live wireless reporting to a center, which is able to record the event and contact the patient and/or physician. Therefore, it provides higher diagnostic yield compared with patient-activated systems.

7. **Signal-averaged electrocardiography (SAECG)** is a collection of 100 to 300 single QRS complexes, which are amplified, filtered for noise, and averaged to determine the presence of late potentials. Late potentials **seem to identify the presence of a reentrant substrate and may indicate an independent risk for the development of future life-threatening ventricular arrhythmias**. SAECG is useful in **predicting inducibility of ventricular arrhythmias by an electrophysiologic study (EPS)**, especially in patients with **ischemic heart disease with structurally normal hearts**. SAECG may also be helpful in identifying patients with arrhythmogenic right ventricular dysplasia or infiltrative cardiomyopathies.

a. **A positive SAECG finding suggests the need for further EP testing**, especially in individuals with known heart disease.

b. The **absence of late potentials has a high negative predictive value.**

8. **EPS** in the assessment of syncope is **mainly recommended** in patients with **coronary artery disease and syncope of suspected arrhythmic etiology with otherwise no indication for implantable cardiac defibrillator (ICD)** implantation. Conversely, EPS is not indicated in patients with a structurally

normal heart, normal ECG, and no palpitations preceding the syncope. Sensitivity and specificity of EPS are generally poor. EPS should also be considered in the following scenarios:

a. Uncertainty about the origin of wide QRS tachycardia, including bundle branch blocks after nonrevealing noninvasive cardiac testing

b. Patient with syncope at high risk of cardiovascular event or with occupational implications that could translate into harm if diagnosis is delayed

c. Known or suspected VT, especially to guide therapy

d. NSVT, mild-moderate left ventricular dysfunction, and late potentials on SAECG, used to stratify prognosis and guide therapy

e. Drug-refractory malignant VT in candidates for ablative therapy

Induced arrhythmia during **EPS does not usually produce syncope in the laboratory**; therefore, a cause-and-effect relationship often has to be assumed. **EPS findings** considered diagnostic in the cause of syncope include:

(1) Sustained monomorphic VT

(2) Sinus bradycardia with corrected sinus node recovery time over 525 ms

(3) Spontaneous or pacing-induced infranodal block or infrahisian block

(4) Baseline His ventricle (HV) interval >100 ms or significant prolongation after procainamide challenge

(5) Paroxysmal SVT with symptomatic hypotension

The limitations and disadvantages of EPS are high cost, invasive nature, lower specificity if a more aggressive electrical stimulation protocol is used, and poor prediction of bradyarrhythmias.

9. Adenosine triphosphate (ATP) test has been suggested to aid in the diagnosis of unexplained syncope. Patients are injected with a 20-mg bolus of ATP and are kept in a supine position with

continuous ECG monitoring. Asystole lasting >6 seconds or AV block lasting >10 seconds is considered abnormal. ATP test may be able to diagnose syncope caused by transient AV block. However, it has not been able to reproduce sinus arrest. This test remains in the investigational phase, and outcome data are not yet available.

Patients with known or suspected dysautonomia syndromes can be referred to autonomic evaluation to rule out neuropathies, vitamin deficiencies, HIV and other infections, and porphyria.

V. TREATMENT. The treatment of syncope hinges on preventing recurrent episodes, decreasing physical harm from syncopal events, and lowering mortality. Therapy must be individualized to the underlying cause or mechanism.

A. Reflex-mediated syncope. The **first step** involves **reassurance about the benign prognosis and patient education to avoid triggers**. It should also include **adjustment of medication regimen** (eg, chronic vasodilator therapy).

1. Nonpharmacologic treatment may be sufficient for those with infrequent and predictable syncopal episodes

a. Blood volume expansion (probably helpful). All patients should be counseled to liberalize salt (10 g salt per day) and fluid intake (2-3 L/d) unless contraindicated (eg, hypertension, heart failure).This increases orthostatic tolerance evidenced in the negativization of previously positive tilt test with intravenous fluid expansion. However, there exists no randomized trial assessing the impact of salt tablets in syncope prevention.

b. Exercise training (debatable effect) seems to increase blood pressure and orthostatic tolerance, but a small trial failed to detect reduction in syncopal recurrences.

c. Tilt training (debatable effect) exposes patients to progressively longer periods of upright posture in order to condition the neural and vascular systems to counter gravitational stress. In one small study on neurally mediated

syncope, tilt training resolved symptoms in 85% of patients during the period of training. However, four randomized trials reported no reduction in the rate of positive tilt test or syncope recurrence.

d. **Counterpressure maneuvers (probably helpful)** should be **recommended in all patients with predictable episodes**. They include isometric arm and leg exercises (eg, crossing leg or hand grip) performed at the first sign of a syncopal episode. They raise peripheral vascular resistance and blood pressure and can prevent the syncopal spell. A recent trial reported a significant risk reduction of 36% in syncope recurrence when these measures were added to conventional therapy.

2. Medical therapy is recommended in patients with frequent and/or unpredictable syncopal episodes as an add-on regimen to lifestyles changes. The majority of long-term randomized studies have failed to show any benefit from most of the medications. These treatments are generally considered second line in reflex-mediated syncope.

   a. **Beta-agonists (probably helpful): Guidelines favor use of midodrine as "pill in the pocket" strategy** in anticipation of known syncope triggers over chronic use in patients without hypertension, heart failure, or urinary retention. Few small open-label studies have reported that midodrine reduces symptoms and increases likelihood of tilt test negativization. Midodrine may decrease syncope recurrence based on one pediatric open-label trial. **Etilefrine consistently provides no** benefit in the prevention of neuromediated syncope.

   b. **Fludrocortisone (debatable effect)** in pediatric studies has shown inconsistent benefit with two trials actually reporting harm. The Prevention of Syncope Trial (POST) II reported a significant benefit with fludrocortisone in adults after 2 weeks of dose stabilization.

   c. **Selective serotonin reuptake inhibitor (SSRI) (probably helpful).** Specifically, **paroxetine** showed promising reduction of syncope recurrence in highly symptomatic patients. Results

have not been confirmed by other trials. Conversely, fluoxetine provides no benefit compared with propranolol or placebo based on one small study.

d. **Beta-blockers.** Randomized controlled trials (RCTs) on the prevention of syncope with beta-blockers have been negative. A meta-analysis with a substudy of POST I and a large observational study showed a benefit with beta-blockers in patients over 42 years old. **Device therapy** has been extensively studied in reflex-mediated syncope. Asystolic pauses are detected in a significant proportion of neuromediated syncope events, whereas carotid hypersensitivity is known to predict the occurrence of sinus pauses. Meta-analysis of randomized double-blind studies revealed **no benefit of pacing in an unselected population with vasovagal syncope**. Nonetheless, International Study on Syncope of Uncertain Etiology 3 trial **reveals that pacing patients >40 years old with recurrent vasovagal syncope with symptomatic asystolic pauses (>3 seconds) or asymptomatic pause (.6 seconds) provides a risk reduction in syncope recurrence (57%)** at 2 years. Similarly, **pacing is thought to be helpful for carotid syncope with bradycardia**. In this setting, dual-chamber pacing is preferred to single ventricular lead pacing, whereas atrial pacing is not recommended. Patients with positive tilt-table test and vasodepressor response do not respond as well to pacing.

B. **OH.** The management of OH benefits from **education and lifestyle changes** as outlined above. Emphasis must be made on **discontinuation of potentially offending drugs, avoidance of sudden changes in position, liberalization of fluid and salt intake, utilization of counterpressure maneuver** if events are predictable, and **use of compression stocking** to prevent orthostatic pooling of venous blood.

1. Contrary to reflex-mediated syncope, **chronic use of midodrine (5-20 mg TID) is recommended** in patients with OH that failed nonpharmacologic regimen.

2. Weaker evidence exists on fludrocortisone, suggesting a decrease in symptoms and higher blood pressure. Additional treatment includes droxidopa in Parkinson disease, octreotide in postprandial hypotension, and erythropoietin in severe anemia.

C. **Cardiac syncope.** The management of cardiac syncope **starts with the correction of electrolyte abnormalities** (eg, prolonged QT from hypomagnesemia or hypocalcemia). Further therapy depends on the underlying mechanism and/or cause of syncope as follows:

1. **Symptomatic bradyarrhythmias and AV blocks require pacemaker implantation.** Patients with an HV interval of >100 ms are at a high risk for **progression to heart block** and may benefit from a pacemaker. Single- and dual-chamber pacemakers decrease risk of recurrence and sudden death in patients with syncope caused by bradyarrhythmias.
2. **Implantable defibrillators** are the best option for patients with malignant or life-threatening ventricular arrhythmias, sustained monomorphic VT, and/or unexplained syncope in the setting of severe left ventricular dysfunction.
3. **Antiarrhythmic therapy** appears to decrease the frequency of syncope; however, it has not been shown to improve survival.
4. Patients with left or right heart outflow obstruction, such as HOCM, should be instructed to avoid exertional activities that precipitate syncope and should be considered for surgical myectomy.
5. Coronary revascularization is strongly indicated in patients with life-threatening arrhythmias (usually polymorphic VT) because of myocardial ischemia.

D. **Driving restrictions.** General guidance for driving restrictions is largely based on expert opinion and supported by limited data. Often, this is a shared decision made between provider and the patient to balance risk of syncope and injury with patients need to drive for family or work purposes. Untreated syncope of any etiology needs evaluation and management prior to return to driving. Patients with syncope with EF <35% and without an ICD are unfit to drive.

Otherwise, symptom free waiting time can vary based on etiology and frequency of syncope.

E. Referral practices. Syncope can be managed by a variety of providers, including cardiologists, neurologists, emergency physicians, and general and geriatric internists. Special populations such as patients with autonomic pathology, adult congenital heart disease, ages >75, or athletes are likely better managed with specialists.

VI. PROGNOSIS. Reflex- and OH-mediated syncope are not associated with increased mortality, but harm may occur in association with a syncopal event. Conversely, **patients with cardiac syncope or unknown etiology have higher rates of mortality and sudden death**. Unexplained syncope has a mortality rate of 6% to 10% over 3 years and 24% over 5 years. Meanwhile, cardiac syncope confers mortality rate of 50% over 5 years and 30% in the first year after diagnosis.

Syncope presents usually as a single event with **only 20% recurring, but 2-year recurrence rate is 30% in older patients**. The best predictor of recurrence for vasovagal episode is the number of events in the prior year. **Cardiac syncope has a higher risk of recurrence** compared with other syncope etiologies. In a meta-analysis of patients presenting to the ED with syncope, recurrence increases linearly over time from 0.3% at 30 days to 22% at 2 years follow-up.

VII. POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS). This is a poorly understood syndrome characterized by exaggerated increase in heart rate of ≥30 beats/min or ≥40 if 12 to 19 years of age, with postural changes. Heart rate is often ≥120 beats/min. Patients may also feel fatigue, dyspnea, tremulousness, lightheadedness, and exercise intolerance, but do not typically experience OH or syncope. Patients typically present at age 14 to 45 years, and it predominantly affects females. They often have multisystem complaints, such as fibromyalgia, chronic fatigue syndrome, sleep disorders, and gastrointestinal symptoms.

A. Etiology. POTS is thought to be a syndrome with multiple overlapping etiologies, with each etiology having varying importance

in individual patients. There is also suggestion of different genetic forms of the disease.

1. **Partial dysautonomia** refers to autonomic impairment in some parts of the nervous system, with efforts by the still-functioning nervous system to compensate.
2. **Increased sympathetic activity.** Studies have shown that patients with POTS have elevated arterial norepinephrine levels and decreased norepinephrine clearance.
3. **Hypovolemia.** Studies have shown reduced blood volume and reduced erythrocyte volume. The cause of these findings is not clear, but some have postulated problems with the renin-angiotensin-aldosterone axis, possibly because of renal denervation.
4. **Changes in venous function.** Patients with POTS have been shown to have increased venous pooling and a decrease in stroke volume on standing.
5. **Primary baroreflex abnormalities** may also cause the increase in heart rate without change in blood pressure that is seen on standing.

   In clinical practice, two main forms of the disease have been identified: the dysautonomic or peripheral form with inability to increase systemic vascular resistance with orthostatic stress and the hyperadrenergic or central form with abnormal biofeedback mechanism above the baroreceptor level.
6. **Diagnosis.** There are no established criteria for the diagnosis of POTS. The characteristic finding is an **increase in heart rate of .30 beats/min** or ≥40 if 12 to 19 years of age **or a rise in heart rate to .120 beats/min in the first 10 minutes of tilt as their diagnostic criterion**. OH does not typically occur. It is important to rule out other conditions, such as autonomic neuropathy, central dysautonomia, dehydration, and medication effects.
7. **Treatment.** Because of the heterogeneous etiologies of POTS, treatment can be very challenging and often requires multiple

attempts with different regimens. There are no large controlled studies of therapy.

1. **Volume expansion** using oral fluid intake of about 2 to 3 L fluids/d, a high-salt diet ~10 g/d, wearing compression stockings, and fludrocortisone may improve symptoms.
2. **Adrenoreceptor agonists** such as midodrine may improve symptoms in patients with mainly peripheral autonomic denervation; studies have shown improvement in heart rate response and symptoms during tilt testing.
3. Patients with **mainly hyperadrenergic symptoms** may see improvement with **beta-blockers**. In one placebo-controlled, randomized crossover study, low-dose propranolol (20 mg) improved tachycardia and reduced symptoms, but high-dose propranolol (80 mg) did not change or worsened symptoms.
4. **Pyridostigmine**, an acetylcholinesterase inhibitor, has been used to attenuate tachycardia.
5. **Other centrally acting drugs**, such as SSRIs, clonidine, and methyldopa, have been used with some success, but experience with their use is very limited.

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SUGGESTED READINGS

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CHAPTER 34

Assessing and Managing Cardiac Risk in Noncardiac Surgical Procedures

Todd J. Brophy and Ajay Bhargava

I. INTRODUCTION

A. Background. The risk of perioperative cardiac events varies considerably depending on the patient's baseline risk and the type of operation. Over the past four decades, much work has been done to improve our understanding of a patient's individual perioperative risk. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force Committee developed practice guidelines aimed at providing an evidence-based approach to perioperative evaluation. These guidelines were updated in 2014.

B. Objective. The purpose of preoperative evaluation is to **assess current medical status and cardiac risks posed by the planned operation** and **recommend strategies that may influence short- and long-term outcomes**.

1. The physician should obtain as much information as possible by means of **history and physical examination**. It is not prudent to order noninvasive tests for every patient. Noninvasive tests are requested only if the results are likely to influence treatment and outcome.
2. **As a general rule, preoperative intervention is rarely needed unless it is indicated in the absence of the proposed surgery.** Patients with clinically stable heart disease may not need extensive preoperative testing.
3. **An emergency procedure** is one in which there is limited time for clinical evaluation prior to surgery because of a life-threatening

condition, usually <6 hours. In most cases, proceeding with surgery while optimizing perioperative care is preferred to delaying for additional testing.

4. Communication is vital among primary physicians, consulting physicians, anesthesiologists, and surgeons for short- and long-term care of patients.

II. CLINICAL RISK ASSESSMENT

A. History

1. The clinician needs to identify cardiac conditions that place a patient at increased risk. Pertinent symptoms include angina, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, palpitations, and syncope.
2. Attention is directed at serious **comorbid conditions**, such as diabetes mellitus, peripheral vascular disease, history of stroke, renal disease, and pulmonary disease.
3. **Functional capacity** is determined on the basis of the patient's ability to perform certain daily tasks (**Table 34.1**). Although the most recent ACC/AHA guidelines incorporate metabolic equivalents (METs) in the stepwise approach to cardiac assessment, the use of more formal activity scales such as the Duke Activity Status Index (DASI) or Specific Activity Scale can also help identify patients with poor exercise tolerance who may be at elevated risk for perioperative cardiac events.

TABLE 34.1 Estimated Energy Requirements for Various Activities

1-4 METs
Eat, dress, or use the toilet.
Walk indoors around the house.
Walk on level ground at 2 mph (3.2 km/h).
Do light housework such as washing dishes.
4-10 METs
Climb a flight of stairs.

Walk on level ground at 4 mph (6.4 km/h).
Run a short distance.
Heavy work such as vacuuming or lifting heavy furniture.
Play games such as golf or doubles tennis.
More Than 10 METs
Participate in strenuous activities such as swimming, singles tennis, basketball, or skiing.

MET, metabolic equivalent.

B. Physical examination

1. The physical examination includes checking blood pressure in both arms (supine and standing) and evaluation of carotid arterial pulse (character, volume, and upstroke), jugular venous pulsation, cardiac rhythm, heart sounds (murmurs, gallops, or rubs), and extremity pulses.
2. Lung fields are auscultated, and the abdomen is palpated for a possible aneurysm.
3. **High-risk findings** include severe aortic stenosis murmur, elevated jugular venous pressure, pulmonary edema, or S_3 gallop.

C. Active cardiac conditions warrant intensive evaluation and management before proceeding with elective noncardiac surgery and may result in delay or cancellation of the scheduled surgery. Such conditions include unstable coronary syndromes, decompensated heart failure, high-grade atrioventricular block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic bradycardia, and severe symptomatic valvular heart disease.

D. Surgical risk is composed of multiple factors, the most obvious of which include surgical site, operative technique (ie, open, laparoscopic, or endovascular intervention), and duration of surgery. There have been different attempts to categorize surgical risk, ranging from simplified versions like the Revised Cardiac Risk Index (RCRI) (in which “elevated risk” only includes intraperitoneal, intrathoracic, or suprainguinal vascular surgery) to complex and specific risk

estimates such as the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) (in which specific surgery current procedural terminology codes are utilized). The 2022 European Society of Cardiology (ESC) perioperative guidelines for noncardiac surgery also published a table of examples for low, intermediate, and high surgical risk that may also aid in the initial perioperative risk stratification (**Table 34.2**). Regardless of which is utilized, the 2014 ACC/AHA guidelines do suggest the use of a risk prediction tool to help predict perioperative major adverse cardiac events (MACE).

TABLE 34.2 2022 ESC Surgical Risk Estimates for 30-Day Perioperative MACE

Low Surgical Risk (<1%)	Intermediate Surgical Risk (1%-5%)	High Surgical Risk (>5%)
Breast	Carotid CEA or CAS (asymptomatic)	Adrenal resection
Dental	Carotid CEA (symptomatic)	Aortic and major vascular surgery
Thyroid	Endovascular aortic aneurysm repair	Carotid CAS (symptomatic)
Eye	Head or neck surgery	Duodenal-pancreatic surgery
Gynecologic (minor)	Intraperitoneal: cholecystectomy, hiatal hernia repair, splenectomy	Liver resection, bile duct surgery
Orthopedic (minor, including meniscectomy)	Intrathoracic (nonmajor)	Esophagectomy
Reconstructive	Neurologic or orthopedic (major, including hip and spine)	Open lower limb revascularization (acute limb ischemia) or amputation
Superficial surgery	Peripheral arterial angioplasty	Pneumonectomy (VATS or open surgery)
Urologic (minor)	Renal transplantation	Pulmonary or liver transplant
VATS minor lung resection	Urologic or gynecologic (major)	Repair of perforated bowel

Low Surgical Risk (<1%)	Intermediate Surgical Risk (1%-5%)	High Surgical Risk (>5%)
		Total cystectomy

MACE estimate includes a 30-day risk of CV death, MI, and stroke.

CAS, carotid artery stenting; CEA, carotid endarterectomy; CV, cardiovascular; ESC, European Society of Cardiology; MACE, major adverse cardiac events; MI, myocardial infarction; VATS, video-assisted thoracoscopic surgery.

Adapted from Halvorsen S, Mehilli J, Cassese S, et al. 2022 ESC guidelines on cardiovascular assessment and management of patients undergoing non-cardiac surgery. *Eur Heart J*. 2022;43(39):3826-3924; Original data from Glance LG, Lustik SJ, Hannan EL, et al. The surgical mortality probability model: derivation and validation of a simple risk prediction rule for noncardiac surgery. *Ann Surg*. 2012;255(4):696-702.

III. RISK PREDICTION TOOLS. Cardiac risk is a function of patient characteristics and the proposed operation. Two contemporary risk calculators have been incorporated into the guidelines to estimate perioperative cardiac risk. In addition to informing patient-physician discussion, these risk calculators serve to stratify patients. To simplify risk stratification, current guidelines recommend identifying low- and elevated-risk groups. Procedures with a risk of MACE ≥1% are considered *elevated risk*. Further testing is not recommended for patients with low risk of MACE.

A. RCRI, developed in 1999 by Lee et al, is well validated, simple, and widely used. It has six predictors of risk for major cardiac complications (**Table 34.3**). In the original derivation and validation study, a patient with 0 to 1 risk factors was considered low risk (≤1% risk of the combined outcome of cardiac death, nonfatal myocardial infarction [MI], and nonfatal cardiac arrest). Subsequent pooled risk estimates (Duceppe et al, 2017) were significantly higher than the 1999 RCRI study, with risk estimates of 3.9% and 6.0% for 0 and 1 risk factors, respectively. However, the increased event rates were likely influenced by the use of more sensitive troponin assays rather than creatine kinase-MB (CK-MB) as well as the inclusion of emergent and urgent surgery patients.

TABLE 34.3 Revised Cardiac Risk Index

Six Independent Predictors of Major Cardiac Complications
High-risk surgery (intrathoracic, intraperitoneal, or suprainguinal vascular procedures)
History of ischemic heart disease (history of MI or a positive exercise stress test, current complaint of chest pain thought to be due to MI, use of nitrate therapy, or ECG with pathologic Q waves; do not count prior coronary revascularization procedure unless one of the other criteria for ischemic heart disease is present)
History of heart failure
History of cerebrovascular disease
Diabetes mellitus requiring insulin therapy
Serum creatinine >2.0 mg/dL (177 mcmol/L)
Rate of Cardiac Death, Nonfatal MI, and Nonfatal Cardiac Arrest According to the Number of Predictors
No risk factors: 0.4% (95% CI 0.1%-0.8%)
One risk factor: 1.0% (95% CI 0.5%-1.4%)
Two risk factors: 2.4% (95% CI 1.3%-3.5%)
Three or more risk factors: 5.4% (95% CI 2.8%-7.9%)
Rate of Cardiac Death and Nonfatal MI, Cardiac Arrest or Ventricular Fibrillation, Pulmonary Edema, and Complete Heart Block According to the Number of Predictors and the Nonuse or Use of Beta-Blockers
No risk factors: 0.4%-1.0% vs <1% with beta-blockers
One to two risk factors: 2.2%-6.6% vs 0.8%-1.6% with beta-blockers
Three or more risk factors: >9% vs >3% with beta-blockers

CI, confidence interval; ECG, electrocardiogram; MI, myocardial infarction.
Adapted with permission from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100(10):1043-1049.

B. American College of Surgeons NSQIP Myocardial Infarction and Cardiac Arrest risk prediction rule, developed in 2011 by Gupta et al, assesses the risk of postoperative MI or cardiac arrest. This tool includes adjusted odds ratios for different surgical sites and was shown to have superior discriminative power to the RCRI, particularly for patients undergoing vascular surgery. The calculator

is available online: http://surgicalriskcalculator.com/miorcardiacarrest.

IV. SUPPLEMENTAL PREOPERATIVE EVALUATION

A. Routine laboratory tests such as serum creatinine, hemoglobin, platelets, potassium, liver profile, and oxygen saturation are important in determining whether a patient needs special attention. Such patients include those with bleeding risk, renal failure, or liver disease.

B. A 12-lead electrocardiogram **(ECG)** is reasonable for patients with known coronary heart disease, significant arrhythmia, peripheral arterial disease, cerebrovascular disease, significant structural heart disease, or in patients with higher risk surgeries without symptoms. Routine preoperative resting ECG is not recommended for asymptomatic low-risk patients.

C. Echocardiography. Echocardiograms can provide information about certain pathologic conditions (eg, left ventricular [LV] dysfunction, aortic stenosis) that predispose to increased perioperative cardiac risk. Routine use of echocardiography is not recommended. However, assessment of LV function is reasonable for patients with dyspnea of unknown etiology, physical examination concerning significant valvular disease, or patients with known heart failure and change in clinical status.

V. STEPWISE APPROACH TO PREOPERATIVE CARDIAC ASSESSMENT.

The ACC/AHA Task Force developed an **algorithm for preoperative cardiac evaluation** to help physicians systematically identify clinical predictors and determine if noninvasive testing is indicated prior to the noncardiac surgery (**Figure 34.1**). Since the most recent ACC/AHA perioperative guidelines were updated in 2014, other societies, including the ESC and the Canadian Cardiovascular Society (CCS), have published perioperative guidelines placing additional emphasis on preoperative biomarker assessment to assist risk stratification of intermediate- and high-risk noncardiac surgery.

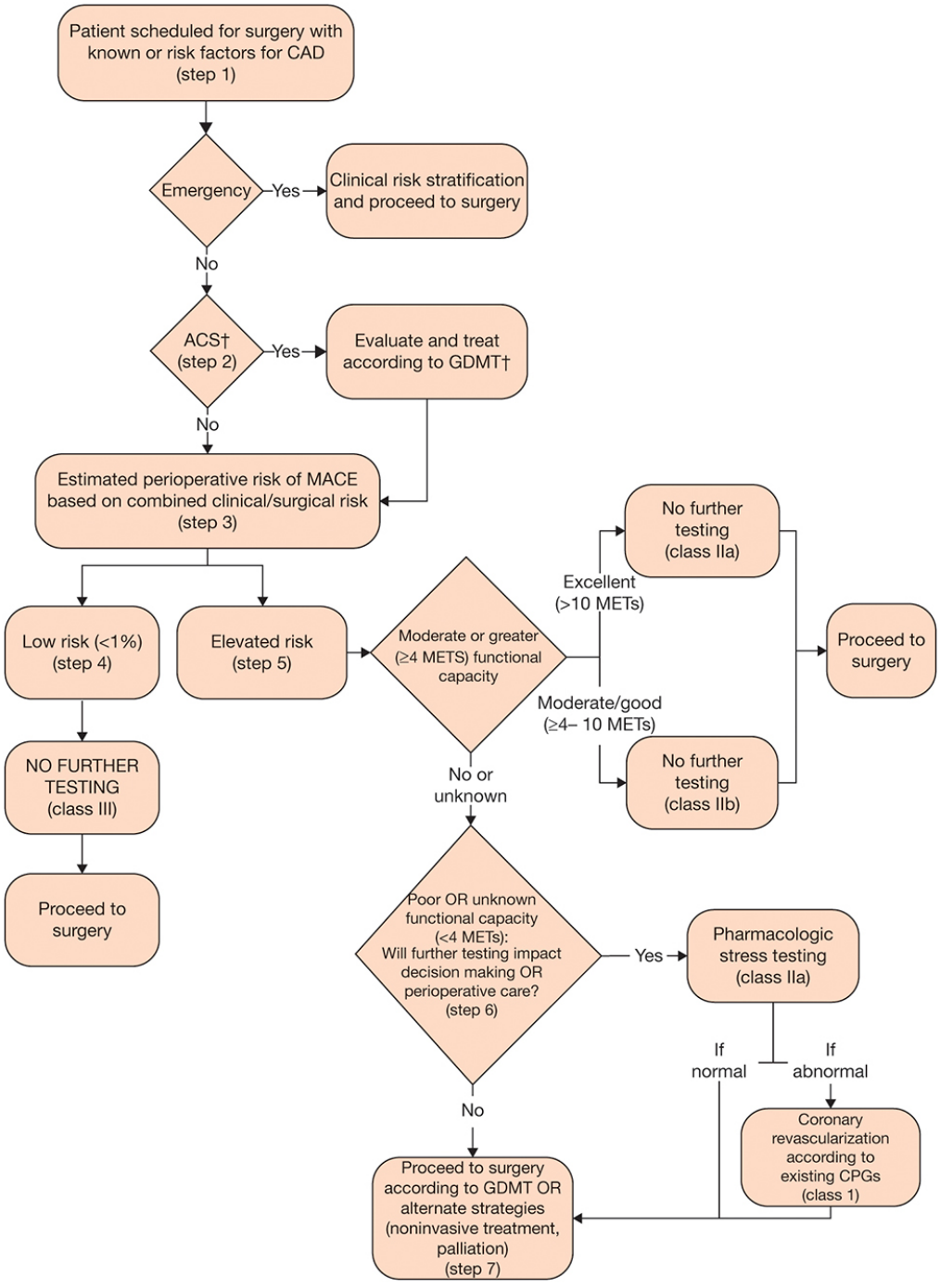

FIGURE 34.1 A stepwise approach to preoperative cardiac evaluation of a patient undergoing a noncardiac surgery. ACS, acute coronary syndrome; CAD, coronary artery disease; CPG, clinical practice guideline; GDNT, guideline-directed medical therapy; MACE, major adverse cardiovascular events; METs, metabolic equivalents. (Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of

Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;64(22):e77-e137. Copyright © 2014 American College of Cardiology Foundation and the American Heart Association, Inc. With permission.)

VI. NONINVASIVE CARDIAC STRESS TESTING. There is no evidence that noninvasive diagnostic testing improves surgical outcomes. A patient's baseline functional capacity should guide the decision to pursue additional preoperative stress testing. Overall, **preoperative noninvasive cardiac stress testing should be reserved for patients who are candidates for these tests, regardless of the planned surgery**.

The recommendations from the 2014 ACC/AHA guidelines are summarized as follows:

A. Patients with elevated risk and **moderate to good function capacity** (≥4-10 METs) may **proceed to surgery** without further exercise testing (class IIb).

B. Patients with elevated risk and **poor functional capacity** (<4 METs) may reasonably undergo **noninvasive pharmacologic testing if it will change management** (class IIa).

C. Routine noninvasive testing is not recommended in patients who are undergoing low-risk surgery.

The **different modalities for stress testing** are detailed in Section IX.

VII. PREOPERATIVE CORONARY REVASCULARIZATION. There are **no prospective randomized controlled trials (RCTs) supporting "prophylactic" coronary revascularization** prior to noncardiac surgery. The **Coronary Artery Revascularization Prophylaxis trial** randomized 510 patients with established coronary artery disease (CAD) at high risk for perioperative cardiac complications to undergo either revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or no revascularization before elective major vascular surgery. There were no differences in perioperative and long-term cardiac outcomes between groups, excluding those with left main disease, LV ejection fraction (LVEF) <20%, and severe aortic stenosis.

A. Indications for revascularization before noncardiac surgery are the same in which revascularization is recommended in the general population:

1. Stable angina with left main disease
2. Stable angina with three-vessel disease (especially with EF <50%)
3. Stable angina with two-vessel disease with significant proximal left anterior descending artery stenosis and either EF <50% or ischemia on noninvasive testing
4. High-risk unstable angina or non–ST-segment elevation MI
5. Acute ST-elevation MI

B. Patients with **asymptomatic ischemia** (based on functional study) do not appear to benefit from preoperative revascularization prior to noncardiac surgery.

C. Routine prophylactic revascularization should not be performed in patients with stable CAD before noncardiac surgery.

D. Small observational studies suggest that patients who undergo **CABG** should wait for at least 4 weeks before proceeding with noncardiac surgery.

III. MANAGEMENT OF PATIENTS WITH PRIOR PERCUTANEOUS CORONARY INTERVENTION ON DUAL-ANTIPLATELET THERAPY. The risks of bleeding, ischemic events (ie, stent thrombosis), and consequences of surgical delay must be considered in patients with prior PCI scheduled to undergo noncardiac surgery. In 2016, the ACC/AHA released a focused update providing recommendations and incorporating recent data demonstrating the safety of shorter duration dual-antiplatelet therapy (DAPT) with newer generation drug-eluting stents. These recommendations were further supported in the 2021 ACC/AHA/Society for Cardiovascular Angiography & Interventions (SCAI) Guideline for Coronary Artery Revascularization in light of additional clinical trial. Recommendations for the timing of surgery are incorporated into a treatment algorithm outlined in **Figure 34.2**.

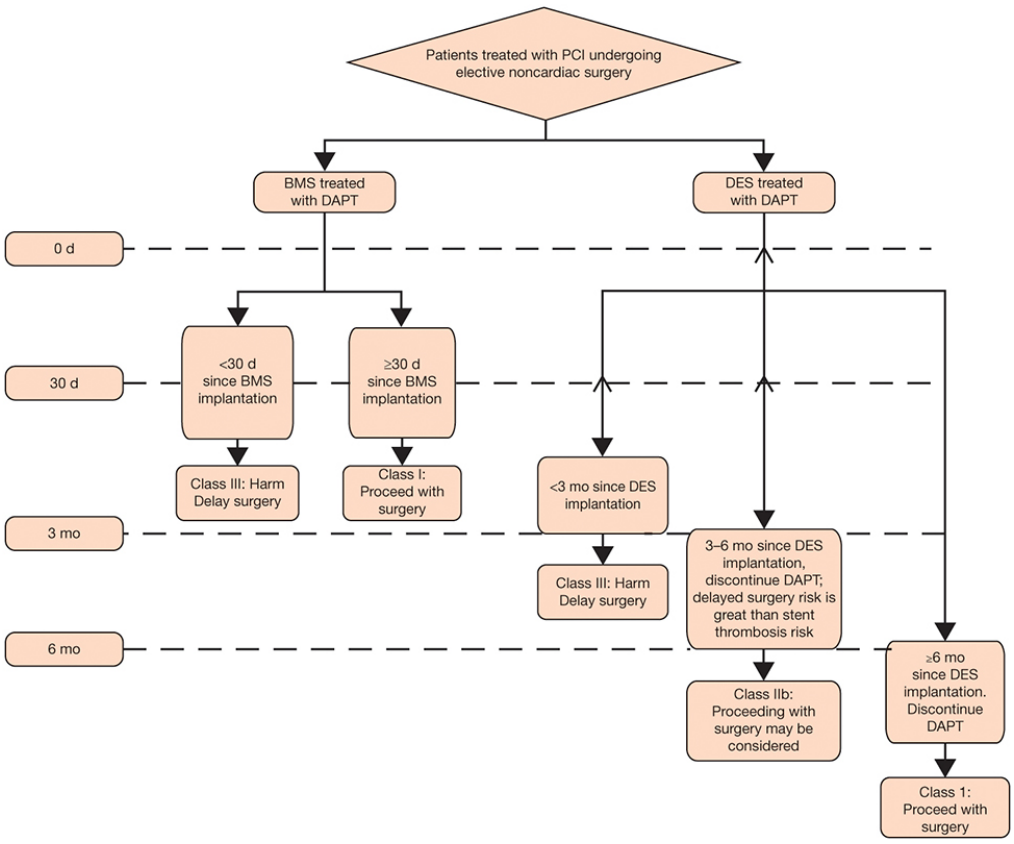

FIGURE 34.2 Timing of elective noncardiac surgery in patients with coronary stents. BMS, bare-metal stent; DAPT, dual-antiplatelet therapy; DES, drug-eluting stent; PCI, percutaneous coronary intervention. (Adapted from Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual-antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention, 2011 ACCF/AHA guideline for coronary artery bypass graft surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease, 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction, 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes, and 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134(10):e123-e155.)

If $P2Y_{12}$ inhibitor therapy needs to be held in patients being treated with DAPT following stent placement, **continuation of aspirin therapy is recommended if possible**. $P2Y_{12}$ inhibitor therapy should be resumed

postoperatively as soon as possible. There is **no convincing evidence demonstrating the efficacy of "bridging" therapy** with intravenous antiplatelet or anticoagulant therapy during temporary discontinuation of DAPT.

IX. MANAGEMENT OF SPECIFIC PREOPERATIVE CONDITIONS

A. Valvular heart disease. In general, the indications for evaluation and treatment of valvular heart disease are similar to those in the nonpreoperative setting. Symptomatic stenotic lesions are associated with increased perioperative morbidity, whereas symptomatic regurgitant valve diseases can usually be managed medically and with close monitoring perioperatively.

1. **Severe aortic stenosis,** if stable and asymptomatic, can be managed with perioperative hemodynamic monitoring and close attention to avoidance of significant periprocedural hypotension. For symptomatic patients, management options include surgical valve replacement, transcatheter aortic valve replacement (TAVR), or balloon valvuloplasty as a short-term bridge. The management strategy should be individualized, because there are no data regarding the efficacy and safety of these options for patients undergoing noncardiac surgery.
2. **Mitral stenosis** when asymptomatic is managed medically with heart rate control and hemodynamic monitoring. When mitral stenosis is severe and symptomatic, mitral valvuloplasty or valve replacement is considered before a high-risk operation is performed.
3. For patients with **aortic or mitral regurgitation**, the medical regimen is optimized with diuretics and afterload reduction.
4. Appropriate **prophylaxis for bacterial endocarditis** is administered for patients with valvular disorders according to the guidelines.
5. Perioperative anticoagulation management for patients with prosthetic heart valves is detailed in Chapter 18.

B. Arrhythmias. High-risk conduction disorders listed above as active cardiac conditions require further evaluation before proceeding with

noncardiac surgery. The following points are important to remember when evaluating arrhythmias in the preoperative setting:

1. Identification of any **underlying cardiac disease, drug toxicity, or metabolic disturbances** that could be the cause of the arrhythmia is very important.
2. Patients with a preoperative history of **atrial fibrillation** who are clinically stable generally do not require special evaluation, other than adjustment of anticoagulation. The decision to interrupt anticoagulation depends on balancing the competing risks of periprocedural bleeding with thrombotic events, and the 2017 ACC Expert Consensus Decision Pathway regarding periprocedural management of anticoagulation addresses this common clinical scenario.
3. The indications for antiarrhythmic therapy and cardiac pacing are similar to those in the nonoperative setting. Antiarrhythmic agents, especially for common conditions such as supraventricular tachycardia (SVT) or atrial fibrillation/flutter, are usually continued throughout the perioperative period without interruption.
4. Frequent premature ventricular beats and asymptomatic nonsustained ventricular tachycardia are not associated with increased perioperative cardiac risk.

C. **Permanent pacemakers and implantable cardioverter-defibrillators (ICDs).** Patients who are completely pacemaker dependent should have their device checked within 3 to 6 months before surgery. A concern in pacemaker-dependent patients is the potential for interaction between intraoperative electrocautery and their device. **Electromagnetic interference, usually with monopolar electrocautery, may cause transient inhibition of pacing and/or inappropriate ICD shocks**. These devices should be reprogrammed to an asynchronous mode (VOO or DOO) and tachyarrhythmia detection and therapies inactivated for ICDs. In general, placing an external magnet over a pacemaker initiates VOO pacing at the manufacturer's default rate, whereas an external magnet disables tachyarrhythmia detection and therapies for ICD without

inhibiting pacing. This knowledge can be especially useful in the setting of urgency if a device cannot be reprogrammed in a timely manner. If a device is inactivated during surgery, the patient should remain on a continuous cardiac monitor throughout the procedure with external defibrillator equipment available. It is imperative to ensure that devices are interrogated postoperatively and reprogrammed to the appropriate settings.

D. Cardiomyopathies and pulmonary hypertension. Patients with restrictive cardiomyopathy, hypertrophic obstructive cardiomyopathy, peripartum cardiomyopathy, and pulmonary hypertension represent a high-risk surgical population. Multidisciplinary management including a specialist familiar with these conditions is recommended to optimize management perioperatively.

X. PERIOPERATIVE MEDICAL THERAPY

A. Beta-blockers. Given their physiologic impact on heart rate, myocardial wall stress, and myocardial energetics, as well as the known benefits of beta-blockers in acute MI, there was interest in the perioperative use of beta-blockers to prevent cardiac complications in noncardiac surgery. In 1999, a high-profile study was published in the *New England Journal of Medicine* by Poldermans et al that concluded perioperative bisoprolol reduced perioperative cardiac death and nonfatal MI in high-risk patients undergoing vascular surgery. In 2012, concerns regarding the scientific integrity of work conducted by Poldermans called into question the evidence base for perioperative beta-blocker therapy. The revised 2014 ACC/AHA clinical practice guidelines took this into account, excluding data from the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography and PeriOperative ISchemic Evaluation trials in a systematic review, which did not substantially affect the estimates of risk or benefit. Overall, preoperative beta-blockers appear to reduce the risk of cardiac events but are consistently associated with bradycardia and stroke. Based on current evidence, the guidelines are summarized as follows:

1. **Patients on chronic beta-blocker therapy should be continued on beta-blockers perioperatively** (class I).
2. It may be reasonable to begin perioperative beta-blockers in patients with intermediate- or high-risk myocardial ischemia on noninvasive stress testing (class IIb).
3. It may be reasonable to begin beta-blockers prior to surgery in patients with three or more RCRI risk factors (class IIb).
4. If beta-blockers are initiated, it may be reasonable to begin therapy in advance to assess safety, preferably more than 1 day before surgery (class IIb).
5. **Do not begin beta-blocker therapy on the day of surgery** (class III).

B. Alpha$_2$-agonists are **not recommended** to prevent cardiac events in patients undergoing noncardiac surgery.

C. The role of **calcium channel blockers** is not well defined and requires further research. Calcium channel blockers with negative inotropic effects, including diltiazem and verapamil, should be avoided in patients with depressed EF or clinical heart failure.

D. Statins. Current evidence, limited to small RCTs and observational studies, suggests statin therapy reduces cardiac events in patients undergoing noncardiac surgery. Patients already taking statins should continue therapy at the time of surgery. Guidelines state that it may be reasonable to initiate perioperative therapy in statin-eligible patients undergoing vascular surgery or other high-risk procedures. The timing and duration of perioperative therapy remains unclear.

E. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) do not appear to influence perioperative outcomes, but patients maintained on these medications were noted to have more frequent transient intraoperative hypotension in retrospective data and a large meta-analysis. Therefore, the ACC/AHA guideline provided a class IIa recommendation for both continuation and interruption of ACE inhibitors and ARBs in the perioperative period, with the recommendation to resume postoperatively as soon as feasible for those patients who have their

medications held. It may be reasonable to preferentially continue these agents for patients who have a strong indication, such as heart failure with reduced ejection fraction (HFrEF).

F. **Aspirin.** In patients without stents, the value of perioperative aspirin is unclear. It may be reasonable to continue aspirin therapy in patients with high-risk CAD or cerebrovascular disease where the risks of potential ischemic events outweigh the risks of bleeding.

XI. PERIOPERATIVE HEMODYNAMIC MONITORING

A. **Pulmonary artery catheters** are occasionally used in high-risk patients (severe valvular disease, combined shock states, advanced heart failure) who are undergoing procedures associated with significant hemodynamic stress. The ACC/AHA guidelines advise to assess the benefit versus risk when considering the use of pulmonary artery catheters. Catheter-guided volume optimization is not routinely recommended because multicenter randomized trials have not shown an outcome benefit with the use of pulmonary artery catheters.

XII. POSTOPERATIVE MONITORING AND MANAGEMENT OF EVENTS

A. **Postoperative MI.** Perioperative tachycardia, hypertension, bleeding, hypovolemia, vasodilatation, hypoxia, and hypercarbia lead to increased myocardial stress. Myocardial injury, as defined by elevated cardiac troponin, is common following noncardiac surgery and is predictive of increased morbidity and mortality. However, **only a small proportion (<5%) of these events are type 1 MIs** (primary coronary event, such as a plaque rupture or thrombotic occlusion). **The majority of cases are secondary to type 2 MI** related to myocardial oxygen supply-demand mismatch, of which there is no specific therapy beyond supportive care and risk factor management. Differentiating the two conditions can be difficult in the postoperative setting, particularly when patients are intubated, sedated, and/or receiving pain medication. Nonspecific findings, such as congestive heart failure (CHF), hypotension, nausea, or ST-segment depression, may be the only clues to myocardial ischemia. Current guidelines

only recommend measurement of troponin levels in the presence of **signs or symptoms suggestive of myocardial ischemia or MI**.

B. The management of **postoperative heart failure and pulmonary edema** is similar to that in nonoperative settings. ECG and troponin should be checked to rule out MI.

C. Arrhythmias. Perioperative arrhythmias are common, especially among older patients and after thoracic surgeries. For patients with arrhythmias, the metabolic profile and medications should be reviewed, and any underlying reversible conditions should be corrected, including hypoxia, fever, bleeding, pain, and infection. Beta-blockers and calcium channel blockers can reduce postoperative tachyarrhythmias. Postoperative atrial fibrillation is common following cardiothoracic surgery as well as noncardiac surgery, with recent observational evidence suggesting an increased risk of MACE. Further studies are needed to address the optimal strategies for the prevention and management of postoperative atrial fibrillation.

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CHAPTER 35

Cardiac Trauma

Ramya Vajapey and Andrew Higgins

I. INTRODUCTION. Traumatic injuries remain one of the leading causes of death worldwide, particularly among younger patients; of these, thoracic trauma is a significant contributor to morbidity and mortality. Cardiac and aortic injuries are the predominant cause of hemorrhagically mediated death among patients with trauma. Cardiac trauma can be divided into blunt trauma (ie, motor vehicle accidents and falls) and penetrating trauma (ie, primarily, knife and gunshot wounds). Cardiac trauma occurs most commonly in the setting of motor vehicle accidents, interpersonal violence, cardiopulmonary resuscitation (CPR), falls from great heights, as well as sporting and industrial accidents. Cardiac trauma can be easily overlooked in the presence of distracting injuries, because it can occur in the absence of chest pain or visible wounds. As many as 50% of people with cardiac injuries die in the field, but advances in diagnostic testing and surgical techniques have improved the prognosis of patients who reach emergency centers alive. Definitive management requires rapid mobilization of the surgical team and transport to the operating room.

Initial attention is focused on the airway, breathing, and circulation, and the primary survey is performed according to the published Advanced Trauma Life Support guidelines. The cardiac physical examination should assess vital signs, peripheral pulses, murmurs, signs of heart failure, distended neck veins, and the presence of pulsus paradoxus. Routine laboratory evaluation should include cardiac biomarkers, and a portable chest radiograph should be performed rapidly. **Transthoracic echocardiography (TTE) at the bedside is the preferred modality for the initial assessment of cardiac trauma with point-of-care ultrasound (POCUS).** The Focused Assessment with

Sonography for Trauma is a widely applied technique using bedside ultrasound to rapidly assess blunt trauma at multiple body sites, including the heart. An electrocardiogram (ECG) is indicated to evaluate for suspected coronary dissection or traumatic coronary thrombosis. **A normal ECG** has a high negative predictive value for blunt cardiac injury, and the addition of cardiac enzymes should also be considered as part of a routine trauma evaluation. Plain films of the chest have limited utility for diagnosis of blunt cardiac injury but may have a role in penetrating trauma demonstrating the presence of a hemothorax, foreign body, and/or a displaced or distorted cardiomediastinal silhouette, as a widened mediastinum or an inward displacement of atherosclerotic calcification from the aortic margin may be seen with aortic dissection on chest x-ray. The role of **cardiac computerized tomography (CT)** using intravenous contrast is expanding, and it remains the diagnostic study of choice to evaluate suspected trauma and/or dissection of the aorta and great vessels, along with transesophageal echocardiography (TEE).

II. BLUNT TRAUMA

A. Blunt cardiac trauma generally occurs in the setting of motor vehicle accidents, but it may also be related to falls, blows from blunt objects, or CPR. This has many possible manifestations including dysrhythmias, contusions, rupture, and coronary artery injury.

B. Blunt trauma may injure the **pericardium**, **myocardium**, **valves or subvalvular apparatus**, **coronary arteries**, or the **great vessels**. The clinical presentation is generally one of **tamponade** or **hemorrhage**, depending on whether the pericardium is intact. Although hypotension and tachycardia are seen in both scenarios, tamponade is suggested by elevated neck veins, muffled heart sounds, and pulsus paradoxus and is rapidly confirmable by a bedside echocardiogram. A new murmur coupled with signs of heart failure should raise clinical suspicion for injury to the valves or subvalvular apparatus. **Myocardial contusions** can present with **electrical disturbances, acute myocardial injury, or heart failure**. Angiography has traditionally been the criterion standard for diagnosing significant

blunt trauma–associated cardiac injury. However, current guidelines recommend initial evaluation with CT scan of the chest with intravenous contrast because of comparable sensitivity and ready availability.

1. **Pericardium.** Increased shear forces during blunt trauma may lead to lacerations or tears in the pericardium. Clinically, the patient may experience pleuritic chest pain, and an ECG may reveal the typical findings of pericarditis. Pericarditis or pericardial effusion may develop weeks or even months after blunt chest trauma as manifestation of post–cardiac injury syndrome. Management is with analgesia, anti-inflammatory therapy, and consideration of corticosteroids in select cases. Late cases of constriction occasionally develop after traumatic injury to the pericardium, which might require pericardiectomy.
2. **Myocardium**
   a. **Myocardial rupture.** The myocardium can be injured by several mechanisms in sudden deceleration injuries. Compression between the sternum and the spinal column, as well as sudden overdistention with blood after abdominal injuries, may lead to myocardial rupture. The thin walls and large diameter of the right atrium predispose it to rupture, and **more than 50% of cases of cardiac rupture involve the right atrium**. The left atrium may be involved in as many as 25% of cases, with the remainder involving the thicker walled right (RV) and left ventricles. Most victims die immediately, but some series suggest that survival may approach 40% if patients arrive with intact vital signs. Management requires prompt thoracotomy and definitive surgical repair. Emergency pericardiocentesis is relatively contraindicated, because it can lead to pericardial reaccumulation and arrest, and is generally only considered as a desperate measure to temporize an arresting or periarrest patient when trained personnel are unavailable to perform a thoracotomy.
   b. **Myocardial contusion.** Blunt chest wall trauma may lead to **focal injury and necrosis of cardiac myocytes**, known as

myocardial contusion. Definitive diagnosis is based on histology, and, therefore, the true incidence and clinical significance of myocardial contusion remain controversial. Patients may complain of precordial pain, but symptoms are usually difficult to interpret in the setting of chest wall trauma and associated injuries. A number of studies have investigated the use of ECG, cardiac enzymes, and TTE in diagnosing myocardial contusion, but none of these tests have been found to be sensitive or specific for the diagnosis. The ECG may be normal or may show nonspecific ST-T wave changes or findings consistent with pericarditis. Elevations in serum troponin levels and creatine kinase–myocardial band (CK-MB) isoenzymes are observed in some patients, but interpretation of a CK-MB may be confounded by concomitant skeletal muscle CK-MM release, especially when total CK >20,000 U/L. TTE may reveal a small effusion or focal wall motion abnormalities; RV involvement is somewhat more common than left ventricular involvement due to its more anterior position. In addition, there are case reports of myocardial dysfunction/heart failure and stress-induced cardiomyopathy following blunt chest injury in athletes. Patients with contusion are thought to be at increased risk for arrhythmic death during the recovery period, because the injured, inflamed myocardium behaves much like a scar tissue as a substrate for slowed conduction and unidirectional block in the development of reentry cycles. However, findings on ECG, TTE, or laboratory tests are insensitive in predicting outcomes. From a practical standpoint, the diagnosis of cardiac contusion does not generally alter management, because treatment is predominantly supportive with careful observation and analgesia. However, making the diagnosis should alert physicians to the potential for arrhythmias. Most centers perform a baseline ECG and monitor patients with blunt chest wall trauma for at least 12 hours before discharge. For athletes, return-to-play decision should be based on clinical circumstances and shared decision-making.

3. **Valvular insufficiency.** Injury to cardiac valves, papillary muscles, or chordae tendineae during blunt cardiac trauma may lead to acute valvular regurgitation. A review of 546 autopsies after blunt trauma suggested that valvular injury may occur in as many as 9% of cases, with a slight increase in frequency in patients with preexisting valvular heart disease. The **aortic valve is most commonly involved**, followed in decreasing frequency by the mitral and tricuspid valves. A new murmur, hypotension, and fulminant pulmonary edema should suggest the diagnosis. The differential diagnosis of a new holosystolic murmur (occasionally with a new right bundle branch block or right-axis deviation on the ECG) should also include a traumatic ventricular septal defect. An emergency TTE and evaluation for urgent surgical intervention are mandated. Acute tricuspid regurgitation is generally well tolerated with lower extremity edema and fatigue as the presenting symptoms, although it occurs relatively rarely.
4. **Coronary arteries.** Blunt trauma occasionally leads to **thrombosis** or **dissection** of a coronary artery and subsequent myocardial infarction; however, these types of injuries are exceedingly rare. Nevertheless, patients with infarctions related to trauma are at risk for all the mechanical complications associated with atherosclerotic disease, such as left ventricular aneurysm or pseudoaneurysm formation, ischemic mitral regurgitation, and ventricular septal defect. In rare cases, blunt trauma contributes to the formation of an arteriovenous fistula between the coronary artery and another structure, such as the coronary sinus, great cardiac vein, right atrium, or RV. Clinically, the patient may have a loud, widely radiating murmur, and ligation of the coronary artery or bypass surgery may be necessary. Multidetector CT has been shown to be helpful in differentiating blunt cardiac injury from acute myocardial infarction, a distinction that is important regarding possible initiation of anticoagulation and need for urgent cardiac catheterization.
5. **Commotio cordis.** Most commonly described in the context of sudden cardiac death in children and adolescents after relatively

low-impact chest wall trauma (most commonly, a baseball or hockey puck striking the chest) have received significant media attention, particularly after an episode involving a professional athlete. The mechanism is unclear, but it appears that a blow to the chest during an electrically vulnerable period of cardiac repolarization may induce ventricular tachycardia or ventricular fibrillation. Victims have been surprisingly refractory to cardiac defibrillation, and survival has historically been poor, though this may be partially mediated by under-reporting in more self-limited cases and is anticipated to improve with more widespread adoption of automated external defibrillators in athletic facilities. Autopsy reports consistently show no evidence of underlying structural heart disease.

6. **Great vessels.** The aorta may also be injured in motor vehicle accidents and falls when sudden deceleration leads to tears or disruption of the vessel. Not surprisingly, most patients with aortic rupture die immediately, but 10% to 20% may reach emergency centers alive if the bleeding is limited by clot or by the pleura. **Aortic rupture typically occurs at the proximal portion of the descending aorta**, where the aorta is tethered against the spine by intercostal arteries and the ligamentum arteriosum. Patients frequently present with chest or back pain and hypotension, and a high index of suspicion is often needed to make the diagnosis. Increased pulse pressure in the upper extremities and diminished pulse pressure in the lower extremities may be found on examination. The chest radiograph may reveal a widened mediastinum, large left pleural effusion, loss of the aortic knob contour, or deviation of the esophagus to the right. A normal chest radiograph, seen in as many as 25% of patients, does not rule out acute aortic pathology.

   CT aortography with intravenous contrast is generally the first-line imaging modality for the diagnosis of ascending aortic dissection and other suspected traumatic injury to the aorta. TEE is also useful and has the advantage that it can be performed rapidly at the bedside in a critically ill patient who is not suitable for

transport. TEE requires sedation and may not be feasible in patients with maxillofacial or cervical spine injuries. Although TTE cannot be used to exclude the diagnosis of aortic dissection, a limited and focused study can be performed more rapidly at the bedside than any other test, and visualization of a flap in the aortic root or ascending aorta secures the diagnosis. Magnetic resonance angiography is an alternative modality but is not well suited for unstable patients because of the time required to perform the study. Definitive surgical repair is indicated for ascending aortic dissection or traumatic aortic rupture. Recent guidelines suggest a preference toward endovascular repair when institutional expertise and anatomy are suitable. If possible, the timing of surgery should be delayed until adequate resuscitation and heart rate and blood pressure control have been achieved. Given the risk of rupture and exsanguination, aggressive reduction of systolic blood goal between 105 and 120 mm Hg is recommended. Beta-blockers can be utilized to reduce inotropic state of the heart, decreasing left ventricular contractility and shear stress, and the impact force of ejected blood on the aorta. Patients with persistent hemodynamic instability despite aggressive measures should be taken emergently to the operating room.

III. PENETRATING TRAUMA

A. Gunshot wounds and stabbings are the most common types of penetrating trauma. The prognosis depends entirely on the extent of injury and the number of chambers involved. Overall mortality is estimated at 60% to 93% for gunshot wounds, 22% to 62% for knife injuries, and 25% for bolting instruments (ie, nail guns). Less frequently, iatrogenic catheter-induced injury can occur in the setting of temporary or permanent pacemaker placement.

B. As with blunt cardiac trauma, the clinical presentation tends to be one of **tamponade** or exsanguinating **hemorrhage**, depending on the integrity of the pericardium. **However, unlike the case of blunt trauma, tamponade carries a favorable prognosis in penetrating trauma**. One series described a survival rate of 73% among patients

with penetrating trauma with tamponade versus 11% among those without. Thrombus within the pericardium is thought to stabilize the rapid hemorrhagic shock associated with penetrating injuries. Pericardial lacerations may also seal spontaneously. Bleeding from the muscular, thicker walled left ventricle is also more likely to be self-limited, whereas injury to the relatively thin RV or right atrium is more likely to be catastrophic and fatal. Knife wounds tend to be smaller and focal, whereas gunshot wounds tend to be larger and extensive and more likely to present with frank hemorrhage.

C. **The RV is the chamber most often involved in penetrating trauma** because of its anterior location in the chest. As described for blunt trauma, penetrating trauma may result in laceration of the pericardium or myocardium, valves, coronary arteries, or the aorta.

D. **Diagnosis.** In an unstable patient, a TTE should be obtained rapidly at the bedside. Although images may be suboptimal, both the sensitivity and specificity of TTE for identifying cardiac abnormalities in this setting are 85% to 90%. A portable chest radiograph may reveal the presence of a pneumothorax or hemothorax.

E. **Management.** After the diagnosis of penetrating cardiac trauma has been made, the patient should be transported as rapidly as possible to the operating room for definitive surgical repair. The infusion of saline and blood products should be continued as needed. Warming of fluids is often needed to prevent hypothermia associated with massive volume resuscitation. There is no role for serial pericardiocentesis in patients with trauma and pericardial effusion, but emergency pericardiocentesis is occasionally necessary if there are delays in reaching the operating room. Injuries in close proximity to coronary arteries may be repaired using biocompatible glues to avoid vessel injury.

IV. SPECIAL CONSIDERATIONS

A. **Indwelling foreign bodies and missile embolization.** Missile embolization from bullet fragments, air gun pellets, or shrapnel is an extremely rare complication from gunshot wounds or battlefield

injuries. Data from the Vietnam conflict suggest that this phenomenon complicates 0.3% to 0.4% of all vascular missile injuries. Clinical suspicion for embolization should be raised in a scenario of multiple penetrating entrance wounds or a single penetrating entrance wound without a corresponding exit wound. The majority of patients with right heart or pulmonary embolization are asymptomatic, but up to 17.4% of patients develop chest pain, dyspnea, or hemoptysis. Up to 4% of patients may exhibit cardiac arrhythmias. Patients with undiagnosed indwelling foreign bodies may also develop subacute bacterial endocarditis as a latent presentation. Metallic missile fragments are usually radiopaque and detected on plain x-rays or a noncontrast CT scan. Intracardiac indwelling foreign bodies should be evaluated by TEE, especially when endocarditis is suspected. Ultimately, the decision to remove asymptomatic indwelling foreign bodies is made on a case-by-case clinical basis considering operative logistics and weighing the risk against the potential benefit.

B. Device implants. An awareness of device-related complications in the setting of cardiac trauma is important, given the expanding patient population with pacemakers and/or implantable defibrillators. Common complications in the setting of blunt trauma would include pocket hematoma, lead dislodgement, or fracture. Penetrating trauma could expose the generator and/or tunneled leads and lead to bleeding or secondary infection. Lead perforation is an uncommon but life-threatening complication manifested as tamponade. Hypotension and bradycardia should prompt concern for lead fracture or dislodgement, especially if the patient is known to be pacemaker dependent. Emergent transcutaneous or transvenous pacing is indicated if the underlying bradyarrhythmia is not hemodynamically tolerated. Device interrogation can also be performed at the bedside to assess pacer dependence and the functional status of all leads using computer equipment provided by the major manufacturers.

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CHAPTER 36

Cardiovascular Manifestations of Systemic Disease

Medhat Farwati and Heba Wassif

I. INTRODUCTION.

Several systemic diseases involve the cardiovascular system, with important therapeutic and prognostic implications. It is vital for cardiologists to recognize, prevent, and manage cardiovascular involvement in various systemic diseases. Patients with inflammatory rheumatic diseases have an increased risk of developing cardiovascular manifestations. The increased risk of cardiovascular pathology in these patients is not only due to traditional cardiovascular risk factors (age, gender, family history, smoking, sedentary lifestyle, cholesterol) but also due to chronic inflammation and autoimmunity. This chapter reviews the cardiovascular manifestations of autoimmune systemic disorders, including coronary artery disease (CAD), myocardial disease, pericardial disease, valvular disease, cardiac arrhythmia, and conduction disease. In addition, the impact of vasculitis and inherited connective tissue disorders on cardiovascular disease is addressed.

II. RHEUMATOLOGIC DISORDERS

A. Rheumatoid arthritis (RA)

is one of the commonest forms of chronic inflammatory polyarthritis, resulting in joint destruction and deformation. There has been evidence of increasing prevalence and incidence of RA in recent years. The World Health Organization (WHO) reported that around 18 million people worldwide were living with RA in 2019, with a predominance in women. The most common cardiovascular manifestations of RA are as follows:

1. **Pericarditis** can present in nearly 50% of patients with RA. It can vary from acute pericarditis and chronic asymptomatic effusive pericarditis to cardiac tamponade or chronic constrictive

pericarditis, with significant hemodynamic consequences. Most cases with uncomplicated acute pericarditis will respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroid therapy may be needed for patients with severe pericarditis. In addition, interleukin-1 (IL-1) inhibitors such as anakinra and rilonacept are being increasingly used for patients with recurrent or refractory pericarditis.

2. **CAD.** Although mortality has decreased among patients with RA over the past decades, it remained higher than in the general population. Cardiovascular disease is the leading cause of death in these patients because of accelerated atherosclerosis, likely a result of higher prevalence of traditional risk factors, in addition to chronic systemic inflammation and the use of corticosteroids. After controlling for traditional risk factors of atherosclerosis, ***patients with RA have been shown to have 2 to 3 times greater risk of CAD*** compared with controls. In the large prospective Nurses' Health Study, women with RA were found to have a 2-fold higher risk of myocardial infarction (MI) compared with controls. In a more recent study, a meta-analysis of 15 studies found that individuals with RA had a 60% greater risk of myocardial ischemia than the general population. The role of disease-modifying agents such as methotrexate has been variable based on the study population with the trend toward risk reduction. In addition to disease-modifying drugs to reduce systemic inflammation, aggressive lifestyle modification, including tight control of blood pressure and low-density lipoprotein (LDL) cholesterol, is warranted.
3. **Cardiomyopathy.** RA can cause granulomatous inflammation of the myocardium leading to cardiomyopathy or involve the conduction system resulting in varying degrees of heart block. Rarely, secondary amyloidosis can occur in RA, leading to an infiltrative cardiomyopathy. In this setting, other end-organ involvement is usually present, particularly renal disease. Cardiac magnetic resonance imaging (MRI) and technetium-99m-pyrophosphate scintigraphy may provide clues to the diagnosis;

however, biopsy is typically required for pathologic confirmation of light chain amyloidosis (AL) in these patients. For further reading, refer to Chapter 9, Section II under the "Heart Failure and Transplant" section.

4. **Valvular disease.** Prevalence of valvular disease in patients with RA is variable depending on patient population ranging from 3% to 70%, on average 30%. However, clinically significant valve disease is rare. Valvular lesions are more prevalent in patients with seropositive RA and significant extra-articular nodular disease. Aortic valve involvement is more common, ranging from valve thickness or sclerosis to hemodynamically significant aortic stenosis (AS). In a recent study of ~73,000 patients with RA from the Veterans Health Administration (VHA) and Centers for Medicare & Medicaid Services (CMS), RA was associated with an increased risk of developing AS (hazard ratio [HR] 1.48; confidence interval [CI] 1.41-1.55), with the subsequent risk for aortic valve intervention and AS-related death, compared to a control group without RA. More studies are needed to assess the prevalence and outcomes of valvular heart disease in this population

B. **Systemic lupus erythematosus (SLE)** is a systemic autoimmune disease that occurs more commonly in women and is characterized by a wide range of organ involvement, including arthritis, dermatitis, glomerulonephritis, serositis, and hematologic abnormalities. Drug-induced lupus can occur with various cardiac medications, including procainamide, quinidine, and hydralazine, and this is associated with the development of antihistone antibodies. SLE can affect the cardiovascular system in various ways:

1. **CAD. Premature coronary atherosclerosis** has been shown to occur commonly in patients with SLE compared with age-matched controls. CAD can also manifest as coronary arteritis, thrombosis in the presence of antiphospholipid antibody (APLA) syndrome (see Section II.C), or, rarely, embolism from Libman-Sacks endocarditis. Importantly, long-term outcomes of patients with MI including the risk of mortality, heart failure, recurrent MI, and

coronary intervention are higher than matched patients without autoimmune conditions.

2. **Valvular disease** is the most common type of cardiac involvement in SLE. The **characteristic valvular lesions in SLE are nonmobile, noninfectious vegetations on the atrial aspect of the mitral valve or the arterial aspect of the aortic valve, referred to as Libman-Sacks endocarditis**. Studies have shown that valvular involvement is very common in SLE and occurs in >50% of patients. The most common valvular abnormality is valvular thickening, followed by vegetations and valvular regurgitation or stenosis. The vegetations can embolize and cause stroke or MI in rare cases (**Figure 36.1**). From a histopathologic perspective, it is important to note that vegetations in Libman-Sacks endocarditis primarily consist of clumps of fibrin with plasma cells and lymphocytes as opposed to infecting organisms in infective endocarditis. Serial echocardiography should be performed to monitor for progression of valve disease, with some experts suggesting annual echocardiography even for asymptomatic patients (no formal guidelines). Treatment is mainly driven by the extent of valvular injury. In cases with severe valve damage, surgical intervention may be warranted and is ideally deferred until the active flare is adequately treated with reevaluation afterward.

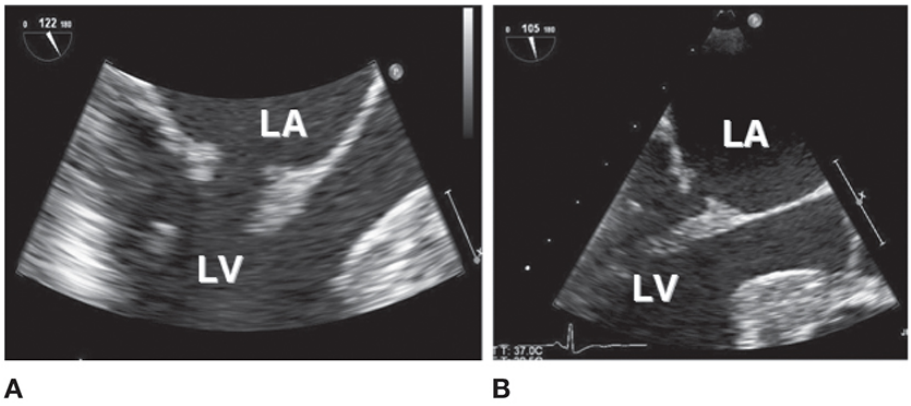

FIGURE 36.1 Transesophageal echocardiogram demonstrating vegetations (Libman-Sacks endocarditis) on the atrial aspect of

anterior and posterior mitral valve leaflets in a patient with systemic lupus erythematosus. **A.** Zoom view of the valve leaflets. **B.** A less detailed image of the leaflets. LA, left atrium; LV, left ventricle.

3. **Pericarditis** is **very common in SLE** and has been shown to occur in >50% to 60% of patients. Associated pericardial effusion is usually exudative, with elevated protein and low glucose concentration, and infection must be ruled out in the setting of concomitant immunosuppressive therapy. Cardiac tamponade is less common with a reported incidence of ~2.5% but may be the presenting manifestation in some patients. The incidence of subsequent chronic constrictive pericarditis is even more rare, with only a handful of cases reported in the literature. In general, the management of inflammation in lupus pericarditis is generally similar to patients without lupus. NSAIDs can be tried first in mild cases of pericarditis. Colchicine can be tried alongside NSAIDs. Systemic steroids can be considered in patients who are not responsive to NSAIDs and colchicine. In addition, the management of these patients necessitates adequate control of underlying autoimmune disease activity. This includes timely treatment with immunosuppressants such as mycophenolate mofetil (MMF), followed by a maintenance regimen to prevent recurrent flares. There are data to suggest that MMF is superior to azathioprine in this setting.
4. **Myocardial dysfunction** in patients with SLE can result from ischemia, valve disease, or long-standing hypertension. Patients with peripheral skeletal myositis have an increased risk of lupus myocarditis. While myocarditis remains an important cause of morbidity and mortality in patients with SLE, its prevalence has decreased owing to the widespread adoption of more effective immunosuppressive regimens. In general, myocarditis presents in a similar manner in patients with SLE compared to the general population. Symptoms include low-grade fever, dyspnea, orthopnea, palpitations, and fluid retention. Laboratory workup may reveal an elevated erythrocyte sedimentation rate (ESR) as well as a rising titer of anti–double-strand DNA (anti-dsDNA)

antibodies in addition to elevated troponin levels. Dilated left ventricle (LV) with reduced systolic function and wall motion abnormalities may be found on echocardiography. Cardiac magnetic resonance (CMR) and positron emission tomography (PET) scan can aid in diagnosis in these patients. The role of endomyocardial biopsy is controversial. This is owing to the perceived procedural risk and the low yield of sampling the right ventricle, as lupus myocarditis predominantly affects the LV.

5. **Conduction system disease** with **complete heart block can occur in infants born to mothers with SLE, particularly those with anti-Ro and anti-La antibodies**. Women with SLE contemplating pregnancy should undergo screening for these antibodies prior to pregnancy and, if present, should undergo fetal echocardiography to screen for conduction abnormalities and myocardial dysfunction. There is some evidence suggesting a role for intrauterine dexamethasone in reversing fetal myocarditis and slowing conduction disease.

C. **APLA syndrome** is characterized by the **presence of APLAs or lupus anticoagulant, recurrent venous or arterial thrombosis, and miscarriages**. APLAs can occur independently, referred to as primary APLAs, or can be associated with other autoimmune diseases such as SLE (10%-30%) and are then referred to as secondary APLAs. Valvular disease is common in APLAs and is characterized by noninfectious vegetations similar to those seen in SLE (Libman-Sacks endocarditis). Management of arterial or venous thrombosis or significant valvular vegetations includes anticoagulation therapy with warfarin. Monitoring anticoagulant effect while on heparin or warfarin may be challenging, due to prolonged partial thromboplastin time or international normalized ratio at baseline, in which case monitoring of anticoagulant effect can be done using activity levels of factors II and X.

D. **Scleroderma** or systemic sclerosis is a rare autoimmune disorder, characterized by vasospasm, microvascular occlusion, and fibrosis of skin and multiple organs. Cardiovascular involvement can occur in progressive as well as limited scleroderma.

1. **Pericardial disease** in the form of fibrinous pericarditis is present in over 70% of patients on autopsy studies, although it is clinically manifest as symptomatic pericarditis in only about 15% to 30% of patients. Small pericardial effusions can be detected in about 40% of patients by echocardiography but are rarely significant. Acute pericarditis may be treated with NSAIDs, with close monitoring of renal function. Corticosteroids are reported to be associated with an increased risk of inducing scleroderma renal crisis. It remains debated whether this is a true mechanistic effect directly related to corticosteroids or it is merely a product of confounding by indication as patients with more severe disease are more likely to both develop renal crisis and receive steroids.
2. **Pulmonary hypertension (PH)** is responsible for significant morbidity and mortality in patients with scleroderma and is more common in the limited type. Autopsy studies have shown histopathologic changes consistent with PH in 65% to 80% of patients with scleroderma; however, <10% of patients manifest PH clinically. Patients with scleroderma and PH appear to have a worse prognosis compared with those with primary PH, with a 2-year survival of <50%. Early diagnosis and treatment may lead to better clinical outcomes; therefore, several studies assessed the role of PH screening in patients with systemic sclerosis. Based on findings from the DETECT study, several authorities recommend echocardiographic screening for patients with high-risk features (eg, disease duration >3 years, diffusing capacity for carbon monoxide [DLCO] <60% predicted, elevated N-terminal pro-B-type natriuretic peptide [NT-proBNP], anticentromere antibody). If patients are found to have an intermediate or high risk for PH on echocardiography, right heart catheterization is recommended to confirm the diagnosis and elucidate the likely mechanism. Drugs for PH, such as prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan), and phosphodiesterase inhibitors (sildenafil and tadalafil), have been studied in patients with scleroderma and PH.

Combination therapies including the use of warfarin may improve survival in patients with PH from systemic sclerosis.

3. **Myocardial involvement** with patchy fibrosis can occur in patients with scleroderma. Epicardial coronary arteries are usually normal on angiography; however, ischemia can occur secondary to microvascular vasospasm. Diastolic dysfunction has been commonly found in these patients. Electrical abnormalities such as frequent ectopy, supraventricular arrhythmias, and nonsustained ventricular tachycardia (VT) can occur in patients with progressive systemic sclerosis. The risk of sudden cardiac death is higher in those with a history of syncope.

E. Seronegative spondyloarthropathies include HLA-B27 antigen–associated arthropathies, such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease–associated arthritis. These disorders occur more commonly in males. **Proximal aortitis with or without aortic regurgitation and conduction disturbances are most commonly associated with ankylosing spondylitis and reactive arthritis**. Proximal aortitis can lead to thickening, stiffness, and dilatation of the aortic root with aortic regurgitation. Aortic or mitral valve thickening with nodularities of the aortic cusps and thickening of the anterior mitral valve leaflet resulting in a characteristic subaortic bump are commonly observed valvular abnormalities in patients with ankylosing spondylitis. Extension of the subaortic inflammation and fibrotic process into the basal septum can result in conduction abnormalities such as heart block, which is usually at the level of the atrioventricular (AV) node. Other less common cardiac abnormalities include pericarditis, diastolic dysfunction, and supraventricular arrhythmias.

F. Dermatomyositis (DM) and polymyositis (PM) are idiopathic inflammatory myopathies characterized by proximal skeletal muscle weakness and elevated levels of muscle enzymes, such as creatine kinase and aldolase. Cardiovascular manifestations of DM and PM include pericarditis, conduction abnormalities, and congestive heart failure secondary to myocarditis that can be focal or generalized and

may be steroid responsive. Cardiac MRI with delayed gadolinium enhancement may be useful in monitoring response to therapy. Coronary vasculitis is a rare manifestation. Management of DM and PM includes corticosteroids, and adjunctive therapies include methotrexate, azathioprine, and intravenous immunoglobulin (IVIg).

III. SYSTEMIC VASCULITIDES

A. Giant cell arteritis (GCA), also referred to as temporal arteritis, **is the most common vasculitis in patients older than 50 years**. It is more prevalent in women compared with men and in those of Northern European descent. GCA usually affects the extracranial branches of the aorta, sparing the intracranial vessels. Transmural inflammation of the vessels is followed by intimal hyperplasia, luminal occlusion, and end-organ ischemia. Branches of the external and internal carotid arteries are particularly susceptible, and the typical clinical presentation of GCA includes new-onset headache, scalp and temporal artery tenderness, jaw pain, acute visual loss, and polymyalgia rheumatica. Concomitant elevation in ESR is almost always present. Temporal artery biopsy is the gold standard for diagnosis and shows transmural chronic granulomatous inflammation with destruction of elastic laminae. Treatment with corticosteroids should be initiated as soon as possible, without waiting for temporal artery biopsy. GCA is associated with thoracic and abdominal aortic aneurysms. According to one study, patients with **GCA are 17 times more likely to develop thoracic aortic aneurysm** and 2.4 times more likely to develop abdominal aortic aneurysm compared with age-matched controls. Rare cardiovascular manifestations include pericarditis, myocarditis, and coronary vasculitis. Studies have shown that MRI or fluorine-18-deoxyglucose (^{18}FDG) PET can be useful for the detection of large vessel vasculitis. Transthoracic echocardiography and abdominal ultrasonography are useful in screening for thoracic and abdominal aortic aneurysms. Low-dose aspirin should be added to corticosteroids, because it has been shown to reduce the rate of blindness and stroke in patients with GCA.

B. Takayasu arteritis (TA) is also a large vessel vasculitis like GCA, but it occurs in young women, particularly of Indian, Japanese, and African American descent. It typically affects the aorta and its major branches (**Figure 36.2**). In TA, arterial stenoses are more common than aneurysms. Clinically, TA is characterized by claudication (upper extremities more common compared with lower extremities), "pulselessness" or asymmetric pulses, and blood pressure. Systemic symptoms such as fever, malaise, arthralgias, myalgias, night sweats, and elevated ESR may indicate active disease. Renal artery stenosis can be associated with hypertension. Cardiac manifestations include aortic regurgitation secondary to aortic root dilatation and, rarely, coronary arteritis. Diagnosis is based on imaging studies that show vascular involvement typical of TA. Imaging modalities such as MRI and PET enable visualization of inflammation in the vessel wall. Therapeutic strategies include corticosteroids, immunosuppressants such as cyclophosphamide or methotrexate in steroid-resistant cases, and anatomic correction using an endovascular or surgical approach when feasible.

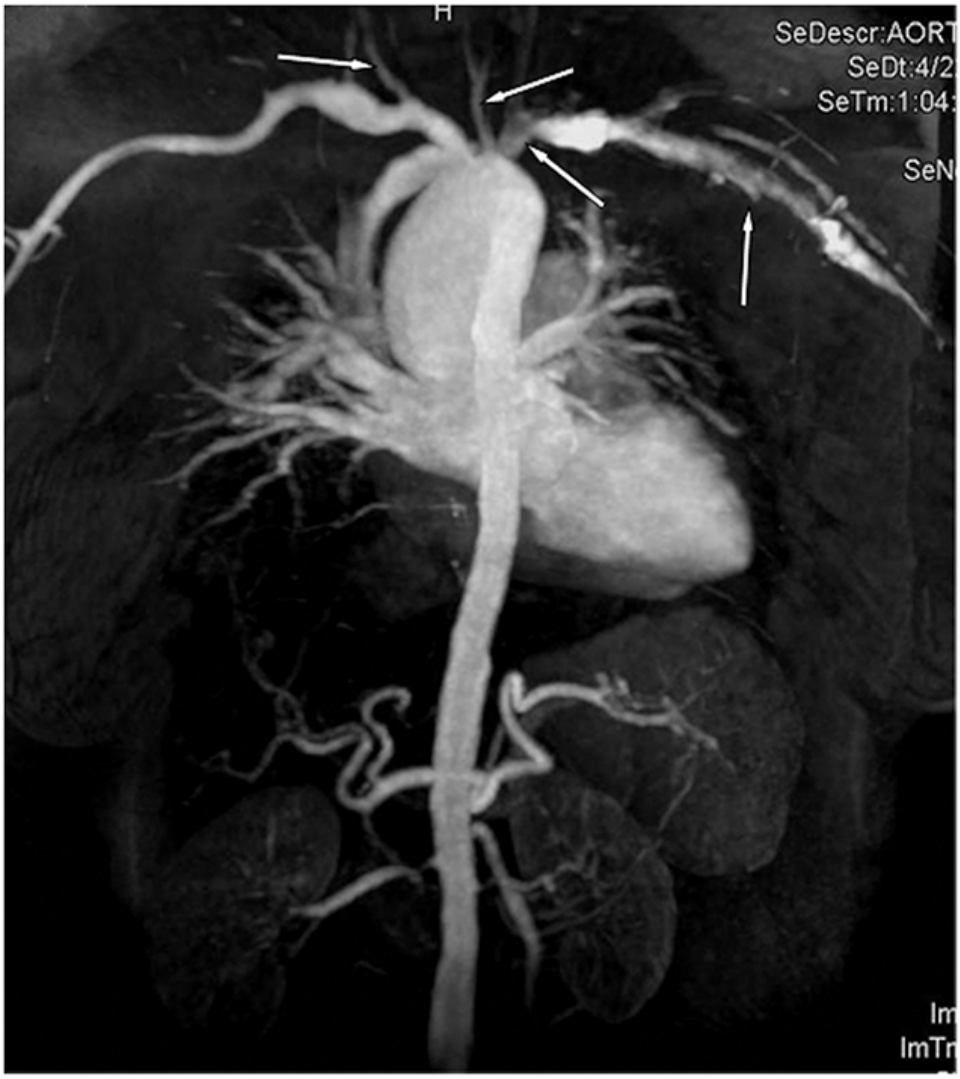

FIGURE 36.2 Magnetic resonance angiogram in a patient with Takayasu arteritis demonstrating severe diffuse narrowing of both common carotid arteries and severe disease in the left subclavian artery (arrows).

C. Kawasaki disease is an acute febrile illness that affects children, usually below the age of 5 years, with the highest incidence in those of Asian descent. Cardiovascular manifestations include pericarditis, myocarditis, aortitis, aortic regurgitation, and arrhythmias. Coronary vasculitis can occur, which, if left untreated, can lead to coronary aneurysm formation in about 4 weeks. Aneurysms larger than 8 mm are referred to as giant aneurysms, and these can thrombose acutely, leading to MI and sudden death. Treatment with aspirin and single-

dose IVIg (dose 2 g/kg) reduces the formation and progression of coronary aneurysms. Recommendations by the American Heart Association (AHA) include long-term follow-up and consideration of anticoagulation for children with multiple giant coronary aneurysms or known obstructive lesions, chronic low-dose aspirin therapy, and coronary artery bypass or percutaneous intervention if lesions are severe and symptomatic.

D. **Idiopathic aortitis** is commonly associated with disorders such as TA and GCA in addition to rheumatologic diseases such as SLE, Behçet disease, seronegative spondyloarthropathies, antineutrophil cytoplasmic antibody–associated vasculitides, Cogan syndrome, and sarcoidosis. Although most cases of aortitis are noninfectious in etiology, infectious causative agents such as *Staphylococcus*, *Streptococcus*, *Salmonella*, and *Syphilis* must be considered. Aortitis can be diagnosed for the first time in surgically excised specimens after aortic surgery. In a 20-year review of over 1,200 aortic surgical specimens at Cleveland Clinic, 52 (4.3%) were clinically and pathologically classified as idiopathic aortitis. Of these, 67% were women. In 96% of cases with idiopathic aortitis and aneurysm formation, aortitis was limited to the thoracic aorta. In 96% of cases, signs of systemic illness were not present at the time of aortic surgery. In 31% (16/52), aortitis was associated with a remote history of vasculitis and a variety of other systemic disorders such as GCA, TA, SLE, and Wegener granulomatosis. Over a mean follow-up of 41 months, new aneurysms were found in 6 of 25 patients not treated with corticosteroids. It is prudent to follow these patients with serial imaging to identify new aneurysms. Treatment with corticosteroids requires evidence of an ongoing systemic inflammatory disease.

E. **Churg-Strauss syndrome (CSS)** is a rare small vessel vasculitis characterized by asthma, peripheral eosinophilia, pulmonary infiltrates, and varying degrees of cutaneous, renal, neurologic, and cardiac involvement. Cardiovascular manifestations are common in CSS and are responsible for significant morbidity and mortality in these patients. The most common cause of death is congestive heart failure secondary to cardiomyopathy, the cause of which may be

small vessel vasculitis or eosinophilic infiltration of the myocardium followed by fibrosis or a combination of both pathologic processes. Other cardiac manifestations include myocarditis and pericarditis with or without pericardial effusion. Therapy mainly includes corticosteroids, but other immunosuppressants may be needed.

F. **Polyarteritis nodosa** is a rare nongranulomatous disease affecting medium-sized arteries that leads to weakening of the vessel wall secondary to necrotizing changes with aneurysm formation or intimal proliferation and stenosis. Cardiac manifestations include angina, MI, congestive heart failure, and arrhythmias, such as supraventricular tachycardia. Treatment is similar to CSS and primarily includes corticosteroids.

IV. CONNECTIVE TISSUE DISEASES

A. **Marfan syndrome** was first described over 100 years ago by Antoine-Bernard Marfan, a French pediatrician. It is **an autosomal dominant connective tissue disease secondary to mutations in the fibrillin-1 (FBN1) gene** that encodes major constituent proteins of microfibrils, which form a significant component of the extracellular matrix. It is a common heritable condition with an estimated prevalence of 1 per 3,000 to 5,000 individuals. About 25% cases have no family history and are a result of de novo mutations. However, genetic evaluation of first-degree relatives is recommended in all instances. The diagnosis of Marfan syndrome is based on the Ghent criteria, based on the consensus by an international expert panel, which has been revised recently with more weight on cardiovascular manifestations. In the absence of family history, the presence of aortic root aneurysm or aortic dissection and ectopia lentis establishes the diagnosis of Marfan syndrome. In the absence of either of these two, the presence of *FBN1* gene mutation or a combination of systemic manifestations listed above is required. Cardiovascular manifestations of the Marfan syndrome are as follows:

1. **Aortic aneurysm and dissection.** Defect in microfibrils results in degeneration of elastic fibers in the aortic media (sometimes inappropriately referred to as “cystic medial necrosis”), with the

resultant aortic aneurysm formation. This typically occurs at the level of the aortic root and involves the sinuses of Valsalva. The aortic root diameter should be serially monitored with echocardiography or computed tomography/MRI. According to the current guidelines, annual imaging is recommended if stability in aortic root size is documented. If the baseline aortic diameter is >4.5 cm or if there is significant growth from baseline, more frequent imaging should be considered. **Elective surgical repair** should be considered if the maximal cross-sectional area in square centimeters of the ascending aorta or root divided by the patient's height in meters exceeds a ratio of 10, because shorter patients have dissection at a smaller size and 15% of patients with Marfan syndrome have dissection at an aorta size smaller than 5.0 cm. This threshold is smaller than for other disorders with aortic aneurysm, given the greater tendency for aortic dissection at smaller diameters in patients with Marfan syndrome. Indications for earlier repair at sizes <5.0 cm include rapid growth defined as >0.5 cm/y, family history of aortic dissection at a diameter <5.0 cm, the presence of significant aortic regurgitation, or in female patients contemplating pregnancy with an ascending aortic diameter >4.0 cm. If the aortic root is <4 cm, then the risk of dissection is considered low, and pregnancy can be allowed with beta-blocker therapy and careful monitoring with serial echocardiography throughout pregnancy. Aortic regurgitation usually occurs secondary to aortic root dilatation. Aortic dissection in Marfan syndrome is usually type A, that is, starts in the ascending aorta and can extend to a variable degree distally. About 10% of dissections in Marfan syndrome begin distal to the origin of the left subclavian artery (type B). Type A dissection necessitates immediate repair, given the high risk of life-threatening complications if not treated promptly. Medical management in patients with Marfan syndrome includes **beta-blockers**, which have been shown to reduce the risk of aortic dilatation and aortic dissection. The beneficial effect of beta-blockers is largely due to the reduction in heart rate and the rate of pressure increase in the aorta, which leads to less stress on the

aortic wall. **Angiotensin receptor blockade (ARB)** with losartan has been shown to slow the rate of aortic root dilatation in animal models of Marfan syndrome, secondary to mitigation of excessive transforming growth factor-beta signaling. However, the evidence for its use in humans is less compelling, although a trial of its use in children with Marfan syndrome suggested efficacy similar to beta-blockade in reducing aortic dilatation. Certainly, it seems appropriate to consider its use in patients with Marfan with adequate blood pressure on beta-blockade. **Calcium channel blockers** have been associated with higher risk of dissection and should be avoided. Because of the risk of acute aortic dissection, patients with Marfan syndrome should be counseled to avoid isometric exercise, including heavy weight lifting, contact sports, and competitive athletics. This is important as there is no data to support that medical therapy including beta-blockers, ARBs, or angiotensin-converting enzyme (ACE) inhibitors can protect athletes from aortic dissection or rupture during intense sport activity. That being said, the 2015 AHA/ACC (American College of Cardiology) scientific statement on aortic diseases including Marfan syndrome states that it is reasonable for athletes with Marfan syndrome to participate in low (class IA) and moderate (class IIA) static/low dynamic competitive sports if they do not have an aortic diameter >40 mm, moderate-to-severe mitral regurgitation (MR), or LV systolic dysfunction with an ejection fraction (EF) <40%. **Mitral valve prolapse** commonly occurs in patients with Marfan syndrome and is more common in women. The incidence is as high as 60% to 80%, and progressive MR occurs in about 25% of patients. The valve leaflets are usually thickened and redundant, and occasionally ruptured chordae or prolapse may be present. Progressive untreated MR can lead to LV dilatation, congestive heart failure, and PH. Tricuspid valve prolapse can occur concomitantly. Standard management for chronic severe MR is indicated in symptomatic patients, with repair of the mitral apparatus if possible, but replacement may be necessary when the leaflets are very redundant or there is severe annular calcification or chordal damage.

2. **Dilated cardiomyopathy**, independent of, or out of proportion to, valvular abnormalities, can occur in patients with Marfan syndrome. This has been hypothesized to be secondary to a potential role of fibrillin mutations in the reduction of myocardial function.
3. **Arrhythmias**, both supraventricular and ventricular, can occur in patients with Marfan syndrome, with a reported prevalence of ~15% in the literature. The most common arrhythmia is atrial fibrillation, followed by VT. Postural tachycardia syndrome (POTS) was also reported in ~5% of patients.

B. **Loeys-Dietz syndrome (LDS)** is an **autosomal dominant connective tissue disease** with similarities to Marfan syndrome but with important genotypic and phenotypic differences. It is caused by mutations in the genes encoding transforming growth factor-beta receptors 1 and 2 (*TGFBR1* and *TGFB2*). Type I LDS is characterized by arterial tortuosity and aneurysms, most often in the aortic root but can involve other arteries, hypertelorism (widely spaced eyes), and bifid uvula or cleft palate or both. Patients are predisposed to more **aggressive and widespread vascular disease**, including aneurysm formation and dissection, compared with Marfan syndrome, with a mean age of death of 26 years. Patients with LDS can develop aortic dissection at aortic diameters <5 cm; hence, **elective repair is recommended at much smaller aortic root dimensions (4.2 cm) compared with Marfan syndrome**. Surgical repair has not been associated with tissue fragility in patients with LDS. More than 50% of patients with LDS can develop aneurysms of other vessels; hence, yearly surveillance imaging of the entire vascular tree has been recommended.

C. **Ehlers-Danlos syndrome, type IV or vascular form**, is a rare autosomal dominant disorder associated with mutations in the gene for type III procollagen (*COL3A1*). Arterial rupture or dissections are the major causes of mortality in these patients and can occur in the thoracic or abdominal vessels, including aortic rupture or dissection. Digestive and uterine complications may also occur. The median age of survival was about 48 years in a study of 220 patients with this

disorder. In the same study, 25% of patients had a medical or surgical complication by the age of 25 years and >80% had such complications by the age of 40 years. In contrast to LDS, tissues are friable in Ehlers-Danlos syndrome, and surgical repair after ruptured aneurysm or dissection can be complicated by hemorrhage or poor wound healing. The role of prophylactic surgical repair for unruptured aneurysms is unclear. Pregnant women have a 50% chance of transmitting the disorder to the child and about 11.5% risk of mortality. Pregnancy should be considered high risk, and women should be counseled against it mainly due to the elevated risk of aortic dissection (WHO Risk Class IV).

D. **Family screening.** Based on the 2010 ACC/AHA guidelines, counseling with genetic testing is recommended to screen first-degree relatives of patients with a gene mutation known to be associated with aeropathy, including *FBN1, TGFBR1, TGFBR2, and COL3A1.* Individuals with positive genetic testing should then undergo aortic imaging.

V. OTHER SYSTEMIC DISEASES

A. **Sarcoidosis** is an idiopathic systemic granulomatous inflammatory disease affecting mainly the lungs but can involve the lymph nodes, skin, eyes, heart, kidneys, musculoskeletal system, nervous system, and endocrine system. **Cardiac involvement is found in 25% of patients with sarcoidosis on autopsy, but only 5% of patients have clinically apparent cardiac involvement**. The most common sites of cardiac involvement are the basal interventricular septum, AV node and the His bundle, focal regions in the ventricular free walls, and the papillary muscles. Classically, regional wall motion abnormalities are present in a non–coronary artery distribution. Cardiovascular manifestations of sarcoidosis are as follows:

1. **Arrhythmias** can vary from conduction disturbances, including heart block to fatal ventricular arrhythmias. Complete heart block is the most common abnormality in patients with clinically evident sarcoidosis and is found in 20% to 30% of patients. First-degree heart block and bundle branch blocks are also seen.

Granulomatous infiltration of the ventricular myocardium can set up foci of automaticity, leading to ventricular arrhythmias. VT is the most common arrhythmia and is reported in about 20% of patients with sarcoidosis. Sudden cardiac death caused by an arrhythmia is one of the leading causes of death (>60%) in patients with sarcoidosis.

2. **Congestive heart failure** may occur secondary to widespread infiltration of the myocardium. It may also occur because of arrhythmias, cor pulmonale from long-standing PH, valvular abnormalities, or a combination of these abnormalities. Progressive congestive heart failure is the second most common cause of death in patients with sarcoidosis.
3. **Pericardial** involvement can manifest as pericarditis, pericardial effusion, and constrictive pericarditis.

Diagnosis of cardiac sarcoidosis may be difficult. Endomyocardial biopsy with finding of noncaseating granulomas has high specificity, but poor sensitivity owing to the patchy nature of myocardial involvement, particularly in the basal septum, whereas the location of biopsy is often the apical septum. Electrocardiogram often reveals conduction abnormalities but has poor sensitivity. Echocardiographic findings include increased ventricular septal thickness (secondary to granulomatous expansion) or wall thinning (because of fibrosis), aneurysms, regional wall motion abnormalities, and, eventually, ventricular dilatation. Contrast-enhanced MRI and ^{18}FDG PET are more sensitive modalities for detecting early cardiac involvement, and findings correlate with disease severity. These imaging modalities can be used in evaluating response to therapy. Corticosteroid therapy can halt cardiac disease progression and improve survival; however, it does not prevent sudden cardiac death. Pacemaker implantation is often necessary in cases of symptomatic heart block or asymptomatic high-grade conduction disease. Implantable cardioverter-defibrillator implantation is recommended for primary prevention in patients with cardiac sarcoidosis at risk for sudden cardiac death, such as those with a

history of nonsustained VT or low EF. Cardiac transplantation for cardiac sarcoidosis is rarely used, because the disease can recur in the transplanted heart. However, it may be considered in young patients with severe end-stage heart failure or resistant VT.

B. Whipple disease is a rare disease caused by a systemic infection with *Tropheryma whipplei*, a gram-positive bacterium that is ubiquitously present in the environment. Cardiac involvement is not uncommon and may present as aortic or mitral valve insufficiency, as well as culture-negative infective endocarditis. Diagnosis is usually secured by histologic examination of the affected cardiac valve. Treatment consists of antibiotics (eg, ceftriaxone, trimethoprim-sulfamethoxazole, or tetracycline) with variable rates of success and long-term recurrence.

C. Immunoglobulin light-chain (AL) amyloidosis is a rare systemic disease characterized deposition of fragments of monoclonal light chains (fibrils) in multiple tissues, including the heart. Amyloidosis may occur either in isolation or as a manifestation of an underlying plasma cell dyscrasias. For further reading, refer to Chapter 9, Section II under the "Heart Failure and Transplant" section.

D. Antirheumatic drugs and cardiovascular disease. Over the past few decades, there has been a significant advancement in drug therapy for numerous rheumatic disorders. Data are emerging regarding the impact of antirheumatic drugs and cardiovascular outcomes.

1. **Tumor necrosis factor-alpha (TNF-alpha) antagonists** have become an important therapy for patients with active RA. There is some evidence to suggest that treatment with TNF-alpha antagonists may slow the progression of atherosclerosis and subsequently cardiovascular events in this population. Advanced congestive heart failure with New York Heart Association (NYHA) class III or IV is a contraindication for the use of these medications
2. **IL-6 inhibitors.** Tocilizumab, an IL-6 inhibitor, has been increasingly used to treat patients with RA and GCA. It is proposed that the vascular protective properties of IL-6 inhibition

might lead to improved endothelial function and arterial stiffness. Conversely, these medications affect lipids unfavorably and have been associated with increased LDL cholesterol. Long-term clinical trials are needed to establish the net effect of these medications on cardiovascular outcomes.

3. **Methotrexate** has been a mainstay treatment for patients with RA for many years with proven efficacy. Several studies have suggested a cardiovascular benefit of methotrexate, possibly owing to improved endothelial function. In a recent analysis of ~20,000 patients with RA, methotrexate was associated with 20% reduction in all cardiovascular events, including MI.
4. **Hydroxychloroquine** is an antimalarial drug with anti-inflammatory properties that is commonly used in the treatment of SLE, RA, and Sjögren syndrome. Several studies suggested some cardiovascular benefits of hydroxychloroquine, including lowering the cholesterol levels and potentially improving endothelial function and aortic stiffness. Retinal damage is a feared side effect, and therefore, baseline ophthalmologic examination with monitoring afterward is indicated. Cardiovascular side effects are rare and may include conduction abnormalities as well as cardiomyopathy with distinct histopathologic features (absence of myocyte injury with vacuolization and curvilinear bodies).
5. **Anti-CD20 medications.** Rituximab, an anti-CD20 medication, is frequently used to treat patients with active RA, SLE, as well as various forms of vasculitis. Small observational studies investigating the impact of rituximab on lipid profile and endothelial function have yielded mixed results. Large clinical trials are needed to establish the relationship between rituximab and cardiovascular outcomes in these patients. Although uncommon, rituximab infusions have been associated with adverse cardiovascular events; thus, it is advised to exercise caution when using these medications in patients with established cardiovascular disease.
6. **Janus kinase (JAK) inhibitors.** Tofacitinib, a JAK inhibitor, is a disease-modifying drug that has been approved for the treatment

of adults with RA. This medication, however, has been linked to increases in lipid levels and unfavorable metabolic profile. In a recent large clinical trial, tofacitinib was associated with a higher risk of major cardiovascular events (HR 1.33) compared to a TNF inhibitor, without an added benefit in efficacy.

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CHAPTER 37 Pericardial Disease

Tiffany Dong and Allan Klein

I. INTRODUCTION. The pericardium is a double-layered, flask-shaped sac containing the heart and the initial part of the great vessels. The outer fibrous layer adjoins adjacent intrathoracic structures, whereas the inner mesothelial portion forms a parietal and a visceral layer, between which lies the pericardial cavity. Normally, this contains <50 mL of serous pericardial fluid, but this may expand substantially in pathologic states. The pericardium serves as a barrier to infection and injury. It also permits the unimpeded expansion, within a protective range, of the ventricle during diastole. Normally, the pericardium readily transmits changes in intrathoracic pressure to the heart with important hemodynamic consequences. Finally, the pericardium can modulate cardiac reflexes and coronary tone via secretion of prostaglandins. The most common pericardial diseases identified in clinical practice include acute/recurrent pericarditis, pericardial effusion, cardiac tamponade, effusive-constrictive pericarditis, and constrictive pericarditis. They may result from local or systemic processes.

II. ACUTE PERICARDITIS. Acute pericarditis is a pericardial syndrome presenting with inflammation of the pericardium. It most often affects males 16 to 65 years old. It accounts for 0.2% of cardiovascular admissions. Despite relatively generally good prognosis, pericarditis usually **recurs between 15-30% of patients** without proper treatment with risks for deleterious complications along with a decrease in quality of life. Etiologies of acute pericarditis are shown in **Table 37.1**. With the advent of COVID messenger RNA (mRNA) vaccines (Pfizer and Moderna), rare cases of pericarditis and myocarditis have been reported. Young males appear more at risk and typically present within a week of their subsequent dose. COVID vaccine–associated pericarditis typically resolves with traditional anti-inflammatory therapy.

TABLE 37.1 Causes of Acute Pericarditis

	Causal Agent	Presentation	Special Laboratory	Treatment
Infectious				
Viral	Coxsackievirus B and echovirus are the most	Most common cause of acute pericarditis	Routine serology not recommended	ASA/NSAID plus colchicine Steroids not recommended

	Causal Agent	Presentation	Special Laboratory	Treatment
	common causal agents.	Prodromal upper respiratory symptoms		
Bacterial	Staph and strep usually following pneumonia or empyema	Patient looks toxic. Chest pain and rub are not necessarily present.	Urgent pericardiocentesis Effusion analysis/cultures and blood culture	Drainage and antibiotics Adjust regimen based on cultures
Tuberculosis (TB)	Pericardial involvement occurs in 1% of pulmonary TB.	Immunocompromised Patient from TB-endemic area High rates of pericardial constriction	CT/MRI chest Sputum/gastric aspirate urine TB culture TB testing in effusion Pericardial/pleural biopsy	Triple therapy for 6 mo Consider adjunctive steroids in HIV-negative patients. Consider intrapericardial urokinase.
Fungal	*Histoplasma*, *Aspergillus*, *Blastomyces*, *Candida* ssp.	*Histoplasma* more likely in immunocompetent patients	Pericardiocentesis Fungal antibodies Staining and culture of pericardial fluid	
Noninfectious				
Idiopathic	Unknown, although many of them are viral	Self-limited		ASA/NSAID plus colchicine
Post–myocardial infarction (post-MI)	Myocardial necrosis	Usually 2-4 d after MI Post-MI pericarditis is a surrogate of extensive myocardial necrosis.	Effusion >10 mm should trigger myocardial rupture investigation.	Supportive ASA and colchicine in selected cases Steroid contraindicated
Dressler syndrome	Unknown, but thought to be an autoimmune reaction	Usually 6-8 wk after MI		ASA/NSAID plus colchicine Steroid contraindicated
Postpericardiotomy	Unknown, also believed to be autoimmune	6-8 wk after surgery Incidence varies from 10% to 40%.		Preventive colchicine ASA/NSAID plus colchicine
Uremic	Unknown, likely retention of uremic toxins	ESRD before or within 8 wk of dialysis Majority of cases have rub and large		Intensive dialysis NSAID and steroids for nonresponder Effusion aspiration in

	Causal Agent	Presentation	Special Laboratory	Treatment
		pericardial effusion.		refractory cases Colchicine contraindicated
Neoplastic	Usually metastatic (lung, breast, lymphoma, and leukemia)	Highly suspicious for tamponade	CT/MRI Effusion cytology Pericardial biopsy considered for confirmation	Antineoplastic treatment Extended pericardial drainage
Autoimmune	SLE, RA, Sjögren, vasculitis, FMF, TRAPS	Rarely first manifestation of autoimmune disease Poor response to therapy	Autoimmune panel (ANA, ENA, ANCA)	Treatment targeted to underlying condition
Inflammatory	Sarcoidosis, Still disease		ACE and 24-h urinary calcium (sarcoid) Ferritin	Treatment targeted to underlying condition
Drugs	Hydralazine, procainamide, doxorubicin, phenytoin, penicillin, immune checkpoint inhibitors			Discontinuation of offending drug For immune checkpoint inhibitors, glucocorticoids should be used in addition to drug cessation.

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; ASA, acetylsalicylic acid; CT, computed tomography; ENA, extractable nuclear antigens; ESRD, end-stage renal disease; FMF, familial Mediterranean fever; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; TRAPS, tumor necrosis factor receptor-1 syndrome.

A. Clinical presentation. Clinical diagnosis of acute pericarditis is made when two of the following criteria are met—chest pain, pericardial rub, electrocardiogram (ECG) changes, and pericardial effusion. In doubtful situations, magnetic resonance imaging (MRI) with gadolinium enhancement may be of value in illustrating pericardial inflammation.

1. **Chest pain** (>85% of cases) is usually affected by respiration and is retrosternal **improved by sitting up and leaning forward**.
2. **Pericardial rub** (<33% of cases) is described as a scratchy and high-pitched sound—often evanescent with changes in quality and intensity on serial examination. Commonly, there is a biphasic rub consisting of atrial and ventricular systolic components. It is best heard during held expiration or

inspiration with the patient leaning forward while placing the diaphragm of the stethoscope at the left lower sternal border.

3. **ECG** changes (up to 60% of cases) evolve through four stages. These may be absent in tuberculosis and neoplastic pericarditis. In the setting of a large effusion, ECG may show **electrical alternans, low voltage,** or both.
   a. **Stage 1:** Diffuse—usually upsloping and concave ST-segment elevation with upright T waves and PR-segment depression in all leads, except V_1 and aVR. There is often reciprocal PR-segment elevation with ST-segment depression in aVR—the "knuckle" sign (**Figure 37.1**).

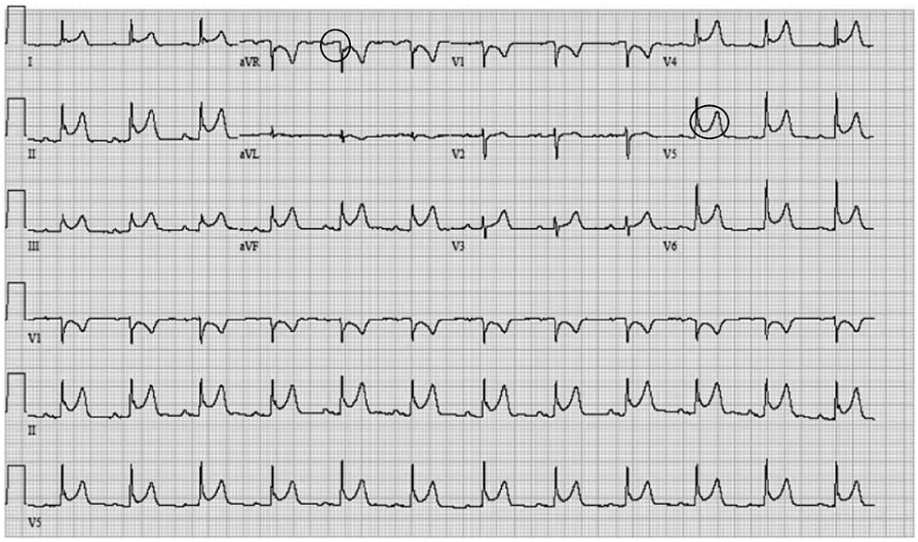


FIGURE 37.1 Stage 1 electrocardiographic changes in acute pericarditis. Note PR-segment elevation in lead aVR ("knuckle" sign) and diffuse ST elevation and the upsloping nature of ST segments when compared with acute myocardial infarction. (Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. *J Am Soc Echocardiogr*. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

   b. **Stage 2** occurs several days later with the resolution of previous PR and ST changes accompanied by T-wave flattening.
   c. **Stage 3** is characterized by T-wave inversion.
   d. **Stage 4** follows after several days to weeks with upright T waves again.
4. **Pericardial effusion**—new or worsening effusion

B. Timeline and definition of pericarditis

1. **Acute** pericarditis is defined as pericarditis lasting <4 to 6 weeks.

2. **Recurrent** pericarditis occurs when pericarditis symptoms recur after a symptom-free period of 4 to 6 weeks.
3. **Incessant** pericarditis is an illness that persists beyond 4 to 6 weeks.
4. **Chronic** pericarditis is reserved for cases lasting longer than 3 months.

C. Diagnostic workup. In all cases with suspicion for pericardial disease, it is recommended to obtain the following:

1. **Routine blood tests:** white blood cells (WBCs), renal and liver function tests
2. **Inflammatory markers and markers of myocardial injury.** Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP/ultrasensitive CRP [usCRP]) are supportive of the diagnosis of acute pericarditis and can help in monitoring the disease process. Troponin I or T elevation supports myocardial involvement or myopericarditis.
3. ECG
4. **Chest x-ray (CXR)**—enlarged bottle-like cardiac silhouette occurs with large pericardial effusion (usually >300 mL). X-ray may also reveal underlying mediastinal, pleural, or pulmonary disease.
5. **Transthoracic echocardiogram (TTE)** within a day of presentation to assess for effusion (only in 40% of cases), tamponade/constrictive physiology, increased pericardial brightness, and wall motion abnormality (if myocardium involved)
6. **Routine testing to identify the underlying cause is not recommended.** Testing should be conducted only if the clinical scenario suggests an underlying etiology. Such testing includes bacterial culture, tuberculin test, viral serologies, fungal tests, thyroid function tests, autoimmune panel, cardiac biomarkers, and/or cytology.

D. General indications for imaging

1. **Echocardiography is the first-line imaging** modality and is routinely indicated in acute/recurrent pericarditis.
2. **Advanced imaging with cardiac MRI or computed tomography (CT)** (**Table 37.2**). **Cardiac MRI** can detect edema and inflammation with positive T2-weighted STIR images and late gadolinium enhancement (LGE). The degree of inflammation is linked to the severity and prognosis of pericarditis. Advanced imaging may be considered in the following scenarios:

TABLE 37.2 Pericarditis Findings per Imaging Modality

Echocardiography
Many cases have normal echocardiogram. Pericardial effusion with/without tamponade physiology (3% of cases) +/− Constrictive physiology Increased pericardial brightness

Intrapericardial masses Wall motion abnormalities (5% of cases of myopericarditis) and/or decreased strain
Cardiac Computed Tomography
Noncalcified thickened pericardium with effusion Irregular pericardium is a sign of severe inflammation. Iodine contrast enhancement supports inflammation. Pericardial effusion can be classified as transudative or exudative based on Hounsfield units.
Cardiac Magnetic Resonance Imaging
Noncalcified thickened pericardium with effusion Increased T2 STIR suggests pericardial edema. Increased LGE suggests pericardial inflammation. Increased T2 STIR signal and increased LGE an acute process with ongoing edema and neovascularization. T2 STIR disappears with chronic or resolving pericarditis, while pericardial LGE indicates chronic inflammation when T2 STIR is absent. Loss of normal sliding motion of parietal layer over visceral layer may suggest pericardial adhesions.

LGE, late gadolinium enhancement; SE, spin-echo; STIR, short-tau inversion recovery time.

- Atypical presentation
- Equivocal echocardiogram with poor prognostic features
- Concern for myocardial involvement as in myopericarditis or perimyocarditis
- Failure of medical therapy or in the assessment of response to therapy
- Concern for chronic pericarditis and constriction
- Chest trauma–associated pericarditis
- Investigation of secondary cause of pericarditis—concomitant ischemia, neoplasm, lung infection, and so on

E. Differential diagnosis. Chest pain from acute pericarditis can mimic aortic dissection, pulmonary embolism, pneumothorax, myocarditis, or acute coronary syndrome. ST elevations in pericarditis are usually upsloping and concave with upright T waves in contrast to horizontal or downsloping convex ST elevation seen in acute ST-elevation myocardial infarction. Echocardiography may help in making the distinction by assessing for wall motion abnormalities, which are usually absent in acute pericarditis.

F. Criteria for admission. Patients with acute pericarditis must be managed in the hospital if there exists a poor prognostic factor and/or concerns of underlying condition driving the illness.

1. Major prognostic factors

- Fever >38 °C
- Subacute symptoms
- Large pericardial effusion (echo-free space around the heart >20 mm)

- Cardiac tamponade
- Failure to respond to medical therapy after 1 week

2. **Minor prognostic factors** include myopericarditis, immunosuppression, trauma, and oral anticoagulant therapy.

G. Management

1. **Physical activity should be limited** until resolution of symptoms and normalization of CRP, ECG, pericardial LGE, and changes on echocardiogram. In addition, athletes should restrict exertion for a minimum of 1 to 3 months.
2. **The first-line treatment** for acute pericarditis is **nonsteroidal anti-inflammatory drugs (NSAIDs)/aspirin and colchicine** as an adjunct therapy until resolution of symptoms and normalization of CRP (**Table 37.3**). The choice of NSAID/aspirin is based on patient tolerance, side effects, comorbidities, and physician expertise. Ibuprofen is the preferred agent with a reasonable safety profile. Intravenous ketorolac may be used for inpatients unable to take oral medications or for severe pain. Patients should be on a proton pump inhibitor while on high-dose NSAIDs. **The addition of colchicine speeds resolution of symptoms and decreases the risk of incessant or recurrent episode by half.** For etiology-specific treatments, see **Table 37.1**.

TABLE 37.3 First-Line Treatment for Acute Pericarditis

Medications	Dose
Ibuprofen	• 600-800 mg orally 3 times a day until symptoms resolution and CRP normalization. Should consider taper over 1-2 wk • Favored NSAID in general given best safety profile
Aspirin	• 750-1,000 mg orally 3 times a day until symptoms resolution and CRP normalization. Should consider taper over 1-2 wk • Favored in patients with concurrent indication for ASA (eg, coronary artery disease)
Colchicine	• 0.6 mg orally twice a day for 3 mo if first episode or 6 mo if recurrence. In patient <70 kg is adjusted to 0.6 mg orally a day

ASA, acetylsalicylic acid; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug.

3. Steroid use during the first episode increases the odds of recurrence by 4-fold. Therefore, this is not recommended as first-line treatment for acute pericarditis. Low-dose corticosteroids (prednisone 0.2-0.5 mg/kg for a month) in combination with colchicine should be considered only in the setting of aspirin/NSAID contraindication or another indication for steroid therapy, such as a steroid-sensitive autoimmune condition.

4. Most patients with idiopathic or viral pericarditis should have a 1-month follow-up to ensure resolution of symptoms and assess for constrictive changes. Patients with pericardial effusion should have serial echocardiograms to follow the size and resolution of the effusion.

H. Complications. Complications usually relate to the underlying cause and not the number of recurrences. For instance, the overall rate of constrictive pericarditis is lower than reported after a first episode of pericarditis.

1. **Recurrent pericarditis:** This is defined as a **recurrent episode of pericarditis after a symptom-free period of at least 4 to 6 weeks** (following taper of medication) from the initial episode. **Rate of recurrence after an episode of acute pericarditis is 15% to 30%.** The recurrence rate increases to 50% after the first recurrence.
   a. **Independent factors for recurrence** identified in trials include **steroid use, LGE on MRI, and CRP elevation** at presentation. Other risk factors proposed include fever, subacute presentation, immunosuppressed host, myopericarditis, large effusion, tamponade physiology, prior chest trauma, incomplete treatment course, and delayed response to therapy.
   b. Clinical presentation and management are similar to acute pericarditis. Exercise limitation is recommended similar to acute pericarditis.
   c. The combination of aspirin/NSAID (weeks to months) and colchicine (6 months) halves rate of subsequent recurrent episode of pericarditis.
   d. **Triple therapy with low-moderate-dose corticosteroids** (prednisone 0.2-0.5 mg/kg), **aspirin/NSAID, and colchicine is only considered after first-line regimen failure**. A very slow taper is recommended once symptoms have resolved and CRP has normalized. Interleukin-1 (IL-1) inhibitors are now considered to be given ahead of steroids in a new paradigm shift in management.
   e. **IL-1 inhibitors** are approved for recurrent pericarditis (**Figure 37.2**). Randomized controlled trials have demonstrated efficacy for anakinra and rilonacept for recurrent pericarditis with a reduction in recurrence, normalization of CRP, and the ability to taper background inflammatory therapy, particularly steroids. Anakinra is dosed with 100 mg subcutaneously or intravenously once a day, while rilonacept is dosed 160 mg subcutaneously weekly with an initial week dose of 320 mg (two doses of 160 mg in two separate sites). Use should be considered in those with their second recurrence and/or those who are colchicine resistance or steroid dependent. Canakinumab has shown efficacy in case series, but no randomized trials have been published for recurrent pericarditis. Furthermore, it is currently unclear the duration of treatment with these IL-1 inhibitors however it is generally given for greater than 12 months. Adverse

side effects include injection site reactions and upper respiratory infections. For rilonacept specifically, other rare side effects are neutropenia and hyperlipidemia. Prior to initiation, patients should be screened for pregnancy, latent tuberculosis, human immunodeficiency virus (HIV), and hepatitis B and C.

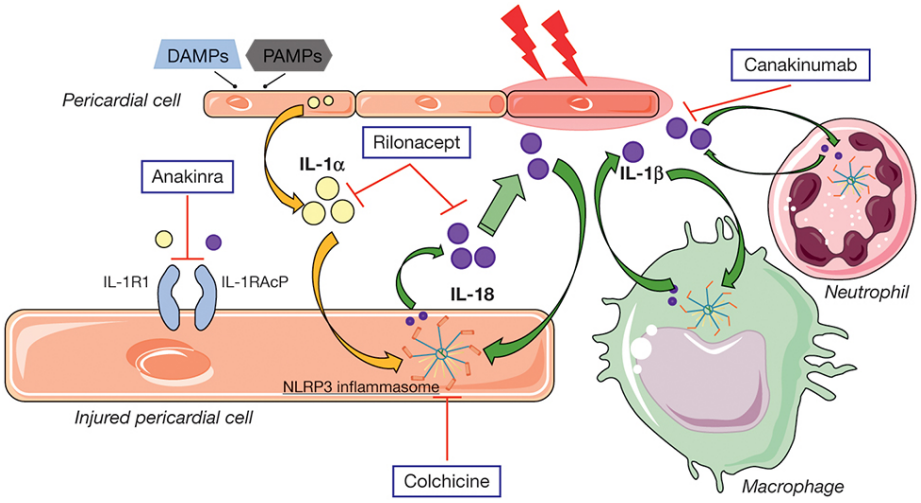


FIGURE 37.2 Mechanism of action for interleukin-1 inhibitors for recurrent pericarditis. (Adapted by permission from Taylor & Francis from Vecchié A, Del Buono MG, Mauro AG, et al. Advances in pharmacotherapy for acute and recurrent pericarditis. *Expert Opin Pharmacother*. 2022;23:681-691. Copyright © 2022 Taylor & Francis Group. With permission.)

f. Radical is considered a last resort for refractory severe symptoms.

2. **Pericarditis with myocardial involvement:** Myopericarditis is defined as acute pericarditis with secondary elevation of myocardial biomarkers in the absence of new left ventricular (LV) impairment. If either new focal or diffuse myocardial impairment with LV impairment (ejection fraction [EF] <40%) is identified, then the event is defined as perimyocarditis.
   a. **Hospitalization is recommended for patients with myocardial involvement.**
   b. **Cardiac MRI should be obtained, beyond the routine pericarditis workup to further characterize myocardial involvement.**
   c. Coronary angiogram should be pursued in those cases with convincing angina and/or increased risk of coronary events.
   d. **Activity restriction for at least 6 months** is recommended in those patients with myopericarditis, given an increased risk of ventricular arrhythmias.
   e. **Empiric treatment with the lowest efficacious dose of aspirin/NSAIDs** is recommended. There is no enough evidence to support the use of colchicine in this setting.

f. If LV systolic function is depressed (perimyocarditis; LV EF <40%), optimal guideline-directed heart failure management is recommended.

g. In general, myopericarditis seems to have good prognosis with no increased risk of death or heart failure.

3. **Cardiac tamponade occurs in up to 11% of cases**, mostly in neoplastic and postsurgical cases. It should be suspected in any patient with acute pericarditis presenting with dyspnea, tachycardia, and hemodynamic instability.

4. **Incessant pericarditis.** Incessant pericarditis is pericarditis that persists lasting more than 4 to 6 weeks. Anti-inflammatory therapy is warranted with NSAIDs, colchicine, and, possibly, steroids with pericardiectomy reserved as the last-line therapy for refractory symptoms. Given the success of IL-1 inhibitors in recurrent pericarditis, these medications may also be considered for treating incessant pericarditis.

5. **Constrictive pericarditis.** Acute pericarditis evolves into constrictive pericarditis only in 1% to 2% of cases, but rarely follows recurrent pericarditis. It is more commonly seen in purulent and tuberculous pericarditis (20%-30% of cases).

III. **PERICARDIAL EFFUSION.** Any process that interferes with the production and/or reabsorption of pericardial fluid may lead to the **accumulation of >50 mL within the pericardial cavity,** leading to a pericardial effusion. Effusions can be classified based on the onset, size, localization, composition, and hemodynamic compromise as described in **Table 37.4**.

TABLE 37.4 Classification of Pericardial Effusion

Onset
Acute (<3 mo)
Chronic (>3 mo)
Size
Trivial (<50 mL): Echo-free space only in systole Mild (50-100 mL): Echo-free space <10 mm
Moderate (100-500 mL): Echo-free space 10-20 mm
Large (>500 mL): Echo-free space >20 mm
Localization
Circumferential
Loculated
Composition
Transudate

Exudate Hemopericardium Pyopericardium
Hemodynamic Impact
None
Effusive constrictive
Tamponade

Effusions with inflammatory signs are likely related to **acute pericarditis**. **Neoplastic process** is more likely the **cause of effusions, causing tamponade** without systemic inflammation. **Large effusions without tamponade or inflammatory signs** are usually due to **chronic idiopathic etiology**.

The **most common causes** of pericardial effusion in developed countries **include idiopathic (50%), neoplastic (10%-25%), infections (15%-30%), iatrogenic (15%-20%), and autoimmune (5%-15%)** (**Table 37.5**).

TABLE 37.5 Causes of Pericardial Effusion

Idiopathic
Infections
• **Viral infections:** Coxsackieviruses A, B5, and B6, echovirus, adenovirus, mumps virus, hepatitis B virus, infectious mononucleosis, influenza, varicella, human immunodeficiency virus
• **Bacterial (purulent):** *Staphylococcus, Streptococcus, Haemophilus influenzae, Salmonella, Neisseria gonorrhoeae, Neisseria meningitidis, Mycoplasma pneumonia, Legionella pneumophila, Rickettsia*, psittacosis, Lyme disease, tularemia
• **Tuberculosis**
• **Fungal infections:** Histoplasmosis, aspergillosis, blastomycosis, coccidioidomycosis, fungal endocarditis
• **Other infections:** Amebiasis, *Echinococcus*
Immunologic/inflammatory disorders
• Rheumatic fever
• Systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis, scleroderma
• Polymyositis, dermatomyositis
• Polyarteritis nodosa, granulomatosis with polyangiitis, giant cell arteritis
• Sarcoidosis, amyloidosis
• Inflammatory bowel disease, Whipple disease
• Behçet syndrome, Reiter syndrome, familial Mediterranean fever

- Tumor necrosis factor receptor-1–associated periodic syndrome and immunoglobulin G4 related diseases

Acute myocardial infarction

- Delayed post–myocardial-pericardial injury syndromes
- Post–myocardial infarction syndrome (Dressler syndrome)

Metabolic

- Uremia, myxedema, hypoalbuminemia

Trauma

- Postpericardiotomy syndrome
- Indirect trauma to the chest
- Percutaneous cardiac interventions
- Perforation of the heart by indwelling catheters

Neoplastic

- **Primary:** Mesothelioma, teratoma, fibroma, leiomyofibroma and sarcoma, lipoma and angioma
- **Metastatic:** Breast carcinoma, bronchogenic carcinoma, lymphoma, leukemia, melanoma

Drugs

Hydralazine, minoxidil, heparin, warfarin, phenytoin, phenylbutazone, cromolyn sodium, dantrolene, methysergide, doxorubicin, procainamide, penicillin, colony-stimulating factor, interleukin-2

Radiation

Dissecting thoracic aneurysm

A. Clinical presentation

1. Clinical presentation ranges **from asymptomatic to tamponade**.
2. **Major determinants of clinical presentation are the underlying etiology of pericardial effusion, volume of effusion, and rate of accumulation.**
3. Rapid accumulation of a small pericardial effusion (80-200 mL) tends to lead to early symptoms including tamponade, whereas a slowly developing effusion may lead to the development of large amounts of pericardial fluid before the onset of symptoms.
4. Often, pericardial effusions are incidentally identified on imaging.
5. When symptomatic, the most common complaints are:
   a. Chest discomfort/fullness
   b. Progressive dyspnea
   c. Orthopnea

d. Patients can also complain of compressive symptoms such as dysphagia (esophagus), hoarseness (recurrent laryngeal nerve), hiccups (phrenic nerve), and/or nausea/vomiting.

6. Physical examination may reveal muffled heart sounds with large effusions. **Ewart sign** can be identified in some patients (dullness to percussion, bronchial breath sounds, and egophony below the angle of the left scapula).
   a. Sinus tachycardia and low blood pressure are ominous signs of tamponade.
   b. Patients with tamponade have **pulsus paradoxus** (>10 mm Hg fall in systolic blood pressure during inspiration) and **Beck triad** (jugular venous distention, muffled heart sounds, and hypotension).

B. Management. Most pericardial effusions can be managed as an outpatient. Initial **assessment for tamponade** should assess for signs of tamponade, such as tachycardia, tachypnea, and hypotension. **Hospital admission is recommended** for those patients with **high-risk features**.

1. **High-risk features**
   a. **Concern for tamponade**
   b. **Large, chronic effusion**
   c. **Suspicion for underlying bacterial or neoplastic process**
2. Workup for suspected pericardial effusion should include:
   a. **Routine workup** for pericardial disease as described before. An echocardiogram is essential in the assessment of tamponade physiology.
   b. Rule out chronic medical conditions based on clinical presentation (eg, hypothyroidism, chronic kidney disease, cancer screening). If pericarditis is identified, there is no need to pursue workup for chronic conditions.

C. General indication for imaging

1. **TTE** is the modality of choice and routinely recommended in patients with suspicion for or known effusions to diagnose and risk stratify the patients. The following are the echo findings of pericardial effusion:
   a. **Persistent intrapericardial echo-free space throughout the cardiac cycle** on M-mode is associated with effusions >50 mL. Conversely, an echo-free space seen only during systole may represent a normal amount of pericardial fluid (trivial effusion).
   b. **Small effusions** tend to localize posteriorly distal to the atrioventricular ring with echo-free space <10 mm.
   c. **Moderate effusions** surround the heart with an echo-free space of 10 to 20 mm.
   d. **Large effusions** are circumferential with greater anterolateral expansion and echo-free space width >20 mm. Anteroposterior or lateral heart swings can be seen in large effusions.

e. **Loculated effusions** with echo densities, stranding, or adhesions suggest exudate over transudate.

f. Two-dimensional (2D) echocardiography parasternal long-axis image with echo-free space between the descending aorta and heart helps differentiate a pericardial effusion from the left pleural effusion.

g. Anterior epicardial fat is differentiated from an anterior effusion based on higher echo density than myocardium and movement in synchrony with heart.

h. Cardiac tamponade physiology is described later in this chapter.

2. **Advanced imaging with CT or MRI may be considered an adjunct in equivocal cases with suspicion for complex effusion, pericardial thickening, or pericardial masses.** Both studies provide better assessment of localization, size, and characteristics of the fluid than echocardiography.

   a. **Cardiac CT is able to further characterize effusions based on CT attenuation:** <10 HU suggests simple transudate; 20 to 60 HU suggests purulent, malignant, or myxedematous effusions; and 60 to 80 HU supports chylopericardium or hemorrhage. Features of pericardial thickening on CT are similar attenuation to effusion, high-attenuation nodularities, lack of movement with position changes, and pericardial enhancement with contrast.

   b. **Cardiac MRI can better differentiate pericardial thickening from small pericardial effusion** compared with cardiac CT. Transudative effusions have low-intensity signal on standard dark-blood images and exhibit high-intensity signal on bright-blood cine images. Meanwhile, exudative collections have high-intensity signal on both T1 and T2 images.

D. Management

1. **Treatment should be targeted to the underlying etiology.** Cases with evidence of acute pericarditis should be treated accordingly. Unfortunately, anti-inflammatory therapies in isolated effusion with no sign of inflammation (eg, elevated ESR, CRP/usCRP, and LGE) are generally ineffective.

2. **Pericardiocentesis (echocardiography or CT guided) is recommended if there**

   a. Are significant symptoms

   b. Is suspicion for bacterial/neoplastic etiology

   c. Is large chronic effusion

   d. Is tamponade physiology

   e. Slow pericardial drainage (30 mL/24 hours) has shown to decrease the risk of reaccumulation

3. Pericardiectomy or **pericardial windows** are indicated in effusions with recalcitrant symptoms, loculated effusion, or when biopsy is needed.

E. Prognosis and follow-up. Evidence suggests that the presence of a small effusion is associated with a worse prognosis when adjusted for age and gender. Prognosis is further impacted by the underlying condition. Moderate and large effusions carry a worse prognosis because they are often caused by bacterial or neoplastic conditions. Up to 30% of large chronic effusion progress to tamponade. Similar to acute pericarditis, idiopathic effusions even if recurrent have a low risk of progression to constriction.

The following is the recommended echocardiographic follow-up for pericardial effusions:

1. No follow-up for small asymptomatic effusions
2. Moderate idiopathic effusions should be monitored with echocardiography every 6 months.
3. Large effusions should have follow-up with echocardiography every 3 to 6 months.

IV. CARDIAC TAMPONADE. Cardiac tamponade is a potentially fatal condition characterized by impaired ventricular diastolic filling caused by an increase in intrapericardial pressures because of the accumulation of pericardial fluid, pus, blood, or gas. The spectrum of tamponade ranges from compensated tamponade to cardiogenic shock.

The development of cardiac tamponade is determined by the **interplay** between **pericardial stiffness** (infiltrations, calcification, or fibrosis), **size of effusion, and rate of fluid accumulation** (**Figure 37.3**).

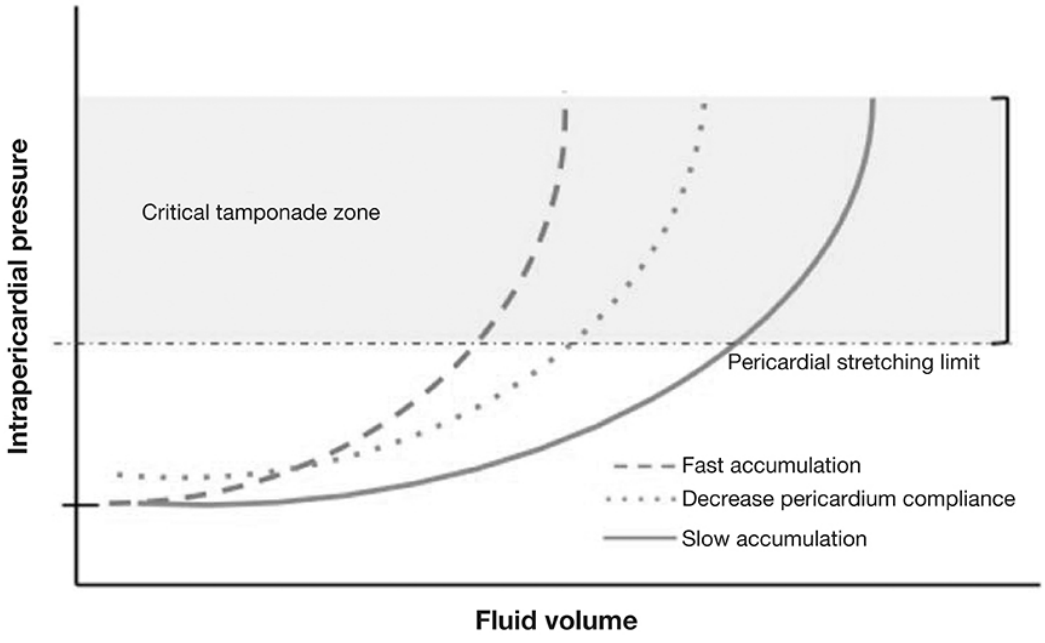


FIGURE 37.3 Pericardial pressure-volume curves. Accumulation of pericardial fluid over time causes minimal changes in intrapericardial pressures until the pericardial stretch limit is reached (flat line), causing exponential increase in intrapericardial pressure. A slower fluid accumulation rate (solid line) takes longer to reach the limit contrary to a rapid filling (dashed line) because there is more time for the pericardium to stretch and activate compensatory mechanisms. The pericardial compliance (dotted line) plays a key role in pericardial tamponade because a decrease in compliance moves the curve to the left. (Adapted from Klein AL, Abbara S, Agler DA, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

A. Pathophysiology

1. The pericardium is able to distend in response to fluid accumulation until a limit on its ability to stretch is reached. Beyond this, small increments in pericardial fluid volume result in large increases in intrapericardial pressure.
2. **Intracardiac volume becomes fixed,** and there is equalization of intracardiac diastolic pressures with those within the pericardium. This causes an absolute reduction in intracardiac volumes, **ventricular diastolic filling, and stroke volumes**.
3. The **cardiac output is initially maintained** by a heightened adrenergic tone, resulting in a resting tachycardia and peripheral vasoconstriction.
4. The **right ventricle (RV) and LV compete for the fixed cardiac volume**. On inspiration, the negative intrathoracic pressure increases the RV venous return, albeit reduced compared with normal, with concomitant reduction in LV filling via a **reduction of pulmonary vein to LV pressure gradient**. This causes a delay in mitral valve opening, a decrease in mitral inflow velocity, left septal bulge, and **further stroke volume reduction,** causing a drop in systolic blood pressure **(pulsus paradoxus)**. The opposite changes occur in expiration.
5. Finally, in **severe tamponade**, **compensatory mechanisms fail**, resulting in a **decreased cardiac output**. Reduced coronary perfusion may cause **subendocardial hypoperfusion**, further compromising cardiac output.

B. Clinical presentation

1. The signs and symptoms of cardiac tamponade all reflect a low cardiac output: restlessness, agitation, drowsiness, or stupor; decreased urine output; dyspnea; chest discomfort and syncope or near syncope; and weakness, anorexia, and weight loss with a chronic effusion.
2. Physical examination usually reveals **Beck triad** (jugular venous distention, distant heart sounds, and hypotension). The following findings are commonly seen in cardiac tamponade:
   a. Compensatory **tachycardia** because of low output state and decreased diastolic filling

b. Tachypnea that reflects elevated pulmonary venous pressure

c. **Elevated central venous pressure** is characterized by a prominent *x* descent and an attenuated or absent *y* descent.

d. **Diminished heart sounds** because of decreased transmission through the fluid-filled pericardium. A pericardial friction rub may be present in some cases.

e. **Pulsus paradoxus (inspiratory drop in systolic blood pressure >10 mm Hg)** as described above. Pulsus paradoxus is **not specific to cardiac tamponade** but may be seen in severe obstructive pulmonary disease, RV infarction, pulmonary embolism, or asthma.

f. **Hypotension** (in severe cases)

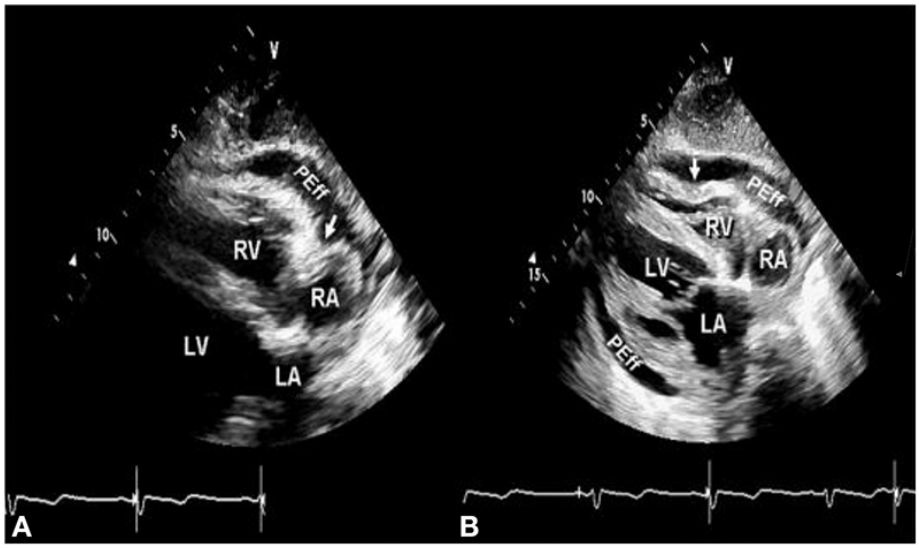
C. Management. It is recommended that all patients with suspected or confirmed tamponade physiology be admitted to hospital and to an intensive care unit setting if hemodynamic compromise is present. All patients should complete routine pericardial disease workup. **TTE must be performed emergently** when the diagnosis of cardiac tamponade is suspected.

D. General indication for imaging

1. **TTE with Doppler** is the initial imaging method of choice. A transesophageal echocardiogram (TEE) is indicated in the postoperative patient with clinical signs of tamponade and inadequate surface images or in whom fluid is not present in the pericardium. Echocardiographic signs of cardiac tamponade include the following:

   a. **Presence of pericardial effusion.** A small pericardial effusion may cause tamponade acutely, whereas a chronic pericardial effusion leading to tamponade is typically much larger.

   b. **Right atrial (RA) collapse** (**Figure 37.4**) typically in late diastole (near peak of R wave) and continues into ventricular systole (sensitive, but specificity only 82%). It is best seen in the parasternal short-axis view, the subcostal view, and the apical four-chamber view. **The longer the duration of diastolic collapse, the more specific it is for tamponade (ie, greater than 1/3 cardiac cycle).**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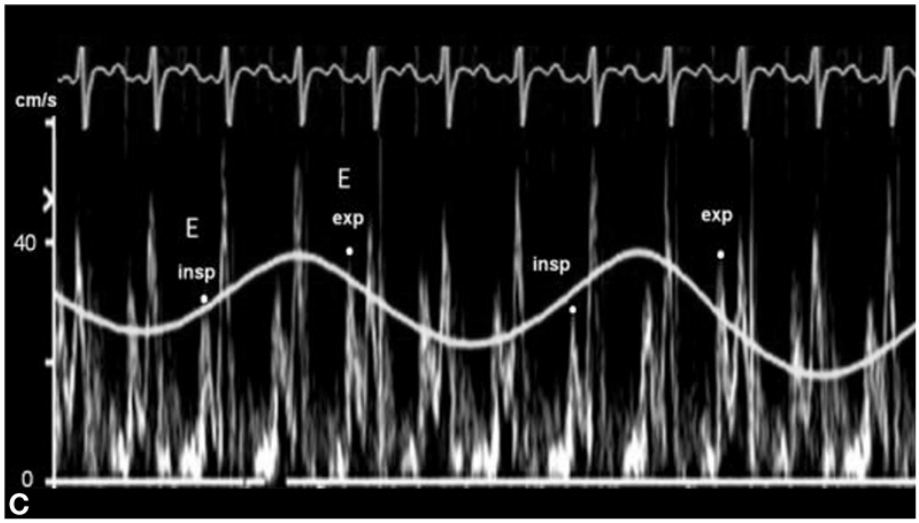
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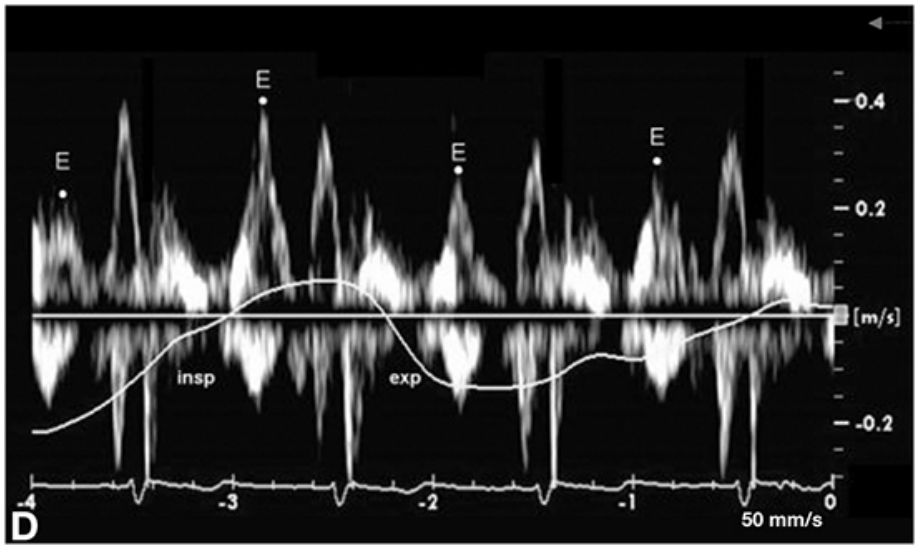
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FIGURE 37.4 Two-dimensional subcostal view of the heart and pulsed Doppler recordings of mitral and tricuspid inflow in a patient with cardiac tamponade. **A.** Atrial collapse is signaled by an arrow occurring at end of diastole (near top of QRS). **B.** RV collapse is signaled by an arrow in early diastole. **C.** Doppler recording of mitral inflow with a respirometer (white line) showing respirophasic flow velocity variation (white dots), with expiratory decrease in peak mitral E-wave velocity exceeding 30%, as is typical in significant tamponade. **D.** Doppler recording of tricuspid inflow with a respirometer (white line) showing respirophasic inflow velocity variation (white dots). These respiratory changes are opposite to those seen in mitral flow velocity. exp, expiration; insp, inspiration; LA, left atrium; LV, left ventricle; PEff, pericardial effusion; RA, right atrium; RV, right ventricle. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

c. **RV early diastolic collapse** or inversion (**Figure 37.4**). Most commonly seen in the anterior RV free wall and infundibulum near the end of T wave with patients in supine position. The parasternal long- and short-axis views of the heart are the best for evaluating this sign. M-mode recording through the RV helps to outline the timing and duration of the event. **Isolated RV diastolic collapse appears to occur before the onset of clinical tamponade.** Conditions that raise RV intracavity volume and RV pressure delay the occurrence of RV diastolic collapse until higher intrapericardial pressures are reached. It has **poor sensitivity in surgical patients** because of the loculated nature of their effusions and the presence of adhesions.

d. **Left atrial diastolic collapse**—a rare but specific sign of tamponade

e. **Abnormal inspiratory increase in RV dimensions** and decrease in LV dimensions

f. **Exaggerated respiratory variation of atrioventricular inflows** detected on pulsed Doppler (**Figure 37.4**): **Expiratory reduction in tricuspid peak E-wave velocity of >60%** and **inspiratory reduction in mitral peak E-wave velocity of >30%**. The respirophasic variation of atrioventricular inflow must be considered only in the context of chamber collapse, inferior vena cava (IVC) dilatation, and/or abnormal hepatic vein flow.

g. **Expiratory blunting or reversal of diastolic hepatic vein flow**

h. **IVC plethora**

2. **CT and TEE** is highly sensitive for detecting hematoma in this setting. Following cardiac surgery, a localized pericardial hematoma rather than fluid may impair filling of the heart. It commonly occurs around the RA and is difficult to diagnose using TTE. **CT or TEE should be considered** in cases where **pericardial hematoma is suspected** but TTE images are nondiagnostic.
3. **Advanced imaging with cardiac CT and MRI** are second-line imaging modalities reserved for subacute complex cases (equivocal postsurgical cases,

regional tamponade, or concern for loculated effusions).

a. **Right heart catheterization (RHC)** is occasionally used in "borderline" cases to confirm the diagnosis of tamponade, quantify the hemodynamic compromise, and assess conditions after pericardiocentesis. Classic diagnostic finding is the **equalization (within 4 mm Hg) of average diastolic pressure in the cardiac chambers,** which is raised usually between 10 and 30 mm Hg.

E. Management

1. Prompt **drainage of pericardial fluid is the most important intervention**. The timing and method of drainage ultimately depend on the etiology of the effusion, the patient's level of acuity, and the availability of trained physicians.
2. The options include pericardiocentesis under echocardiographic, fluoroscopic or CT guidance, and surgical drainage. The latter is preferred if there is a high likelihood of recurrence, in purulent effusions, in loculated effusion, or with urgent bleeding into the pericardium. Generally, if the patient is hemodynamically compromised, percutaneous drainage is performed because induction of anesthesia may lead to a further drop in cardiac output and complete hemodynamic collapse.
3. If the fluid is loculated and not easily accessible through a pericardial window, CT-guided needle drainage is occasionally helpful.
4. Additional management includes volume expansion (albeit to a tolerated limit), inotropic support if the patient is hypotensive, and avoidance of diuretics or vasodilators.

V. CONSTRICTIVE PERICARDITIS.

This is the result of a noncompliant pericardium, usually as a consequence of inflammation, fibrosis, or calcification, which encases the heart leading to heart failure because of impaired diastolic ventricular filling. Pericardial thickening is commonly seen; however, up to 20% of cases have a normal pericardial thickness.

Constrictive pericarditis can be caused by any pericardial process (**Table 37.6**). The most common cause of constrictive pericarditis in developed countries is viral or idiopathic pericarditis (42%-49%), followed by post–cardiac surgery (11%-37%) and radiation therapy (9%-31%). Meanwhile, in developing countries, tuberculosis pericarditis is the leading cause of constriction. There has been a paradigm shift in evaluating and thus treating pericardial disease. The spectrum from acute pericarditis to constrictive pericarditis with or without an underlying inflammatory component should be elucidated (**Figure 37.5**).

TABLE 37.6 Common Causes of Constrictive Pericarditis

Idiopathic	• Accounts for 42%-49% of cases

	• It is the most common cause of constriction in developed countries. • Rate of progression into chronic constriction is <1%.
Infectious diseases Viral (eg, coxsackievirus B and echovirus), bacterial, tuberculosis, fungal, and parasitic	• Tuberculosis is the main cause of constriction in developing countries. • Bacterial and tuberculous pericarditis have the highest chances of progression into constriction (20%-30%).
Post–cardiac surgery	• Accounts for 11%-37% of cases • Risk factors include intraoperative hemorrhage into the pericardium, postoperative pericarditis, and the occurrence of postpericardiotomy syndrome.
Radiation	• Risk factors include duration of therapy, total amount of radiation administered, and volume of the heart in the radiation field. • Delay onset up to 20 y after radiation therapy • In contrast to other causes of constrictive pericarditis, there may be myocardium dysfunction from radiation damage.
Immunologic disorders Rheumatoid arthritis, systemic lupus erythematosus, scleroderma, and sarcoidosis	• Account for 3%-7% of cases of pericardial constriction • Only 3%-5% of autoimmune pericarditis evolve into chronic constriction.
Neoplastic disease Breast cancer, lung cancer, lymphoma, mesothelioma, and melanoma	• Causes constriction via infiltration of pericardium
Miscellaneous	• Accounts for <10% of all cases of constriction • Includes trauma, drug, and uremic pericarditis

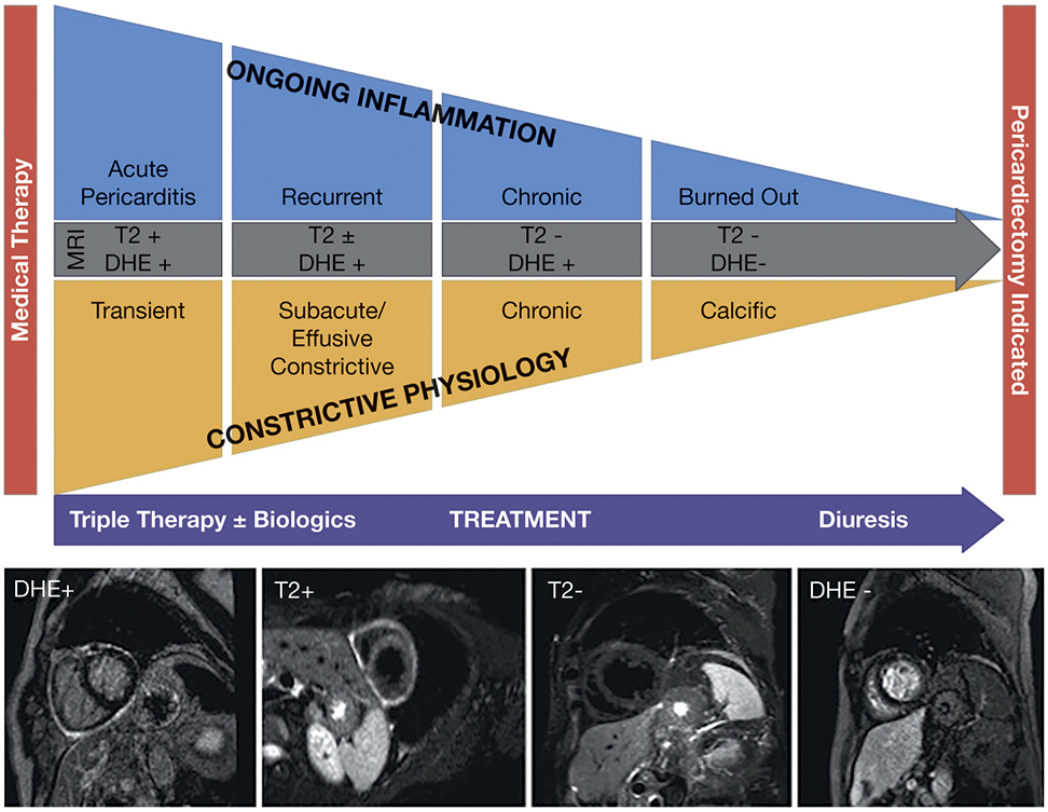


FIGURE 37.5 Spectrum of pericardial disease. Use cardiac magnetic resonance sequences especially T2 and delayed hyperenhancement (DHE) to distinguish between spectrum of ongoing inflammation and constrictive physiology. (Reproduced from Chetrit M, Xu B, Kwon DH, et al. Imaging-guided therapies for pericardial diseases. *JACC Cardiovasc Imaging*. 2020;13:1422-1437. Copyright © 2020 Elsevier. With permission.)

A. Pathophysiology

1. Constrictive pericarditis can be classified into the following specific subforms:
   a. **Transient constrictive pericarditis usually follows an episode of acute pericarditis with effusion** but can also follow any pericarditis, pericardiectomy, and chemotherapy or be associated with autoimmune diseases. **It accounts for 9% to 17% of all constrictive pericarditis**. It is defined as a transient form of **constriction because of inflammation rather than scarring that spontaneously resolves or resolves after 3 to 6 months of anti-inflammatory therapy**. Therefore, symptoms of constriction may be accompanied by those of pericarditis with signs of inflammation (ESR, CRP/usCRP, LGE). Prompt recognition and treatment may be important to prevent potential evolution into chronic constrictive pericarditis.
   b. **Effusive-constrictive pericarditis** is described in patients with pericardial tamponade in whom intracardiac pressures remain elevated (RA pressure

fails to decrease by 50% or to less than 10 mm Hg) despite pericardiocentesis. There is a predominant involvement of the visceral pericardium (epicardium), called constrictive epicarditis by some authors. Some patients may have resolution with a conservative approach, but others require extensive epicardiectomy, which should be performed at experienced pericardial centers as it is technically challenging.

c. **Chronic constrictive pericarditis** is defined as persistent constriction after 3 to 6 months duration.

2. The encasement of the heart by **nondistensible pericardium limits the cardiac filling to a fixed volume**. In early diastole, the **ventricles expand normally with rapid early filling** secondary to the elevated pulmonary and systemic pressures. Once the **ventricles reach the confines of the rigid pericardium, diastolic filling comes to an abrupt halt** because of an immediate increase in ventricular pressure. **Nearly all ventricular filling occurs in the second phase of diastole (early rapid filling),** with little contribution from the third phase (diastasis) and the fourth phase (atrial systole). **The hallmark of constrictive pericarditis, although nonspecific, is the ultimate equalization of end-diastolic pressures in all four cardiac chambers.**
3. **The stiff pericardium also prevents the transmission of intrathoracic pressures** to the cardiac cavities during the respiratory cycle (intrathoracic-intracardiac pressure dissociation), which causes significant respirophasic variation of ventricular preload with associated enhanced ventricular interdependence.
4. **During inspiration**, the **right heart preload and tricuspid inflow velocity increase** because of the negative intrathoracic pressure. Conversely, **left heart preload and mitral inflow decrease** as a consequence of full transmission of the negative pressure to the pulmonary vein in contrast to partial or no transmission into the left heart chambers. This leads to a **full RV and an emptier LV encased by a stiff pericardium**, which causes a **leftward shift of the ventricular septum**.
5. The opposite occurs **on expiration**, a positive intrathoracic pressure **reduces right-sided preload and tricuspid inflow**. Meanwhile, the increased thoracic pressure is fully transmitted to the pulmonary venous circulation, but not to the left heart, **increasing LV filling pressures and mitral inflow**. This will ultimately lead to a **full LV and emptier RV,** causing **rightward septal shift and late diastolic flow reversal in the hepatic veins**.
6. The myocardium is generally normal; and **myocardial relaxation and systolic function are usually spared**. However, myocardial function may occasionally be compromised by tethering of the myocardium to the pericardium.

B. Clinical presentation. The **early symptoms** of constrictive pericarditis are often insidious and nonspecific, including **malaise, fatigue, and decreased exercise tolerance**. As the **disease progresses**, patients complain predominantly **of right-sided heart failure symptoms,** including peripheral edema, hepatic congestion, ascites, and worsening exercise tolerance.

The physical examination of a patient with constriction commonly reveals the following:

1. **Increased jugular venous distension**, on occasions so high that it may only be evident by examining the patient upright. Observation of the jugular venous pulsations reveals a **prominent *y* descent that is produced by the rapid ventricular filling in early diastole**. Many patients demonstrate a lack of inspiratory fall in venous distention, known as **Kussmaul sign**.
2. **Muffled heart sounds** because of decreased transmission through the thickened pericardium and **soft first heart sound (S_1)** because mitral and tricuspid valves are nearly closed by the end of diastole.
3. **Occasionally, one may hear a pericardial knock** in early diastole. This represents the abrupt cessation of diastolic filling that occurs when further ventricular relaxation is impeded by the rigid pericardium. The pericardial knock **must be differentiated from other early diastolic sounds,** such as an opening snap, third heart sound (S_3), and tumor plop. In general, the pericardial knock is of a higher frequency, is heard best with the stethoscope diaphragm, and occurs slightly earlier than an S_3.
4. **Decreased breath sounds** at the bases, attributed to pleural effusions
5. **Congestive hepatosplenomegaly.** In severe cases, there may be liver dysfunction and **ascites**.
6. **Peripheral edema**

C. Management. Confirming the diagnosis of constrictive pericarditis often presents a challenge; the clinician must rely on clinical suspicion and integration of imaging techniques to increase diagnostic accuracy. Perhaps, the greatest challenge lies in differentiating constrictive pericarditis from restrictive cardiomyopathy.

D. Routine workup for suspected constrictive pericarditis should include the following:

1. Complete basic workup recommended in all cases of pericardial disease (WBC, liver and renal function, ECG, echocardiogram, inflammatory markers, and cardiac biomarkers).
2. **ECG** usually reveals a low voltage with generalized flattening of the T waves. Atrial fibrillation is a common finding.

3. **Chest radiograph** reveals pericardial calcification in 30% of cases. It is best appreciated with a lateral film, usually involving the RV and atrioventricular groove. **Pleural effusions** occur frequently.
4. **Inflammatory markers** (ESR, CRP/usCRP) are important in identifying cases with transient constrictive pericarditis.

E. General indication for imaging.

1. TTE is routinely recommended as first-line imaging in the diagnostic workup of constriction. In patients with a consistent clinical presentation, an echocardiogram with definitive constrictive physiology may be sufficient. Doppler echocardiography also helps **exclude competing diagnoses**, such as restrictive cardiomyopathy. The following are the characteristic echo findings of constrictive physiology:
   a. **Pericardial thickening** (only approximately two-thirds of cases) is suggested by parallel motion of parietal and visceral pericardium.
   b. Flattening of LV posterior wall endocardium
   c. **Septal bounce** "shudder" (M-mode) described as oscillatory diastolic beat-to-beat movement of the ventricular septum
   d. **Abnormal respirophasic septal shift** (ventricular interdependence) with septal movement to the left in early diastole with inspiration, whereas on expiration, the septum shifts back to the right (**Figure 37.6**). This motion can be appreciated on 2D or M-mode, and it is the most sensitive echocardiographic finding. Simultaneous respirometric recording should be used.

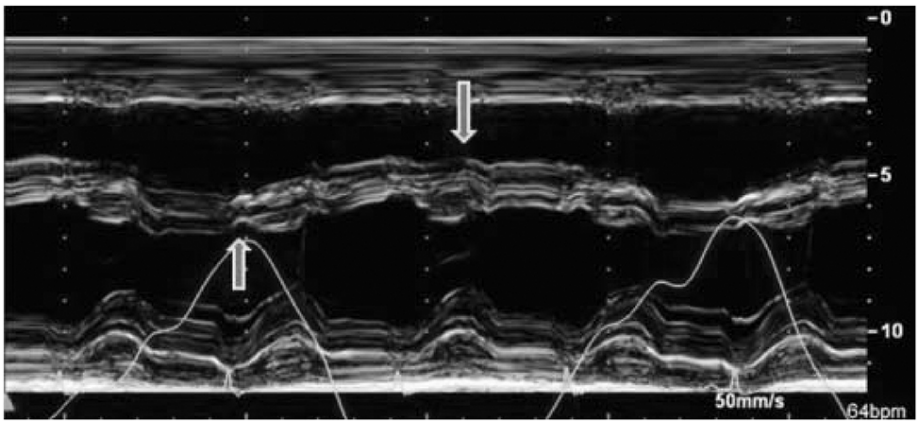


FIGURE 37.6 Respirophasic ventricular septum movement in a patient with constrictive pericarditis using M-mode echocardiogram with additional respirometric recording. The ventricular septum moves toward the left ventricle with inspiration (upward arrow) and toward the right ventricle with expiration (downward arrow). (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc*

Echocardiogr. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

e. IVC plethora

f. High early E-wave velocity, short deceleration time, and **decreased A wave** ($E/A \geq 2$) suggesting predominant grade 3 diastolic filling or restrictive filling

g. Increased respirophasic variation of atrioventricular inflows with major changes during first beats on inspiration and expiration (**Figure 37.7**). Findings suggestive of constrictive physiology include the following:

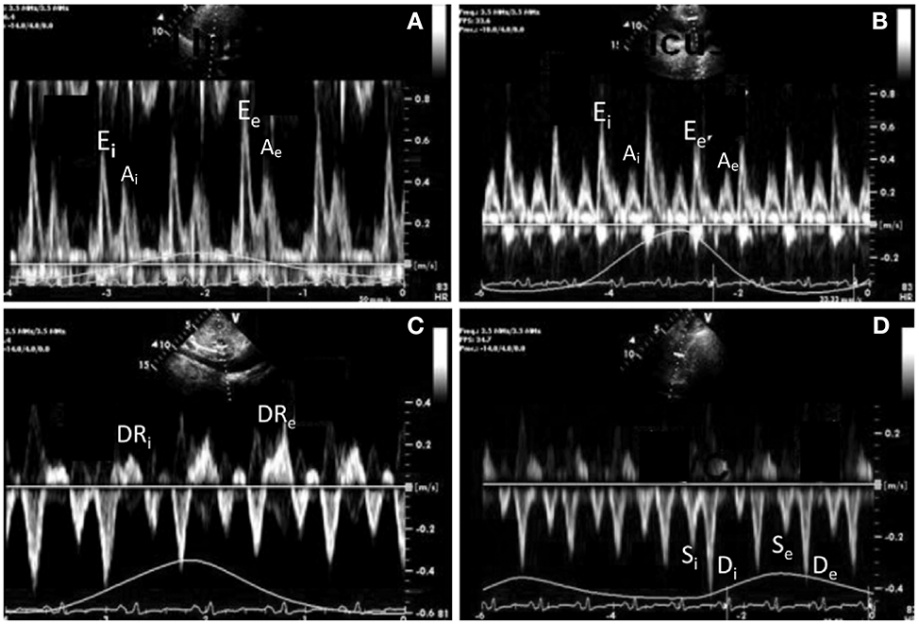


FIGURE 37.7 Pulsed Doppler recordings of mitral (**A**), tricuspid (**B**), superior vena cava (SVC) (**C**), and hepatic vein (**D**) inflow velocities, with simultaneous respirometric recording, in a patient with constrictive pericarditis. The peak early diastolic filling velocity (E) to peak late diastolic filling velocity (A) ratio is increased (>1). **A.** Mitral inflow velocities markedly increase during expiration (E_e and A_e) and decrease with inspiration (E_i and A_i). **B.** Tricuspid inflow velocities increase with inspiration (E_i and A_i) and decrease with expiration (E_e and A_e). Similar changes are not observed in normals and those with restrictive disease. Patients with restriction have an increased E/A ratio; but there is no significant respirophasic variation. **C.** SVC flow velocities showing increased diastolic reversal flow (DR_e) during expiration. **D.** Hepatic vein flow velocity showing an increase in both peak systolic (S_i) and diastolic (D_i) flow velocities with inspiration. During expiration, there is a marked drop in both velocities (S_e and D_e) and an increase in diastolic reversal flow. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

- **Inspiratory reduction of peak mitral E-wave velocities >25%**
- **Inspiratory increase in tricuspid E-wave velocities >40%**
- Opposite changes occur during expiration.

h. Respiratory variation in **pulmonary venous flow during diastole** mirrors peak mitral E-wave changes during respiration. **Pulmonary venous peak diastolic flow velocity variability of >20% is supportive of constriction, but not necessary for diagnosis.**

i. **Expiratory hepatic diastolic flow** reversal with **hepatic diastolic reversal-to-forward flow velocity ratio during expiration of >0.79** is characteristic of constrictive physiology. Conversely, hepatic diastolic flow reversal on inspiration is suggestive of restriction (**Figure 37.6**).

j. Doppler velocities of the medial mitral valve annulus in early diastole (*e′*) are **normal or slightly increased** (>8 cm/s). Conversely, restrictive cardiomyopathies have decreased *e′* velocities **at both medial and lateral mitral annuli** (<7 cm/s), reflecting abnormal myocardial relaxation (**Figure 37.8**).

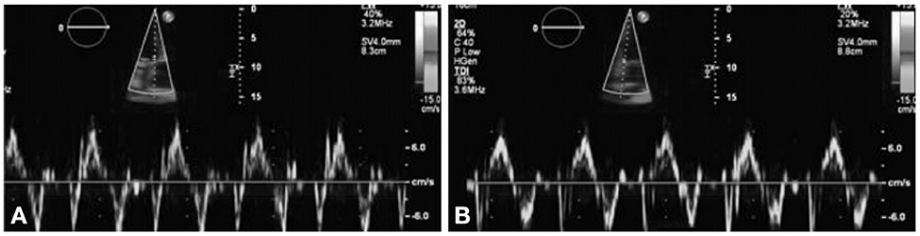


FIGURE 37.8 Annular tissue velocities of medial (**A**) and lateral (**B**) mitral annulus in a patient with constrictive pericarditis. **A.** The medial *E′* velocity is 12 cm/s, and the lateral *E′* velocity is 8 cm/s. Lateral *E′* is lower than septal *E′* in constrictive pericarditis, which is attributable to perimyocardial tethering of the lateral left ventricular free wall. (Adapted from Klein AL, Abbara S, Agler DA. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease. *J Am Soc Echocardiogr*. 2013;26(9):965-1012.e15. Copyright © 2013 Elsevier. With permission.)

k. **Annulus paradoxus,** defined as an inverse relationship of *E*/*e′* compared to pulmonary capillary wedge pressure (PCWP) in patients with constrictive pericarditis

l. In constrictive pericarditis, the relationship between the lateral and medial mitral annuli *e′* velocities is often reversed **called annulus reversus. Contrary to normal, *e′* peak velocity at the medial annulus is typically higher than peak *e′* velocity at the lateral annulus**. This is attributed to tethering of the LV lateral free wall to the pericardium in constriction.

m. **Superior vena cava (SVC) flow** allows for differentiation of chronic obstructive pulmonary disease (COPD) and constrictive pericarditis. Similar to constriction, patients with COPD have respiratory variation in *E* velocities on TTE. This is attributed to swings in intrathoracic pressures. Due to marked changes in the intrapleural pressure leading to exaggerated decreases in RA pressures, patients with COPD have marked increase in inspiratory SVC systolic forward flow velocity with changes of >35% noted during respiration. This is not seen with constriction because the intrapleural and RA pressures are dissociated. This finding in constriction is similar to Kussmaul sign.

n. **Strain imaging** in constrictive pericarditis is characterized by preserved global longitudinal strain but reduced **circumferential deformation with more pronounced involvement of anterolateral wall of the ventricles compared with the septum,** which is known as **strain reversus**. This strain pattern can reverse after pericardiectomy. Conversely, restrictive cardiomyopathy commonly presents with a uniform strain reduction, affecting longitudinal, radial, and circumferential ventricular deformations. Decreased LV anterolateral strain over septal strain ratio could be used to differentiate constrictive pericarditis from restrictive cardiomyopathy. Regional longitudinal strain ratios are decreased in constrictive pericarditis compared to normal controls or patients with restrictive cardiomyopathy.

o. In summary, the **key echocardiographic criteria in the diagnosis of constrictive pericarditis** (**Figure 37.9**) include an abnormal septal motion (ventricular interdependence) with either spared or elevated *e′* velocity of medial mitral annulus (>8 cm/s) and/or hepatic vein expiration reversal flow ratio of >0.79, in addition to increased respirophasic variation of atrioventricular inflows and IVC plethora.

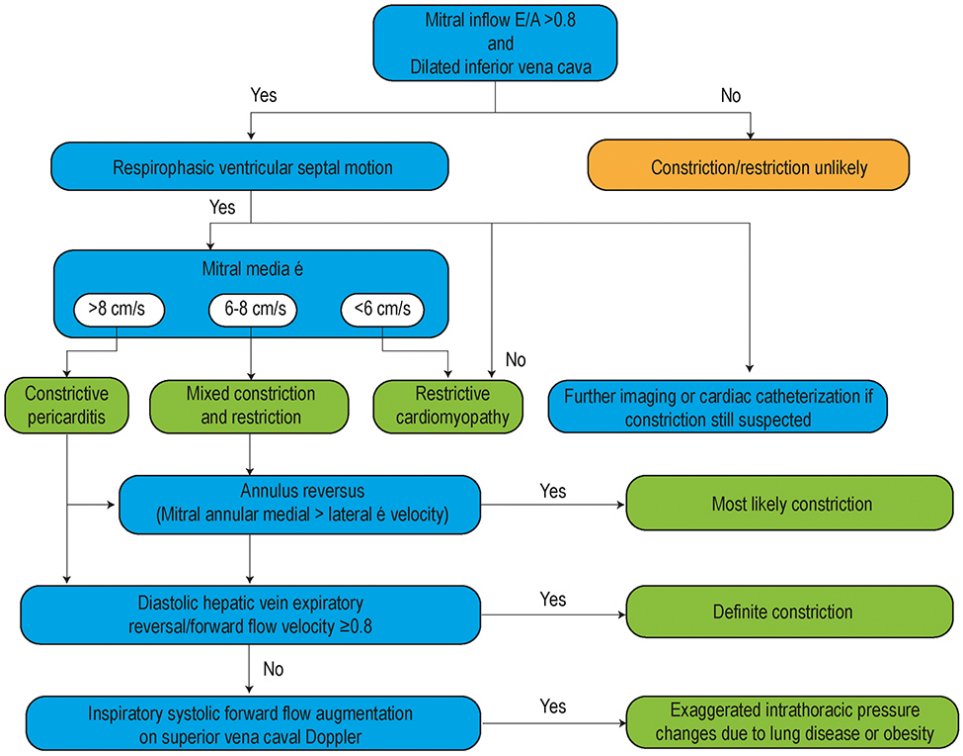
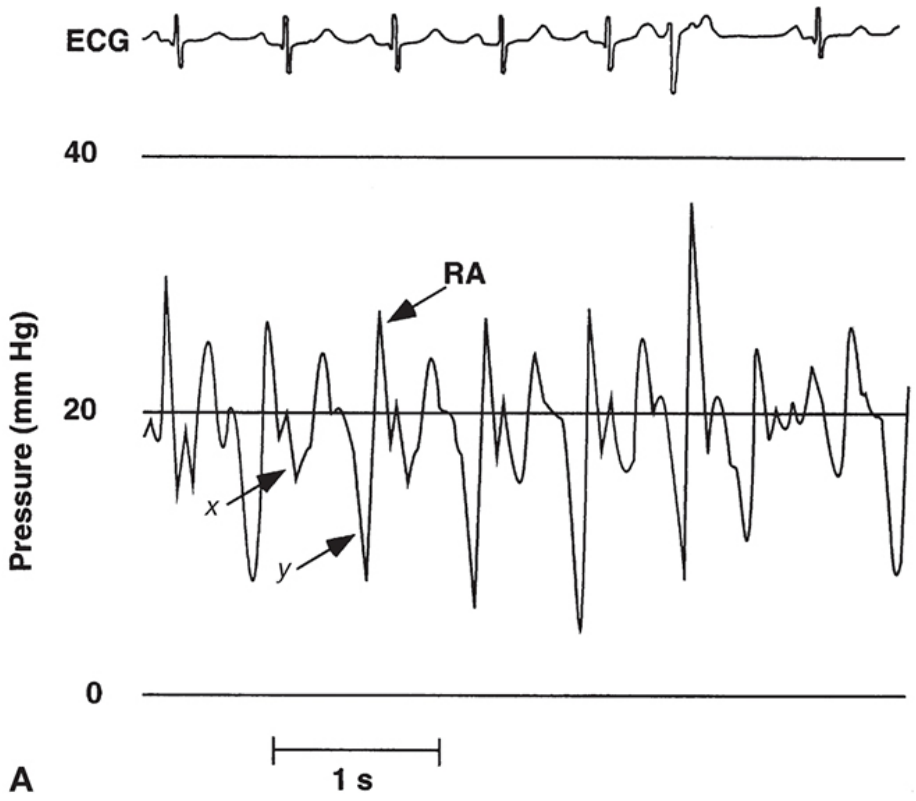


FIGURE 37.9 Echocardiographic flow chart for diagnosing constriction. (Reprinted from Klein AL, Wang TKM, Cremer PC, et al. Pericardial diseases: International position statement on new concepts and advances in multimodality cardiac imaging. *JACC Cardiovasc Imaging*. 2024 Aug;17(8):937-988. Figure 23., with permission from Elsevier.)

2. **Cardiac MRI** provides both anatomic and hemodynamic information in constrictive pericarditis, without the radiation associated with cardiac CT. MRI may demonstrate features of ventricular interdependence such as septal bounce and respirophasic variation in septal excursion. It can assess pericardial thickening and is the best modality to assess pericardial inflammation. It is excellent at tissue characterization and quantifying LV and RV systolic function, which is of value in patients where there is diagnostic uncertainty. Nonetheless, MRI is inferior to cardiac CT in assessing pericardial calcification. In addition, it is important to assess for the presence of inflammation on MRI, which would warrant anti-inflammatory therapy rather than surgery. Increased T2 short-tau inversion recovery time (STIR) and late gadolinium enhancement on MRI are signs on ongoing inflammation that can be seen in acute, recurrent, or even some cases of constrictive pericarditis.
3. **Cardiac CT** in constrictive pericarditis provides a superior 3D delineation of the pericardium in comparison with echocardiography. A thickened pericardium >4 mm (80% of cases) is supportive of the diagnosis, although normal pericardial thickness does not exclude constrictive pericarditis. Indirect findings include tubular deformation of RV with normal LV and IVC plethora.

Cardiac CT is the best modality for assessing pericardial calcification, which may assist in surgical planning.

4. **Cardiac catheterization** assists in both diagnosing constrictive pericarditis and differentiating it from restrictive cardiomyopathy. In general, both RHC and left heart catheterization are performed to obtain simultaneous ventricular pressure readings. It is recommended when noninvasive testing fails to provide a definitive diagnosis and in difficult cases.
   a. **RA pressure** waveform has been described as having a **W-shaped configuration**. This morphology is produced by a prominent *a* wave as the atria contract against an elevated ventricular pressure, an exaggerated *x* descent, and a steep *y* descent, because of rapid ventricular filling in early diastole (**Figure 37.10**).



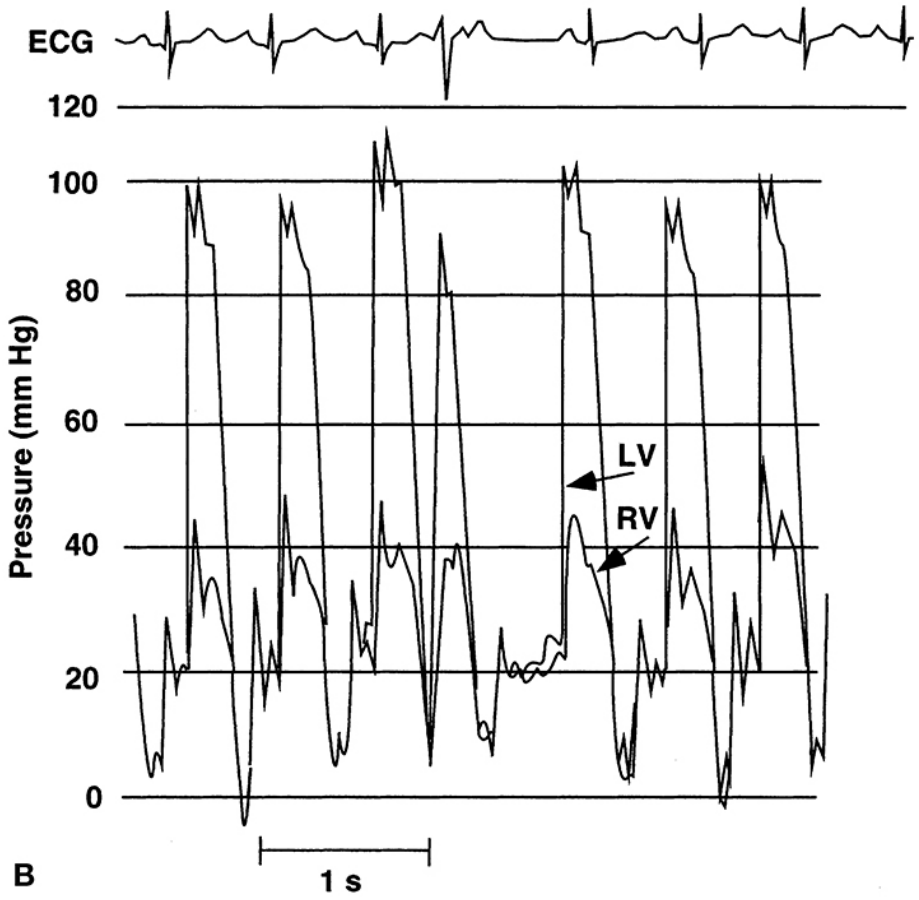


FIGURE 37.10 Right atrium (RA), right ventricle (RV), and left ventricle (LV) pressure waveform in constrictive pericarditis. **A.** The preserved *x* descent and the prominent *y* descent contribute to the classic W-shaped atrial waveform. **B.** Note the equalization of left ventricular and right ventricular end-diastolic pressures, generally within 5 mm Hg of one another. The rapid early diastolic filling and subsequent abrupt cessation of flow because of the rigid pericardium produces a dip-and-plateau waveform (square root sign), appreciated best in this waveform following the premature ventricular contraction. ECG, electrocardiogram. (Adapted with permission from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Williams & Wilkins; 1996:801-822.)

b. Ventricular pressure waveforms demonstrate the classic **dip-and-plateau** physiology, commonly referred to as the **square root sign** (**Figure 37.10**). The **initial downward deflection** reflects the drop in pressure during the isovolumic relaxation period. The subsequent **upward deflection** reflects early diastolic filling. The **terminal plateau** represents the cessation of flow that occurs once the limit of the rigid pericardium has been reached.

c. There is also equalization (within 5 mm Hg) of elevated end-diastolic pressures in both ventricles. The RV systolic pressure is generally <50 mm Hg, with an RV end-diastolic pressure that is more than one-third of RV

systolic pressure. These findings assist in **differentiating constrictive pericarditis from restrictive cardiomyopathy, where RV systolic pressure** is often elevated to >**55 mm Hg**.

d. **The ratio of the RV/LV systolic pressure-time area during inspiration versus expiration** (systolic area index) greater and equal to 1.1 has been shown to be **a useful measure of enhanced interventricular interaction** (**Figure 37.11**). The presence of ventricular discordance due to interventricular dependence on RHC distinguishes constriction from restriction.

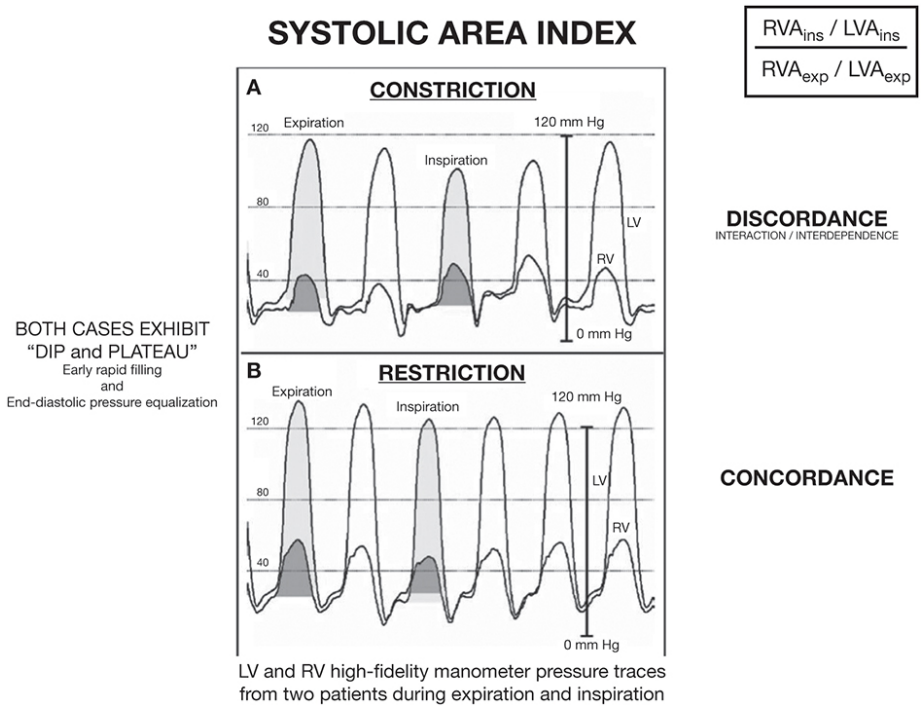


FIGURE 37.11 Respiratory ventricular interaction between right ventricle (RV) and left ventricle (LV) systolic area indexes in patients with constriction (**A**) and restriction (**B**). Note that in constrictive pericarditis patients (**A**), there is a rise in the area of RV pressure curve (darker shaded area) and a reduction in the area of LV pressure curve (lighter shaded area), whereas in patients with restrictive cardiomyopathy, there is a drop in the area of RV pressure curve during inspiration, with no change in the area of LV systolic pressure curve. LVA_{exp}, LV systolic area in expirations; LVA_{ins}, LV systolic area in inspirations; RVA_{exp}, RV systolic area in expirations; RVA_{ins}, RV systolic area in inspirations. (Adapted from Talreja DR, Nishimura RA, Oh JK, et al. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol*. 2008;51(3):315-319. Copyright © 2008 American College of Cardiology Foundation. With permission.)

e. **Hypovolemia can mask characteristic features of constrictive pericarditis**, and fluid challenge may be required to unmask ventricular interdependence in patients who are volume depleted.

5. Current recommendations favor a multimodality approach (echocardiography, cardiac MRI, cardiac CT, and cardiac catheterization) based on clinical presentation and patient characteristics to enhance diagnostic accuracy and improve management. The following are suggested situations where integration of imaging may be used:

   a. **Equivocal diagnosis of constriction on echocardiogram.** In this scenario, cardiac catheterization is almost always necessary to confirm diagnosis.

   b. **Suspicion for transient constrictive pericarditis** (elevated inflammatory markers and constriction symptoms for less than 3 months). Cardiac MRI should be strongly considered in these cases to assess for inflammation. The presence of pericardial edema detected by T2 STIR signal and LGE signal is indicative of inflammation. There is emerging evidence supporting anti-inflammatory therapy for 3-6 months as an initial strategy in a patient with inflammatory constrictive pericarditis or effusive-constrictive pericarditis.

   c. **Cases where assessment of pericardial calcification is warranted.** For instance, recurrent constriction after pericardiectomy or cardiac surgery. Cardiac CT is the imaging modality of choice for surgical planning. Cardiac CT should be limited otherwise to patients who are unable to undergo cardiac MRI.

   d. **Preoperative simultaneous RHC and left heart catheterization** can be done not only to assess ventricular interdependence not only to confirm the diagnosis in complicated cases (radiation heart disease) as in mixed constriction/restriction but also to get an accurate assessment of the cardiac index, which may assist in surgical planning.

F. **Differentiating constrictive pericarditis from restrictive cardiomyopathy.** Constrictive pericarditis is a potentially curable disease, whereas treatment options in restrictive cardiomyopathy are often limited to medical therapy. There are several key findings by echocardiography, cardiac catheterization, and cardiac MRI that can be used to differentiate these two clinical entities and are described in **Table 37.7**.

TABLE 37.7 Key Findings Used to Differentiate Constriction From Restriction

Investigation	Constrictive Pericarditis	Restrictive Cardiomyopathy
Echocardiography		
Annular tissue velocity (*e´*)	Preserved except at lateral mitral annulus and right lateral tricuspid	Reduced

Investigation	Constrictive Pericarditis	Restrictive Cardiomyopathy
	annulus. Annulus reversus with septal *e´*>lateral *e´*	
Diastolic dysfunction	Present	Present; More likely to have *E*/*A* ratio >2 with short DT
Respirophasic interventricular septal shift	Present	Absent
Respirophasic variation in transvalvular flow	Present	Absent
Respirophasic changes in hepatic venous flow	Reversal of forward flow during expiration	Reversal of forward flow during inspiration
LV wall thickness	Normal	Normal or increased
Perimyocardial slippage (motion of LV, RV, and atrial free wall)	Reduced	Normal or reduced
Cardiac Catheterization		
Elevated LV filling pressures	Present (equalization of diastolic pressures in all four chambers that are more suggestive of constriction)	Present
RVSP	<50 mm Hg RVEDP >1/3 RVSP	>50 mm Hg (LVEDP >RVEDP)
LV/RV discordance	Present	Absent
Cardiac Magnetic Resonance Imaging		
Respirophasic shift of interventricular septum	Present	Absent
Pericardial thickening or enhancement	Normal or increased	Normal
Myocardial scarring detected by post–gadolinium enhancement	Absent unless coexisting cardiomyopathy	Present

E/*A*, transmitral *E* Doppler to *A* Doppler; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; RV, right ventricular; RVEDP, right ventricular end-diastolic pressure; RVSP, right ventricular systolic pressure.

G. Management. Radical pericardiectomy is the preferred treatment for constrictive pericarditis, although there are certain clinical scenarios in which medical therapy is appropriate.

1. Patient with **constrictive pericarditis and signs of inflammation** (elevated inflammatory markers and/or evidence of inflammation on cardiac CT or MRI)

should be treated initially with trial of **anti-inflammatory therapy for 3 to 6 months** before recommending surgical intervention. This may include NSAIDs and colchicine, as well as steroids, or IL-1 inhibitors for refractory cases. Patients with known etiology should undergo appropriate medical treatment (ie, antituberculosis for tuberculosis or disease-modifying agents for lupus).

2. Patient with **effusive-constrictive pericarditis** should have **pericardiocentesis and trial of medical therapy** before recommending pericardiectomy.
3. Patients who have **New York Heart Association class I symptoms** may initially be treated with **diuretics and a low-sodium diet. However, diuretic therapy must be used cautiously as significant drop in intravascular volume may lead to a decrease in cardiac output. Ultimately, some of these patients require pericardiectomy. Often, a metabolic stress echo may help assess functional capacity in these patients.**
4. Medical therapy is also appropriate in **patients with severe comorbid illnesses** that limit life expectancy and/or place them at an unacceptably high risk for operative mortality.
5. **Pericardiectomy provides symptomatic improvement in more than 90% of patients**. However, pericardiectomy carries an **operative mortality of <1.5%** at specialized centers. The etiology of constrictive pericarditis can predict perioperative mortality. Patients who have constrictive physiology because of viral or idiopathic pericarditis have better outcomes than those who have radiation-induced constrictive pericarditis. Those patients with a poor preoperative functional class are at highest risk for perioperative death; therefore, most physicians advocate **early surgical intervention**. In addition, the presence and extent of pericardial calcification increases the difficulty of surgery.

VI. CONGENITAL ABSENCE OF PERICARDIUM. Congenital pericardial agenesis (CPA) is due to failure of the pleuropericardial membranes to fuse leading to complete or partial agenesis of the pericardium. It is very rare with a male predominance. Typically, congenital absence of the pericardium occurs in isolation but can occur with other congenital disorders, such as atrial septal defects and Vertebrae, Anus, Heart, Trachea, Esophagus and Renal (VATER) syndrome. The most common form is complete left sided (70%) followed by complete right sided (17%), complete bilateral (9%), and partial (3%-4%).

A. Clinical presentation

1. Often asymptomatic and found incidentally
2. Atypical chest pain, dizziness, dyspnea, palpitations
3. Trepopnea in partial agenesis
4. Migrating apical beat and/or posterolaterally displaced apex

5. Anecdotal reports of sudden cardiac death due to compression of coronaries by pericardial rim

B. Diagnostic workup

1. ECG for complete shows a right-axis deviation with incomplete right bundle branch block (RBBB) and poor R-wave progression. Electrical alternans of QRS and P waves can also occur. ECG is typically unremarkable in partial.
2. CXR shows a posterior and leftward shift of heart with the loss of the right border (Snoopy sign) in complete left agenesis. There may also be lung tissue in between the aorta and the pulmonary artery as well as between the heart and the left hemidiaphragm. CXR in partial CPA is typically normal.
3. TTE views may be difficult to obtain due to displacement of the heart in complete CPA.
   a. For left CPA, the RV can appear falsely enlarged in the parasternal long views. In addition, the LV posterior wall motion is exaggerated, resulting in paradoxical motion of the interventricular septum. The apical four-chamber view shows a "teardrop" heart due to lateral displacement, elongated atria, and widened ventricles, while the apical two-chamber view shows outward bulging of the inferior wall.
   b. TTE in partial CPA is typically normal, although abnormalities include regional wall motion bulging or wall motion abnormalities and herniation of appendages.
4. CT or cardiac MRI can confirm the diagnosis. ECG-gated cardiac CT with contrast has higher sensitivity in detecting pericardial defects due to higher spatial resolution. Cine sequences demonstrate excessive systolic motion of the apex. Similar to TTE and CXR, both CT and cardiac magnetic resonance (CMR) can identify displacement of the heart as well as lung tissue between the aorta and the pulmonary artery.

C. Treatment

a. Most do not require intervention.
b. Intervention is indicated if there are symptoms or complications, such as chamber herniation or ischemic disease. Surgery involves patch closure, total pericardiectomy, or enlargement of a defect to alleviate herniation.

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CHAPTER 38

Cardiac Tumors

David S. Katzianer and Jay Ramchand

I. INTRODUCTION. Cardiac neoplasms are **rare** in comparison with other forms of heart disease. Although secondary tumors of the heart are, by definition, malignant, primary tumors may be either benign or malignant. **Primary cardiac tumors are rare, occurring approximately 30 times less frequently than cardiac metastases.** In a large series of more than 12,000 autopsies, primary cardiac tumors occurred with an incidence of less than 0.1%. Most of these primary tumors are benign, with cardiac myxoma being the most common. Cardiac sarcomas, followed by lymphomas, are the most common primary malignant tumors.

II. CLINICAL PRESENTATION. Patients may present with nonspecific constitutional symptoms or with cardiovascular symptoms from tumor interference with valvular function (regurgitation, stenosis), myocardium (decreased contractility, arrhythmias), and/or pericardium (pericardial effusion/constriction) or from tumor embolization. Notably, the majority of cardiac tumors are found incidentally on echocardiography or chest imaging performed for other indications.

A. Constitutional symptoms. Many tumors, especially myxomas, are associated with a wide variety of systemic manifestations. Fever, chills, malaise, cachexia, skin rash, and weight loss are not uncommon. Associated laboratory abnormalities, including leukocytosis, thrombocytosis or thrombocytopenia, hypergammaglobulinemia, as well as elevated erythrocyte sedimentation rate and C-reactive protein levels are frequently present as well. These findings may be attributable to the constitutive production of **inflammatory cytokines** by the tumor or due to release

from tumor autonecrosis. Myxoma cell production of **interleukin-6** and elevation of **antimyocardial antibodies** have been documented, with levels of these serum markers normalizing after tumor resection.

B. **Embolic phenomena.** Tumor embolization may account for the initial presenting symptoms, via either direct embolization of tumor fragments or thromboemboli released from the tumor surface. The type of emboli is dependent on tumor **location** as well as the presence of intracardiac shunts. **Right-sided** tumors and left-sided tumors with left-to-right shunts can result in pulmonary emboli and, if untreated, may result in cor pulmonale. It can be difficult to differentiate pulmonary tumor emboli from those of venous thromboembolic disease, though certain characteristics can help differentiate tumor emboli from venous thromboembolism. First, tumor emboli may result in completely unilateral defects. Second, defects caused by tumor emboli generally do not resolve with time or with anticoagulation. **Left-sided** tumor emboli may result in visceral infarction, limb ischemia, myocardial infarction, or transient ischemic attack/stroke. In addition, multiple vascular aneurysms may develop. Of the benign primary cardiac tumors, embolization is most frequently noted with cardiac myxomas and even more so if the tumor has a villous surface. The brain is the most common site for systemic embolization in primary cardiac neoplasms, involving both hemispheres in approximately 40% of cases. Embolic findings in a young person, in sinus rhythm and without valvular disease or endocarditis, should raise suspicion for the presence of an embolic source related to an intracardiac mass.

C. **Direct cardiac invasion/mass effect.** Signs and symptoms are related to tumor location and size. Intramyocardial tumors, which are most often found in the left ventricular free wall and intraventricular septum, generally remain asymptomatic when the tumor size is small but can result in arrhythmias, conduction abnormalities, and sudden cardiac death if they become larger. The appearance can on occasion mimic hypertrophic cardiomyopathy. Rarely, ventricular rupture can be the initial presentation. Tumors of the left atrium, especially if mobile, may prolapse into the mitral valve, resulting in obstruction of

atrioventricular (AV) blood flow. This results in signs and symptoms similar to mitral stenosis, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, and fatigue. Importantly, **syncope and sudden death** may also occur.

III. PHYSICAL EXAMINATION. Physical examination may show signs of pulmonary venous congestion. A fourth heart sound (S_4) may be present, as may a widely split, **loud first heart sound** (S_1). The loud S_1 may be heard with left atrial tumors and is caused by late closure of the mitral valve, when the left ventricular-left atrial pressure crossover occurs at a higher pressure. Although this finding is also seen with mitral stenosis and preexcitation, the absence of a diastolic rumble or a short PR on an electrocardiogram (ECG) should raise the possibility of left atrial tumor. Left atrial tumor may cause a holosystolic murmur at the apex radiating to the axilla (if tumor causes mitral incompetence) as well as a diastolic murmur (if the tumor obstructs mitral flow simulating mitral stenosis). The pathognomonic **tumor plop** manifests as an early diastolic sound, after an opening snap but before a third heart sound (S_3). Tumors of the **right atrium** often result in systemic venous congestion. Once significant pulmonary hypertension occurs, **hypoxemia, clubbing, and polycythemia** may develop as a result of right-to-left shunting. Right atrial tumors and intracavitary **right ventricular** tumors may present as right heart failure. A diastolic rumble that varies with inspiration may be noted and is due to tricuspid valve obstruction. The **P2** is delayed and may have varying intensities. Jugular venous pressure waveform examination may demonstrate **prominent a waves and Kussmaul sign**. Recurrent pulmonary emboli can potentiate pulmonary hypertension. **Left ventricular** tumors, when not intramural, can result in signs and symptoms of pulmonary venous congestion or low-output states. Upon examination, findings may mimic aortic stenosis, subvalvular stenosis, or hypertrophic cardiomyopathy.

IV. DIAGNOSIS. Because no clinical sign or symptom is specific, more advanced diagnostic methodology is universally required.

A. **ECG.** In isolation, ECG provides a little added clue to the diagnosis. However, changes in rhythm or voltage or the development of new AV block on serial tracings may be the first sign of either the extension of a primary cardiac tumor or the development of secondary cardiac involvement.

B. **Radiography.** Chest radiography may be helpful in identifying epicardial tumors. Cardiomegaly, mediastinal widening, or cardiac silhouette irregularities may suggest the diagnosis. Calcifications are seen occasionally. Pulmonary congestion or oligemia may be noted in patients with large left or right intracavitary tumors, respectively.

C. **Echocardiography.** Transthoracic echocardiography (TTE) is usually the primary diagnostic tool in most patients, with a sensitivity ranging from 55% to 93% (based on the TTE machine properties, mass, location, and size). TTE will often allow for an initial assessment of the size, mobility, and location of the mass, in addition to the presence or absence of a pericardial effusion. If a tumor is strongly suspected or a mass is noted by TTE, transesophageal echocardiography (TEE) should be considered. TEE provides improved sensitivity (~97%) and specificity, particularly with atrial masses, and allows for superior visualization of anatomic details, such as contour, cysts, calcification, and the presence of a stalk. Three-dimensional echocardiography is also increasingly helpful in evaluation because of its ability to visualize complex cardiac masses. Echocardiographic contrast agents can be used to define vascularity in the evaluation of cardiac masses. Echocardiography additionally allows for assessing the hemodynamic significance of the mass in the case of valvular or vascular obstruction. In comparison to other imaging modalities, echocardiography is generally widely available and does not result in radiation exposure.

D. **Radionuclide imaging.** Positron emission tomography scanning may be useful in known metastatic disease to look for cardiac involvement.

E. **Computed tomography (CT).** CT, especially multislice CT with contrast, is often used in the diagnosis and evaluation of cardiac masses. It can define tumor extension, assess tumor calcification, and

evaluate adjacent extracardiac structures (lungs, mediastinum, and great vessels). CT additionally plays a vital role in preoperative planning.

F. Cardiac magnetic resonance (CMR). Like CT, CMR has an important role in the evaluation of cardiac tumors. Specifically, it characterizes size, shape, and surface features, as well as evaluates tissue composition—giving information regarding the type of tumor that is present. Magnetic resonance imaging (MRI) has the highest soft tissue contrast of the imaging modalities, and it is particularly helpful in distinguishing thrombus from tumor. It is also the most sensitive imaging modality for detecting the extent of tumor infiltration. MRI similarly can aid in surgical planning.

G. Angiography. Cardiac catheterization is **not necessary in most cases**. However, in the following scenarios, the risk and cost of angiography may be worthwhile: clarifying inadequate noninvasive imaging, defining blood supply for suspected malignant tumors (**Figure 38.1**), and evaluating coexistent valvular or coronary artery disease that could alter surgical approach. The major additional risk of angiography is embolization of tumor or thrombus. A transseptal approach is relatively contraindicated in cases of suspected left atrial myxoma, given the high frequency of involvement of the fossa ovalis and the accompanying risk of embolization.

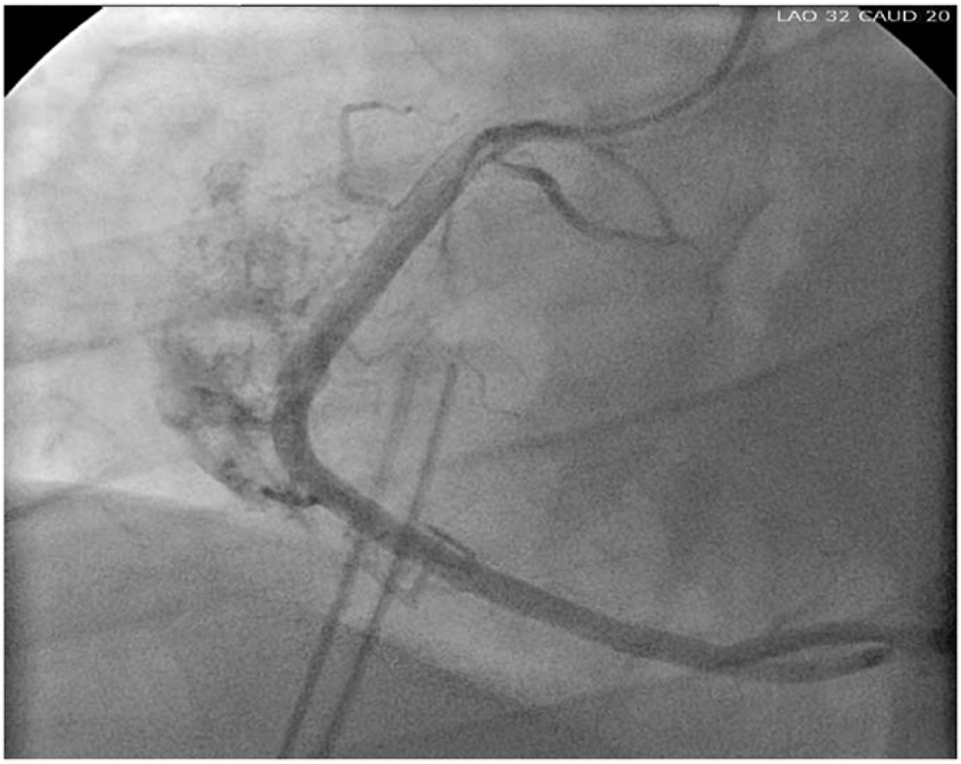

FIGURE 38.1 Coronary angiogram showing collateral blood flow supplying a suspicious mass. It turned out to be a malignant sarcoma in the right atrium.

H. Endomyocardial biopsy (EMB). Limited data exist on the utility of EMB in the management of cardiac tumors. Generally, diagnosis is made from noninvasive imaging; however, EMB can be considered if imaging is equivocal or if a tissue sample is required prior to treatment decisions (ie, chemotherapy).

V. PRIMARY CARDIAC MALIGNANCIES

A. Benign neoplasms. A description of specific benign cardiac tumors is given in subsequent text. Relative proportions are given in **Table 38.1**.

TABLE 38.1 Relative Proportion of Benign and Malignant Tumors in Adults by Tumor Type

Benign Tumor	% of Group	Malignant Tumor	% of Group
Myxoma	46	Angiosarcoma	33
Lipoma	21	Rhabdomyosarcoma	21
Papillary fibroelastoma	16	Mesothelioma	16
Hemangioma	5	Fibrosarcoma	11
Fibroma	3	Lymphosarcoma	6
Atrioventricular nodal mesothelioma	3	Osteosarcoma	4
Rhabdomyoma	2	Thymoma	3
Teratoma	1	Neurogenic sarcoma	3
Granular cell tumor	1	Leiomyosarcoma	1
Neurofibroma	1	Liposarcoma	1
Lymphangioma	1	Synovial sarcoma	1

1. **Myxomas** (**Figure 38.2**). Myxomas are the most common among the primary benign cardiac tumors in adults, accounting for approximately 50% of them. **The mean age at the time of diagnosis is 50 years, and approximately 70% of myxomas occur in women.** Most myxomas are sporadic (90%) and present typically as a lobular left atrial mass attached to the **interatrial septum (often in the region of the fossa ovalis)** via a pedicle. It is important to note that **tumors located on the posterior wall of the left atrium are usually not benign**. Approximately 75% of myxomas arise in the left atrium. Less frequently, myxomas may be found in the right atrium (10%-15%), either ventricle (3%-4% in each ventricle), or arising from the AV valves.

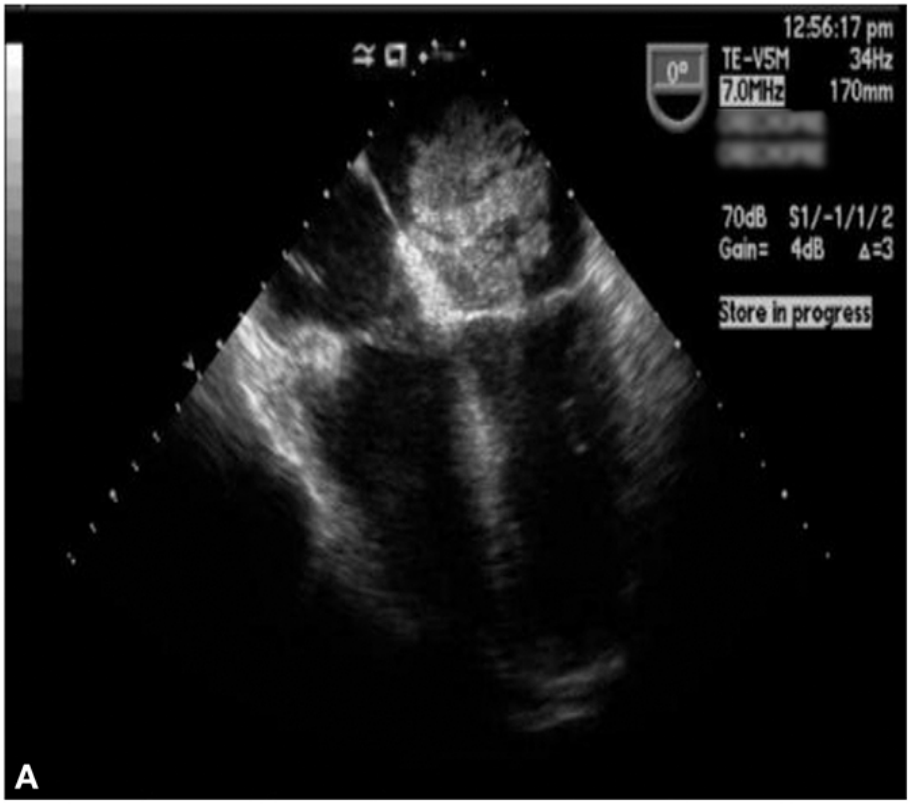
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FIGURE 38.2 **A.** Large, mobile protruding left atrial tumor arising from the atrial septum seen on transesophageal echocardiography. **B.** Pathology was consistent with atrial myxoma.

a. Generally, surgical resection of myxomas is preferred, regardless of tumor size due to the risk for embolic or cardiovascular complications with conservative management. Annual follow-up with echocardiogram is recommended following myxoma resection for at least 4 years because 10% to 15% of these tumors may recur. **Atrial myxomas are rarely inherited as part of the autosomal dominant Carney complex**, which consists of both cardiac and noncardiac myxomas, spotty pigmentation (ie, pigmented nevi), and endocrine overactivity (pituitary, adrenocortical, and endocrine testicular tumors). Patients with the Carney complex typically present in the third decade, often have bilateral tumors, and have high recurrence rates following resection. If a myxoma syndrome is suspected, **screening echocardiography is recommended** for all first-degree relatives, particularly if the index patient is young, has multiple tumors, or has typical noncardiac features of the genetic syndrome.

b. **Pathologically**, cardiac myxomas may be either smooth, round, gelatinous, or friable and irregular in appearance. They sometimes contain a hemorrhagic core and frequently attach via a sessile or pedunculated base. The typical diameter at presentation is 4 to 8 cm, and the typical mass is 15 to 180 g. **Histologically**, myxomas have characteristic patterns of "lipidic" cells within glycosaminoglycan-rich myxoid stroma. **Ultrastructurally**, myxoma cells resemble embryonic mesenchymal cells. **Immunohistochemically**, they demonstrate variable activity for endothelial cell markers, with reliable positivity to vimentin, indicating a mesenchymal derivation. Myxomas also produce vascular endothelial growth factor, likely contributing to angiogenesis and tumor growth.

2. **Papillary fibroelastomas.** They are the second most common primary cardiac tumors in adults, and grossly, these benign tumors resemble sea anemones, with frond-like arms protruding off a central stalk. Histologically, these have a superficial papillary growth of the endocardium with a central avascular fibroelastic core. They are avascular and typically pedunculated. These most commonly are located on **either surface of the aortic valve**, at the midportion of the valve, whereas the atrial side of the mitral valve is the second most common location (see **Figure 38.3**). Rarely, they may present on the endocardial surfaces. Although these tumors are not associated with valvular dysfunction, in approximately 30% of cases, thrombus, with subsequent emboli, develops. Surgical resection is generally recommended for patients with a symptomatic presentation with embolization or in an asymptomatic patient with large, mobile tumors (1 cm or greater in diameter). Papillary fibroelastomas tend to present with embolic complications in **middle-aged patients**. Anticoagulation may be considered if recurrent embolization occurs in a nonsurgical candidate. Fibroelastomas may be differentiated from Lambl excrescences, which are also commonly found on the aortic valve, by their location on the midportion of the valve as opposed to the closure lines in the case of Lambl excrescences.

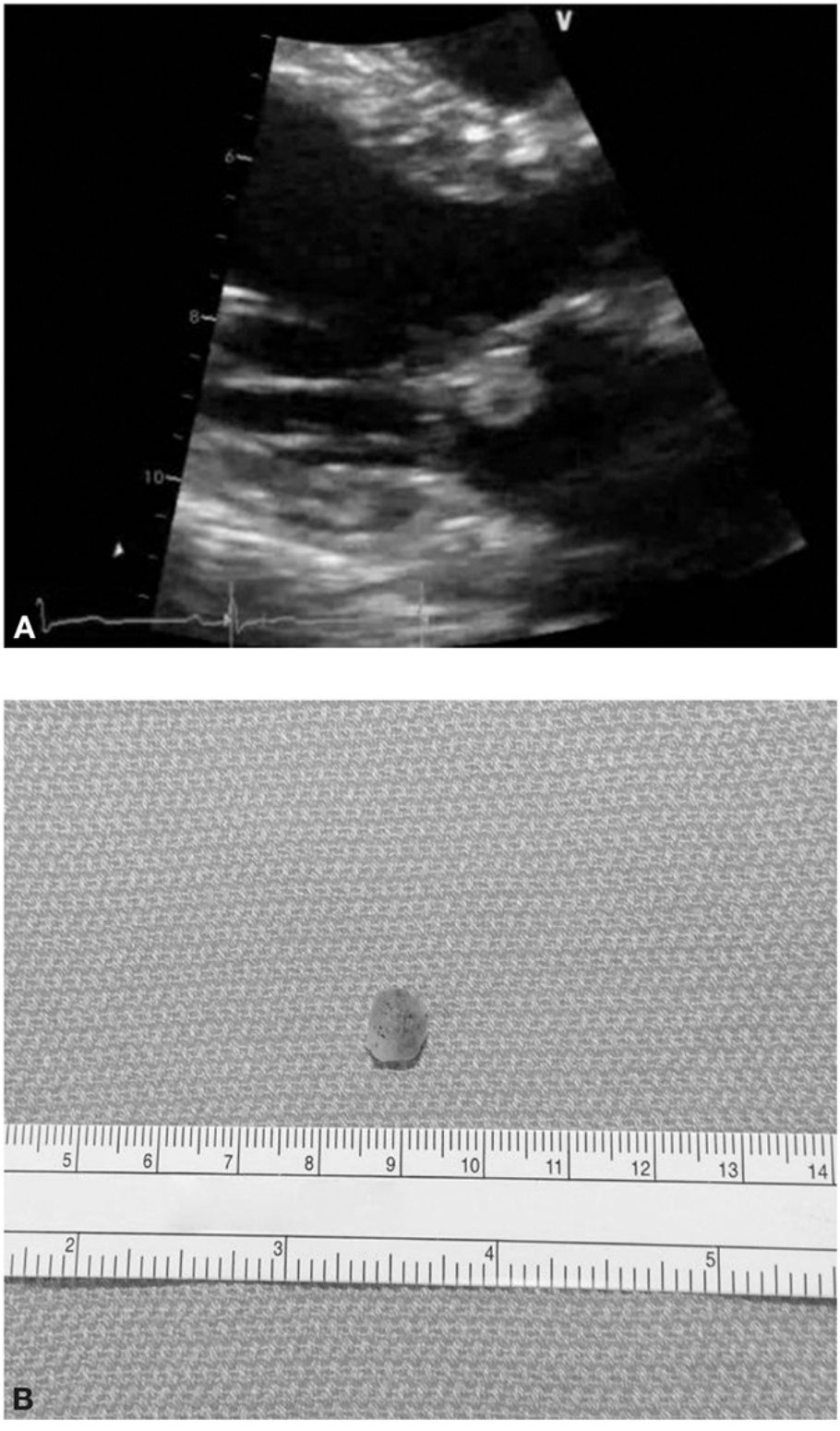

FIGURE 38.3 **A.** Mobile mass on the atrial surface of the mitral valve on parasternal long-axis view of mitral valve on transthoracic

echocardiography. **B.** Pathology was consistent with mitral valve fibroelastoma.

3. **Rhabdomyomas.** Rhabdomyomas, the most common benign tumor in **children** and **infants** (responsible for 50%-60% of cases), are frequently located within one of the ventricles. Rhabdomyomas are tumors of cardiac myocytes and are nearly always **multiple**, and most patients have at least one intracavitary, obstructing lesion. The most common presentation for this type of cardiac tumor in adults is arrhythmia; however, it may be clinically silent if the tumors are small. There is a clear association with **tuberous sclerosis**: 80% of patients with rhabdomyoma have the disease, and 60% of patients with tuberous sclerosis have rhabdomyomas. In some cases, rhabdomyomas may regress spontaneously during childhood, and thus, surgery is indicated in the case of significant symptoms.
4. **Fibromas.** Generally, fibromas are found in **pediatric** populations as well; these benign connective tissue tumors are almost universally **intramural**. They are usually firm, circumscribed but unencapsulated, and may grow to **several centimeters**. They have a preponderance for the left ventricle and, unlike rhabdomyomas, do not spontaneously regress. The **Gorlin syndrome** includes cardiac fibromas, multiple basal cell carcinomas, jaw cysts, and skeletal abnormalities.
5. **Lipomas.** These benign tumors occur at **all ages**, with men and women affected equally. Tumors range in size depending on their location. Fifty percent of tumors are found in the subendocardium, whereas the remainder are subepicardial, intramuscular, or valvular. Many tumors are **clinically silent** and identified only at autopsy. Subendocardial tumors may result in symptoms related to cavity obstruction, whereas subpericardial tumors can lead to compression of the heart and/or development of pericardial effusion. Intramyocardial tumors may result in arrhythmias or conduction disturbances and, possibly, sudden death. Valvular lipomas can lead to valvular insufficiency and heart failure. Lesions are generally **well encapsulated** with a center of

predominantly benign fatty cells. Without pathologic confirmation, lipomas can be confused with lipomatous hypertrophy of the interatrial septum. Both MRI and CT are useful in diagnosing cardiac lipomas based on the characteristic features of fatty tissue with these techniques.

6. **Hemangiomas/lymphangiomas.** These tumors are **very rare** and consist of benign collections of endothelial cells. Usually, they are located within the intraventricular septum or AV node and, as such, may present as heart block, sudden cardiac death, or hemopericardium.
7. **Pericardial cysts** are typically benign congenital lesions that are noncontiguous with the pericardial space. These usually require no further workup or management; however, rarely, these can result in cardiac tamponade and right heart or left heart failure due to the resultant mass effect on cardiac structures.
8. **Paragangliomas** are tumors arising from the neural crest chromaffin cells and are usually located in the retroperitoneum or adrenal gland as a pheochromocytoma. Very rarely, these can originate as primary cardiac tumors from any cardiac chamber, with the left atrium and pulmonary artery most commonly affected. Symptoms can be related to catecholamine excess in hormonally active tumors. These tumors are highly vascularized, and preoperative biopsy should be avoided when suspected due to the risk of bleeding. Surgical resection is preferred for cardiac paragangliomas, with perioperative treatment of catecholamine excess indicated in those with hormonally active tumors.

B. **Malignant neoplasms.** Histologically, **primary malignant tumors are virtually always sarcomas**. Suggestive **characteristics** include rapid growth, mediastinal invasion, hemorrhagic pericardial effusion, precordial pain, and pulmonary vein extension. Primary malignant neoplasms make up approximately 25% of all primary cardiac tumors. Cardiac sarcomas are the most common primary malignancies of the heart. Sarcomas are typically present in young adults with a mean age of 46 years and are associated with a poor prognosis with a median survival of 6 to 12 months.

1. **Sarcomas**
    a. **Angiosarcomas.** Almost always found within the right atrium, angiosarcomas are highly aggressive tumors that often take the form of broad-based, lobular masses. Hemorrhagic pericardial effusions are not uncommon. Histologically, these tumors have ill-defined vascular channels lined with atypical endothelial cells. The blood flow through the tumor may produce a continuous precordial murmur. Despite resection and/or adjuvant chemotherapy, clinical deterioration is rapid. **Angiosarcomas have a peak incidence in the fourth decade of life and are more common in men**.
    b. **Rhabdomyosarcoma.** These sarcomas **are more common in children and may affect any cardiac chamber**, though commonly affect the valves. Tumors are generally infiltrative, but on occasion, they may develop polypoid extensions, which can cause them to be mistaken for myxomas. Prognosis is poor. Treatment for rhabdomyosarcomas typically consists of a combination of surgical resection, chemotherapy, and radiation.
    c. **Other.** Fibrosarcomas, leiomyosarcomas, osteosarcomas, lymphosarcomas, liposarcomas, and other undifferentiated sarcomas represent the remainder of primary cardiac malignancies. These tumors are very rare and are generally infiltrative, involving multiple cardiac chambers.
2. **Mesothelioma.** The typical location of primary cardiac mesothelioma is the **pericardium** as they originate from the pericardial mesothelial cell layer. Generally, very diffuse, these tumors lead to symptoms consistent with pericarditis or hemorrhagic effusion. They may occasionally infiltrate the **AV node**, leading to conduction disturbances, sudden cardiac death, or tamponade. Much like cardiac sarcomas, these tumors carry a very poor prognosis.
3. Primary cardiac lymphoma is rare, with an incidence of 1% of primary cardiac malignancies. The mainstay of treatment is systemic chemotherapy. Untreated primary cardiac lymphoma portends a poor prognosis.

VI. SECONDARY CARDIAC MALIGNANCIES. As mentioned previously, most malignancies of the heart are secondary and, by definition, **metastatic**. The overwhelming majority of metastatic cardiac tumors occur in the **pericardium** and are usually **carcinomas**, as opposed to sarcomas. Because of increased prevalence, **the most commonly found metastatic tumor to the heart is lung cancer**. The typical presentation is of pericardial effusion or tamponade or pulmonary vein obstruction from direct extension. After metastatic lung cancer, breast cancer, lymphoma, leukemia, and renal cell carcinoma are the most common offenders. The tumor with **the greatest propensity to metastasize to the heart is melanoma**, followed by germ cell tumors and leukemia (**Table 38.2**). A new complaint referable to the heart in a patient with known extracardiac malignancy should prompt a thorough investigation to rule out cardiac malignancy.

TABLE 38.2 Metastatic Tumors to the Heart by Absolute Number and Greatest Propensity

Primary Tumor	Absolute Number	Primary Tumor	Number per 100 Tumors
Lung	180	Melanoma	46
Breast	70	Germ cell	38
Lymphoma	67	Leukemia	33
Leukemia	66	Lymphoma	17
Esophagus	37	Lung	17
Uterus	36	Sarcoma	15
Melanoma	32	Esophagus	13
Gastric	28	Kidney	11
Sarcoma	24	Breast	10
Oral	22	Oral	9
Colon	22	Thyroid	9

VII. DIFFERENTIAL DIAGNOSIS. Establishing the correct diagnosis is imperative. A thorough differential diagnosis of **nonmalignant conditions** must be considered and ruled out. Possibilities include

pericardial cysts, teratomas, lipomatous hypertrophy of the interatrial septum, thrombus, and sarcoid. Unfortunately, the final diagnosis in many cases must still be made pathologically.

III. THERAPY AND PROGNOSIS. The primary therapy for most benign tumors remains **operative resection**, given the associated risk of lethal obstruction, arrhythmia, or embolization; however, conservative management may sometimes be pursued depending on the tumor subtype. Most surgeons perform excision with extracorporeal circulatory support in order to directly visualize the tumor, as well as a careful search for metasynchronous tumors. In higher risk patients, more extensive resection is recommended. The femoral or azygous vein is usually cannulated, as opposed to the right atrium, to avoid potential tumor fragment embolization. Mitral valve repair or replacement is usually unnecessary in the absence of associated bacterial endocarditis. An analysis reviewing 106 operations for sporadic atrial myxomas noted only one perioperative death. Survival at 25 years is no different when compared with age- and sex-matched controls. There are limited data regarding the use of a minimally invasive or robotic approach to cardiac tumor resection. Small series suggest that parasternal or partial sternotomy access does not compromise the safety or efficacy while allowing for shortened hospitalization and better cosmetic results. Long-term follow-up is not yet available for this approach.

Regardless of the type of surgical resection or whether the tumor is sporadic, annual **follow-up noninvasive imaging is recommended** in all patients after resection. Recurrence rates of 12% to 22% have been quoted in patients with family histories, syndromes, and multiple tumors at original presentation versus 1% for patients with sporadic, isolated myxomas. Primary malignant tumors generally portend dismal prognoses. They are rarely cured by surgery because of the large amount of cardiac tissue involved. Adjuvant therapy (ie, chemotherapy and radiation) after resection does not affect the prognosis, although it may slow progression in individual cases. **Palliative resection** is advocated for obstructive symptoms. **Cardiac transplantation** has been performed for patients with both benign and malignant tumors, but thus far, the series have been too small to reliably predict outcomes.

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CHAPTER 39

Common Genetic Issues in Cardiovascular Disease

Weili Zheng and W. H. Wilson Tang

I. INTRODUCTION. Genetic abnormalities have been associated with all types of cardiovascular disease. Recently, new DNA sequencing technologies and ultra-high throughput genotyping have expedited the pace of cardiovascular genomics, leading to improved understanding of underlying pathophysiology and their connections with salient phenotypic features.

The following is a cardiologist's practical approach for a modern approach to identifying and managing genetic cardiovascular conditions. Note that cardiovascular disease may also play a prominent role in genetic syndromes (eg, Friedrich ataxia, Becker/Duchenne muscular dystrophy) as well as lysosomal storage diseases (eg, Fabry, Danon, Pompe). Chromosomal abnormalities can also have serious implications, including congenital cardiac abnormalities of varying severity. Syndromic, metabolic, and congenital abnormalities are covered in the congenital heart disease chapters (Chapters 29-32, 36).

II. METHODOLOGY TO IDENTIFYING GENETIC DISORDERS IN CARDIOVASCULAR DISEASE. Given that a significant minority of patients with otherwise nonspecific etiologies of cardiovascular disease (ie, nonischemic cardiomyopathy [CM], myocarditis, severe hyperlipidemia [HLD]) have an underlying genetic abnormality, cardiologists should consider a familial component in all forms of cardiovascular diseases. In addition, with the emergence of direct-to-consumer testing (eg, 23-and-Me), patients seeking consultation for genetic abnormalities uncovered will become an increasingly common reality. Familiarity with common cardiovascular genetic conditions, as well as comfort with intake of family history, use of standard cardiovascular gene testing panels, and referral to genetic counselor are basic competencies of the practice of cardiogenetics. This is key to appropriate diagnosis, deploying cascade testing, and screening procedures for appropriate disease management and prevention.

A. Indications for Genetic Testing. Clinical suspicion for genetic causes of cardiovascular disease should be high if on clinical presentation, a **patient's burden of disease is out of proportion with underlying risk factors, especially with younger age of onset** (ie, a young person without behavioral risk factors who has a dilated cardiomyopathy [DCM] or conduction deficits) **or if there is a strong family history of affiliated conditions**.

If genetic etiology is suspected, it is crucial to conduct a relevant family history to gauge further clinical suspicion. If genetics testing is completed, a comprehensive family history spanning three generations is recommended to assess the need for cascade screening.

A comprehensive workup, including for ischemic disease, should be undertaken along with considerations for genetic testing. Moreover, in patients who are discovered to have advanced cardiovascular disease (eg, late-stage CM or high-degree atrioventricular [AV] block) or acute cardiovascular event (eg, myocarditis), if workup does not reveal identifiable age-appropriate etiology (eg, ischemia), genetic workup is also reasonable.

B. Interpretation of Genetic Testing. Genetic testing can be ordered directly by the clinical provider or through a referral to a genetics counselor, although the latter is often preferred and recommended due to the benefits of pretest counseling and comprehensive evaluation of family history. The typical genetic panel for cardiovascular diseases contains ~100 of the most relevant pathogenic variants, including all 44 medically actionable genes identified by the American College of Medical Genetics and Genomics (ACMG, the so-called "ACMG SF v3.1"). Out-of-pocket expenses for genetic testing have dropped considerably and should no longer be considered a limitation for most patients.

In addition to current widely available panels, it is anticipated that polygenic risk scores for specific cardiac disease may emerge for clinical use in the near future, which can inform the aggressiveness of interventions taken in pursuit of secondary prevention. Moreover, whole-exon sequencing may emerge for those who are negative on typical panels, to further screen for rare or splice variants that are pathogenic.

On a genetic panel, variants will be characterized as pathogenic, benign, or uncertain significance. **Figure 39.1** shows the standard written convention of a non-truncating genetic variant, which usually occurs in a missense mutation.

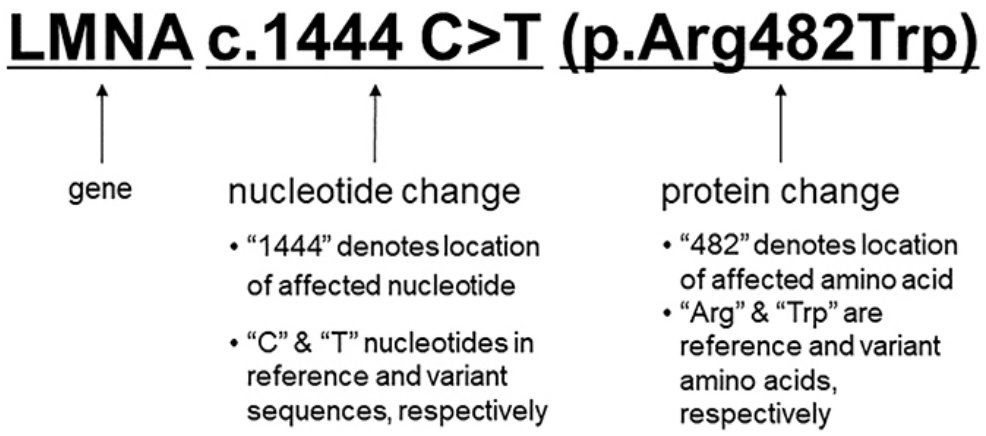

FIGURE 39.1 Human genomic variant nomenclature.

This is an example of a nontruncating variant, which usually occurs in a missense mutation. On the other hand, **truncating variants** usually involve frameshift, splice, nonsense, or large deletion mutations that lead to encoding of a nonfunctional protein, or a complete degradation of protein translation, causing **loss of function**. Truncating variants are almost always **pathogenic or likely pathogenic**. Other definitions are found below:

Heterozygous variant. Most conditions found on cardiovascular panels are autosomal dominant. As a result, a heterozygous variant encompasses one pathogenic and one normal allele and typically results in less severe disease expression.

Variant of unknown significance (VUS). A variant for which not enough information is known whether to characterize as benign or pathogenic

C. Post-test counseling. If a positive pathogenic variant is identified, clinical management changes should be made appropriately. Typically, a more aggressive approach to screening and treatment is required in such patients (ie, earlier implementation of goal-directed medical therapy in CM, more frequent serial screens for aortopathy with earlier cutoff for surgical intervention, cardiac magnetic resonance imaging [MRI] screening for scar to risk-stratify implantable cardioverter-defibrillator [ICD] placement). Lastly, for patients who have VUS, the clinician should engage in regular updates (~every 3-5 years) to ensure a VUS has not been reclassified as a pathogenic variant.

D. Clinical and genetic screening for at-risk relatives. In addition to clinical management, **cascade genetic testing is recommended** for all first-degree

relatives. In addition, at-risk relatives who test positive should undergo clinical surveillance at appropriate intervals depending on the condition.

If the index patient declines genetic screening, or if such results are inconclusive (eg, VUS present), clinical and genetic screening of first-degree family members is recommended.

III. GENES INVOLVED IN INDIVIDUAL CARDIAC DISEASE PROCESSES

A. Familial hyperlipidemia (FH). FH is a well-characterized entity defined by markedly elevated serum low-density lipoprotein (LDL) predisposing to premature coronary atherosclerosis. The dyslipidemia is often severe, unresponsive to standard lifestyle interventions. In FH, **clinical suspicion should be high for** any individuals who suffer **early-onset atherosclerotic cardiovascular disease (ASCVD) (<50 years old in males, <60 in females)**, have **LDL levels over 190 mg/dL,** or have **uncontrolled LDL levels despite maximal HLD therapy**. The full Dutch Lipid Clinic Network Criteria for FH are listed in **Table 39.1**; by criteria, a positive genetic test also fulfills the definite FH diagnosis. In patients with confirmed FH, aggressive pharmacologic intervention including a statin, ezetimibe, +/− proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor is needed to meet LDL goals; **LDL levels should be reduced to <70 mg/dL for acceptable reduction of ASCVD risk, and ideally <55 mg/dL**.

TABLE 39.1 Dutch Lipid Clinic Network Diagnostic Criteria for Familial Hypercholesterolemia

DLCN Criteria	Points
History	
Premature CAD[a]	2
Premature ischemic CVA and/or PAD[a]	1
Family History	
1° relative w/premature ASCVD or LDL ≥130 mg/dL	1
1° relative w/tendon xanthoma or arcus cornealis	2
Physical Examination	
Tendon xanthoma	6
Arcus cornealis before age 45	4

DLCN Criteria	Points
Serum Cholesterol (Prior to Treatment)	
LDL >330 mg/dL	8
LDL 250-329 mg/dL	5
LDL 190-249 mg/dL	3
LDL 155-189 mg/dL	1
Genetic Testing	
Mutation in LDLR, apo B, PCSK9	8
DLCN Criteria Scoring	**Total Points**
Definite FH	>8
Probable FH	6-8

apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CVD, cardiovascular disease; DLCN, Dutch Lipid Clinic Network; FH, familial hyperlipidemia; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; PAD, peripheral artery disease; PCSK9, proprotein convertase subtilisin/kexin type 9.
[a]Premature: males <55 years, females <60 years.

The overall **prevalence of FH is approximately 1 in 200**, with three genes implicated in the majority of cases: *LDLR* (LDL receptor), *APOB* (apolipoprotein B), and *PCSK9*. In approximately 20% of cases, the cause is unknown, although other etiologies such as elevated lipoprotein(a) [Lp(a)] can be implicated.

1. The ***LDLR*** gene is located at 19p13.2 and encodes the **LDLR**. These receptors in the liver take up circulating LDL and regulate the amount of cholesterol in the blood. This is the most common form, **encompassing ~60% to 80% of FH**, with approximately 1,700 mutations in the *LDLR* gene affecting many aspects of *LDLR* function such as reducing the number of LDLR produced in the cells or interfering with the receptor when removing LDLs from the blood. Alterations in the gene range from point mutations to gene rearrangements. **Typically, if left untreated, these patients and affected family members have a 20-fold risk of ASCVD**. The majority of individuals are **heterozygous**; those with homozygous patterns of inheritance are more severely affected and are

more likely to be diagnosed during childhood. Consanguinity increases the risk of homozygous inheritance.

2. The ***APOB*** gene is located at 2p32.3 and encodes for the production of two forms of the apo B protein, a component of lipoproteins, **apo B-100** and **apo B-48**. The most common pathogenic mutation is a point mutation in the apo B component of the LDL molecule, which results in the inability of LDL to bind to its LDLR. The Arg3500Gln (R3500Q) is the most common substitution in the apo B (*APOB*) gene, more common in Northern European populations, and encompasses **~2% to 5% of patients with FH**. The R3500W is another *APOB* gene mutation identified in East Asian populations as a common cause of FH. Overall, the **phenotype of apo B mutations appears to be less severe than in the FH caused by *LDLR* mutations**. Mutations in the *APOB* gene occur in 5% to 10% of cases of FH, with a country variation in incidence. In some countries such as Japan, Russia, Spain, and Finland, the *APOB* genetic mutations have not been identified in FH cases.
3. The ***PCSK9* gene**, located at 1p32.3, is responsible for increasing degradation of the LDLR. Approximately **1% to 2% of FH** involves the *PCSK9 gene.* Mutations in *PCSK9*, such as D129N, D374H, D374Y, E 32K, E670G, F216L, R215H, S127R, D374Y, and R496W, confer gain in function and cause FH.
4. The ***LPA* gene**, located at 6q25.3, encodes for **Lp(a)**, an atherogenic protein made in the liver that is similar in structure to LDL, with the exception of addition apo A, bound to ApoB100 by disulfide bond. As a result, Lp(a) makes up a component of the non–high-density lipoprotein (HDL) cholesterol levels found in the standard lipid panels. **Elevated Lp(a)** levels have been shown to carry **independent risk of ASCVD at levels>50 mg/dL or >100 nmol/L**. Though elevated, Lp(a) exists as a distinct entity outside the FH umbrella, **Lp(a) levels >200 mg/dL confer a risk of ASCVD equivalent to that of FH,** with **doubled prevalence (1/100 patients)**. As such, **screening for elevated serum Lp(a) levels should take place concurrently with FH screening**, as well as in cases in which there is **less than expected lowering of LDL cholesterol despite adherence to conventional therapy**. Currently, Lp(a) levels are also not amenable to standard lipid-lowering agents, though new medications such as antisense oligonucleotides show promise, with significant reductions of over 50% in Lp(a) levels.

5. The ***LDLRAP1*** gene is located at 1p36.11 and encodes for **LDLR adaptor protein 1**. More than 10 mutations are known to cause this condition. These mutations either result in the production of a nonfunctional version of the LDLRAP1 protein or do not make any protein. This is inherited in **recessive** manner with milder phenotype than the autosomal dominant form of the disease and more amenable to treatment with conventional therapies.

B. Connective tissue abnormalities and disease of the aorta. Genetic mutations affecting the connective tissue and extracellular matrix typically affect multiple organ systems, but often, the most devastating and lethal effects arise from cardiovascular complications, such as aortic dissection and rupture. Below are a number of conditions described, with associated **Table 39.2**. More detailed descriptions of the conditions are found in Chapter 27.

TABLE 39.2 Familial (or Syndromic) Aortopathies

Condition	Genes	Prevalence	Role in Diagnosis	Aortic Diameter for Elective Replacement (See Chapter 27 for Details)
Ehlers-Danlos syndrome	Vascular type: COL3A1 Cardiovalvular type: *COL1A2*	1 in 50-200,000	Confirm clinical diagnosis and subtype classification	4.5 cm
Loeys-Dietz syndrome	***TGFBR1, TGFBR2,*** *SMAD3, TGFB2, TGFB3, SMAD2*	~1 in 100,000	Major criterion for diagnosis and subtype classification	4.0-4.5 cm
Marfan syndrome	*FBN1*	1 in 15,000	Major criterion for diagnosis	4.5-5.0 cm

1. **Marfan syndrome.** Marfan syndrome is caused by defects in the extracellular matrix and leads to abnormalities of organs of the cardiovascular, skeletal, and ocular systems. The genetic defect is in the **fibrillin-1 (*FBN1*) gene** on chromosome 15q21.1, which is responsible for producing microfibrils, a key component allowing for the elastic

properties of extracellular tissue. It is inherited in an **autosomal dominant** manner; over 1,800 mutations in the *FBN1* gene have been recognized, affecting various aspects of cellular processing of FBN1, resulting in both truncating and nontruncating variants. As a result, there is **variable penetrance**—an *FBN1* gene mutation can have wide variation in the onset and severity of cardiac symptoms. The classic features of **tall stature, arachnodactyly, dolichostenomelia, pectus excavatum, ectopia lentis**, and a positive family history all support a diagnosis of Marfan syndrome. The cardiovascular system is affected, and the **most common cause of death** in these patients is from **aortic dissection and aortic rupture**. Other common problems include aortic dilation with aortic valve regurgitation, mitral valve prolapse (MVP), tricuspid valve prolapse, and arrhythmias. **A Marfan syndrome will present with dissection at a younger age and without traditional risk factors (eg, hypertension)**.

2. **Ehlers-Danlos syndrome (EDS).** EDS is a group of connective tissue disorders caused by defects in collagen formation. In 2017, the International ED Consortium proposed a new classification with 13 subtypes based on clinical features and linked to mutations in collagen-related genes. Except for the hypermobility type, the definitive diagnosis for each of these subtypes is based on genetic testing and the presence of a causative gene. The cardiovascular system is involved in two subtypes: the vascular and the cardiovalvular.
    a. The vascular subtype (vEDS) has an **autosomal dominant** pattern of inheritance and accounts for approximately 5% of all EDS cases. The gene, ***COL3A1***, is localized to chromosome 2q32.2 and encodes for type III collagen. In vEDS, hypermobility and skin hyperextensibility may not be evident—**diagnosis requires genetic testing for evidence of *COL3A1* gene mutation**. Vascular complications include dissections of the carotids and the vertebral arteries, as well as rupture of the abdominal vessels such as the renal and hepatic arteries, especially at a younger age. **Aortic dissections are the primary cause of death and often involve both the thoracic and abdominal aortas**. Up to one quarter of cases have evidence of aortic aneurysmal involvement.
    b. The cardiac-valvular subtype (cvEDS) has an **autosomal recessive** pattern of inheritance. The ***COL1A2*** gene, involved in this subtype, is localized to chromosome 7q21.3 and encodes for a component of type

I collagen known as the pro-alpha2(I) chain. **This leads to premature and progressive aortic and mitral valve degeneration.** In cvEDS, hypermobility and skin hyperextensibility may not be evident—**diagnosis requires genetic testing for evidence of *COL1A2* gene mutation**.

3. **Loeys-Dietz syndrome.** Loeys-Dietz syndrome is a connective tissue disorder characterized by **hypertelorism, cleft palate**, and vascular disease in the form of **arterial aneurysms and dissection**. It is inherited in an **autosomal dominant** pattern. In many cases, it is the result of a de novo mutation. There are six types of Loeys-Dietz syndrome classified according to the gene involved: type I from *TGFBR1* (chromosome 9q22.33), type II from *TGFBR2* (chromosome 3p24.1), type III from *SMAD3* (chromosome 15q22.33), type IV from *TGFB2* (chromosome 1q41), type V from *TGFB3* (chromosome 14q24.3), and type VI from *SMAD2* gene (chromosome 18q21.1). Mutations in these genes interfere with the transforming growth factor-beta pathway. Phenotypically, the **characteristics are similar to those in Marfan syndrome**, and also, these patients appear similar (with the exception of the craniofacial abnormalities) to patients with vEDS. Clinically, patients are at **high risk for aortic dissection**. However, Loeys-Dietz appears to have much lower intraoperative mortality during corrective vascular surgery. Both genetic testing to identify the mutation and clinical findings (eg, aortic root enlargement or dissection) are needed for definitive diagnosis.

C. **CMs.** Primary disease of the myocardium affects both systolic and diastolic function and often results in heart failure or other adverse events over time. **It is estimated that up to 25% of nonischemic CMs have a genetic etiology**. Most are inherited in an autosomal dominant manner. **Table 39.3** lists some of the genetic variants associated with phenotypes of CM.

TABLE 39.3 Inherited Cardiomyopathies

Condition	More common Genes	Less Common Genes (<1% Prevalent in Cases)	Diagnostic Yield of Genetic Testing	Additional Testing/Therapy for Proband (Index Patient)	Clinical Screening for At-Risk (Gene +), Asymptomatic Patients, ie, Family Members of Proband
Dilated CM	***TTN***, ***LMNA***, DSP, MYH7, TNNT2	BAG3, RBM20, TNNC1, TNNI3, TPM1, SCN5A, PLN	25%-40%	Cardiac MRI, consideration for ICD	Echo + ECG: Every 1-2 y at 6-12 years old Every 1-3 y at 13-19 years old Every 2-3 y at 20-49 years old Every 5 y at 50+ years old
Hypertrophic CM	***MYBPC3***, ***MYH7***, TNNI3, TNNT2, TPM1	MYL2, MYL3, ACTC1, PRKAG2, PLN, LAMP2, GLA	30%-60%	Cardiac MRI, consideration for ICD	Echo + ECG: Every 1-2 y at 6-12 years old Every 2-3 y at 13-17 years old Every 3-5 y at 18+ years old
Arrhythmogenic CM	***PKP2, DSP, LMNA,*** DSC2, DSG2	TMEM43, DES, FLNC, JUP, PLN, RYR2, SCN5A, TMEM43, TTN	60%-65%	Implementation of ICD	NA
TTR-type cardiac amyloidosis	TTR	NA		Technetium PyP scan, AL amyloidosis screening	Echo + ECG: Every 1-2 y, until 10 y prior to predicted age disease onset

Condition	More common Genes	Less Common Genes (<1% Prevalent in Cases)	Diagnostic Yield of Genetic Testing	Additional Testing/Therapy for Proband (Index Patient)	Clinical Screening for At-Risk (Gene +), Asymptomatic Patients, ie, Family Members of Proband
					Every 6-12 mo thereafter

CM, cardiomyopathy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; MRI, magnetic resonance imaging; PyP, pyrophosphate; TTR, transthyretin.

1. **DCM.** DCM is characterized by dilation of one or both of the ventricular chambers, resulting in severe systolic dysfunction; its **prevalence has been estimated to be as high as 1 in 250**, and **genetic cause is thought to account for 25% to 40% of DCM** cases. In many cases, the pattern of inheritance is autosomal dominant. However, recessive, X-linked, and mitochondrial patterns of inheritance are also seen, especially in syndromic conditions resulting in secondary DCM (eg, Danon, Duchenne/Becker, Fabry). When ordering genetic testing for DCM, it is important to order concurrent panels for hypertrophic cardiomyopathy (HCM) and arrhythmogenic cardiomyopathy (ACM) due to gene overlap that exists for those conditions. **Most importantly, familial DCMs can be responsive to modern goal-directed medical therapy for heart failure with reduced ejection fraction (EF), and treatment should be instituted aggressively to optimize prognosis** (see Chapter 7).
    a. Mutations in the sarcomere protein genes account for approximately **10% to 20%** of idiopathic DCM. **The *TTN* gene encoding for titin is the most commonly mutated gene in DCM**. More than 35 variants of *TTN* have been associated with DCM; many of these are *TTN*-truncating variants with variable penetrance.
    b. **Mutations in *LMNA* gene, which encodes lamin A and lamin C, account for ~5% of familial DCM.** Lamin mutations result in accelerated senescence within the heart, resulting in eventual fibrosis and manifesting in **severe conduction system disease**. Patients with LMNA are also at risk for ventricular tachycardia (VT) and require additional scrutiny into whether ICD is warranted, even if goal EF 35% is not met. An LMNA risk calculator exists as a clinical

decision-making tool to inform patients and cardiologists of VT risk (lmna-risk-vta.fr).

c. Mutations in the *dystrophin* and *EMD* gene, classically associated with Duchenne and Emery-Dreifuss muscular dystrophy, respectively, have been identified in X-linked recessive DCM, that is, female carriers of the gene. These mutations may manifest as DCM in adulthood, usually after age 30. Mutations in the *ALMS1* and *GATAD1* genes are transmitted in an autosomal recessive pattern.

2. **HCM.** HCM (see Chapter 10) is prevalent in approximately **1 in 500 people** and is a highly variable and heterogeneous disease process. The characteristic phenotype is an asymmetrically hypertrophied myocardium with a small ventricular chamber and, occasionally, a left ventricular (LV) outflow tract pressure gradient (with systolic anterior motion of the mitral valve) and/or an intracavitary gradient. However, HCM phenotypic variants exist, such as concentric hypertrophy, mid-ventricular, and apical ventricular hypertrophy. In addition, the clinical variability of HCM is not only limited to the presenting phenotype but also related to the age of presentation, clinical course, and eventual outcomes, making it very challenging to properly identify a phenotype of interest. Nonetheless, there remains a very real severe risk of sudden cardiac death in a segment of patients. Consider should be made for ICD placement if there are increased risk factors. In this case, MRI is the test of choice as it can reveal the presence of scar that can form nidus for VT/VF (ventricular fibrillation).

a. **The majority of mutations in two genes: *MYH7* on chromosome 14 and *MYBPC3* on chromosome 11.** These genes encode proteins of the cardiac sarcomere unit, specifically the product of *MYH7* is beta-myosin heavy chain, whereas *MYBPC3* encodes myosin-binding protein C.

b. In addition, **1,400 known mutations in at least 50 separate genes have been identified**. These genes include *TNNT2* (troponin T), *TNNI3* (troponin I), *MYL2* (myosin light chains), *MYL3* (myosin light chain 3), *TPM1* (alpha-tropomyosin), and *ACTC* (actin).

c. Mutations in other sarcomeric as well as nonsarcomeric genes and Z-disc encoding genes have also been identified in HCM. **The importance of properly characterizing a phenotype as heterogeneous as HCM has been illustrated by the example of glycogen storage diseases mimicking the appearance of HCM**.

Mutations in the genes for adenosine monophosphate–activated protein kinase gamma2 (PRKAG2) and lysosome-associated membrane protein 2 (LAMP2) were found in phenotypes that closely resembled HCM but were differentiated based on serum protein levels and ventricular preexcitation. **Moreover, the lysosomal storage diseases such as alpha-galactosidase A deficiency (Fabry) also manifest as HCM and can often go undetected**.

3. **Restrictive CM (cardiac amyloidosis [CA]):** The most common type of CA is caused by mutations in the transthyretin (TTR) gene, causing amyloid deposits in the heart. CA is covered more extensively in Chapter 9. In cases where TTR-CA has been identified, **genetic testing should be sent to identify hereditary genotype, for which cascade screening would be recommended in first-degree relatives**. At-risk relatives may also be eligible for therapies to prevent progression of CA at an earlier stage.
4. **ACM.** Formerly known as arrhythmogenic right ventricular cardiomyopathy (ARVC), ACM is a primary abnormality resulting in **fibrofatty infiltration of the myocardium, primarily the right ventricle**. Clinical manifestations include **right ventricular dysfunction and lethal ventricular arrhythmias**. Diagnosis often requires a battery of tests, including an electrocardiogram demonstrating repolarization abnormalities and an epsilon wave, MRI or computed tomography demonstrating fibrofatty infiltration of the right ventricle, and endomyocardial biopsy. Often, a positive family history of the disorder is present. Management will involve **placement of an ICD** in high-risk patients (ie, significant VT burden, positive genetic testing, or low EF). ACM is usually inherited in an ***autosomal dominant*** with incomplete penetrance (in most cases). Thirteen chromosomal locations have been identified for ACM, and mutations associated with ACM have been identified in specific genes at 11 of these locations. Eleven of these genes encode five desmosomal proteins (desmoplakin, desmoglein, plakophilin-2, desmocollin 2, and plakoglobin) and six nondesmosomal proteins (desmin, titin, transmembrane protein 43, transforming growth factor-beta3, ryanodine receptor 2, and alpha-catenin). The specific genes for ARVC3 and ARVC6 have not yet been identified, although the chromosomal loci are known. Other genes have been reported as being implicated in ARVC: PLN encodes for phospholamban, LMNA encodes lamin A/C, and *SCN5A* gene encodes for sodium channels. In ACM,

eight mutations in the *DSP* gene, encoding desmoplakin, have an autosomal dominant pattern of inheritance, whereas mutations in the same *DSP* gene with an autosomal recessive inheritance result in Carvajal syndrome. Similarly, in ARVC12, mutations in the *JUP* gene encoding plakoglobin have an autosomal dominant pattern of inheritance, whereas mutations in the same *JUP* gene with an autosomal recessive inheritance result in Naxos disease, a variant associated with the triad of ACM along with dermatologic manifestations, such as wooly hair and palmoplantar keratoderma.

5. **Left ventricular noncompaction (LVNC).** LVNC is a relatively rare congenital abnormality of the myocardium, resulting in a trabeculated appearance of the LV cavity. It **is characterized by spongy myocardium that results from arrest in endomyocardial morphogenesis**. It is seen in <1% of adults. This disorder can occur either isolation or in association with other congenital anomalies or with chromosomal abnormalities. These chromosomal abnormalities are rare and include chromosomal deletion, trisomy, Robertsonian translocation, and mosaicism. When LVNC is present with a congenital abnormality, the cause is related to the gene associated with that abnormality. Over time, it is thought that noncompaction can proceed to DCM with severe systolic dysfunction. LVNC is inherited mainly through an autosomal dominant mode of transmission, but X-linked transmission is also seen. **Mutations in two sarcomere genes, *MYH7* and *MYBPC3,* which are also implicated in HCM, are responsible for almost one-third of LVNC cases**. The genes that have been reported mainly encode for sarcomeric, Z-disc, and nuclear-envelope proteins as well as mitochondrial proteins. A mutation in the alpha-dystrobrevin (*DTNA*) gene on chromosome 18q12.1 has been linked to LVNC1. Mutations for LVNC2 and LVNC3 have been identified on chromosome 11p15 (LVNC2) and chromosome 10q23 (LYNC3), respectively. LVNC variants have been mapped specifically to mutations of the sarcomere genes: LVNC4 is linked to mutation in the *ACTC1* gene (chromosome 15q14), LVNC5 to a mutation in the *MYH7* gene (chromosome 14q12), and LVNC6 is caused by mutation in the *TNNT2* gene (chromosome 1q32). Mutation in the *MIB1* gene (chromosome 18q11) is linked to LVNC7, whereas LVNC8 is caused by mutation in the *PRDM16* gene (chromosome 1p36), and LVNC9 is brought about by mutation in the *TPM1* gene (chromosome 15q22). Mutation in the *MYBPC32* gene

(chromosome 11p11) is implicated in LYNC10. There is also an X-linked form of LVNC, Barth syndrome, caused by mutation in the *TAZ* gene on chromosome Xq28 that encodes tafazzin (TAZ), a mitochondrial protein.

D. Arrhythmogenic disorders. Disorders of the conduction system of the heart lead to significant clinical manifestations, most notably ventricular arrhythmias and sudden cardiac death. The entities below in **Table 39.4** have been well described, and their respective genetic abnormalities have been characterized.

TABLE 39.4 Inherited Cardiac Arrhythmias

Condition	Genes	Prevalence	Role of Genetic Testing in Diagnosis	Role of Genetic Testing in Management
Brugada syndrome	SCN5A (most common)	1 in 2,000	Can support clinical diagnosis	Aids with identification of family members at risk for the condition
Catecholaminergic polymorphic ventricular tachycardia	RYR2	1 in 10,000	Major criterion for diagnosis and subtype classification	Aids with identification of family members at risk for the condition
Long QT syndrome	KCNQ1, KCNH2, SCN5A	1 in 5,000-20,000	Confirm clinical diagnosis and subtype classification	Causative gene may affect recommended treatment/therapeutic decisions and risk assessment; aids with identification of family members at risk for the condition

1. Brugada syndrome. Brugada syndrome was initially described by Josep and Pedro Brugada in 1992. Clinically, ventricular arrhythmias and sudden cardiac death can occur, particularly in middle-aged men. Characteristic electrocardiographic features can help make the diagnosis; in some cases, certain drugs, including sodium channel blockers and tricyclic antidepressants, or stress conditions such as fevers, can unmask the abnormality on a surface electrocardiogram. Brugada syndrome is typically inherited in an ***autosomal dominant*** pattern with incomplete penetrance. A de novo mutation can occur in approximately 1% of cases. Mutations in more than 15 genes have been identified as causing Brugada syndrome: *SCN5A, SCN1B, SCN2B, SCN3B, SCN10A, RNGRF,*

GPD1-L, HCN4, KCNE3, GPD1L, HCN4, KCNE3, KCND3, KCNJ8, KCNE5, CACNA1C, *CACNB2, CACNA2D1, TRPM4, SLMAP,* and the *PKP2* gene. The *SCN5A* gene with approximately 300 known mutations is the gene most commonly associated with Brugada syndrome and accounts for approximately 25% of cases. It has been mapped to chromosome 3p22.2 and is a voltage-gated sodium channel gene. *SCN1B* (chromosome 19q13.12), *SCN2B (*chromosome 11q23.3), *SCN3B (*chromosome 11q24.1), and *SCN10A* (chromosome 3p22.2) are also voltage-gated sodium channel genes. The *RANGRF* gene on chromosome 17p13 encodes a protein involved in the function of the Nav1.5 cardiac sodium channel. *GPD1-L,* an NAD-dependent glycerol-3-phosphate dehydrogenase gene, is associated with chromosome 3p22.3. *HCN4*, on chromosome 15q24, is a hyperpolarization-activated cyclic nucleotide–gated potassium channel 4 gene. *KCNE3* (chromosome 11q13.4), *KCND3* (chromosome 1p13.2), and *KCNJ8* (chromosome 12p12.1) are voltage-gated potassium channel genes also. *KCNE5* (chromosome Xq22.3) is an X-linked potassium voltag*e–gated channel gene. CACNA1C (chromosome 12p13.33) and CACNB2 (chromosome 10p12.33-10p12.31) are two subunits* of *the L-type voltage-dependent ca*lcium c*h*annels, whereas *CACNA2D1* gene (chromosome 7q21.11) and *TRPM4* gene (chromosome 19q13.33) are other calcium voltage–gated genes. The *SLMAP* gene (chromosome 3p14.3) is implicated in encoding an element of a conserved striatin-interacting phosphatase and kinase co*mplex*. *PKP2* gene (chromosome *12p11*.21) encodes plakoph*ilin 2.* In addition, some modifier genes have also been identified. Genetic testing in Brugada syndrome is used to confirm a clinical diagnosis. A negative result does not necessarily exclude the diagnosis. It may reflect that the individual does not have the condition, but it may also mean that the individual has either a mutation in a gene not part of the testing panel or a mutation in a Brugada-associated gene not included in the panel or the mutation is yet undiscovered. Approximately only one-third of clinically diagnosed cases are found to have a genetic cause despite the large number of genes associated with Brugada syndrome.

2. **Catecholaminergic polymorphic ventricular tachycardia (CPVT):** CPVT is characterized by ventricular arrhythmias triggered in response to sympathetic activity, such as physical activity or emotional stress. It is predominantly caused by mutations in the ***RYR2* gene**, located at 1q43, which encodes for ryanodine receptors that function as calcium

transporters in between ions. The *RYR2* gene is passed in an **autosomal dominant** manner and accounts for up to ~50% of cases, with other more minor genes such as *CASQ2* forming a minority of cases.

3. **Long QT syndrome (LQTS).** LQTS encompasses a range of disorders characterized clinically by **syncope and sudden cardiac death, with electrocardiographic abnormalities in the QT interval and the T-wave morphology**. LQTS is usually inherited in an **autosomal dominant** pattern. Recessive inheritance, seen in Jervell and Lange-Nielsen types 1 and 2, is rare. De novo mutations are uncommon. There are approximately 15 different types of LQTS based on the type of gene involved. Of these known genes, *KCNQ1* (LQT1), *KCNH2* (LQT2), and *SCN5A* (LQT3) are the most frequently identified and account for approximately 75% of cases. Each of the remaining 12 genes account for less than 1% of cases. Approximately 20% of clinically diagnosed LQTS are not linked to a variant in a known gene. The various forms of LQTS are often distinguishable by clinical features and genetic abnormalities. One such distinguishing feature is that those with LQT1 are typically at higher risk during periods of exercise, whereas those with the LQT3 variant are at higher risk during sleep. The *KCNQ1* gene encodes the catecholamine-sensitive portion of the potassium channel responsible for conducting the delayed rectifier current (I_{Ks}) in the LQT1 variant, whereas the *SCN5A* gene is affected in the LQT3 variant. The underlying defect involving the sodium channel results in a prolonged depolarization current, whereas defects involving the potassium channel result in a longer QT duration secondary to the inability to reestablish repolarization within the myocyte. The autosomal recessive phenotypes (Jervell and Lange-Nielsen types 1 and 2) are associated with bilateral sensorineural hearing loss.

   Hundreds of mutations are involved in LQTS. However, most of the prognostic information available is based on the gene involved and not the specific mutation. Having the genotypic information can help in prognosis and in determining response to therapy. The rates of ventricular arrhythmias and sudden cardiac death vary based on the gene involved, as does the response to therapy. This information may be particularly helpful in trying to decide between medical therapy, ICD implantation, or both.

E. Valvular heart disease

1. **MVP** involves myxomatous degeneration of the valve tissue, leading to redundant tissue and weakening of both the valve and subvalvular apparatus. Prolapse of the mitral valve occurs primarily because of abnormalities in the connective tissue matrix of the valve itself. Clinically, this manifests as displacement of the mitral valve leaflets into the left atrium during systole and may progress to mitral regurgitation and eventual congestive heart failure with occasional rupture of the chordae. Although surgical repair and replacement have improved the long-term prognosis of this disorder, understanding the genetic basis of this disease may allow the earlier diagnosis and development of therapies to prevent progression.

   Presentation of MVP may vary even within members of the same family. Nonsyndromic MVP (see Chapter 16) is a common disorder that appears to have a strong genetic component, and the familial form is most commonly inherited in an ***autosomal dominant pattern*** with variable penetrance dependent on sex and age. The following chromosomal locations have been identified with MVP (**Table 39.5**). Additional mutations in this gene and their links to MVP are being investigated. In 2015, three loci, 2q35, 17p13, and 22q12, associated with MVP were identified.

TABLE 39.5 Genetics of Mitral Valve Prolapse

Gene	Chromosome Location	Comments
MMVP1	16p12.1-11.2	Autosomal dominant
MMVP2/DCHS1	11p15.4	Autosomal dominant; R2513H loss-of-function missense mutation in gene encoding calcium-dependent cell-cell adhesion molecules (cadherin superfamily)
MMVP3	13q31.1-32.1	Autosomal dominant
XMVD/FLNA	Xq28	X linked; P637Q missense mutation

2. In addition, it occurs in an idiopathic form, and it is also associated with other valvular syndromes such as bicuspid aortic valve (BAV) and connective tissue diseases, which typically affect cardiovascular function such as Marfan syndrome (syndromic MVP), osteogenesis imperfecta, and EDS. Certain subtypes of MVP are also arrhythmogenic and are

associated with channelopathies, leading to the risk of sudden cardiac death.

3. **Aortic valve disease.** Aortic valve disease (see Chapter 15) can be divided into two different types based on clinical characteristics: **BAV and calcific trileaflet aortic valvular disease**. Calcific aortic valvular disease is typically a disease of the older patients. It was thought to be affected by those risk factors predisposing toward coronary artery disease (CAD) but more recently is recognized as a separate condition from atherosclerosis. BAV is believed to be a congenital abnormality with an ***autosomal dominant*** mode of transmission with reduced penetrance. The prevalence of BAV in first-degree relatives of affected individuals has been reported as being as high as 9%. **BAV is present in 0.2% to 2% of the population** and is typically discovered earlier on in life and is frequently associated with disease of the aorta. What BAV and calcific aortic valvular disease have in common is the eventual progression to calcification of the aortic valve itself. **Mutations in the *NOTCH1* gene located on chromosome 9 at q34.3 have been implicated in BAV development**. NOTCH1 is a transmembrane protein with transcriptional regulatory activity that is vital not only for aortic valve development but also for calcification. It is thought that mutations in this gene may allow the normally repressed transcription factor Runx2 to facilitate the development of valvular endothelial cells into osteoblast-like cells and promote valvular calcification. Mutations in the *ACTA2* gene on chromosome 10q23.3, which codes for actin, have also been linked to BAV. Mutations in ubiquitin fusion degradation 1–like gene, located at 22q11.21, have also been implicated in BAV. This gene codes for a signaling protein that is prevalent during embryonic formation of cardiac outflow tracts. Another gene implicated in BAV is the *GATA5* gene on chromosome 20q13.33 encoding for a protein that is a transcription factor containing two GATA-type zinc fingers. This protein is necessary for cardiovascular development. Recent studies have identified associations between loss-of-function mutations of the *GATA5* gene and BAV. In 2014, Qu et al reported that a loss-of-function mutation in the *NXK2-5* gene, location 5q35.1, was associated with BAV in a Chinese family. The *NXK2-5* gene encodes a homeobox-containing transcription factor that is involved in cardiac embryologic development. Mutations in this gene are known to cause atrial septal defect and tetralogy of Fallot. Three additional loci associated with BAV have been

identified on the long arms of chromosomes 5, 13, and 18, but no specific genes have been discovered. Interestingly, in 2014, researchers using a targeted next-generation sequencing approach identified variants in 26 genes not previously implicated with BAV in humans. It is evident that many different genes are implicated in BAV and calcific aortic valvular disease, including Lp(a), for which increases in serum levels have been shown to be correlated with earlier onset and more severe calcific aortic valve.

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CHAPTER 40

Heart Disease in Women

Ambreen Fatima Ali and Leslie Cho

I. INTRODUCTION. Cardiovascular disease (CVD) is the leading cause of death of women in the United States, accounting for 28% of all deaths in women. Despite aggressive campaigns by the American Heart Association (AHA) and other organizations, only 44% of the women surveyed in 2019 listed coronary heart disease (CHD) as a leading cause of death for women. This is a stark decrease from 2009 when 65% of women identified CVD as the leading cause of death for women. Although there was an overestimation of cancer-related mortality in the survey, the decline in awareness of CVD risk is alarming. Minority women, particularly Black and Hispanic, are consistently less aware of their CV risk, which is higher than for age-matched White women.

Gender-related differences exist in the presentation and outcome of CVD. Although men have a high age-specific incidence of CVD in most age groups, the difference decreases after age 55 years as the incidence of CVD continues to increase in postmenopausal women while it plateaus in men. There was an encouraging decline in CV mortality in women between 1999 and 2011, but a concerning 7% increase in CV mortality in women was seen in 2017. Based on the AHA Heart Disease and Stroke Statistics Report in 2021, the prevalence of CHD and myocardial infarction (MI) in women is 6.2% and 2.1%, respectively. Women are older at the time of first MI (mean age 72.0 vs 65.6 years) and have higher in-hospital mortality with ST-elevation MI (STEMI) (7.4% vs 4.6%) and with non–ST-elevation MI (NSTEMI) (4.8% vs 3.9%). Women experience longer door-to-balloon time and lower rates of guideline-directed medical therapy and intervention than men. Medicare data show women have higher early mortality after acute MI

(AMI) compared with men, although the gap decreases a month post-AMI.

A 2022 review on ischemic heart disease in young women showed mortality in women aged 35 to 54 years has increased from 27% to 32% over the past 2 decades. While obstructive coronary artery disease (CAD) remains the predominant etiology of AMI, up to 15% of these young women have nonobstructive coronaries. Women hospitalized with AMI have greater in-hospital mortality than men, particularly in younger women aged <50 years. All of this necessitates the need to better understand the differences in CVD risk, pathology, and treatment between men and women. This chapter summarizes the current understanding of the gender-specific features of CVD and outcomes.

II. GENDER DIFFERENCES IN PATHOPHYSIOLOGY. There appear to be gender-based differences in the atherosclerotic process in men versus women. **Women, in general, have more diffuse atherosclerosis with less plaque volume and luminal obstruction than males**. The underlying mechanism of coronary obstruction also appears to differ—while plaque rupture remains the dominant cause of AMI in women, they have significantly more plaque erosion compared to men, as shown by a histopathologic study in 1999, where 25% of women had plaque erosion compared to 18% of men. Although plaque burden may be similar, women have less calcium in plaque, a thinner fibrous cap, and smaller necrotic core. Vasoreactivity, thrombosis, and inflammation are influenced by a variety of hormones, present in varying quantities in men and women. Women have smaller coronary arteries than men, and interestingly, women taking androgens have much larger coronary arteries than their age-matched controls. It is well established that estrogen confers protection from CAD in premenopausal women. The exact mechanisms by which this occurs are not fully understood; however, it is likely multifactorial, with estrogen signaling involved in the regulation of vasomotor tone, inhibition of smooth muscle cell proliferation, and maintenance of favorable metabolic conditions, including regulation of obesity, hypertension (HTN), and lipid profile. Animal studies suggest estrogen decreases oxidative stress via upregulation of the production of prostacyclin PGI_2, a molecule known

to retard the progression of atherosclerosis. In addition, women have higher levels of fibrinogen and factor VII, which may contribute to sex-related differences in endothelial function and hemostasis.

A. **Myocardial infarction in the absence of obstructive coronary artery disease (MINOCA).** This is a clinical syndrome with chest pain, electrocardiographic (ECG) changes, and troponin elevation in the setting of normal or nonobstructive coronary arteries on left heart catheterization (LHC). Incidence is estimated to be about 5% to 6% of all AMI, and women make up about 50% of MINOCA population while overall accounting for 25% of all AMI. Patients with MINOCA also have fewer traditional CAD risk factors. It is putatively caused by microvascular coronary dysfunction—the coronary microvasculature fails to appropriately vasodilate in response to increased myocardial oxygen requirements, perhaps because of hormonal signaling. Other proposed mechanisms for MINOCA include plaque disruption with distal embolization of thrombus, coronary vasospasm, supply-demand mismatch, and spontaneous coronary artery dissection (SCAD) (see below). A 2019 Scientific Statement from AHA recommends the management of MINOCA with conventional cardioprotective medications, including aspirin (ASA), statins, angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers (ACEI/ARBs), and beta-blocker (BB). For vasospastic angina, calcium channel blockers and nitrates can be used. Most patients with MINOCA will require additional studies (cardiovascular magnetic resonance imaging [CMRI], intravascular ultrasound [IVUS], optical coherence tomography [OCT], and physiologic testing) to rule out alternative diagnoses. A majority of the studies report better prognosis of patients with MINOCA compared with patients with AMI.

B. **Stress cardiomyopathy**, also known as Takotsubo cardiomyopathy or "broken heart syndrome," is another CVD affecting predominantly postmenopausal women. Stress cardiomyopathy is diagnosed when patients, often in the setting of severe emotional distress or physical trauma, present with chest pain, ST elevation on ECG, abnormal cardiac biomarkers, and characteristic appearance of an akinetic,

ballooning apex on echocardiography or left ventricular (LV) ventriculogram. The degree of wall motion abnormality is often out of proportion to the degree of troponin elevation. Diagnosis is by a process of exclusion, including angiography, which often reveals normal coronary vessels or nonobstructive mild disease. The etiology of stress cardiomyopathy is not fully elucidated but is believed to result from catecholamine toxicity with excessive sympathetic stimulation of the basal segment of the heart. Microvascular dysfunction and/or coronary vasospasm may also contribute to the pathophysiology of stress-induced cardiomyopathy. Recent data suggest prognosis may be dependent on the nature of the trigger—physical versus emotional, with physical triggers associated with worse prognosis and lower recovery. Overall, however, the prognosis in most patients remains very favorable, and most patients will recover ventricular function to baseline within weeks to months with guideline-directed medical treatment.

C. **SCAD** is defined as coronary artery dissection in the absence of atherosclerosis, trauma, or iatrogenic causes. Women comprise 87% to 95% of patients with SCAD, with a mean age of 44 to 53 years. Single-center studies estimate the prevalence of SCAD around 4% of all AMI cases. The current understanding of ***pathophysiology*** is the development of hematoma within the tunica media and compression of a true lumen leading to ischemia. For this, two mechanisms are hypothesized: “inside-out” hypothesis suggesting blood enters subintimal space after disruption of endothelial lining, or “outside-in” hypothesis with de novo hematoma formation in the tunica media. The latter is favored by more recent evidence from angiographic and OCT data. When compared to patients with AMI, patients with SCAD have lower rates of risk factors for CVD including HTN and hyperlipidemia, rates of which are comparable to age-matched populations. This raises suspicion for other causative mechanisms, particularly genetic predisposition, arteriopathies, and sex hormones, given overwhelming majority of cases are in women. However, studies have not been able to establish any distinct genetic susceptibility, but there are more observed cases in patients with

connective tissue disorders. Sex hormones have been implicated in the development of SCAD; however, there is the condition seen in women with or without children and regardless of menopausal status. SCAD in pregnancy is discussed in the chapter on pregnancy and the heart. Most cases present similar to atherosclerotic acute coronary syndrome (ACS), including chest pain, ECG changes, and cardiac biomarker elevation. Coronary angiography is the mainstay of diagnosis and, in challenging cases, can be aided by invasive coronary imaging.

Three types of SCAD are defined:

- Type 1 has a linear filling defect.
- Type 2 is the most common and has a long segment of vessel narrowing with distal tapering.
- Type 3 mimics atherosclerotic lesions.

Management is largely conservative, using medical therapy with BB, ARB/ACEI, and therapy for heart failure if indicated. However, in cases of left main dissection or clinically unstable patients, urgent coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is indicated. Fibromuscular dysplasia (FMD) has been associated with SCAD. FMD is a nonatherosclerotic, noninflammatory vascular disease that can manifest as tortuosity, aneurysm, stenosis, or dissection. FMD is the most common extracoronary vascular abnormality identified among patients with SCAD, and concomitant FMD in patients with SCAD is estimated to around 17% to 86%.

D. Aortic disease. The prevalence of thoracic aortic disease is higher in men, and the estimated 70% cases of symptomatic or clinically significant aortic disease are in men. This is likely explained by the protective effect of estrogen. Aortic walls of women have upregulation of estrogen receptor-alpha (ER-α), which provides vasoprotective effect and decreased vessel inflammation. However, as would be expected, this protection is at least partially lost after menopause. Conversely, women with degenerative aortic aneurysms have a faster rate of aneurysm growth. Another issue is the cutoffs for aortic dilatation are not differentiated between both sexes, despite

women being smaller in height and body surface area. Men tend to get more inherited aortic disease; however, women have a higher incidence of autoimmune conditions with accompanying vasculitis. Takayasu arteritis remains an almost exclusively female disease. A particular challenge in women with aortic disease is surveillance. Cross-sectional imaging is the benchmark for assessing aortic dilatation; however, regular computed tomography (CT) scans in young women can cause significant cumulative radiation exposure to breast tissue, and MRI is preferred. From a presentation and outcome standpoint, women with dissection have delayed presentation and delayed time to diagnosis compared to men (median time from presentation to diagnosis of 6.40 vs 3.96 hours; $P < .001$). Fortunately, postoperative mortality for women remains comparable to that of men. An area specific to women where risk stratification for aortic disease becomes paramount is preconception planning. Women with inherited aortic diseases such as Marfan syndrome, Loeys-Dietz syndrome, and vascular Ehlers-Danlos are recommended to have elective aortic surgery if prepregnancy aorta is >4.5 cm, although variations in recommendations exist between different disorders. Furthermore, threshold for aortic surgery may be lower if there are independent risk factors for dissection (ie, rapid aortic growth or a family history of aortic dissection). For prepregnancy aortic dimensions between 4.0 and 4.5 cm, surveillance is recommended every trimester. Aortic dissection remains the most feared complication, and up to half the dissections in women aged <40 years are associated with pregnancy. There is at least a 4-fold risk of dissection and rupture with pregnancy and delivery, and planned cesarean delivery is recommended for significant aortic dilatation >4.5 cm in most cases. Most of all, aortic disease in pregnancy can be at high risk or at times prohibitive condition and needs to be managed in conjunction with maternal-fetal medicine and cardio-obstetrics to ensure safety for both the mother and the baby.

E. **Heart failure.** There are gender differences in the incidence and outcomes of heart failure, particularly with regard to heart failure with preserved ejection fraction (HFpEF), which is much more

common in women. This is further discussed in the chapter on heart failure.

III. GENDER DIFFERENCES IN RISK FACTORS

A. Diabetes mellitus. Diabetes affects more women than men after the age of 60 and confers a greater relative risk of CVD in women. Diabetes increases the rate of CAD 3 to 7 times in women, while men with diabetes have only a 2- to 3-fold increased risk of CAD. Type 2 diabetes is associated with other components of the metabolic syndrome, all of which increase the risk for CVD. Diabetes also remains a strong risk factor for the development of heart failure in women. Diabetes eliminates the 10-year gender difference in the development of CAD.

B. HTN. Women have a different trajectory of developing HTN when compared with men. Younger women have lower blood pressure (BP) but appear to have a steeper increase in BP over time, and women over the age of 65 have higher rates of HTN than men, with more than 73% of women aged 65 to 74 years diagnosed with HTN. A woman's risk of developing HTN increases if they are obese, has a family history of HTN, or is postmenopausal. Women with HTN have a higher risk of both CAD and congestive heart failure than men with HTN. This risk for CVD related to HTN rises steeply with age, although most studies show that treatment attenuates this risk.

C. Hyperlipidemia. Lipid fractions in women are affected by their menopausal status. Premenopausal women have lower low-density lipoprotein cholesterol (LDL-C) levels and higher high-density lipoprotein cholesterol (HDL-C) levels than age-matched men. As women age, LDL-C increases, HDL-C decreases, and triglycerides increase. Total cholesterol and LDL-C are less predictive in women, unlike HDL-C, which is inversely associated with the risk.

D. Cigarette smoking. This is the single most important preventable risk factor. Smoking leads to more CVD deaths than any other risk factor, likely owing to its effects of increasing inflammation, thrombosis, and oxidation of LDL-C. Smoking also has an antiestrogen effect, inducing unfavorable changes in lipid levels.

There is a 6 to 9-fold increased risk of MI in female smokers compared with age-matched nonsmokers; in fact, the risk from smoking is equivalent to the risk of weighing about 42 kg more than a nonsmoking woman. Women who smoke have a higher risk of CVD compared with men smokers, particularly for women less than 55 years of age. However, with smoking cessation, the risk is cut in half after 1 year without smoking and eventually declines to the level of nonsmoker risk.

E. Obesity and metabolic syndrome. Approximately 34% of American women are obese, and this number continues to climb. Trends of metabolic syndrome in the United States showed increased metabolic syndrome in women in 2016 compared to 2011 (37% from 32%). There has been a particular increase in metabolic syndrome in young individuals from 16% to 21%. In women, obesity and body fat distribution (ie, abdominal circumference) are independent risk factors for CAD. As shown by an examination of a cohort of 115, 195 women from the Nurses' Health Study, the risk of death from CVD increased with increasing body mass index (BMI).

F. Estrogen/menopause. Postmenopausal women have more CVD risk factors, such as obesity, HTN, and hyperlipidemia, likely owing to the precipitous decline in estrogen levels. The predominant source of estrogen changes from estradiol in the premenopausal state to the much weaker hormone estrone (produced by the conversion of androgens in peripheral adipose tissue) during menopause. Animal studies have shown that estrogen can have favorable CV effects, reducing cellular hypertrophy, enhancing vessel wall elasticity, and providing antioxidant and anti-inflammatory actions.

As part of the Women's Ischemia Syndrome Evaluation study results, endogenous estrogen deficiency in young women was shown to be a strong risk factor for CHD, with a 7.4-fold increased risk. Because of the protection from CAD afforded for premenopausal women, there was early enthusiasm for the use of hormone replacement therapy (HRT) to prevent CVD in postmenopausal women, sparked by data from observational studies. However, multiple randomized, placebo-controlled trials over recent years have

shown evidence of increased risk for CVD with HRT, such that it is no longer recommended for primary or secondary prevention of CVD.

G. Physical inactivity. As women age, they become less physically active than their male counterparts. This contributes to weight gain and predisposes to the development of diabetes and HTN. In addition, with the cessation of estrogen production with menopause, there is increased abdominal fat deposition, further predisposing to CAD. There is a strong inverse association between the activity level and the incidence of CV events (**Tables 40.1** and **40.2**).

TABLE 40.1 Risk Classification of Cardiovascular Disease in Women

High Risk	At Risk	Optimal Risk
• Known CAD	• Subclinical atherosclerosis (eg, coronary calcification, carotid plaque, or thickened intima media)	• Fasting blood glucose <100 mg/dL (untreated)
• Cerebrovascular disease	• Cigarette smoking	• Nonsmoker
• Peripheral arterial disease	• Poor diet	• Healthy (Dietary Approaches to Stop Hypertension [DASH]-like) diet
• End-stage renal or chronic kidney disease	• Physical inactivity	• Physical activity goal for adults <20 y of age: >150 min/wk moderate intensity, >75 min/wk vigorous intensity, or combination
• Diabetes	• Obesity (especially abdominal location)	• BMI <25 kg/m^2
• 10-y Framingham global risk >10%	• Dyslipidemia (total cholesterol >200 mg/dL, HDL-C <50 mg/dL, or treated for dyslipidemia)	• Total cholesterol <200 mg/dL (untreated)

High Risk	At Risk	Optimal Risk
	• HTN (SBP >120 mm Hg, DBP >80 mm Hg, treated HTN, or history of pregnancy-induced HTN) • Family history of premature CAD (<55 y in men, <65 y in women) • Metabolic syndrome or history of preeclampsia or gestational diabetes • Poor exercise capacity on exercise treadmill test and/or abnormal heart rate recovery after stopping exercise • Family history of premature CVD occurring in first-degree relatives in men <55 y of age or in women <65 y of age • Autoimmune diseases (eg, SLE or RA)	• BP <120/<80 mm Hg (untreated)

BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; RA, rheumatoid arthritis; SBP, systolic blood pressure; SLE, systemic lupus erythematosus.
Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404-1423. Copyright © 2011 American Heart Association, Inc. With permission.

TABLE 40.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women

Lifestyle Interventions	Major Risk Factor Interventions	Preventive Drug Interventions
Class I Recommendations		
Smoking cessation (B)	Maintain optimal BP (<120/80 mm Hg) with lifestyle modification (B)	ASA in high-risk women (known CAD, cerebrovascular disease, PAD, AAA, ESRD, CKD, diabetes, and 10-y Framingham risk >20%) (A)
Exercise: 150 min/wk of moderate-intensity exercise (eg, brisk walking), 75 min/wk of vigorous-intensity exercise (eg, running), or combination (B)	Pharmacotherapy for BP ≥140/90 mm Hg (≥130/80 mm Hg in CKD or diabetes). Thiazide should be initial agent unless compelling indications for beta-blockers and/or ACEI/ARB exist (eg, ACS/MI) (A)	Clopidogrel therapy for high-risk women intolerant of ASA (B)
Weight loss to BMI <25 kg/m^2 and waist circumference ≤35” (B)	Control of lipids through lifestyle modification (LDL-C <100 mg/dL, HDL-C >50 mg/dL, triglycerides <150 mg/dL, and non–HDL-C [total cholesterol—HDL-C] <130 mg/dL) (B)	Beta-blockers for at least 1 y and up to 3 y in women after MI and ACS, with normal LV function. Use indefinitely if LV dysfunction present (A)
CV rehabilitation in those with recent ACS or PCI, angina, and recent CVA, PAD, or CHF (B)	Pharmacotherapy of lipids in those with CAD (A), diabetes, or 10-y absolute risk >20% (B) to goal LDL-C <100 mg/dL	ACEIs in those after MI or with clinical CHF, LV dysfunction (LVEF ≤40%), or diabetes (A). If intolerant of ACEI, ARB can be substituted (B)
Diet counseling to promote intake of fruits and vegetables, whole grain and high-fiber foods, and fish at least 2 times per	Pharmacotherapy of lipids in those with LDL-C ≥130 mg/dL after lifestyle modification and presence of multiple risk	Aldosterone blockade after MI in symptomatic women with LVEF ≤40% who are

Lifestyle Interventions	Major Risk Factor Interventions	Preventive Drug Interventions
week. Limit consumption of saturated fat, cholesterol, alcohol, sodium, and *trans*-fatty acids (B)	factors (or if LDL-C ≥160 mg/dL in those with multiple risk factors, even if Framingham risk <10%) (B). Pharmacotherapy of lipids in those with LDL-C ≥190 mg/dL regardless of other risk factors Maintain HbA1c <7% in those with diabetes (B).	without renal dysfunction or hyperkalemia and who are already on an ACEI and beta-blocker (B)
Class IIa Recommendations		
	Goal LDL-C <70 mg/dL is reasonable in the very high risk (known CAD + multiple major risk factors, severe and poorly controlled risk factors, or diabetes) (B)	
Class IIb Recommendations		
Omega-3 fatty acid in the form of fish or capsule (eg, EPA 1,800 mg/d) may be considered in women with hypercholesterolemia or hypertriglyceridemia for primary or secondary prevention (B).	Pharmacotherapy with niacin or fibrates when HDL-C is low or non–HDL-C is elevated in high-risk women (after LDL-C goal reached) (B)	Low-dose ASA therapy (81 mg daily or 100 mg on alternate days) in women ≥65 y if benefits outweigh risk of bleeding (B)

AAA, abdominal aortic aneurysm; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASA, aspirin; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cerebrovascular; CVA, cerebrovascular accident; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.
Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American

Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404-1423. Copyright © 2011 American Heart Association, Inc. With permission.

H. Female-specific risk enhancers. In the 2020 Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women, led by the American College of Cardiology (ACC) CVD in Women Committee, CVD risk factors unique to women have been described as follows:

1. **Pregnancy-associated conditions.** Adverse pregnancy outcomes can occur in up to 20% of pregnancies and are associated with a 2- to 4-fold increase in future CVD risk. Pregnancy and CVD are discussed in detail in the Cardio-Obstetrics chapter.
   a. **Gestational HTN.** Hypertensive disorders of pregnancy are associated with the development of incident HTN. Women with preeclampsia are at 3.7-fold risk of HTN, 2.2-fold risk of ischemic heart disease, and 1.5-fold risk of mortality. Preeclampsia was also introduced as a "risk enhancer" in the 2018 ACC/AHA Lipid Guidelines and in the 2019 ACC/AHA Prevention Guidelines.
   b. **Gestational diabetes.** Women with gestational diabetes mellitus (GDM) can have up to 20-fold increased risk of future diabetes, 2-fold increased risk of HTN, and ischemic heart disease.
   c. **Preterm birth.** Delivery before 37 weeks of gestation is associated with a 2-fold increased risk of CVD and CV mortality. The risk of CVD is higher with more preterm and earlier preterm births. Women with **pregnancy loss** are also at increased risk of CVD.
2. **Premature menopause.** Physiologic decline in estrogen and associated changes, including body fat distribution, reduced glucose tolerance, higher BP, dysregulation of lipids, and potential vascular inflammation contribute to higher CVD risk in postmenopausal women. Premature menopause confers the increased CVD risk earlier in women. Data from the United Kingdom Biobank cohort reports an increased risk of CVD with premature menopause before age 40.

3. **Polycystic ovarian syndrome (PCOS).** Although PCOS is a common condition in young women of reproductive age, its associated effects of decreased insulin sensitivity, and a predisposition to metabolic syndrome, likely drive the increased risk of CVD in future. In addition, psychological factors including anxiety, depression, and eating disorders are prevalent with PCOS and independently confer additional risk.
4. **Autoimmune disease.** Women are more likely to have autoimmune diseases, particularly rheumatoid arthritis and systemic lupus erythematosus (SLE). Given the inflammatory milieu created by such disorders, it is not surprising that women with autoimmune disease have much higher prevalence and earlier incidence of CVD.

I. **Novel risk factors.** Traditional risk factors are known to underestimate CHD risk in women. For this and other reasons, research has been focused on identifying other novel biomarkers that can better define a woman's risk. Multiple biomarkers have been investigated (eg, high-sensitivity C-reactive protein [hsCRP], brain natriuretic peptide, and fibrinogen), but the greatest promise appears to be with hsCRP. As part of the Women's Health Study, over 27,000 healthy American women had their CRP and LDL-C levels measured. The women were then followed for a mean of 8 years for the occurrence of the primary end point (MI, ischemic stroke, coronary revascularization, or death from CVD). Although minimally correlated with each other, both CRP and LDL-C levels had strong linear relationships with CVD events, with CRP being the stronger predictor. Each biomarker tended to identify different high-risk groups, but better prognostic values were obtained when both were used together. Routine measurement of hsCRP is not currently recommended, but these data suggest hsCRP may add benefit to the risk assessment of women with intermediate CV risk.

IV. **GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS.** CVD often manifests differently in women than in men, potentially because of underlying differences in pathophysiology. This is particularly true for women with

diabetes. Women usually present at an older age and have more comorbidities than do men. As such, once the diagnosis of CAD is made, women are at higher risk for adverse outcomes.

A. Like men, women can present with typical symptoms of angina, such as substernal **chest pain** and **dyspnea on exertion** that is relieved by rest. These symptoms more often occur in older women, who present more similarly to men.

B. Women are more likely than men to present with **atypical chest pain**; shortness of breath; neck, shoulder, or arm pain; diaphoresis; and nausea/vomiting.

C. Women are more likely to have subtle symptoms that require detailed history-taking to elicit, such as **chest "pressure or tightness,"** lightheadedness, palpitations, or fatigue. Women most often have symptoms that occur at rest, wake them from sleep, or occur in times of psychological stress.

D. Women more often present acutely without preexisting prodromes of symptoms or with **sudden cardiac death**.

V. GENDER DIFFERENCES IN ASSESSMENT

A. Exercise ECG. Guidelines suggest that women at low risk for CAD are not candidates for diagnostic testing, whereas women who are intermediate to high risk capable of performing 5 metabolic equivalents or greater should undergo an exercise ECG. As with men, an abnormality is identified if there is ≥1 mm of ST-segment depression or elevation. Generally, exercise ECG has lower sensitivity and specificity than other modalities, and this is even more prominent in women (sensitivity and specificity of 31%71% and 66%-88%, respectively). This difference is not well understood, but it has been attributed to several factors, including lower ECG voltage and more frequent resting ST and T-wave changes. In general, women are more likely than men to have a false-positive stress test; however, a negative exercise stress test has a negative predictive value of ~80%.

B. Stress echocardiography (transthoracic echocardiography [TTE]). Stress TTE tends to have higher specificity and lower

sensitivity than stress perfusion imaging, as wall motion abnormalities occur later than perfusion abnormalities. However, stress TTE has the advantages of eliminating radiation exposure, decreasing cost, and providing the ability to assess LV function and cardiac structures. It has been shown to be a cost-effective strategy for determining CV risk in patients at intermediate risk.

C. **Stress myocardial perfusion scan.** Because of the limited sensitivity and specificity of exercise ECG in women, other modalities are frequently employed to assess the risk of CAD. The most frequently used test is the single-photon emission computed tomography (SPECT) scan, a radionuclide-based technique. Because alterations in myocardial perfusion generally occur earlier than ECG changes or wall motion abnormalities, this test is more sensitive than exercise ECG or echocardiography for estimating risk in either gender. For those individuals unable to exercise or attain target heart rates, regadenoson or dipyridamole can be used as a pharmacologic stress agent. Limitations of SPECT are critical in women, given soft tissue attenuation artifact from breast and excess adipose tissue, some of which can be mitigated by CT attenuation correction. Women also have smaller hearts, and with limited resolution of SPECT, minor areas of ischemia are more likely to be missed.

D. **Coronary angiography.** Diagnostic coronary angiography is the gold standard for diagnosing CAD in both men and women. When evaluated by LHC, however, women more often have minimal to no obstructive CAD. Women tend to experience more frequent vascular complications such as bleeding and renal failure related to diagnostic LHC when femoral approach is utilized. This may be related to older age at the time of presentation, smaller body size, smaller vessel size, and higher prevalence of diabetes. A radial approach is favored for diagnostic and interventional coronary procedures as there is less risk of bleeding complications than femoral catheterizations.

E. **Coronary artery calcium (CAC) score.** Recent studies have shown a highly predictive role of coronary calcium scoring in women for assessing the risk of CVD, which has different characteristics when compared to men. A large analysis by CAC Consortium, which

assessed approximately 63,000 asymptomatic men and women, showed women had fewer calcified lesions, greater lesion size, and higher plaque density when compared with men. In undetectable CAC, both sexes had comparable mortality. However, where CAC was detectable, women had higher risk of CV mortality compared to men. CV mortality was also higher in women compared with men if the lesions were longer than 15 mm, there were five lesions or more, or if there was multivessel involvement. Moreover, CAC density was correlated with mortality in men, but not in women. The relationship between CAC and CVD in women holds true for women with diabetes as well.

F. **Coronary CT angiography (CTA)** is a unique noninvasive modality that identifies the burden of obstructive and nonobstructive CAD. Since women have a higher likelihood of having nonobstructive yet significant CAD and a relatively higher complication rate with invasive angiography, CTA offers to improve diagnostic certainty noninvasively while impacting treatment decisions. Diagnostic accuracy of CTA in ruling out significant CAD has been demonstrated for both sexes, even with low-intermediate pretest risk. CTA, however, does show lower sensitivity for detecting stenosis in small distal segments in women when compared with men (54% vs 89%). This is attributed to the overall smaller vasculature size in women. CTA, however, does surpass or is at least equal to functional stress testing in detecting significant CAD in women. In the PROMISE trial, CTA was associated with a lower rate of nonobstructive disease on invasion angiography compared with the stress test, showing increased congruence between the CTA and invasive angiography. In sex-specific analysis of the PROMISE trial, abnormal CTA in women had higher hazard ratio for major adverse cardiovascular event (MACE) compared to women with the abnormal stress test (5.9 vs 2.3). CTA also showed higher diagnostic certainty of identifying angina promptly in the SCOT-HEART trial. CTA also allows for plaque characterization, including extent, severity, and composition.

G. Cardiac magnetic resonance (CMR) imaging is a robust, reliable, and reproducible imaging modality for the assessment of tissue characterization, cardiac anatomy, and cardiomyopathies. It is a particularly advantageous imaging modality in women over cardiac CT, fluoroscopy, and nuclear testing, as it does not involve exposure to ionizing radiation. Premenstrual women with radiation-sensitive breast tissue and pregnant women are at the highest risk of detrimental radiation effects. CMR helps in accurate volumetric assessment, and prior CMR data show women have smaller absolute and indexed volumes of LV and right ventricle (RV), and smaller atria compared to men, with similar or higher ejection fraction. There are several sex-specific applications of CMR. As discussed above, ischemic disease presents differently in women with a much higher frequency of MINOCA. CMR provides incremental value to establishing this diagnosis, and studies show establishment of diagnosis in up to 87% of cases as it can distinguish between small infarct versus Takotsubo CM versus myocarditis, among other things. Another niche use of CMR in women is in peripartum cardiomyopathy. We know that the degree of both LV and RV dysfunction correlates with outcomes, and CMR can accurately assess ventricular dysfunction and size, particularly RV dysfunction. Since most women will require periodic imaging, CMR supplements echocardiography with the goal of minimizing radiation exposure in young women. The presence of late gadolinium enhancement (LGE) on CMR is also predictive of outcomes in subsequent pregnancies. Another notable sex-specific role of CMR is in cancer therapy–related cardiac dysfunction, especially after treatment of breast cancer, which is a female-predominant disease. Echocardiography can miss subtle changes in cardiac function and volumetric changes, which are more accurately assessed by CMR. CMR is comparable to multigated acquisition (MUGA) scan for LV function; however, the latter introduces ionizing radiation. CMR strain is also shown to decrease with anthracycline use, as well as increased T2 signal intensity and anthracycline and trastuzumab therapy. Other sex-specific uses of CMR include pregnancy risk stratification in congenital heart disease and aortic disease, assessment of CVD

associated with systemic autoimmune conditions, and aortic disease requiring serial imaging, where the risk of radiation exposure is to be minimized.

VI. GENDER DIFFERENCES IN THERAPIES. Most CVDs can be prevented if risk factor modification occurs early and aggressively. Until recently, most of the clinical trial data, on which the guidelines for the prevention and treatment of both genders are based, were derived from trials conducted largely in men. This information had been extrapolated to women because gender-specific trial data were lacking. Because of this uncertainty, more recent clinical trials have offered insights into gender-specific results, allowing for evidence-based guidelines for disease prevention and treatment in women. However, with only a few exceptions, the guidelines are the same for both men and women. The gender-specific results are highlighted here; for a full discussion, see appropriate sections of other chapters.

A. ASA. Aspirin (ASA) is the principal antiplatelet agent in patients with CAD. Its benefit in secondary prevention, as well as in ACS, STEMI, and after revascularization (CABG or PCI), is well known and discussed elsewhere. However, there are very few gender-specific data in these instances, so most recommendations are extrapolated from trials conducted largely in men. The role of ASA in primary prevention of CAD is controversial. Early data suggested that ASA may be protective as primary prevention for future CVD events in women, as it is in men. However, as part of the Women's Health Study, nearly 40,000 healthy women older than age 45 were randomized to either ASA 100 mg on alternate days or placebo, and they were followed for the incidence of CV events (nonfatal MI, nonfatal stroke, or CV death) over 10 years. Despite a 24% reduction in ischemic stroke, ASA had no benefit over placebo in reducing MI or CV death. However, ASA did appear protective as primary prevention in those women aged 65 years or above, because it significantly decreased the risk of both MI and stroke in this age group. In addition, ASA is protective in women with elevated lipoprotein (a) levels, which is an independent risk factor for the development of early CAD. Long-term 15-year follow-up, however,

showed low-dose ASA was ineffective or harmful for most healthy women, but there may be a benefit in women older than 65 years. More recent randomized trials (ASCEND, ARRIVE, and ASPREE) show a lack of net benefit, and the prevention of vascular events may even be superseded by the harm from bleeding complications. The 2019 ACC/AHA Guideline on Primary Prevention of CVD now states that the majority of healthy individuals should not get ASA for primary prevention. The guidelines do not give sex-based recommendations. In certain cases of individuals with high risk of atherosclerotic CVD (ASCVD), uncontrolled risk factors, and low bleeding risk, low-dose ASA can be considered after a risk discussion with the patient.

B. Thienopyridines. Thienopyridines, the most common of which is clopidogrel, have proven beneficial, when given with ASA, to reduce the rate of stent thrombosis after PCI. Clopidogrel has also shown benefit in secondary prevention of CAD, ACS, and STEMI (discussed in detail elsewhere). Few of the clinical trials using clopidogrel have given gender-specific data, but there are some data available for specific settings.

In the substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial, in which the patients received PCI, 2,658 patients with non-ST-segment elevation ACS undergoing PCI were randomly assigned to ASA plus clopidogrel or placebo for 9 months. Of the study population, 30.2% were women. Clopidogrel plus ASA long-term therapy improved outcomes in those patients who received PCI. This was more significant in men, but a definite trend toward benefit in women was evident as well. Similar results were seen for women in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, where 29% of the 2,116 patients were women. The CREDO trial showed benefit of post-PCI therapy with ASA and clopidogrel out to 1 year of therapy, again with a trend toward benefit in women.

C. P2Y12 inhibitors. Although there have been no specific trials looking at P2Y12 effectiveness in women, the data from the cardinal trials for prasugrel (TRITON-TIMI 38) and ticagrelor (PLATO)

provide insight. In TRITON-TIMI 38, comparing prasugrel versus clopidogrel in patients with ASA-treated ACS, there was no significant difference between the genders, although men showed higher absolute (2.4% vs 1.6%) and relative (21% vs 12%) reductions in MACE at 15 months. In PLATO, comparing ticagrelor versus clopidogrel in patients with ASA-treated ACS, no significant gender difference was seen in CV events by 1 year.

D. Statins. The primary prevention efficacy of statins in women has been controversial due to low event rates in women in clinical trials; however, meta-analysis suggests that women achieve similar clinical benefit from statins as men. This is potentially due to underlying differences in atherogenesis between the sexes. The Cholesterol Treatment Trialists' collaboration performed a meta-analysis of 27 statin trials including 174,000 patients where 27% were female. This meta-analysis showed that for equivalent reductions in LDL-C, men and women have similar relative risk reductions in vascular events. Furthermore, a post hoc subgroup analysis of the PROVE IT-TIMI 22 suggested that women may have greater risk reduction than men with lesser degrees of LDL-C reduction. In the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin, multivariable analysis showed greater decreases in plaque volume for women compared to men, across both rosuvastatin and atorvastatin treatment groups.

The 2018 ACC/AHA Guidelines on Lipid Management and the 2019 ACC/AHA Guidelines for Primary Prevention of Cardiovascular Disease include sex-specific recommendations for lipid management. They recommend statin therapy as the mainstay for the following:

- Clinical ASCVD
- Severe hypercholesterolemia (LDL >190 mg/dL)
- Diabetes mellitus in adults
- Primary prevention in adults between 45 and 70 years at high risk (20%) and some individuals at intermediate risk with risk enhancers, elevated CAC, and after clinician-patient risk discussion

There is concern that women are more likely to develop statin-associated muscle symptoms and consequently less likely to tolerate adequate therapy, but we do not have data on sex-specific adverse events.

E. Nonstatin therapy. In recent years, the introduction of PCSK9 inhibitor (PCSKi) monoclonal antibodies has dramatically changed the landscape of lipid management. This is particularly important for patients who cannot tolerate statins or have very high LDL-C levels refractory to standard therapy. Both the available PCSKi drugs, alirocumab and evolocumab, have been shown to drastically lower LDL-C levels by greater than 50% (ODYSSEY and FOURIER trials, respectively). Although the number of women in these trials was small, subgroup analyses did not show any difference in response to drug between the sexes.

Ezetimibe is another alternative for patients with statin intolerance secondary to adverse effects. The IMPROVE IT trial showed ezetimibe added to a statin provided an additional 25% reduction in LDL-C. On its own, ezetimibe provides a modest 18% reduction in LDL-C.

F. HRT. Currently, there is no role for menopausal hormone therapy (MHT) in CVD prevention. In the 1990s, there was enthusiasm about the preventive role of MHT based on a few observational studies, which demonstrated decreased rates of CVD in postmenopausal women, the data from randomized control trials have presented conflicting results. In 1998, the Heart and Estrogen/progestin Replacement Study (HERS) reported an association between oral HRT and increased rates of coronary disease and stroke. In this study of secondary prevention, 2,763 postmenopausal women with CAD were randomized to either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or placebo daily. After an average 4-year follow-up, there was no significant difference in the primary outcome of nonfatal MI or CHD death, but there was a signal toward early CV events, particularly in the first year after HRT initiation.

This was followed by the landmark primary prevention Women's Health Initiative (WHI) trial published in 2002. WHI had 16,608 healthy postmenopausal women randomized to combined estrogen-progestin or placebo. The aggregated results show an increased risk of CHD, stroke, and venous thromboembolism (VTE) in participants on HRT. Further analyses showed a more nuanced approach—the absolute risk of adverse events was lower for younger women (50-59 years) and higher if HRT was started >10 years after menopause or cessation of estrogen exposure. This supports the "timing hypothesis"—in women who start HRT earlier, there may be a reduced risk of CVD. Data from >10 years of follow-up of HRT impact on bone mineral density show a reduced risk of composite CV outcomes in women on HRT. Both HERS and WHI led to a dramatic decline in HRT prescriptions. Subsequent meta-analyses, however, have shown that early (<10 years postmenopause) HRT may lower all-cause CV mortality. While current gynecology and endocrinology medical society guidelines recommend HRT for menopause symptoms with considerations and timings, no medical societies recommend **HRT for primary or secondary prevention of CVD**.

G. **Stroke prevention.** We know through multiple studies that women are at a higher risk of stroke with atrial fibrillation (AF). A meta-analysis in 2018 that assessed 44 studies (more than 993,000 patients) showed an increased risk of stroke in women compared to men, which increased with advancing age. Hence, it has been incorporated in the CHA2DS2-VASc score with which the recommendation for anticoagulation in women is score 3. Compared to men, women with AF-associated stroke have worse prognosis and disability. In 2018, the European Heart Rhythm Association recommended the use of novel anticoagulants in women due to increased residual stroke risk when treated with vitamin K antagonists and lower bleeding complications with novel anticoagulants.

H. **Lifestyle modification.** The good news for women is that initiating lifestyle modifications can reduce CV risk by reducing the risk of developing diabetes. As part of the Diabetes Prevention Program Research Group, 3,234 patients (68% women) with impaired glucose

tolerance were randomized to placebo, metformin (850 mg twice daily), or lifestyle modification (goal 7% weight loss and at least 150 minutes of physical activity per week). After almost 3 years of follow-up, the lifestyle modification group had a 58% reduction in the incidence of diabetes compared with 31% in the group with metformin. This translates to a decreased risk of CVD. Salt modification and restriction also lead to a higher drop in BP in women compared with men.

VII. EVIDENCE-BASED GUIDELINES FOR HEART DISEASE PREVENTION IN WOMEN.

The ACC/AHA guidelines emphasize the importance of recognizing the wide-ranging spectrum of CVD in women. In general, a woman aged 20 years or above is first classified as at high risk, at risk, or at optimal risk based on the criteria in **Table 40.1**. Several factors should be evaluated, such as medical history, lifestyle, family history of premature CAD, Framingham risk score, and other genetic conditions, before decision regarding the aggressiveness of preventive therapy is finalized.

The guidelines are grouped into three main areas: lifestyle interventions, major risk factor interventions, and preventive drug interventions. **Table 40.2** lists the class I and class IIa recommendations for primary or secondary prevention of CVD in women. These guidelines are suggested as a starting point, with therapy tailored to the needs of each individual patient.

In general, it is suggested that the initial evaluation begins with a complete history, specifically eliciting symptoms of CVD, as well as a complete physical examination, with particular attention to BP, BMI, and waist size. Laboratory evaluation should follow, including fasting lipids and glucose levels. During the evaluation, assessment of Framingham risk should be performed, as well as depression screening in those women with known CVD. **All class I lifestyle interventions** should be employed in **all women**, regardless of risk level.

If the woman is at **high risk** (established CAD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, chronic kidney disease, or Framingham risk >20%), the **class I major risk factor and preventive drug interventions** should be initiated (see

Table 40.2). Consideration should also be given to some of the class II recommendations, particularly the **LDL-C goal of >70 mg/dL**.

There are some interventions that should not be considered. **Table 40.3** lists those therapies that are **contraindicated** based on the results of recent clinical trials.

TABLE 40.3 Class III Interventions (Ineffective, Possibly Harmful in Cardiovascular Disease Prevention in Women)

Hormone replacement therapy or selective estrogen receptor modulators
Antioxidant vitamin supplementation (vitamin E, vitamin C, and beta-carotene)
Folic acid with or without vitamin B_6 or B_{12} (folic acid supplementation should be used in the childbearing years to prevent neural tube defects)
ASA in healthy women <65 y

ASA, aspirin.
Adapted from ACC/AHA guidelines 2011 update. Adapted from Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association. *J Am Coll Cardiol*. 2011;57(12):1404-1423. Copyright © 2011 American Heart Association, Inc. With permission.

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CHAPTER 41

Sports Cardiology

Evan K. Harmon and Michael S. Emery

I. INTRODUCTION. Competitive athletes and highly active people (CAHAP) are a unique and growing population requiring increasingly specialized care within the field of sports cardiology. Historically, the field has emphasized the detection of underlying cardiovascular disease in young athletes, careful assessment of risk for sudden cardiac death (SCD), and counseling with regard to participation in competitive sports (ie, return to play). Though these remain important components in the care of CAHAP, a 2017 review published by the American College of Cardiology (ACC) Sports and Exercise Leadership Council recognized the expanding role of the sports cardiologist in evaluating symptomatic CAHAP and/or managing those with known cardiovascular disease. **These responsibilities require a fundamental understanding of anticipated physiologic and anatomic adaptations of the heart to volume load (eg, dynamic or aerobic exercise), pressure load (eg, static or resistance training), or a combination of the two, collectively referred to as exercise-induced cardiac remodeling (EICR)**. Distinguishing between EICR and true pathology is, therefore, a core principle in the care of CAHAP.

A. Dynamic training. The metabolic requirement of working muscles increases during dynamic exercise (eg, running). To meet demand, the cardiovascular system responds through two principal mechanisms: increased cardiac output (CO) and reduced peripheral vascular resistance (PVR). CO is determined by heart rate and stroke volume (SV) and, in athletes, can increase up to 6-fold during vigorous exercise, compared to resting conditions. The increase in preload and CO during endurance exercise creates volume-related stress on the heart. In addition, exercise-induced reduction in PVR,

through recruitment and dilation of peripheral vascular beds (mainly in working skeletal muscle), also contributes to increased CO.

The augmentation of CO during dynamic exercise is driven by both a rise in heart rate and an increase in SV. The former is mediated by the autonomic nervous system (ie, parasympathetic withdrawal and sympathetic augmentation) and does not increase with conditioning, given it is predominately determined by age. SV, however, is modifiable, as it is determined largely by the end-diastolic volume (ie, chamber size) and, to a lesser degree, by the end-systolic volume (regulated by a sympathetically mediated augmentation of cardiac contractility). End-diastolic volume increases in trained athletes, which augments CO during exercise. Therefore, characteristic findings in the highly trained endurance athlete include a resting bradycardia and a balanced increase in left ventricular (LV) dimensions and wall thickness (eccentric hypertrophy).

B. Static training. Conversely, the sustained contraction of peripheral muscle beds during static, or strength training (eg, weightlifting) acts to compress peripheral blood vessels and causes a marked increase in PVR. This response is further augmented by an exercise-induced surge in sympathetic tone and catecholamine release. During intense strength exercise, the LV may transiently have to work against a peripheral systolic blood pressure of up to 400 mm Hg. However, it should also be noted that this dramatic rise in acute blood pressure is rare, with studies suggesting that the absolute increase in blood pressure from baseline is variable and ultimately dependent on several factors, including the amount of muscle engaged and whether a Valsalva maneuver is performed. Regardless, the increase in PVR is accompanied by only a limited increase in CO; therefore, strength exercise mainly creates a pressure-related stress on the heart.

Importantly, many sports (eg, rowing and cycling) have overlapping physiology, exposing the heart to both volume- and pressure-related stressors. Nevertheless, sports are often classified according to the type(s) of stress placed on the cardiovascular system. For example, the 2015 American Heart Association (AHA)/ACC

Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Abnormalities divide sports into nine categories based on these principles (**Figure 41.1**). **Knowledge of patients' expected cardiac changes according to the demands of their sports is important when evaluating the cardiovascular system of CAHAP**. Furthermore, the degree of cardiac adaptation also varies according to age, gender, ethnicity, and genetic factors. Below, exercise-induced structural cardiac remodeling of the ventricles, atria, and aorta is described.

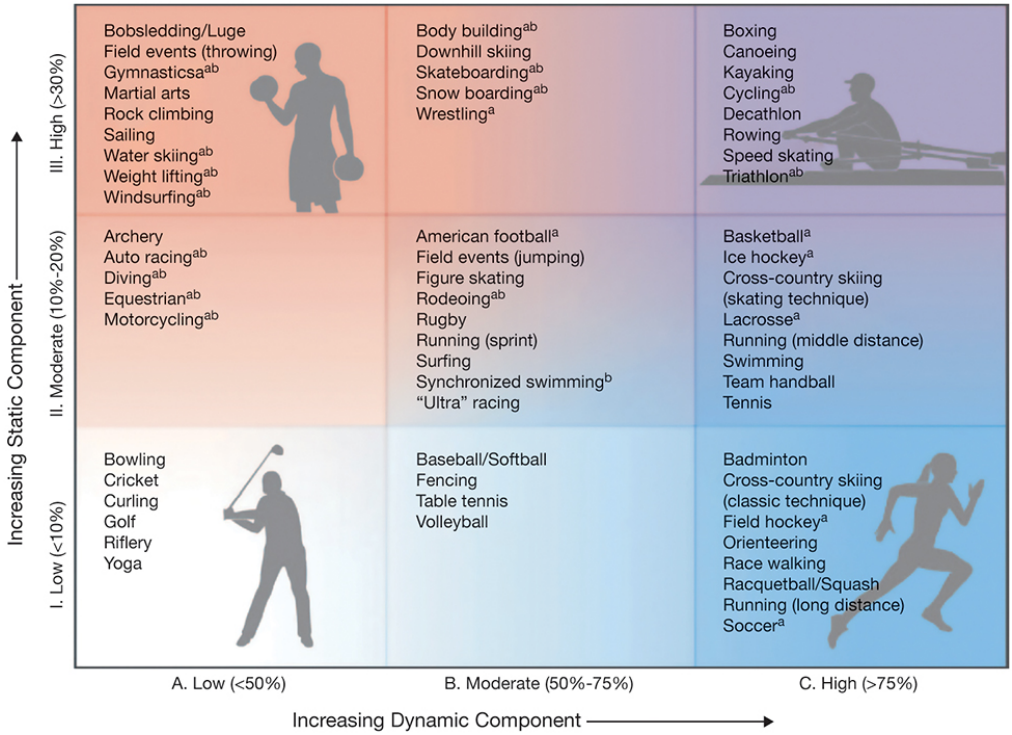

FIGURE 41.1 Classification of sports. This classification is based on peak static and dynamic components achieved during competition. It should be noted, however, that higher values might be reached during training. The increasing dynamic component is defined in terms of the estimated percent of maximal oxygen uptake (VO_2 max) achieved and results in an increasing cardiac output. The increasing static component is related to the estimated percent of maximal voluntary contraction (MVC) reached and results in an increasing blood pressure load. The lowest total cardiovascular demands (cardiac output and blood pressure) are IA (shown in the palest color), while the highest are IIIC. Increasing dynamic load is depicted by increasing blue intensity, while increasing static load is depicted by increasing red intensity. [a]Danger of body collision. [b]Increased risk if syncope occurs. (Reprinted

from Levine BD, Baggish AL, Kovacs RJ, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 1: Classification of sports: dynamic, static, and impact. *J Am Coll Cardiol*. 2015;66(21):2350-2355. Copyright © 2015 American College of Cardiology Foundation. With permission.)

II. STRUCTURAL CARDIAC ADAPTATIONS WITH REPETITIVE EXERCISE. EICR can become evident as soon as 90 days after commencing an intense exercise regimen. These adaptations improve both cardiac efficiency (eg, lower heart rate for a given exercise intensity) and maximal exercise capacity (eg, increase maximal CO).

A. Wall thickness. Repetitive pressure load results in increased LV wall stress and resultant increase in wall thickness with relatively minimal changes in chamber size (ie, concentric hypertrophy). Conversely, repetitive volume load typically produces dilation of the LV, accompanied by a balanced increase in wall thickness (ie, eccentric hypertrophy). This key relationship between LV wall thickness and end-diastolic volume has been described as relative wall thickness (RWT) and distinguishes between eccentric and concentric hypertrophy. RWT is defined by the equation (2 × posterior wall thickness)/(LV internal diameter at end diastole). An increase in RWT would suggest an increase in wall thickness out of proportion to cavity dilatation, whereas a decrease in RWT would suggest an LV chamber dilated out of proportion to its wall thickness. The 2015 American Society of Echocardiography (ASE) guidelines for chamber quantification, therefore, define eccentric hypertrophy as an LV mass indexed to body surface area (BSA) greater than 115 g/m^2 in males and greater than 95 g/m^2 in females with RWT less than or equal to 0.42. An increased LV mass index with RWT greater than 0.42 is diagnostic of concentric hypertrophy. Aside from eccentric and concentric hypertrophy, a third LV geometric phenotype to consider is concentric remodeling, which describes a subset of patients with normal LV mass index but increased RWT (ie, greater than 0.42). Patients with concentric remodeling exhibit abnormal LV geometry but without hypertrophy, which can be either physiologic in

the context of static exercise stress or pathologic in the context of various disease states (eg, myocardial infarction).

When assessing LV geometry in the CAHAP population, sex differences should also be considered. For example, one study of over 1,000 elite athletes in the United Kingdom demonstrated that while the majority of participants exhibited normal LV geometry (70% overall) in the context of dynamic, static, and mixed exercise, the type of remodeling exhibited among those with abnormal LV geometry was sex dependent. Specifically, male athletes tended to exhibit concentric remodeling or hypertrophy, while females tended to exhibit eccentric remodeling, particularly those engaged in dynamic exercise. Similar findings have been described elsewhere, with factors such as testosterone-mediated effects on cardiomyocytes and differences in peak exercise-related blood pressure likely playing a role.

Though RWT considers the relationship between the thickness of the posterior wall and LV chamber size, septal wall thickness is also of interest. Normal distribution of LV septal wall thickness has been investigated in several large series of athletes. In one study of Caucasian elite athletes (n = 947), wall thickness exceeded 12 mm in only 1.7%. Several other series corroborate that a thickness >13 mm is relatively rare in athletes. However, many of these studies were performed primarily in Caucasian male adult athletic cohorts.

It has become clear that a number of **factors must be considered when assessing the athlete with increased wall thickness**, including not only the **sport type and training regimen but demographic factors such as race, gender, and age** as well. For example, Black athletes generally develop more hypertrophy in response to exercise compared to White athletes. In one large study (n = 300), 18% of Black athletes had a septal wall thickness >12 mm, compared to only 4% of White athletes. Furthermore, in this study, 3% of Black athletes, but none of the White athletes, developed significant LV hypertrophy (LVH) (>15 mm). The mechanism behind the augmented LVH response in Black athletes, which is present across sporting disciplines, is not clear, but has been attributed to a combination of genetic, endocrine, and hemodynamic factors.

Because of **phenotypic overlap with mild hypertrophic cardiomyopathy (HCM)**, athletes with a septal wall thickness of 13 to 15 mm are often considered to be in a diagnostic "gray zone." In such cases, other echocardiographic parameters are often useful to differentiate physiologic LVH from HCM. For example, in athletes, **septal wall thickness is typically accompanied by an increase in LV size (>55 mm)**. Importantly, LV chamber size appears to remain <50 mm even in patients with HCM who participate in competitive sports. An LV size >55 mm in patients with HCM, on the other hand, is usually due to progressive myocardial fibrosis and thinning, accompanied by systolic dysfunction and heart failure symptoms. Such advanced HCM is typically not compatible with participation in competitive sports. Importantly, marked LVH is uncommon in very young athletes and should raise the suspicion for HCM, particularly if present before 16 years of age. **Furthermore, physiologic LVH is usually accompanied by normal or even supranormal parameters of diastolic function and should not be asymmetric**.

Myocardial deformation assessment using speckle-tracking echocardiography is one tool that may be a useful adjunct in differentiating HCM from EICR. Typically, strain is normal in CAHAP, while there is a reduction in strain at the site of greatest hypertrophy and fibrosis in HCM. Of note, in <10% of cases, HCM may be limited to the apical segments of the LV, which may be difficult to appreciate on echocardiography. Therefore, when the suspicion for HCM remains despite initial reassuring echocardiographic findings, contrast-enhanced echocardiography or cardiac magnetic resonance (CMR) imaging can be used. CMR is also useful to identify asymmetric areas of hypertrophy and to identify scar using late gadolinium enhancement (LGE). Furthermore, CMR (in conjunction with echocardiography) can be used to identify abnormalities of the mitral valve apparatus, which is seen in up to 75% of patients with HCM. **If the diagnosis remains uncertain despite extensive imaging workup, detraining (ie, exercise reduction or abstinence) may be used as a diagnostic tool**. Detraining may induce regression of physiologic cardiac hypertrophy, whereas HCM-induced hypertrophy typically does not regress after

stopping athletic activity. In a seminal study of six Olympic athletes, septal wall thickness was reduced from 13.8 ± 0.9 to 10.5 ± 0.5 mm following 6 to 34 weeks of voluntary training reduction. Finally, genetic testing for HCM is not a reliable method to rule out the presence of disease, but can be useful as a rule-in test, if positive (**Table 41.1**).

TABLE 41.1 Summary of Cardiac Assessment to Differentiate Cardiac Pathology From Exercise-Induced Cardiac Remodeling

Exercise-Induced Cardiac Remodeling	HCM	DCM	ARVC
12-Lead ECG			
Multiple training-induced features—see International Recommendations for ECG Interpretation in athletes	LVH with TWI extending beyond V_2 (Caucasian) or V_4 (Black) athletes ST depression	Nonspecific ECG changes such as Q waves, poor R-wave progression, ST depression, and TWI	Delayed right precordial S-wave upstroke TWI V_1-V_3 Epsilon waves
Echocardiogram			
Balanced LV and RV dilation and symmetric hypertrophy LVEDD >55 mm Normal diastolic function and strain pattern	Asymmetric wall thickening LVEDD <45 mm Abnormal diastolic function and strain pattern Dynamic outflow obstruction	Typically isolated LV dilation with reduced LVEF Abnormal diastolic function and strain	Typically isolated RV dilation with reduced RVEF associated with regional akinesia, dyskinesia, or aneurysm formation
Magnetic Resonance Imaging			
Balanced LV and RV dilation and symmetric hypertrophy No LGE	Asymmetric hypertrophy. Patchy mid-wall or RV insertion point LGE. Abnormal papillary muscle morphology	Mid- or subepicardial LGE. Dilated LV with thinned myocardium	Dilated RV with regional akinesia, dyskinesia, or aneurysm formation May see patchy LGE

Exercise-Induced Cardiac Remodeling	HCM	DCM	ARVC
	and attachment		
Exercise Stress Testing			
Normal/supranormal exercise capacity LVEF normalizes with exercise in athletes with a borderline low resting LVEF	Exercise-induced LVOT gradient. Abnormal blood pressure response Ventricular ectopy. Reduced functional capacity	Low-normal to abnormal exercise capacity Reduced myocardial recruitment LVEF typically does not completely normalize with exercise	Low-normal to abnormal exercise capacity Poor myocardial recruitment RVEF typically does not completely normalize with exercise.
Additional Workup to Consider in Challenging Cases			
–	Holter monitoring Detraining and genetic testing	–	Signal-averaged ECG Holter monitoring Endomyocardial biopsy

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; ECG, electrocardiogram; HCM, hypertrophic cardiomyopathy; LGE, late gadolinium enhancement; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; RV, right ventricular; RVEF, right ventricular ejection fraction; TWI, T-wave inversion.

B. LV dilatation. Unlike distinguishing between concentric hypertrophy and remodeling described above, the 2015 ASE guidelines do not provide definitive echocardiographic parameters in distinguishing between eccentric hypertrophy and remodeling. The *Journal of the American College of Cardiology* published a 2021 State-of-the-Art Review by Martinez et al that described eccentric remodeling as a physiologic response to dynamic exercise training and sustained increases in CO. However, elite endurance athletes may develop profound LV dilatation without a clear upper limit of normal, and therefore, an assessment of adaptive versus pathologic remodeling

should not rely on chamber size alone. In a large series of young healthy athletes (n = 1,309), representing 38 different sporting disciplines, LV end-diastolic diameter (LVEDD) ranged from 38 to 66 mm (mean 48 mm) in women and 43 to 70 mm (mean 55 mm) in men. More than 40% of male athletes had LVEDD exceeding 54 mm, and 14% had very pronounced dilation exceeding 60 mm. Furthermore, one meta-analysis reported a mean LVEDD of 55 mm (95% confidence [CI]: 54-56) and 52.4 mm (95% CI: 51.2-53.6) in endurance- and resistance-trained athletes, respectively.

It is our experience that LVEDD can be significantly larger in highly trained endurance athletes. Indeed, one study evaluating 286 Tour de France cyclists reported that LVEDD exceeded 60 mm in more than 50% of the athletes. Therefore, when considering the upper normal limit of LV chamber size is usually defined as 58 mm for men, the **diagnostic challenge in differentiating athlete's heart from pathologic changes** (ie, dilated cardiomyopathy) becomes evident. This challenge is compounded by an **occasionally observed low-normal or mildly reduced LV ejection fraction (EF) in highly trained endurance athletes**. For example, in the study mentioned above, 6% of the Tour de France cyclists had an LVEF of ≤52%. In contrast, a study of National Basketball Association players (a sport with a greater static component than cycling), an EF <50% was observed in <1% of athletes. A meta-analysis of studies comparing endurance- and resistance-trained athletes reported a normal EF in both groups, with no significant difference between the two. Mean EF was 63% (95% CI: 61-64) in the endurance-trained athletes and 66% (95% CI: 62-70) in the resistance-trained athletes. Therefore, although an EF that appears low can occasionally be seen in extreme endurance athletes, this finding is not as common as often supposed. When faced with a diagnostic dilemma in an apparently **healthy athlete with LV dilation and reduced EF**, it can be useful to perform an **exercise stress echocardiogram to demonstrate normal myocardial recruitment and supranormal exercise capacity**. Increases in EF >11% or an absolute EF >63% at peak exercise favors EICR as opposed to cardiomyopathy. In addition, the healthy endurance athlete with LV dilation will invariably have four-chamber

dilation, normal diastolic function, and eccentric hypertrophy. Abnormal diastolic function or findings isolated to the LV suggest pathology (**Table 41.1**). Endurance training tends to augment diastolic filling, which can be demonstrated by high E wave and mitral annular tissue velocities. The improved early LV relaxation and filling allows for preservation of SV during exercise at high heart rates. In fact, it has been reported that endurance exercise training can attenuate, or even reverse, the decline in diastolic function typically seen with aging.

C. **Right ventricular (RV) dilatation.** Pressure load–induced cardiac remodeling, seen in strength training, is usually limited to the LV by virtue of mitral valve shielding. However, endurance EICR affects all cardiac chambers, including the RV. The thin-walled RV typically responds to volume overload stress by dilation, without concomitant hypertrophy. However, RV response to exercise stress has been less well characterized than in the LV, and absolute thresholds to define normal ranges are less well described. In a study of 102 endurance athletes, RV chamber dilation exceeded the upper limit of normal in >50% or participants. Importantly, the RV enlargement was accompanied by LV dilation in almost all cases. Isolated RV dilation, on the other hand, is rare in athletes and should raise the suspicion for a pathologic process such as arrhythmogenic right ventricular cardiomyopathy (ARVC). Furthermore, because exercise-induced RV dilation tends to be a global process, any significant regional changes (aneurysmal or saccular dilation, or regional akinesia) warrant further investigation (**Table 41.1**).

D. **Hypertrabeculation.** LV noncompaction is a poorly defined entity that refers to prominent myocardial trabeculations with deep intertrabecular recesses typically observed throughout the LV, though RV noncompaction has been rarely described as well. Pathophysiologically, noncompaction is thought to be the result of incomplete in utero compaction of the fetal ventricular myocardium, though others have noted that the entity may instead arise from the compacted myocardial layer extending into the ventricular cavity in a trabeculated pattern (making “noncompaction” a misnomer

altogether). A subset of patients with hypertrabeculation of the LV develop noncompaction cardiomyopathy, clinically considered to be a genetic cardiomyopathy by the AHA, and which has been associated with heart failure, ventricular arrhythmias, and thromboembolic complications.

However, some patients with LV hypertrabeculation remain asymptomatic, and still others have been observed to form reversible de novo trabeculations in the context of increased cardiac preload and the absence of other cardiomyopathy manifestations. Two populations of particular interest, which have been noted to develop hypertrabeculation of the LV, are pregnant women and CAHAP. It is thought that the hypertrabeculation observed in these populations may be an adaptive response to the shared physiologic stress of increased preload, where increased LV volume itself may simply result in greater echocardiographic exposure of the trabeculations. A cross-sectional European echocardiographic study of over 1,100 competitive athletes found that 18.3% of athletes exhibited increased LV trabeculation (compared to 7.0% in controls), with all athletes remaining asymptomatic and free of adverse cardiovascular events over 4 years of follow-up. In addition, the authors of the Progression of Early Subclinical Atherosclerosis (PESA) study found that subjects in the highest quintile of vigorous physical activity (roughly 2 hours per week) exhibited twice the prevalence of LV noncompaction by conventional CMR compared to those in the lower quintiles.

These studies and others highlight the risk of overdiagnosis of LV noncompaction cardiomyopathy in CAHAP with physiologic hypertrabeculation of the LV. Unfortunately, echocardiography is frequently inconclusive, and therefore, CMR is often employed as an adjunctive imaging modality. A noncompacted-to-compacted myocardium ratio of >2.3 in end diastole has been suggested as a diagnostic CMR cutoff for LV noncompaction, though it is worth noting this threshold was derived from a study comparing images of only seven patients with noncompaction cardiomyopathy to 170 volunteers who were either healthy or had varying alternative pathologies, including hypertensive heart disease, HCM, dilated cardiomyopathy, and aortic stenosis. CMR may also identify LGE

suggestive of myocardial fibrosis or scar, which can be seen in true LV noncompaction cardiomyopathy and may have significant prognostic value. However, the significance of LGE in the CAHAP population presents a persistent diagnostic challenge. The prevalence of LGE on CMR in this population is as high as 30% and is typically found at the RV insertion points to the anterior and posterior interventricular septum. This enhancement is thought to represent physiologic fibrosis formation in response to repetitive dynamic and static load rather than true scar. Therefore, LGE isolated to the RV insertion points in CAHAP in general is likely to be benign and carries no prognostic significance, while a more diffuse pattern or clinical features concerning for underlying cardiomyopathy should raise suspicion for true pathology. Similarly, physiologic hypertrabeculation is typically found in asymptomatic individuals and is associated with preserved systolic function and normal or supranormal diastolic function. Clinical signs or symptoms of heart failure, a personal or family history of malignant ventricular arrhythmias or SCD, or unexplained systemic thromboembolism may all point to underlying LV noncompaction cardiomyopathy.

E. **The aorta. Volume and pressure loads during dynamic and static exercise, respectively, place a significant hemodynamic stress on the aorta**. As a result, CAHAP may exhibit some degree of aortic dilatation in response to both static and dynamic exercise. A meta-analysis showed that the aortic root diameter measured at the sinus of Valsalva and the aortic valve annulus was 3.2 and 1.6 mm greater in athletes (n = 5,580) compared to matched nonathletic controls (n = 727). However, as these data would suggest, the expected increase in aortic dimensions in the CAHAP population is generally considered mild and frequently clinically insignificant. Aortic root dilatation in young CAHAP rarely exceeds 4.0 cm in men and 3.4 cm in women. **Marked aortic root dilation (>4 cm) is unusual in athletes and should be considered pathologic warranting further investigation until proven otherwise**.

Aortic emergencies such as dissection and rupture are rare but potentially preventable contributors to SCD in the CAHAP

population. A thorough history and physical examination remain the most powerful screening tools in this regard. A personal or family history of bicuspid aortic valve (BAV) or genetic aortopathies (Marfan syndrome, Loeys-Dietz syndrome, Ehler-Danlos syndrome, or other familial thoracic aortic aneurysm/dissection) should prompt a transthoracic echocardiogram (TTE). For Marfan syndrome in particular, the Marfan syndrome Systemic Score is a useful tool that can be completed with patients to raise or lower suspicion and guide further testing. In patients found to have aortic root or ascending aortic aneurysms along with risk factors for heritable thoracic aortic disease, the 2022 ACC/AHA Guidelines for the Diagnosis and Management of Aortic Disease recommend genetic testing to identify pathogenic variants. If a pathogenic variant is identified, genetic counseling and testing of at-risk biologic relatives is also recommended, along with TTE screening if a pathologic variant is identified. The 2015 Eligibility and Disqualification Recommendations for Competitive Athletes with Cardiovascular Diseases provide guidelines for determining the safety of athletic participation in patients identified to have aortic pathology, including in cases of Marfan syndrome and BAV.

Another subpopulation of CAHAP of increasing research interest is “masters” athletes, defined as men and women beyond the fourth decade of life who perform routine exercise with competitive athletic goals. In general, SCD due to aortic emergencies is exceedingly rare in the young CAHAP, but whether aortic adaptations persist, worsen, or regress over time, and whether these changes become more clinically relevant as patients age, remains unclear. A cross-sectional study of 442 male and female masters-level endurance athletes (rowers and runners) aged 50 to 75 years found the prevalence of aortic root dilatation greater than 4.0 cm as measured by TTE to be 21%, with 88% of these being male. Given this prevalence is much higher than expected when compared to age- and sex-matched controls, the question has arisen whether long-term exercise itself may be responsible for such vascular remodeling. Furthermore, whether this remodeling is physiologic (akin to eccentric remodeling of the LV in the face of chronic dynamic stress) or pathologic, as

would be suggested in the younger CAHAP, is unclear. Future studies should investigate whether these aortic changes translate to adverse clinical outcomes, though admittedly this will be a significant challenge, given the need to control for multiple possibly confounding comorbidities known to contribute to aortic pathology such as patient age.

Finally, the sports cardiologist may encounter patients who have either (1) been found to have aortic dilatation not meeting surgical criteria and managed expectantly or (2) undergone aortic surgery and wish to return to their previous level of competition and/or exercise. Counseling in this population requires a thorough understanding of the underlying aortic pathology, the type and level of exercise pursued, the presence or absence of expected physical contact, and, if applicable, the surgical repair and results achieved. CAHAP who have been found to have mild aortic root dilatation (eg, 4.0-4.1 cm in tall men, 3.5-3.7 cm in tall women, or Z-scores 2-2.5) and do not exhibit BAV or features of potential heritable aortopathies, participation in all competitive athletics may be considered in the event no genetic aortopathy is subsequently identified. However, these patients may be counseled to avoid "intense" weight training tailored specifically to each athlete's goals and baseline capabilities. In patients who have undergone surgical correction of the aortic root or ascending aorta for aneurysm or dissection, and who have no residual aortic dilatation or dissection, it is reasonable for patients to participate in low static, low dynamic sports that do not include potential for body collision (eg, golf, bowling, cricket). However, in patients with residual aneurysm and/or chronic dissection, participation in any competitive sports should be avoided.

F. Exercise and cardiopulmonary testing. Given the many potential anatomic and physiologic adaptations in the CAHAP population described above, a final point to consider is how EICR may impact the utility, protocols, and results of select exercise testing. In general, two types of exercise testing are typically pursued: exercise stress testing (EST) with and without imaging, and cardiopulmonary exercise testing (CPET). With regard to the former, EST in the

general population serves as a noninvasive assessment for ischemic heart disease and exercise capacity while also providing data useful in cardiac risk stratification and prognostication. Certainly, EST serves a similar role in the management of CAHAP, particularly in those who are symptomatic, but also to monitor the hemodynamic response to exercise, determine the mechanism(s) underlying impaired athletic performance, and inform exercise training regimens. In CAHAP known to have underlying cardiac pathology, EST may also assess for the provocation of symptoms, hemodynamic changes, and/or arrhythmias at various performance levels. These results may play a critical role in informing risks/benefits conversations as they relate to counseling for athletic participation and/or return to play.

Similar to EST, a CPET in CAHAP is often performed either to unmask cardiovascular and/or pulmonary symptoms at maximal stress or to provide objective performance data to aid in training regimen optimization. Unlike EST, however, CPET is able to provide more discrete measurements of maximal oxygen consumption (VO_2 max) and ventilatory threshold, two key determinants of human exercise performance. CAHAP generally has a much larger CO due to increased SV in the context of EICR, which is manifested as a greater VO_2 max. When interpreting the CPET performed in an athlete, the interpreter needs to take into consideration certain physiologic principles that would be considered normal in a CAHAP population but potentially abnormal in the general population (eg, peak VO_2, ventilatory threshold, chronotropic index, oxygen pulse, SpO_2, breathing reserve, and respiratory rate).

A final consideration with regard to both EST and CPET being used in the care of CAHAP is careful attention to stress method and examination protocols. With regard to treadmill stress protocols, the well-described Bruce protocol is often avoided as many CAHAP are able to withstand longer durations of stress and ultimately become limited by calf fatigue with increasing gradation rather than true cardiopulmonary exhaustion. Alternative protocols starting at higher treadmill speeds with more gradual gradient changes such as the Astrand and Costill/Fox protocols are, therefore, more frequently

employed in CAHAP treadmill stress testing. Cycle ergometer testing may be pursued rather than treadmill testing, particularly in CPET studies, owing to reduced electrocardiogram (ECG) artifact, direct measurement of power output, and easier blood pressure measurement. Though cycle ergometer testing yields a V_{O_2} max 8% to 12% less than treadmill testing, it carries the benefit of ramp testing, during which work rate increases linearly across the test duration, allowing for a more precise quantification of exercise capacity as opposed to data obtained during arbitrarily chosen exercise intervals. Though treadmill and cycle stress testing are most commonly employed, testing in certain CAHAP may require a more unique approach. For example, burst/sprint tests, agility tests, and rowing tests have all been pursued in various circumstances. Ultimately, the stress type and intensity pursued will depend on a multitude of factors, including the goals of the test itself, peak workload of the athlete, and logistical capabilities of the stress laboratory.

III. ELECTROPHYSIOLOGIC CARDIAC ADAPTATIONS TO REPETITIVE EXERCISE.

EICR not only affects cardiac structure and mechanical function but can also induce profound cardiac electrophysiologic changes. As a result, an athlete's ECG has the potential to raise alarm for an underlying cardiomyopathy, and false-positive findings have remained one of the major arguments against including the 12-lead ECG as part of the initial preparticipation screening of athletes in the United States. To better identify athletes who need further evaluation and to avoid false-positive test results, several ECG criteria have been proposed. The **Seattle Criteria**, published in 2012, reduced the false-positive rate from as high as 40% in criteria used in the early 2000s, to ~10%. The **International Criteria for ECG** Interpretation in Athletes published in 2017 further reduced the false-positive rate without affecting sensitivity, mainly by no longer categorizing isolated left atrial and right atrial enlargement, RV hypertrophy (RVH), and left- and right-axis deviation as abnormal based on data showing that such ECG findings have a very low diagnostic yield in athletes. Normal and abnormal ECG findings in athletes according to the international criteria are shown in **Figure 41.2**. An

additional category of "borderline" changes is now used; features seen in isolation are considered benign, but if there is more than one borderline feature, further evaluation is recommended.

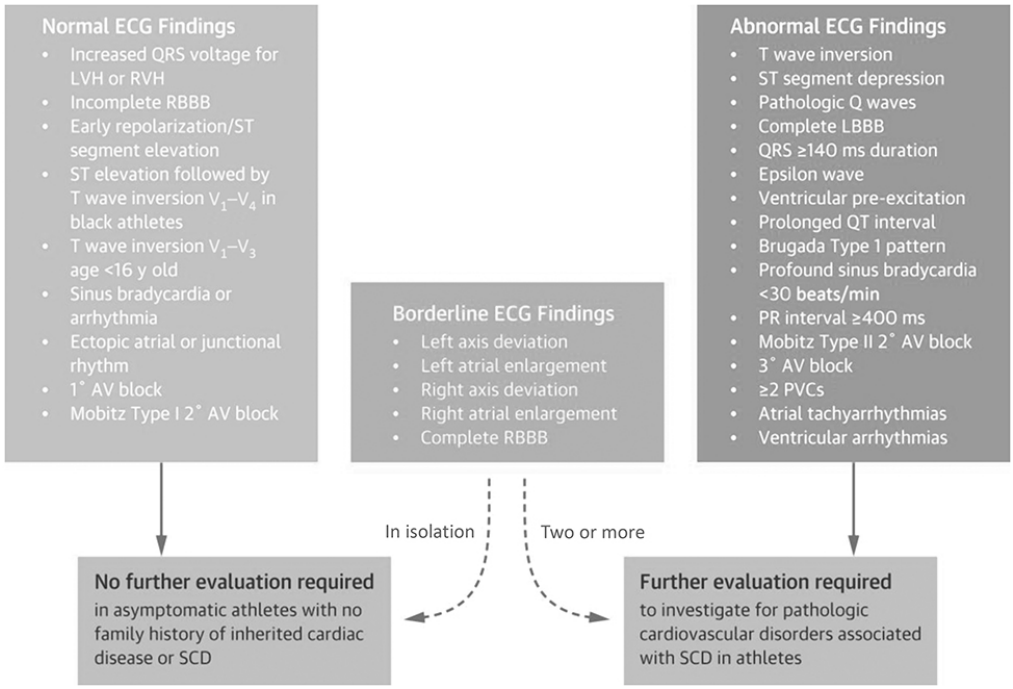

FIGURE 41.2 The international criteria for ECG interpretation in athletes. AV, atrioventricular; ECG, electrocardiogram; LBBB, left bundle branch block; LVH, left ventricular hypertrophy; PVC, premature ventricular complex; RBBB, right bundle branch block; RVH, right ventricular hypertrophy; SCD, sudden cardiac death. (Reprinted from Sharma S, Drezner JA, Baggish A, et al. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol*. 2017;69(8):1057-1075. Copyright © 2017 Elsevier. With permission.)

A. Cardiac rate, rhythm, and conduction changes in athletes.

Extensive exercise may result in profound resting sinus bradycardia (occasionally as low as 30 beats/min), sinus arrhythmia, ectopic atrial and junctional rhythms, first-degree atrioventricular (AV) block, and second-degree Mobitz type I AV block. These changes are attributed mainly to a shift in autonomic balance, with repetitive exercise resulting in a heightened parasympathetic (vagal) tone and concomitant sympathetic withdrawal. When physiologic, these

changes disappear with exercise (a state of heightened sympathetic tone and vagal withdrawal). In the absence of symptoms, such changes are considered normal in athletes. In contrast, second-degree Mobitz type II AV block and third-degree AV block are extremely rare in athletes and are more suggestive of cardiac conduction disease.

Incomplete right bundle branch block (iRBBB) is seen in up to one-third of athletes and has been attributed to RV remodeling and dilation, which results in an increase in cardiac conduction time and is considered a normal variant. Complete RBBB, although seen in only 1% of athletes, is now considered to be a borderline ECG finding according to international recommendations, and when found in isolation, no further evaluation is recommended. Conversely, complete left bundle branch block (LBBB) is not an athletic adaptation and should trigger further evaluation.

Though ventricular arrhythmias have been observed in CAHAP, they remain relatively rare. In one study, 355 competitive athletes with frequent premature ventricular complexes (PVCs) on screening ECG and/or a history of palpitations were further evaluated using 24-hour Holter monitoring. Athletes were subsequently divided into three groups based on the total number of PVCs and/or presence of non-sustained ventricular tachycardia (NSVT): group A (n = 71; >2,000 PVCs/24 hour and/or ≥1 episode of NSVT/24 hour), group B (n = 153, ≥100 to <2,000 PVCs and no NSVT), and group C (<100 PVCs and no NSVT). Overall, 93% of athletes had no significant cardiac abnormalities after extensive further cardiac testing, including TTE, CMR, and exercise ECG. In 7% (n = 26) of athletes, a cardiac abnormality was identified (mitral valve prolapse with mild mitral regurgitation in 11, ARVC in 7, myocarditis in 4, and dilated cardiomyopathy in 4). The prevalence of cardiac abnormalities was 30%, 3%, and 0% in groups A through C, respectively, suggesting that the presence of >2,000 PVCs/24 hour and/or NSVT in CAHAP should trigger further evaluation, as up to 30% of patients will have true underlying pathology.

Perhaps more useful than absolute PVC burden is PVC morphology. Right or left ventricular outflow tract (RVOT/LVOT)

PVCs, as well as fascicular PVCs, are almost always benign in an otherwise structurally normal heart. Outflow tract PVCs typically have an LBBB morphology with an inferior frontal axis, while fascicular PVCs typically exhibit a relatively narrow RBBB morphology (<130 ms) and either a superior axis (if arising from the left posterior fascicle) or inferior axis (if arising from the left anterior fascicle). While these PVC morphologies are typically benign, PVCs with an LBBB pattern and superior axis should prompt investigation for ARVC or sarcoidosis as these likely arise from the RV free wall or moderator band (**Figure 41.3**). In addition, PVCs with an RBBB morphology and wide QRS (>130 ms) may suggest an underlying LV cardiomyopathy. Finally, polymorphic PVCs and/or short-coupled PVCs (ie, PVCs with a coupling interval of <300 ms) are associated with malignant ventricular arrhythmias and warrant further investigation. The initial imaging modality of choice is typically exercise stress echocardiogram, not only to evaluate for underlying structural heart disease but also to determine whether PVCs dissipate or worsen with exercise. Benign PVCs typically disappear with exertion but may return in recovery, unlike complex and, possibly, malignant PVCs, which tend to worsen with exertion. If stress echocardiogram findings are abnormal, CMR is often pursued for greater diagnostic clarity.

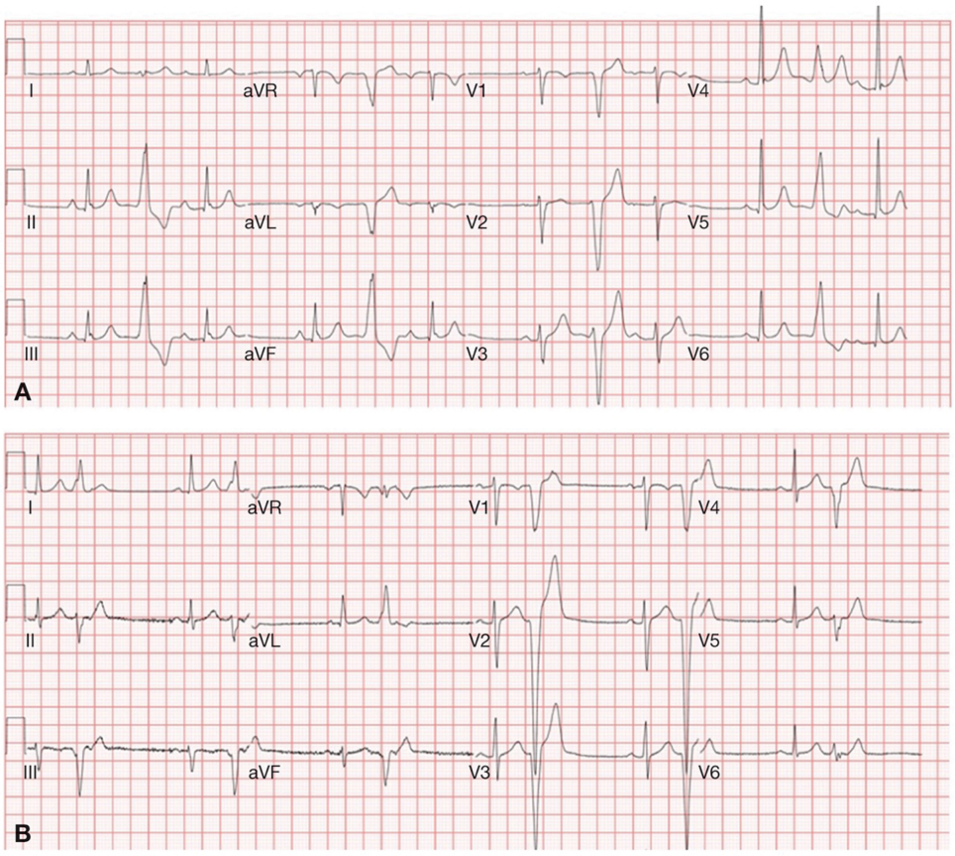

FIGURE 41.3 Interpretation of PVC morphology. **A.** Typical RVOT PVCs in a distance runner, with an LBBB pattern, precordial transition by V_4, and inferior axis. **B.** Right ventricular apical PVCs in a patient with early ARVC. PVC morphology is LBBB with a very late transition and superior axis; ARVC, arrhythmogenic right ventricular cardiomyopathy; LBBB, left bundle branch block; PVC, premature ventricular contraction; RVOT, right ventricular outflow tract. (Reprinted from Darden D, Prutkin JM. Premature ventricular contractions in athletes: insight into evaluation and management. *J Am Coll Cardiol*. 2022; Expert Analysis. Copyright © 2022 Elsevier. With permission.)

B. Voltage criteria for ventricular hypertrophy. Voltage criteria for LVH are common in athletes and present in up to 70% of male athletes. It is particularly common in adolescent athletes (attributed to the thinner chest wall) and Black athletes (attributed to more pronounced underlying ventricular hypertrophy). Increased QRS voltage criteria, when present in isolation, do not warrant further investigation. However, in the presence of pathologic Q waves, ST depression, T-wave inversion (TWI), or symptoms, LVH on ECG

warrants further investigation with an echocardiogram or other testing modalities as clinically indicated, primarily to rule out HCM.

C. **Repolarization changes.** Exercise-induced changes in autonomic tone and/or electrical remodeling may also produce repolarization changes in athletes, including the early repolarization pattern (ERP) and TWI. ERP is present in up to 90% of athletes and is considered a normal variant in asymptomatic athletes. Interestingly, ERP may develop before, and independent of, LVH. Unlike ERP, TWI is one of the more challenging ECG changes to interpret in athletes, as they may be physiologic, or suggestive of an underlying cardiomyopathy such as ARVC or HCM. **Two important components in differentiating between physiologic and pathologic TWI are (1) TWI localization on the surface ECG and (2) understanding the variance in both TWI prevalence and morphology across age, gender, and race**. With regard to the former, TWI is considered to be physiologic in leads aVR, III, and V_1, recognizing that normal variants based on race and age also exist, as described below. Conversely, lateral TWI in leads I, aVL, V_5, and/or V_6, or inferolateral TWI in the aforementioned leads as well as II and aVF, should always prompt further investigation for a potential underlying cardiomyopathy. This is primarily due to the fact that lateral or inferolateral TWI may suggest RV dilatation rather than displacement. TWI isolated to the inferior leads (II, aVF) is of uncertain clinical significance in CAHAP but can be associated with underlying cardiomyopathy and/or valvular disease, namely, mitral valve prolapse. Thus, it may be reasonable to maintain a relatively low threshold for further investigation in these patients.

Demographic factors should also be considered when evaluating TWI, namely, race and age. For example, TWI is present in approximately 5% of White CAHAP and in up to 25% of Black CAHAP. Furthermore, in Black CAHAP, TWI commonly extends to leads V_2 to V_4 and is preceded by domed ST segments, without any evidence of underlying pathology. In contrast, patients with ARVC often exhibit an isoelectric ST segment preceding precordial TWI. **Overall, TWI should be considered abnormal if extending beyond**

V2 in White CAHAP, beyond V4 in Black CAHAP, or if it is accompanied by Q waves or ST depression.

Beyond race, age is another recognized demographic factor that may impact the presence of TWI. Specifically, anterior TWI in leads V_1 to V_3 in prepubertal children and adolescents is considered benign and is referred to as a juvenile pattern. However, a subset of CAHAP may exhibit a persistence of anterior TWI beyond puberty. This "persistent juvenile pattern" is not well-defined, particularly among CAHAP, and there is no definitive age-specific cutoff at which the juvenile pattern normalizes. In general, however, it is quite rare for the pattern to persist beyond 16 years of age. For example, in a study of 1,000 young athletes (<18 years old) compared to 300 nonathlete controls, no subject older than age 16 exhibited TWIs in leads V_2 and V_3.

A final feature of benign TWI to consider is their normalization with exercise. In one study, T waves normalized with submaximal exercise in healthy athletes, and this may offer another diagnostic tool beyond echocardiography and CMR. As a last resort, detraining can be used because TWI typically normalizes in athletes after 6 weeks of exercise restriction. In one study, pathologic TWI was associated with cardiac disease in 44.5% of athletes when extensive investigation was performed using echocardiography, CMR, exercise testing, and 24-hour Holter monitoring. Echocardiography only identified about half of these abnormal cases, which has led many experts, including the authors of the International Recommendations for ECG Interpretation in Athletes, to advocate for more extensive investigations in these athletes, especially CMR (**Figure 41.4**). However, it is unclear how broadly applicable these data are, and further race-, body habitus-, and sport-specific studies are needed.

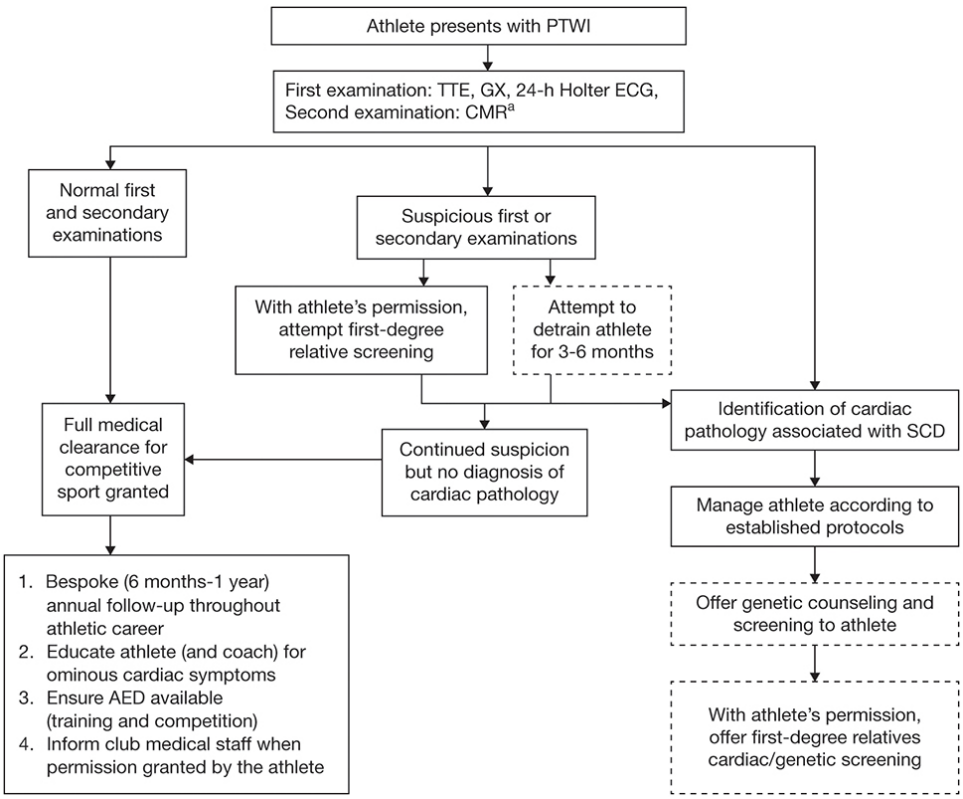

FIGURE 41.4 Algorithm for evaluation of CAHAP presenting with TWI. [a]Note that CMR is routinely recommended even with normal echocardiography. Dotted lines mean that the evaluation can be proposed to CAHAP. 24-Hour Holter ECG indicates 24-hour Holter ECG recording including intensive training session. AED, automatic external defibrillator; ECG, electrocardiogram; GX, maximal exercise test; PTWI, pathologic T-wave inversion; SCD, sudden cardiac death; TTE, transthoracic echocardiography. (Adapted from Schnell F, Riding N, O'Hanlon R, et al. Recognition and significance of pathological T-wave inversions in athletes. *Circulation*. 2015;131(2):165-173. Copyright © 2015 Circulation. With permission.)

D. The QT interval. Athletes have slightly longer QT intervals compared to nonathletes, which has been primarily attributed to physiologic LVH. It has been reported that 6% of athletes have a corrected QTc exceeding the upper limit of normal (470 in men and 480 in women). However, it should be kept in mind that a prolonged QTc in isolation (ie, in the absence of other long QT syndrome criteria) only has a positive predictive value of 7%. Further evaluation is, therefore, essential, and the diagnosis should not be made solely based on the ECG. Of note, QT intervals are notoriously

difficult to measure in athletes because of the common presence of sinus arrhythmia and U waves. In sinus arrhythmia, an average QTc based on several beats should be used, and care must be taken to exclude the U wave. The shape of the T wave should also be carefully investigated for notched or bifid morphologies, as they may be suggestive of a true ion channel disorder.

IV. EXERCISE AT THE EXTREME. It is undisputed that habitual moderate and vigorous exercise promotes health. Paradoxically, for individuals with unrecognized cardiac disease, there is an increased risk of an adverse cardiac event during strenuous exercise. Recognizing this causal relationship, preparticipation screening and eligibility/disqualification guidelines have been implemented in many parts of the world to reduce this risk. A more recent concern is whether, at the extremes of exercise, the cardiovascular benefits of exercise are offset by adverse effects on the cardiac structure and function of otherwise normal hearts. Some have suggested that the benefits of exercise exhibit an inverted J-shaped relationship to overall health, even in individuals without underlying cardiac disease. Proposed mechanisms are that repeated high-intensity exercise, without sufficient recovery time, results in inflammation, myocardial injury, and accelerated atherosclerosis, ultimately leading to fibrosis and adverse cardiac remodeling. Two important potential sequelae to consider are atrial fibrillation (AF) and coronary artery calcification (CAC).

Several studies have shown that sinoatrial node disease, advanced heart block, and AF are more common in veteran athletes than in their sedentary peers. A meta-analysis of six case-control studies comparing 655 competitive athletes to 895 controls in total demonstrated a significantly increased AF prevalence among athletes (23%) compared to controls (12.5%). In addition, a large cohort study of more than 50,000 competitive male skiers found the highest predictors of the development of AF to be an increasing number of completed races and faster race times. These findings and others have suggested that while lower levels of exercise seem to be protective against AF, there may be a threshold at which increasing exercise level begins to pose a risk. It is also worth noting that this link between extreme exercise and AF

development seems to be unique to male CAHAP. A meta-analysis of over 650,000 subjects demonstrated that while intense exercise increased AF risk in men, the opposite was true in women, with intense exercise seemingly having a protective effect. The pathophysiologic link between intense exercise and AF development is unclear but may be related to progressive left atrial dilatation and fibrosis. In general, a rhythm control strategy is generally preferred in CAHAP to minimize symptom burden, recognizing that the use of antiarrhythmic drugs should be in compliance with the patient's athletic governing body when applicable. Approach to thromboembolic risk reduction is highly individualized and often dependent in part on the patient's training regimen and bleeding risk.

A second interesting and somewhat controversial concern of extreme exercise is the potential increased burden of CAC in this population. One study of middle-aged male CAHAP stratified participants into three exercise levels based on metabolic equivalent of task (MET)-minutes per week (<1,000, 1,000-2,000, and >2,000) and found that the >2,000 MET-minutes/week group had a significantly higher prevalence of CAC (68%) and median CAC score (9.4) compared to the least active group (43% and 0, respectively). Another study of over 150 competitive cyclists and runners found that a CAC score >70th percentile was associated with the number of years of exercise training. **However, though these studies and others have suggested extreme exercise may convey elevated CAC risk independent of typical mediators, the clinical significance of these findings is uncertain**. For example, in the study of exercise-level groups, participants in the most active group were most likely to have calcified rather than mixed plaque, possibly suggesting greater plaque stability. Further research is necessary to elucidate whether and to what degree the observed increases in CAC convey an increased risk for adverse cardiovascular outcomes.

There has been an increasingly reported finding of troponin elevation following endurance exercise. One of the larger studies investigating postexercise troponin release was the North Sea Race Endurance Exercise (NEEDED) study, which evaluated 177 recreational athletes completing a mountain bike race. Both troponin I and troponin T levels were elevated in all participants, with a hazard ratio (HR) >150 bpm identified as a significant predictor of troponin elevation at both 3 and 24

hours after exercise. Previously, the intensity of exercise was felt to be a greater contributor to postexercise troponin elevation in CAHAP than duration, but NEEDED seemed to confirm that perhaps duration above a particular intensity threshold plays a significant role. Clinically, this troponin elevation becomes relevant in attempting to distinguish between exercise-related "troponinemia" and a true acute coronary syndrome. In general, however, benign exercise-induced troponin elevations seem to typically have very low peak concentrations that normalize within 24 hours. Similar to CAC, additional research is needed to delineate the mechanism of exercise-related troponin release and its clinical significance.

Finally, despite the discussions and controversies surrounding AF, CAC, and troponin elevation in CAHAP, it should be noted that the literature is currently composed primarily of small, cross-sectional studies evaluating only subsets of lifelong extreme endurance athletes. It should be emphasized that the risk of adverse cardiovascular events is significantly higher in those who lead a sedentary lifestyle compared to individuals who regularly participate in any level of exercise. Further, longitudinal studies of elite athletes including Olympians, Tour De France cyclists, and cross-country skiers have reported an increase in their life expectancy compared to the general population. Overall, the remarkable benefits of regular exercise are well described and should be promoted for most individuals to improve cardiovascular health.

V. ELIGIBILITY AND DISQUALIFICATION FOR ATHLETES WITH CARDIAC DISEASE.

Eligibility and disqualification recommendations for athletes with cardiac abnormalities have been published by the ACC, the AHA, and the European Society of Cardiology. These guidelines are extensive, and a complete overview of this topic is beyond the scope of this chapter; however, it is important to recognize that many of the recommendations are based on the assumption that exercise is a modifiable risk factor for SCD. For most cardiac conditions, this assumption is largely unproven and based on expert opinion. As newer data have emerged, such recommendations have been modified. For example, athletes with implantable cardioverter-defibrillators (ICDs) were previously restricted from all competitive sports with the exception of IA (low static, low

dynamic) sports; however, current guidelines suggest they may now participate in higher static and dynamic component sports after appropriate counseling if free from appropriate device therapies for a period of 3 months. This modification was based on the results of a registry of such athletes who continued to compete against medical advice and demonstrated no increased risk of SCD. Similarly, athletes with long QT syndrome were previously disqualified from most competitive sporting activities until objective data demonstrated a low risk of cardiac events in those who are asymptomatic and are taking appropriate treatment while being managed by experts. Conversely, continued participation in competitive sports has been shown to accelerate progression of certain diseases, such as ARVC, along with increasing the risk of ventricular arrhythmias. Therefore, significant exercise restrictions should be recommended in athletes with ARVC.

It is clear that these return-to-play decisions are nuanced and that many sports cardiologists advocate transitioning away from a strict paternalistic framework for decision-making regarding eligibility to compete for athletes with cardiac disorders in favor of a shared decision-making model. This model incorporates appropriate counseling of the patient and other relevant stakeholders (such as family and team) regarding the risks, benefits, and uncertainties of continued exercise in the context of the underlying cardiac disorders and encourages participation of all parties in reconciling this information with their personal preferences and beliefs. Practically, “five pillars” of shared decision-making have been proposed to guide a successful discussion between sports cardiologists and their patients: knowledge, humility, respect, teamwork, and communication. As described above, knowledge refers to the detailed understanding of expected and unexpected cardiovascular adaptations to exercise required to ultimately discern physiologic from the pathologic. However, the sports cardiologist must also have a knowledge of the patient’s athletic and training goals, the participation requirements of the relevant governing body of the sport in question, and the potential implications of exercise restriction. Because potential underlying pathologies affecting CAHAP span across essentially all cardiac subspecialties, the sports cardiologist should recognize clinical scenarios in which a second opinion or evaluation by

colleagues in a separate subspecialty is warranted. Humility, therefore, may broaden and enhance a patient's evaluation, while also respecting the many diagnostic dilemmas presented in this chapter. Given the time and effort devoted to a patient's training and craft, respect for the patient's goals and priorities is essential in establishing a therapeutic relationship. A thoughtful shared decision-making discussion should also be a team-based approach involving a variety of perspectives from family, coaches, trainers, and the team medical staff. Finally, the sports cardiologist should clearly communicate the risks and benefits of participation and restriction to the patient, and document the outcomes of these conversations as they arise. Adherence to these five pillars may enhance the care for this challenging population and establish a meaningful therapeutic relationship between sports cardiologists and their patients.

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CHAPTER 42

Cardio-Oncology

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I. INTRODUCTION

A. The prevalence of cancer therapy–related disease has increased over the past century due to improved cancer therapies leading to a steady rise in the number of cancer survivors. In parallel, the lengthened survival of patients with cardiovascular disease (CVD) into old age has likewise resulted in malignancy being an ever more frequent comorbidity in this patient population. As an example, more women diagnosed with breast cancer above the age of 65 years die from cardiovascular causes than from breast cancer itself. The coexistence of cancer and CVD is accrued by the presence of shared risk factors for both types of conditions, such as smoking, obesity, hyperlipidemia, sedentary lifestyle, inflammation, and somatic and inherited mutations affecting insulin sensitivity. With a growing number of available agents for cancer treatment over the past decades, ranging from classic cytotoxic chemotherapies to targeted agents and more recently immunotherapy, cardiovascular effects of cancer therapy are increasingly recognized and the diagnosis and management of the effects of cancer and its therapies on the cardiovascular system have become a necessary skill to be a practicing cardiologist.

Cancer therapy–related cardiac dysfunction (CTRCD) can present in a wide range of clinical presentations including acute forms such as pericarditis and tamponade, myocarditis, tachyarrhythmias, heart block, and even cardiac arrest. Chronic presentations tend to involve myocardial damage with decreased ventricular function, reduced left ventricle ejection fraction (LVEF), heart failure (HF) syndrome, arrhythmias, and coronary artery disease (CAD). In addition, vascular toxicities are a frequent complication of cancer therapies due to the already prothrombotic state of cancer added to the toxic effects of many cancer therapies on platelets and the endothelium. Vascular events represent the second most common cause of death in patients with cancer undergoing outpatient therapies. These include venous and arterial thrombosis, acute arterial vasospasm, accelerated atherosclerosis, systemic and pulmonary hypertension, and arteritis.

Initial associations between anthracyclines and myocyte injury leading to dilated cardiomyopathy and LV dysfunction were first reported by Von Hoff in

the 1970s in a seminal paper that paved the way for research in the growing field of cardio-oncology. The later use of trastuzumab, a monoclonal antibody against the human epidermal growth factor-2 (HER2) receptor overexpressed primarily in breast cancer, led to the understanding of different and perhaps indirect mechanisms of cardiac damage from targeted cancer therapies. Many such new targeted therapies have since been linked with adverse cardiovascular toxicity, such as other targeted monoclonal antibodies, tyrosine kinase inhibitors (TKIs), proteasome inhibitors, endothelial growth factor receptor (EGFR) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, mTOR inhibitors, BCR-BAL inhibitors, and other multitarget kinase inhibitors. More recently, the development of immunotherapy with novel immune checkpoint inhibitors (ICIs) anti–programmed cell death-1 (anti-PDL1) and anti–cytotoxic T lymphocyte-4 (anti-CTL4) antibodies, as well as the development of chimeric antigen receptor (CAR) T-cell therapy against CD-19 for lymphomas, have brought to light another range of cardiovascular toxicity from these agents, including myocarditis from the former or cytokine release syndrome (CRS) from the latter. In similar manner, the growing role of radiation oncology in cancer treatment has led to the understanding of radiation-induced heart disease after initial reports of increased CVD in survivors of radiation therapy (RTX) used for Hodgkin lymphoma and breast cancer. High doses of radiation have been linked to a vast array of late-developing cardiovascular toxicity that includes pericardial, valvular, myocardial, coronary, and conduction system disease. This chapter outlines the classification and mechanisms of cancer therapy–related cardiotoxicity, reviews the clinical presentation of multiple cancer agents causing cardiovascular toxicity, and provides strategies for the diagnosis and management of cancer-related cardiac disease.

B. Terminology

1. Several definitions for CTRCD have been proposed, which poses an issue when reporting and recognizing adverse cardiovascular events. For this purpose, the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) were developed to standardize reporting of adverse reactions in oncology clinical trials. Classically, chemotherapy-related cardiac dysfunction is defined as a decrease in the LVEF by echocardiography of greater than 10 percentage points, to a value <53% (normal reference value for 2DE). This decrease should usually be confirmed by repeated echocardiography. LVEF decrease may be further categorized as **symptomatic** or **asymptomatic** depending on clinical repercussions. Function recovery after diagnosis of LV dysfunction can be **reversible** if it returns to within 5 percentage points of baseline; **partially reversible** if improved by at least 10 percentage points but remaining more

than 5 percentage points below baseline; **irreversible** if remaining within 10 percentage points of the nadir; or **indeterminate** if the patient is not available for reevaluation. More recently, the International Cardio-Oncology Society 2021 Consensus Statement provided a holistic definition for multiple cardiovascular toxicities:

a. **Cardiac dysfunction** or structural injury associated with cancer therapy, which can remain asymptomatic or present as clinical HF, each defined ranging from mild to severe (**Table 42.1**). In many studies, cardiac dysfunction related to cancer therapies has been defined as LVEF <50% or an LVEF reduction >10% from baseline.

b. **Myocarditis.** Toxicity or immune-mediated inflammation of the myocardium, associated with various cancer therapies, especially ICIs, defined by major and minor diagnostic criteria (**Table 42.2**)

TABLE 42.1 International Cardio-Oncology Society Consensus Statement Definition and Classification of Cancer Therapy–Related Cardiac Dysfunction (CTRCD)

	Mild	Moderate	Severe	Very Severe
Asymptomatic CTRCD (with or without additional biomarkers, LVEF values are based on 2D echo)	LVEF >50% AND new relative decline in GLS by >15% from baseline AND/OR new rise in cardiac biomarkers	New LVEF reduction by >10 percentage points to an LVEF of 40%-49% New LVEF reduction by 15% from baseline AND/OR new rise in cardiac biomarkers	New LVEF reduction to <40%	
Symptomatic CTRCD (with LVEF and supportive cardiac biomarkers)	Mild HF symptoms, no intensification of therapy required	Need for outpatient intensification of diuretic and HF therapy	HF hospitalization	Requiring inotropic support, mechanical circulatory support, or consideration for transplantation

CTRCD, cancer therapy–related cardiac dysfunction; GLS, global longitudinal strain; HF, heart failure; LVEF, left ventricle ejection fraction.

TABLE 42.2 Definitions for Immune Checkpoint Inhibitor–Associated Myocarditis According to the 2021 Cardio-Oncology Society Consensus Statement

Either Pathohistologic Diagnosis

Multifocal inflammatory cell infiltrates with overt cardiomyocyte loss by light microscopy of cardiac tissue samples

Or Clinical Diagnosis

A troponin elevation[a] (new, or significant change from baseline) with 1 major criterion or a troponin elevation (new, or significant change from baseline) with 2 minor criteria after exclusion of acute coronary syndrome or acute infectious myocarditis based on clinical suspicion

Major Criterion

CMR diagnostic for acute myocarditis (modified Lake Louise criteria)

Minor Criteria

- Clinical syndrome (including any one of the following: fatigue, muscle weakness, myalgias, chest pain, diplopia, ptosis, shortness of breath, orthopnea, lower extremity edema, palpitations, lightheadedness/dizziness, syncope, cardiogenic shock)
- Ventricular arrhythmia and/or new conduction system disease
- Decline in cardiac (systolic) function, with or WMA in a non-Takotsubo pattern
- Other immune-related adverse events, particularly myositis, myopathy, myasthenia gravis
- Suggestive CMR (meeting some but not all the modified Lake Louise criteria)

Modifiers: Severity of Myocarditis

Severe	Hemodynamic instability, heart failure requiring noninvasive or invasive ventilation, complete or high-grade heart block, and/or significant ventricular arrhythmia
Nonsevere (clinically significant)	Symptomatic but hemodynamically and electrically stable, may have reduced LVEF, no features of severe disease
Smoldering (subclinical)	Incidentally diagnosed myocarditis without any clinical signs or symptoms
Steroid refractory	Nonresolving or worsening myocarditis (clinical worsening or persistent troponin elevation after exclusion of other etiologies) despite high-dose methylprednisolone

Recovery from Myocarditis

Complete recovery	Patients with complete resolution of acute symptoms, normalization of biomarkers, and recovery of LVEF after discontinuation of immunosuppression are considered to have achieved complete recovery. CMR may still show LGE or elevated T1 due to fibrosis, but any suggestion of acute edema should be absent.

Recovering	Ongoing improvement in patient clinical symptoms, signs, biomarkers, and imaging parameters, but not yet normalized, while on tapering doses of immunosuppression

[a]Both troponin I and troponin T can be used; however, troponin T may be falsely elevated in those with concomitant myositis.
CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement; LVEF, left ventricle ejection fraction; WMA, wall motion abnormality.

c. **Arrhythmias/QT prolongation.** A QT interval >500 ms, measured by the Fridericia formula, is defined as prolonged. Supraventricular and ventricular arrhythmias are defined as per standard practice.

d. **Hypertension.** Elevation in systolic and/or diastolic blood pressure after initiation of cancer therapy without any other contributing changes. 130/80 and 140/90 mm Hg are defined as diagnostic and therapeutic thresholds, respectively, according to comorbidities.

e. **Vascular toxicity.** Induction or aggravation of vascular disease caused by cancer therapy; vascular toxicity may be transient or sustained, symptomatic, or asymptomatic, as defined by standard criteria.

2. Criteria for temporal classification of cardiotoxicity from cancer therapies are traditionally used when referring to anthracycline toxicity. **Acute cardiotoxicity** has been labeled as occurring within 1 to 2 weeks of receiving active cancer therapy. **Chronic cardiotoxicity** is defined as happening later than 2 weeks and can be further classified into **early onset** if happening within 1 year of completion of cancer treatment or **late onset** at any point after the first year.

3. It is important to note that patients with advanced HF have usually been excluded from cancer therapy trials and patients with cancer have been excluded from cardiovascular trials. Therefore, the cardiotoxic effects of cancer therapies on patients with preestablished CVD have been documented to a lesser degree and thus have lower volume and quality of evidence. On the other hand, the benefits of guideline-directed medical therapy for CTRCD do not have high-quality evidence, and therefore, recommendations for the treatment of CVD in patients with cancer are mostly extrapolated from clinical trials from the general population and have lesser validity and quality of evidence. Likewise, most cardiovascular risk scores and calculators do not take into account cancer as a CVD risk factor; therefore, their validity in cancer patients is limited.

II. **PATHOPHYSIOLOGY OF CANCER THERAPY–RELATED CARDIOTOXICITY.** CTRCD has been classically described as occurring through one or more than three main mechanisms: by direct cardiomyocyte damage (type I cardiomyopathy); alterations

in perfusion, innervation, or hormonal milieu (type II cardiomyopathy); or inflammatory cell infiltration of the myocardium (type III cardiomyopathy). This classification was historically proposed in 2005 to differentiate anthracycline cardiotoxicity (type I), which was felt to be permanent, from trastuzumab toxicity (type II), which was deemed to have a higher likelihood of recovery. However, existing data challenge this classification as cardiac toxicity associated with cancer therapies is usually mediated by more than one of these mechanisms and can be reversible or irreversible, regardless of the offending agent. More importantly, this classification does not account for the growing number of kinase inhibitors used to treat cancer. For the sake of organization and historical relevance, the mechanisms of cardiotoxicity are presented under this classification in this chapter.

A. Type I cardiomyopathy. Direct toxic effect on the cardiomyocyte can occur with various cancer therapies. This represents the most classic form of toxic cardiomyopathy.

1. **Anthracyclines** cause cardiotoxicity by multiple mechanisms including intercalating between base pairs of DNA or RNA inhibiting its synthesis; inhibiting topoisomerase II-B in DNA/RNA transcription and replication; inducing iron-mediated oxidative stress that damages DNA, proteins, and lipids; and histone modification that deregulates epigenomic and transcription processes. Chronic cardiotoxicity is characterized pathologically by vacuole formation, myofibril dropout, and fibrosis, all of which precede the decline in EF. Mitochondrial injury has also been proposed as one of the main factors related to chronic cardiotoxicity from anthracyclines.
2. **TKIs** interfere with the transfer of a phosphate group to a tyrosine residue of a protein, which is a key step in regulating several signaling pathways that control cell function, survival, and proliferation. The first such inhibitor used was **imatinib**, which neutralizes the Break Point Cluster-Abelson-1 (BCR-ABL1) fusion protein present in the Philadelphia chromosome–positive chronic myeloid leukemia (CML). Imatinib is also used for the inhibition of KIT and PDGFRA proto-oncogenes present in gastrointestinal (GI) stromal tumors. Cardiotoxicity is hypothesized to be caused by activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential, release of cytochrome *c* into the cytosol, and reduction of cellular adenosine triphosphate (ATP) content. The incidence of cardiotoxicity varies greatly between TKIs and is classically higher in TKIs inhibiting the VEGF and MEPK/ERK kinase pathways.

B. Type II cardiomyopathy. Unlike type I cardiomyopathy, type II cardiac injury from cancer therapies is mediated by indirect factors causing cardiac injury

instead of direct cellular toxicity to the cardiomyocyte. Examples include vasospasm, injury to the vasculature, or metabolic derangements.

1. Therapy with **5-fluorouracil (5-FU)** and **its oral prodrug capecitabine** can cause profound and diffuse vasoconstriction involving the coronary microcirculation and can lead to a clinical syndrome similar to stress-induced or Takotsubo cardiomyopathy. Vasospasm can lead to myocardial infarction (MI), but metabolic derangements in cell metabolism can also lead to cardiomyocyte damage, especially with 5-FU, which has a metabolite that interferes with Krebs cycle activity. 5-FU is metabolized by dihydropyrimidine dehydrogenase (DPD), and deficiencies in this enzyme have been linked with an increased risk of cardiotoxicity when using this drug.
2. **HER2 inhibitors** were developed as a targeted therapy for HER2 (an oncogene) positive breast cancer (1%-20% of breast cancers) and include trastuzumab, lapatinib, and pertuzumab. While the mechanism of injury of trastuzumab has not been fully elucidated, one of the postulated mechanisms is ERBB2-mediated inhibition of PI3K. Studies of patients receiving both anthracyclines and trastuzumab suggest that the latter impairs the repair response to anthracyclines in cardiomyocytes. Trastuzumab can thus unmask concomitant injury to the myocardium that leads to the HER2 stress response pathway involved in cellular regeneration. HER2 is one of the tyrosine kinases of the epidermal growth factor receptor (ERBB) family, which binds to neuregulin in important cardiac development and physiology pathways and may represent an important pathway in the stress response of the heart. Inhibition of the neuregulin-ERBB signaling pathway may, therefore, impair this stress pathway, leading to impaired recovery or regeneration after cardiac insults.
3. **VEGF** plays an important role in the production of vasodilators nitric oxide and prostacyclin and decreases the production of endothelin-1, a vasoconstrictor. **VEGF inhibitors** can lead to hypertension, decreased cardiac function, HF, and stress-induced cardiomyopathy. The prototypical example is **bevacizumab**, which can lead to impaired vascular reactivity and angiogenic response to ischemia or increased afterload conditions, which explains the higher prevalence of cardiotoxicity in individuals with CAD or hypertension. VEGF inhibitor **sunitinib** inhibits multiple receptor tyrosine kinases including VEGF and platelet-derived growth factor receptors and destabilizes the coronary microvascular endothelial network, reducing coronary flow reserve and contractile reserve.
4. **Proteasome inhibitors** such as bortezomib or carfilzomib are used in the treatment of multiple myeloma. Proteasome complexes degrade multiple

regulatory proteins, including those controlling cell apoptosis, DNA repair, and cell cycle progression, and its inhibition is hypothesized to lead to protein dysregulation leading to cardiac dysfunction.

5. Immunotherapies such as **CAR T-cell therapies** can lead to acute myocarditis with T-cell–mediated cardiac injury as seen in patients treated with the first developed CAR T-cell therapy against melanoma-associated antigen-3 (MAGEA3), which is caused by cross-reactivity to the striated muscle–specific protein titin. Another mechanism of cardiac toxicity in this scenario is related to CRS with anti-CD19 CAR T-cell therapy for large B-cell lymphoma or acute lymphoblastic leukemia. CRS is a pro-inflammatory state characterized by overexpression of tumor necrosis factor (TNF) and interleukin-1beta (IL-1β), which can lead to tachycardia, hypotension, arrhythmias, decreased EF, and even cardiac arrest via mechanisms similar to those involved in sepsis-induced cardiomyopathy.
6. **RTX** tends to cause restrictive cardiomyopathy predominantly. While cardiomyocytes are relatively resistant to radiation injury, the damage of radiation is primordially induced by activation of the coronary microvascular endothelium favoring leukocyte infiltration as well as increased permeability leading to extravasation of blood and deposition of fibrin as amyloid-like structures as well as thrombus formation. This same type of inflammatory reaction can be observed in the valves, the pericardium, and the conduction system.

C. **Type III cardiomyopathy** leads to myocardial damage through inflammatory mechanisms leading to myocarditis. This mechanism tends to present more acutely and with fulminant presentations than types I and II.

1. **Cyclophosphamide** is an alkylating agent that interferes with cell growth by cross-linking DNA. Metabolites of cyclophosphamide can induce endothelial capillary injury, causing edema, hemorrhage, and thrombosis manifesting as hemorrhagic myocarditis, which can present with HF and/or tachyarrhythmias.
2. **ICIs** are monoclonal antibodies directed against T-cell inhibition pathways of effector T cells, specifically the cytotoxic T lymphocyte antigen-4 (CTLA4) and PD1 pathways, which leads to increased immunosurveillance and reactivation of cellular immunity and decreases the underpinning effect of tumoral cells in the immune system. However, upregulation of the T-cell immune surveillance can lead to a broad spectrum of immune-related adverse events. This effect can be caused by direct binding of ICIs to target molecules on nonlymphocytic cells with downstream immune activation, reactivation of T cells against tumor antigens that cross-react with other

organ tissues, or generation of autoantibodies and production of inflammatory cytokines.

III. CARDIOTOXICITY DUE TO CANCER THERAPIES: EPIDEMIOLOGY, CLINICAL PRESENTATION, MONITORING, AND PREVENTION

A. Chemotherapy. See **Table 42.3** for a summary of cancer therapies known to cause cardiovascular toxicity.

TABLE 42.3 Cancer Therapies and Their Associated Cardiotoxicities

Medication	Cancer Therapy Indications	Known Cardiovascular Toxicity
Anthracyclines		
Doxorubicin	ALL, bladder, breast, endometrial, Ewing sarcoma, hepatocellular, HL, NHL, leukemia or lymphoma, MM, osteosarcoma, SCLC, soft tissue sarcoma, thymoma, uterine sarcoma, Waldenström macroglobulinemia	Cardiac dysfunction and heart failure, arrhythmias. Risk is increased with the presence of CVD risk factors, higher doses, and concomitant cardiotoxic therapies.
Epirubicin	Breast cancer, gastric cancer, esophageal cancer, osteosarcoma, soft tissue sarcoma	
Idarubicin	AML	
Mitoxantrone	AML, HL, NHL, prostate cancer, stem cell transplantation	Cardiac dysfunction, arrhythmia, vascular toxicity
Antimetabolites		
5-Fluorouracil (5-FU)	Anal carcinoma, bladder cancer, breast cancer, cervical cancer, colorectal cancer, esophageal cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, SCC	Coronary vasospasm, myocardial ischemia, infarction, arrhythmias, ECG changes, sudden death. Less risk of cardiac toxicity than 5-FU
Capecitabine	Anal carcinoma, breast cancer, colorectal cancer, gastric cancer, hepatobiliary cancer, esophageal cancer, ovarian, fallopian peritoneal cancer, pancreatic cancer, cancer of unknown primary	
Clofarabine	ALL, AML	Arrhythmias, risk of cardiomyopathy with high dose or combination with cyclophosphamide, pericardial effusion, hyper- or hypotension
Alkylating Agents		

Medication	Cancer Therapy Indications	Known Cardiovascular Toxicity
Cyclophosphamide	ALL, breast cancer, CLL, Ewing sarcoma, HL, MM, NHL, SCLC, stem cell transplant conditioning	Hemorrhagic myopericarditis, arrhythmia. Risk usually at very high doses
Busulfan	Essential thrombocythemia, hematopoietic stem cell conditioning regimen, polycythemia vera	Arrhythmias, pericardial effusion, and tamponade
Cisplatin	Bladder cancer, breast cancer, cervical cancer, endometrial carcinoma, esophageal and gastric cancer, head and neck cancer, HL, malignant pleural mesothelioma, MM, NHL, osteosarcoma, ovarian cancer, penile cancer, SCLC, testicular cancer	Endothelial dysfunction, arterial vasospasm, hypertension
Oxaliplatin	Biliary adenocarcinoma, CLL, cancer of unknown primary, colorectal cancer, neuroendocrine tumors (carcinoid), NHL, ovarian cancer, esophageal/gastric cancers, pancreatic cancer, testicular cancer	Endothelial dysfunction, arterial vasospasm, hypertension, QTc prolongation
Microtubule-Binding Agents		
Docetaxel	Adenocarcinoma of unknown primary, bladder cancer, breast cancer, Ewing sarcoma, head and neck cancers, NSCLC, esophageal and gastric cancer, ovarian cancer, prostate cancer, SCLC, soft tissue sarcoma	Asymptomatic bradycardia, complete heart block, SVT, small risk of cardiomyopathy
Paclitaxel		Same as docetaxel and risk of vasospasm-induced angina and myocardial ischemia. May exacerbate risk of anthracycline toxicity
Vinblastine	Bladder cancer, HL, melanoma, NSCLC, soft tissue sarcoma, testicular cancer	Vascular toxicity with vasospasm and acute vascular thrombosis
Vincristine	ALL, CNS tumors, HL, NHL, Ewing sarcoma, gestational trophoblastic tumors, MM, ovarian cancer, primary CNS lymphoma, SCLC, thymoma	
Antitumor Antibiotics		
Bleomycin	HL, testicular cancer, ovarian germ cell cancer	Vascular toxicity, acute thrombosis, vasospastic angina, Raynaud, phlebitis, pulmonary hypertension

Medication	Cancer Therapy Indications	Known Cardiovascular Toxicity
		(most commonly due to pulmonary fibrosis)
Immunomodulatory Drugs		
Thalidomide	CLL, diffuse large B-cell lymphoma, mantle cell lymphoma, MM, myelodysplastic syndrome	Arrhythmias, thrombotic events, edema
Lenalidomide	MM, systemic light-chain amyloidosis, Waldenström macroglobulinemia	Cardiomyopathy, arrhythmias, arterial and venous thromboembolic events, edema
Monoclonal Antibody Tyrosine Kinase Inhibitors (Target)		
Trastuzumab (anti-Her2/ERBB2)	Breast cancer, gastric cancer	Cardiomyopathy, heart failure, usually reversible. Increased risk with concomitant anthracyclines and CV risk factors Arrhythmias
Pertuzumab (anti-Her2/ERBB2)	Breast cancer	
Bevacizumab (anti-EGF-VEGFR2)	Glioblastoma, persistent/recurrent/metastatic cervical cancer, metastatic colorectal cancer (nonsquamous), NSCLC, ovarian (epithelial), fallopian tube or primary peritoneal cancer, metastatic RCC	Hypertension, cardiomyopathy, heart failure, thrombosis, thrombotic microangiopathy, PRES
Ramucirumab (anti-VEGF-VEGFR2)	Metastatic NSCLC, metastatic gastric cancer, metastatic colorectal cancer	Vascular toxicity, hypertension, thrombotic microangiopathy
Aflibercept (anti-VEGF-VEGFR2)	Metastatic colorectal cancer	Hypertension, thrombotic microangiopathy, PRES
Cetuximab (anti-EGFR/HER1)	Colorectal cancer, head and neck cancer, penile cancer, SCC (KRAS wild type)	Arrhythmias, cardiac arrest, vasospastic angina, myocardial infarction, heart failure
Necitumumab (anti-EGFR/HER1)	NSCLC	Vascular toxicity, cardiac arrest
Panitumumab (anti-EGFR/HER1)	Colorectal cancer, KRAS wild type	Hypertension, heart failure, arrhythmias, ST changes and QTc prolongation
Small-Molecule Tyrosine Kinase Inhibitors (Target)		
Dasatinib (BCR-ABL1)	Philadelphia chromosome–positive ALL and CML, GIST	Pulmonary hypertension, pericardial and pleural effusion

Medication	Cancer Therapy Indications	Known Cardiovascular Toxicity
Imatinib (BCR-ABL1)	Philadelphia chromosome–positive ALL and CML, GIST, myelodysplastic syndrome, melanoma, stem cell transplant for CML	Arrhythmias, pericardial effusion, cardiomyopathy, palpitations, chest pain
Nilotinib (BCR-ABL1)	Philadelphia chromosome–positive ALL and CML, GIST	Peripheral vascular disease, ischemic heart disease, QTc prolongation, sudden cardiac death, hypercholesterolemia
Ponatinib (BCR-ABL1)	Philadelphia chromosome–positive ALL and CML	Peripheral vascular disease, ischemic heart disease, thrombotic microangiopathy, hypertensive crisis, arterial and venous thrombotic events
Sunitinib (VEGFR1-VEGFR3)	GIST, pancreatic neuroendocrine tumors, RCC, soft tissue sarcoma, thyroid cancer	Cardiomyopathy, hypertension, thrombotic microangiopathy, thrombotic events, QTc prolongation. Nondihydropyridine calcium channel blockers increase drug levels.
Sorafenib (VEGFR1-VEGFR3)	Angiosarcoma, hepatocellular cancer, RCC, thyroid cancer, GIST	Cardiomyopathy, hypertension, myocardial ischemia, thrombotic events. Nondihydropyridine calcium channel blockers increase drug levels.
Ibrutinib (Bruton tyrosine kinase)	CLL, mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia	Atrial fibrillation, hypertension, heart failure
Erlotinib (EGFR/HER1)	NSCLC, pancreatic cancer	Acute coronary syndrome, heart failure, arrhythmias
Osimertinib (EGFR/HER1)	NSCLC	Cardiomyopathy, heart failure, QTc prolongation, atrial fibrillation, SVT, pericardial effusion and tamponade
Lapatinib (HER2/ERBB2)	Breast cancer	Cardiomyopathy, heart failure, myocardial infarction, atrial fibrillation
Proteasome Inhibitors		

Medication	Cancer Therapy Indications	Known Cardiovascular Toxicity
Bortezomib	Follicular lymphoma, mantle cell lymphoma, MM, systemic light-chain amyloidosis, T-cell lymphoma, Waldenström macroglobulinemia	Cardiomyopathy, heart failure, peripheral artery disease
Carfilzomib	MM, Waldenström macroglobulinemia	Cardiomyopathy, heart failure, pulmonary hypertension, peripheral artery disease

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; CVD, cardiovascular disease; ECG, electrocardiogram; GIST, gastrointestinal stromal tumor; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSCLC, non–small-cell lung cancer; PRES, posterior reversible encephalopathy syndrome; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small-cell lung cancer; SVT, supraventricular tachycardia.

1. **Anthracyclines** can cause acute cardiotoxicity in around 1% of individuals, manifesting as arrhythmias, electrocardiogram (ECG) changes, pericarditis, myocarditis, or HF. It can present as acute cardiotoxicity in less than 5% of cases but tends to present chronically in most cases (see terminology above), usually within the first few months after exposure to anthracyclines. After 1 year of therapy, approximately 7% to 10% of patients can have LV systolic dysfunction, which can also present as late as 10 to 20 years after therapy in the setting of an additional stressor or second hit. Anthracycline-related cardiomyopathy affects survival, and its prognosis has been compared to that of dilated cardiomyopathy. Its development is dose related, and in the case of doxorubicin, the highest risk is reported after a cumulative dose of 200 mg/m^2, although there is no minimum anthracycline threshold. Other risk factors include extremes of age, female sex, presence of other cardiac risk factors (ie, diabetes, hyperlipidemia, hypertension, smoking, low LVEF at baseline, other cardiac diseases), cumulative dose >250 mg/m^2, and concomitant treatment with other cardiotoxic agents, including radiation. A monitoring echocardiogram is recommended 6 to 12 months after completion of therapy for patients with more than one risk factor. Recent trials have shown no or very modest benefit of initiating angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, or angiotensin receptor blockers at the time of treatment with anthracyclines, but other retrospective studies have shown a benefit of starting therapy with beta-blocker and an ACE inhibitor, especially within the first few months after recognizing LV dysfunction. Data on the prevention of anthracycline cardiotoxicity come mostly with the use of **dexrazoxane, a free-radical scavenger, and iron-**

chelating agent, in the pediatric population. However, its use has been approved as a primary preventive strategy for CTRCD for high-risk adults with advanced or metastatic breast cancer who have already received 300 mg/m^2 of doxorubicin or equivalent. In clinical practice, dexrazoxane infusion (dosage ratio dexrazoxane/doxorubicin is 10/1; eg, 500 mg/m^2 ^{d}exrazoxane per 50 mg/m^2 ^{d}oxorubicin) should be considered at least 30 minutes prior to each anthracycline cycle in adult patients with cancer scheduled to receive a high total cumulative anthracycline dose for curative treatment, and in patients with high and very high CTRCD risk (including those with preexisting HF or low-normal or reduced LVEF) where anthracycline chemotherapy is deemed essential. **Liposomal formulations of anthracyclines modify pharmacokinetics and tissue distribution without compromising antitumor efficacy and have shown to be less cardiotoxic than conventional formulations**. Their use should be favored when available. Equivalence dosing and conversion ratios for different anthracyclines are presented in **Table 42.4**.

TABLE 42.4 Anthracycline Equivalence Dose

	Doxorubicin	Epirubicin	Daunorubicin	Mitoxantrone	Idarubicin
Cardiovascular toxicity ratio	1	0.8	0.6	10.5	5
Isoequivalent dose (mg/m^2)	100	125	167	9.5	20

2. **Taxanes** such as paclitaxel and docetaxel inhibit microtubular structures and disrupt tumoral proliferation. When used alone, they have minimal cardiotoxic potential and may induce asymptomatic bradycardia in 30% of patients, complete heart block in 0.1%, supraventricular tachycardia (SVT) (including atrial fibrillation [AF]) in 0.2%, and ventricular fibrillation in 0.3% of patients. These events are usually seen with the first or second cycles of chemotherapy, often within 24 hours of infusion, and are usually self-limited and resolve within 48 to 72 hours. Paclitaxel has been associated with acute coronary syndromes (ACSs) that are often related to vasospasm, in which case ST elevation can resolve with administration of nitroglycerin.
3. **Alkylating agents** such as **cyclophosphamide** are used mainly for breast cancer, lung cancer, and hematologic malignancies. Hemorrhagic myocarditis can present with doses higher than 100 mg/kg. Doses >270 mg/kg for 1 to 4 days or doses of >1.55 g/m^2 are associated with a substantial risk of cardiotoxicity. Acute HF presents in 7% to 33% of patients receiving doses >150 mg/kg, with mortality ranging from 2% to

17% in patients with cyclophosphamide-associated myocarditis. Treatment includes discontinuation of therapy and supportive treatment for myocarditis. Cyclophosphamide has also been known to cause pulmonary veno-occlusive disease.

4. **Platinum-based agents such as cisplatin** and **bleomycin** and **vinca alkaloids** are frequently used for testicular cancer and have been associated with vasospasm. Over two-thirds of patients being treated for testicular cancer with these agents develop angina, and about one-third of patients develop Raynaud phenomenon. Cisplatin therapy (and other platinum-based therapies like oxaliplatin and carboplatin) has been known to cause acute arterial thrombosis related to endothelial erosion from toxicity to endothelial cells, desquamation, and exposure of von Willebrand factor, as well as impairment of endothelial regeneration. Apart from acute arterial thrombosis, cisplatin has also been linked to accelerated atherosclerosis chronically. Patients receiving cisplatin-based therapy have a 2 to 7 times higher risk than normal of CAD, with higher rates of cerebrovascular and peripheral artery disease also seen years after therapy.
5. **Therapy with antimetabolites like 5-FU** has been associated with cardiotoxicity in up to 20% to 30% of patients. The risk is increased in patients with prior ischemic heart disease, hypertension, or kidney dysfunction. Both 5-FU and its oral prodrug, capecitabine, can cause profound and diffuse vasoconstriction that involves coronary microcirculation and may lead to myocardial ischemia, which can present as an ACS or chronic LV dysfunction. Nitrates can be helpful to dilate epicardial circulation, but calcium channel blockers are more efficient in vasodilating microcirculation. The risk of cardiotoxicity is higher when these drugs are infused continuously over 2 days versus when they are infused as a 3-hour bolus. Uridine triacetate, which competes with 5-FU metabolites, can be used for the treatment of life-threatening 5-FU and capecitabine-related cardiotoxicity.
6. **Arsenic trioxide** is a cytotoxic agent used often for chemotherapy-sparing purposes in the treatment of acute promyelocytic leukemia. It is given as an intravenous infusion, and its use has been linked to QTc-interval prolongation >500 ms in up to 40% of patients. Close ECG monitoring is needed as well as discontinuing other QTc prolonging medications prior to initiating therapies. The drug should be withheld for prolonged QTc-interval readings (>450 ms for males and >460 ms for females). In the setting of QTc prolongation, magnesium and potassium should be repleted and dose reduction should be used once QTc normalizes according to infusion protocols.

B. Targeted agents

1. **HER2-targeted therapies** such as trastuzumab, lapatinib, and pertuzumab are used to treat HER2+ breast cancer. Trastuzumab is particularly associated with cardiotoxicity, causing reduced cardiac function in 15% to 20% and symptomatic HF in up to 5% of patients receiving it. Other manifestations of cardiovascular toxicity include hypertension, arrhythmias, and, rarely, sudden cardiac death. Patients at high risk can be identified by an increase in cardiac troponin levels after initiation of therapy, and the risk of LV dysfunction is increased when trastuzumab is given concomitantly with anthracyclines in breast cancer. In contrast to anthracycline-related cardiomyopathy, recovery of cardiac function can be seen after cessation of trastuzumab therapy, although this is only seen in about 25% of patients suffering from cardiac dysfunction. Although randomized clinical trials such PRADA and MANTICORE have been largely equivocal, the expert consensus is that the initiation of standard HF therapies in affected individuals leads to at least partial recovery of LV function. Surveillance for CTRCD should be done with echocardiography at baseline and every 3 months while receiving therapy as well as at the time of completion of therapy. If there is a decrease in LVEF >16% from baseline, protocols recommend withholding therapy for at least 4 to 8 weeks and repeating an echocardiogram to resume therapy only if LVEF returns to normal or if absolute decrease is <15% from baseline. LVEF should be monitored every 6 months for at least 2 years after completing therapy.
2. **VEGF inhibitors** have been associated with a wide array of cardiovascular complications, including hypertension, vascular toxic effects, and cardiomyopathy. **Hypertension** develops in a 20% to 25% of individuals in a dose dependent and transient manner and can be seen as early as 1 week after initiation of therapy with bevacizumab and sunitinib. Cardiomyopathy can develop in 9% to 28% of patients receiving pazopanib or sunitinib, with symptomatic HF presenting in 1% to 8% of these. A preeclampsia-like syndrome has been described in patients receiving VEGF inhibitors presenting with **hypertension, proteinuria, and renal thrombotic microangiopathy**. These patients may be at increased risk of developing subsequent cardiac dysfunction. Aggressive hypertension management is needed before starting therapy with VEGF inhibitors, and blood pressure monitoring should be performed weekly for the first 6 weeks of therapy. Regular urinalysis should be performed as a screening test due to the association of this class of medications with proteinuria. Nondihydropyridine calcium channel blockers (verapamil and diltiazem) should be avoided with sunitinib and sorafenib due to their CYP3A4 system

inhibition leading to increased VEGF inhibitor levels. **VEGF-associated cardiomyopathy** can be seen in 10% to 15% of patients enrolled in clinical trials, is more commonly asymptomatic, and can be reversible in a number of patients. Baseline echocardiography and natriuretic peptide measurement are recommended in moderate- and high-risk patients treated with VEGF inhibitors, and serial evaluation should be considered every 3 months along with natriuretic peptide measurement for high-risk patients. VEGF inhibitors have also been linked to arterial thrombotic events presenting as ACS, stroke, or acute limb ischemia. Inhibition of VEGF with bevacizumab can cause thrombotic as well as bleeding events since antagonizing VEGF may lead to impaired endothelial cell regeneration and thus may facilitate bleeding. Special care must be taken with patients receiving bevacizumab and anticoagulation, as there is a high risk of bleeding, particularly in the setting of GI cancer.

3. **Multiple TKIs** have been developed for cancer treatment. Cardiovascular toxic effects vary from agent to agent and are unique due to "off-target" effects of each medication. While imatinib carries minimal risk of cardiotoxicity, dasatinib has been linked to cardiopulmonary complications, such as pulmonary hypertension and pleural and pericardial effusions; nilotinib and ponatinib are associated with vascular thrombotic events occurring in 3% to 7% patients and include coronary events, ischemic stroke, or peripheral artery thrombosis, all of which are more frequent in patients with other atherosclerotic risk factors. Ibrutinib, which inhibits Bruton tyrosine kinase and is used in B-cell cancers, has been associated with a 3% incidence of AF when compared to other agents and has also been linked to hypertension and HF. However, real-life data have shown the incidence rate of cardiac dysfunction with ibrutinib to be as high as 25%. Trametinib, an MEK inhibitor, has been associated with cardiac dysfunction in 7% of patients, requiring cardiac monitoring during treatment. Several TKIs, including sunitinib, lapatinib, nilotinib, and vandetanib, can lead to QTc prolongation, with an average increase in 15 ms in as much as 18% of patients receiving vandetanib but in <5% of individuals receiving other TKIs. ECG should be measured at baseline and at 2 and 4 weeks after starting therapy with these agents and 2 weeks after any dose increase. Baseline echocardiography, blood pressure measurement, and ECG should be obtained before starting therapy with dasatinib or second- and third-generation TKIs, such as bosutinib, nilotinib, or ponatinib. Repeat echocardiogram should be considered every 3 months in the first year of therapy in high-risk patients and every 6 to 12 months thereafter.

4. The **proteasome inhibitors** bortezomib (reversible inhibitor) and carfilzomib (irreversible inhibitors) may lead to cardiomyopathy and HF in 4% to 7% of patients being treated for multiple myeloma. The risk of cardiomyopathy is greater with carfilzomib, and they have also been linked to hypertension, diastolic dysfunction, or pulmonary hypertension. Proteasome inhibitors have also been linked to accelerated coronary atherosclerosis.

C. Immunotherapies

1. The incidence of ICI-related adverse events is generally higher with CTLA4 inhibition (ipilimumab) and is highest when combined CTLA4 and PDL1 inhibitors (nivolumab, pembrolizumab, cemilimab, avelumab, atezolizumab, durvalumab) are given. While colitis, dermatitis, and pneumonitis present more commonly (all with incidence >10%), myocarditis can present in around 1% of patients on immunotherapy but is associated with the highest mortality (40%) when compared to other organ involvement. In its most severe form, myocarditis can present as HF, cardiogenic shock, and sudden cardiac death. Endomyocardial biopsy is often but not always positive for myocarditis, and cardiac magnetic resonance imaging (MRI) shows late gadolinium enhancement (LGE) and edema in only 23% to 33% of patients, respectively. Apical ballooning can be seen in about 14% of patients, and reversal of LV dysfunction occurs only in about 50% of patients. ICIs can induce arrhythmias, including conduction block, ventricular ectopy, and ventricular tachycardia (VT). Early recognition of myocardial involvement is crucial in order to stop offending agents and initiate timely therapy. Elevations in cardiac troponin and natriuretic peptide levels are a sensitive marker of ICI-induced myocarditis. ECG can be helpful to detect early signs of ICI-related myocarditis, with low voltage suggesting pericardial effusion. Coronary angiography is usually performed to exclude CAD and ACS as the main differential diagnosis. Cardiac MRI can be used to differentiate acute MI from myocarditis, Takotsubo cardiomyopathy, or other forms of cardiomyopathy. Grading of ICI cardiotoxicity is listed in **Table 42.5**.

TABLE 42.5 Grading of ICI-Related Myocarditis According to the 2018 American Society of Clinical Oncology Clinical Practice Guideline

Grade	Criteria
G1	Abnormal cardiac biomarker testing, including abnormal ECG
G2	Abnormal screening tests with mild symptoms
G3	Moderately abnormal testing or symptoms with mild activity
G4	Moderate-to-severe decompensation

ECG, electrocardiogram; ICI, immune checkpoint inhibitor.

Treatment of ICI-related cardiomyopathy includes supportive therapy and immunosuppression. The latter should be instated in all cases of life-threatening myocarditis, lethal arrhythmias such as VT or complete heart block, pericarditis with pericardial tamponade, and acute MI with coronary vasculitis. Recommended therapy for severe, life-threatening adverse effects includes inpatient admission, permanently discontinuing immunotherapy as well as pulse-dose steroids with methylprednisolone 1 g/d for 3 to 5 days. Steroid therapy is instituted until cardiac functions return to baseline and is then tapered over 4 to 6 weeks. Some patients who do not improve within 24 hours might require a quick escalation of immunosuppressive therapies with immunoglobulins, antithymocyte globulin, infliximab (if HF is not present), mycophenolate mofetil, or tacrolimus. Plasmapheresis may be helpful in removing the offending drug due to the long half-life of ipilimumab (14.5 days), pembrolizumab (25 days), nivolumab (26.7 days), and atezolizumab (27 days). The CTLA4 agonist abatacept may be used in cases refractory to steroids. The multicenter clinical trial ATRIUM is underway to assess the use of abatacept in ICI-induced myocarditis. In fulminant cases, advanced mechanical cardiac support with an intra-aortic balloon pump, Impella, or extracorporeal membrane oxygenation (ECMO) may be required until cardiac function recovers.

2. **CAR T-cell therapy** may lead to CRS, which has several effects on cardiac dysfunction as discussed previously, presenting with tachycardia and hypotension, arrhythmias, and decreased LVEF in severe cases. Cardiac arrest is less frequent but may occur even 1 week after therapy initiation. The treatment of choice for life-threatening CRS is an IL-6 antagonist, such as tocilizumab or siltuximab. Patients with circulatory shock may require vasopressor support.
3. The **immunomodulatory drugs thalidomide and lenalidomide** that promote the degradation of two B-cell transcription factors have shown to improve the prognosis of patients with multiple myeloma. However, randomized clinical trials with these drugs showed a high risk of venous thromboembolic disease, especially when combined with high-dose dexamethasone, which led to a protocol modification requiring mandatory thromboprophylaxis with aspirin or anticoagulation when using this combination. They have also led to an increased risk of arterial events, leading to a black box warning of increased risk of MI and stroke in patients with multiple myeloma receiving lenalidomide and dexamethasone. Aspirin therapy or prophylactic doses of low-molecular-weight heparin (LMWH) are

recommended for patients with low risk of venous thromboembolism (VTE) receiving thalidomide- or lenalidomide-based therapy, while high-risk patients for VTE should receive therapeutic doses of LMWH or vitamin K antagonists.

IV. RADIATION-INDUCED HEART DISEASE

A. Epidemiology. Experience from the second half of the 20th century has shown that cancer survivors who undergo RTX to the chest as part of their cancer treatment have a 1.7- to 2-fold increase in cardiovascular death when compared with those who do not undergo RTX. There is a known linear increase in the risk of valvular heart disease with radiation doses above 30 Gray (Gy)/m^2. Standard doses of RTX used for several cancers are listed in **Table 42.6**. Women appear to be at higher risk of radiation-induced heart disease, and there is a relative increase in 7.4% in the risk of coronary events for each Gy of radiation to the chest in patients with previous breast cancer. Radiation-associated cardiotoxicity typically appears 10 to 30 years following treatment. The risk of inducible ischemia on myocardial perfusion imaging increases from 5% at 10 years postradiation to 20% at 20 years postradiation. In patients with Hodgkin lymphoma who undergo radiation, the median time from diagnosis of malignancy to cardiac complications is 19 years. As a rule, left-sided breast cancer has been shown to lead to more heart disease than right-sided breast cancer because radiation to the left breast is in more direct line with the heart. The risk of RTX-induced heart disease can be categorized based on the mean heart dose (MHD) of RTX received, which is not the same as the total RTX dose received (ie, 40 Gy of prescribed dose to approximately 50% of the heart equals 20 Gy MHD) and is presented in **Table 42.7**. The risk of cardiac events increases when RTX is used in conjunction with other cardiotoxic cancer therapies, such as anthracyclines, trastuzumab, or fluorouracil.

TABLE 42.6 Standard Radiation Doses Used for Common Thoracic Cancers

Type of Cancer	Typical Radiation Dose[a]
Stage I lung cancer	54 Gy total
Stage III lung cancer	60 Gy total
Stage I breast cancer	40 Gy total
Advanced-stage Hodgkin lymphoma	30-45 Gy total
Esophageal cancer	50-64 Gy total

[a]This is not equal to the mean heart dose (MHD) of received radiation, which is calculated based on the percentage of heart muscle irradiated.

TABLE 42.7	Risk Stratification Based on Radiotherapy Mean Heart Dose (MHD)
Low risk	<5 Gy MHD
Moderate risk	5-15 Gy MHD or <5 Gy MHD and cumulative doxorubicin dose >100 mg/m^2
High risk	>15-25 Gy MHD or 5-15 Gy MHD and cumulative doxorubicin dose >100 mg/m^2
Very high risk	>25 Gy MHD or >15 Gy MHD and cumulative doxorubicin dose >100 mg/m^2 or Cumulative doxorubicin dose >250 mg/m^2 or Moderate or severe CTRCD during treatment, ICI-related myocarditis, cardiac arrhythmias, or severe vascular toxicities (ACS < stroke, PVD)

ACS, acute coronary syndrome; CTRCD, cancer therapy–related cardiac dysfunction; ICI, immune checkpoint inhibitor; PVD, peripheral vascular disease.

Due to the dose-related risk of radiation-induced heart disease, multiple efforts have been made to decrease the amount of energy received by the heart. Previous protocols for lymphoma included mantle radiation with >30 to 40 Gy using an anteroposterior technique, which exposed other mediastinal and thoracic organs such as the heart and lungs to high doses of radiation. Multiple techniques such as deep inspiratory breath-hold, proton therapy, and radiation limited to involved lymph nodes have helped reduce the dose of RTX received by the heart. Similarly, advances in tangential radiation for breast cancer as well as novel techniques such as three-dimensional conformal radiation with heart blocking and prone positioning have allowed for a reduction in cardiac exposure to radiation. During treatment planning, radiation oncologists select the optimal particle, angle, energy, delivery system, and target coverage to reduce the amount of radiation delivered to the heart and lungs.

B. Clinical presentation. As stated previously, radiation-induced cardiotoxicity can present with a myriad of manifestations involving any component of the heart: coronary arteries, myocardium, pericardium, valvular structures, conduction system, and great vessels.

1. **CAD** is the most common manifestation of radiation-induced heart disease, occurring in up to 85% of patients who receive mediastinal radiation. It typically involves the coronary ostia and proximal vessels, and its location depends on the type of radiation received. Mediastinal radiation is usually associated with left anterior descending (LAD) and right coronary artery (RCA) involvement, whereas left-sided breast radiation is usually associated with LAD involvement. The medical management of radiation-induced CAD should be similar to that of conventional CAD, with aggressive risk factor reduction and antiplatelet therapy. From an interventional perspective,

there are conflicting data, but available evidence suggests that both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have worse outcomes when compared to a population without a history of radiation. CABG poses a series of difficulties in this population as arterial and venous conduits can be fibrotic, scarred, or stenosed, preventing them from being viable grafts; patients are often at high surgical risk due to friable tissue and the presence of adhesions, leading to higher rate of bleeding and poor wound healing; concomitant radiation-induced lung disease can be present, which might increase postoperative mortality; calcification of the aorta is often present, which might impede aortic clamping for cardiopulmonary bypass and increase the risk of mortality and stroke with surgery. Due to the high surgical risk, open heart surgery should often be delayed until the appropriate time to include valvular and pericardial surgery due to the high incidence of both in this population.

2. **Valvular disease** occurs in up to 26% of patients at 10 years and 60% at 20 years after RTX. The median interval between cancer diagnosis and valvular disease is 23 years, with the prevalence and severity of valvular disease being proportional to the amount of radiation received. Patients with a history of chest radiation have a 9.2-fold increased risk of requiring surgery for valve disease when compared to nonirradiated patients. Fibrosis of the valve cusps and leaflets is more common in the left-sided valves, with aortic insufficiency being the most common valve disease encountered, followed by aortic stenosis. Mitral disease usually involves the anterior leaflet predominantly and usually spares the commissures and leaflet tips, with aortomitral continuity calcification being present in most cases. Tricuspid disease can also be present. Management of valve disease associated with RTX remains a controversial subject. There is conflicting data regarding transcatheter aortic valve replacement (TAVR) in this population, but several studies have found increased mortality, cardiac events, and need for pacemaker implantation in patients with radiation-induced heart disease undergoing TAVR when compared to nonirradiated controls. Surgical replacement of the aortic and mitral valves has also been found to have worse outcomes in patients with a history of RTX to the chest, although most of these cases require simultaneous CABG due to the frequency of concomitant CAD. A retrospective study from the Mayo Clinic comparing TAVR versus Surgical aortic valve replacement (SAVR) in radiation-induced aortic valve disease found higher risk scores, lower incidence of postoperative AF, decrease in hospital stay, and lower 30-day mortality in TAVR patients when compared to the surgical counterparts.

3. **Cardiomyopathy** is related to total radiation dose, fraction size, and volume of heart in the radiotherapy field. Radiation-induced myocardial fibrosis along with microvascular and macrovascular injury result in systolic and diastolic dysfunction in ~10% of patients receiving radiation to the chest, with the right ventricle being more susceptible due to its anterior location in the mediastinum. A restrictive physiology pattern is typical, and regional wall motion abnormalities can also be found. As noted previously, a higher prevalence of perfusion abnormalities is found in women receiving RTX for left-sided than right-sided breast cancer, and LAD involvement is more frequently found in these cases. These detrimental myocardial changes can be compounded by cardiotoxicity from anthracyclines or HER2 antagonists.
4. **Pericardial disease** presents most frequently as chronic pericarditis in 8% to 30% of patients several years after RTX to the chest. Acute pericarditis is less common with modern RTX protocols and is more commonly seen with high doses of radiation given for Hodgkin lymphoma. In the long term, collagen and fibrin replace the adipose tissue of the heart, leading to fibrosis of the pericardium and a calcified and rigid pericardial sack, which can result in interventricular dependence and constrictive physiology. Invasive hemodynamic evaluation might be needed to differentiate restriction from constriction, but multimodality imaging can help characterize constriction with annulus reversus or reduced LV free wall strain on echocardiography, pericardial calcification on cardiac computed tomography (CT), and ventricular interdependence with respirophasic septal shift on cardiac magnetic resonance cine imaging. Treatment consists of symptom management with anti-inflammatory medications and diuretics, but definite therapy for proven constriction might require pericardiectomy, which carries a significantly high risk as radiation-induced constrictive pericarditis has been shown to have the worse mortality with a 5-year mortality of 12%. The risks of operating must be weighed against the symptomatic benefits after maximized medical therapy is instituted, and surgery is often delayed and done concomitantly with other surgical indications resulting from radiation-induced heart disease.
5. **Conduction system abnormalities** can develop due to radiation-induced fibrosis in up to 75% of patients receiving RTX. Nonspecific repolarization abnormalities are common during active radiation, but significant conduction abnormalities usually develop decades after exposure, with the most common being right bundle branch block (RBBB). Infranodal blocks and all degrees of atrioventricular (AV) block can also occur. Ectopy and sustained arrhythmias, both supraventricular and ventricular, are also more common in patients with a history of RTX. Autonomic dysfunction has also

been found in patients receiving RTX, and abnormal heart rate recovery times are found in 32% of such patients versus 9% in age-matched controls, as well as higher rates of loss of circadian variability in heart rate, inappropriate chronotropic response to stress, and persistent tachycardia presumed to be secondary to reduced vagal tone. Diagnosis and management for arrhythmias in radiation-induced heart disease follow standard treatment for cardiac arrhythmias.

V. CARING FOR PATIENTS WITH CANCER WITH CARDIOVASCULAR DISEASE.

Cardiovascular care for patients with cancer who are undergoing cancer therapy includes a longitudinal and multidisciplinary approach throughout the patient's cancer pathway. Since cancer and CVD share multiple risk factors, management of such risk factors becomes pivotal for managing both diseases simultaneously. Patients should initially be screened for cardiovascular risk factors or for the presence of CVD to identify those at high risk for cardiovascular complications and tailor monitoring strategies appropriately. The risk of cardiotoxicity is composed of the likelihood of suffering cardiovascular adverse effects and the severity of the repercussions from it based on preexisting cardiac morbidity. The 2017 guidelines from the American Society of Clinical Oncology (ASCO) on the prevention and monitoring of cardiac dysfunction of cancer survivors and the 2022 European Society of Cardiology (ESC) guidelines on cardio-oncology offer recommendations on the prevention and monitoring of cardiovascular toxicity.

A. Initial assessment and monitoring. Prior to starting cancer therapies or undergoing cancer surgery, patients should be assessed and screened for traditional cardiovascular risk factors and preexisting CVD in order to determine the risk of suffering from cardiovascular toxicity from oncologic treatment. Oncologists should screen for physical and metabolic risk factors for CVD (obesity, hypertension, hyperlipidemia, diabetes, tobacco use, alcohol consumption, physical activity, older age) and should aggressively treat modifiable ones. Stratification of the patient from low, moderate, or high risk can be done using the Heart Failure Association and International Cancer and Oncology Society (HFAISCO) baseline cardiovascular toxicity risk stratification, although several other scores have been studied for this purpose. High-risk factors include the presence of any cardiovascular risk factors, borderline low EF (50%-55%), greater than moderate valvular disease, plan for high-dose anthracyclines, high-dose chest RTX, or a combination of low-dose anthracyclines with chest RTX. Patients at high or very high risk should be referred to a cardiologist prior to initiation of cancer therapies.

1. An **ECG** should be obtained for every patient who is scheduled to receive cardiotoxic therapies. Attention to the QTc prolongation should be paid,

especially for patients receiving therapies with potential for QTc prolongation, as well as AV conduction delays or any other signs of cardiac conduction abnormalities.

2. **Baseline and serial serum biomarker measurements of cardiac troponins and natriuretic peptides** can help in baseline stratification and identification of higher risk patients as well as monitoring for subclinical cardiotoxicity. Patients with elevated cardiac troponins are more likely to suffer anthracycline and trastuzumab cardiotoxicity. Patients with elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) at baseline may be at higher risk of mortality and cardiotoxicity after starting therapy.
3. **Baseline echocardiogram** is recommended for all patients receiving cardiotoxic therapies and particularly for patients at high risk of cardiotoxicity. LVEF and global longitudinal strain (GLS) assessment should be done as well as diastolic function and structural assessment of right and left chamber size and function. A change >15% in GLS has a high specificity to predict LV dysfunction in patients receiving cardiotoxic agents. Valvular apparatus morphology and function should also be evaluated.
4. **Genetic testing** has shown promising utility as a tool to predict susceptibility to cardiotoxicity from cancer therapies and has been thoroughly studied in the setting of anthracycline cardiotoxicity, but its use is not recommended nor currently widely available.
5. **Monitoring** for CTRCD varies according to the received therapies and the patient's baseline risk. The 2022 guidelines from the ESC offer comprehensive protocols on the periodic monitoring of CTRCD depending on the cancer therapy–specific regimen. In general, patients require baseline assessment with ECG, serum biomarkers, and echocardiography, with repeat serial assessments during active cancer treatment and routine post-therapy surveillance. The monitoring intervals vary depending on the cardiotoxic risk of the cancer therapy administered and the patient's baseline risk, with more frequent monitoring for higher risk patients and therapies. Repeat testing with ECG, serum biomarkers, and echocardiogram should be done at any point of cancer therapy (during and after) if the patient develops new cardiac symptoms.

B. **Prevention of CTRCD** includes aggressive control of modifiable risk factors and should include limiting alcohol intake, smoking cessation, exercise prescription, and dietary education. Medical therapy for hypertension, hyperlipidemia, diabetes, and chronic kidney disease (CKD) should follow established guidelines for cardiovascular prevention.

1. Meta-analyses and randomized clinical trials looking at the use of **renin-angiotensin-aldosterone system blockers, beta-blockers, and mineralocorticoid receptor antagonists** for primary prevention in patients receiving anthracycline and HER2 inhibitor therapies have shown a significant benefit in preventing LVEF reduction, but no difference in reducing the incidence of clinical HF or other clinical outcomes. Their use should be considered in patients at high and very high risk receiving cardiotoxic cancer therapies.
2. Dexrazoxane and liposomal doxorubicin should be used to prevent anthracycline-related cardiotoxicity as stated previously in the anthracycline section.

C. **The decision to stop cancer therapies** in the setting of CTRCD is never an easy one and should be made through a multidisciplinary discussion involving the patient and the cardiology and oncology specialists. While this decision may vary from case to case, the benefit of continuing chemotherapy must be weighed against the potential risk of cardiac events based on a patient's individual cardiovascular and oncologic risk and the severity of the cardiotoxicity. In general, **moderate to very severe symptomatic CTRCD and severe asymptomatic CTRCD** warrant interruption (at least temporarily) of anticancer therapies and initiation of guideline-directed medical therapy for HF as well as a multidisciplinary discussion about the risks of reinitiating therapy (see **Table 42.1**). **Mild symptomatic and asymptomatic mild-to-moderate CTRCD** should be evaluated by a multidisciplinary team to decide on the benefits and risks of continuing cancer therapies.

D. **Management of ACSs** in patients with cancer poses certain therapeutic challenges. Patients with cancer are at increased risk for major cardiovascular events due to shared risk factors, a pro-inflammatory and prothrombotic state from cancer, and the added cardiotoxicity and risk of vascular events from some cancer therapies. They are also at higher risk of bleeding, especially in the setting of GI, genitourinary, and pulmonary cancers, and may have frequent thrombocytopenia secondary to cancer therapies or myeloid malignancies. In addition, the need for cancer surgeries makes PCIs especially high risk if there is a need to discontinue dual-antiplatelet therapy (DAPT) soon after stent placement. In general, guidelines recommend an invasive strategy in patients with cancer presenting with ST-elevation MI (STEMI) or high-risk non–ST-elevation MI (NSTEMI) with a life expectancy >6 months, while a conservative noninvasive strategy should be considered in patients with ACS and poor prognosis with life expectancy <6 months, although this distinction is not always readily made. The duration of DAPT should be individualized, considering shorter durations for patients with high risk of bleeding. In the

acute setting, aspirin is not recommended if platelets are <10,000/mcL, while clopidogrel and prasugrel/ticagrelor are not recommended if platelets are <30,000/mcL or <50,000/mcL, respectively. Clopidogrel is preferred to prasugrel and ticagrelor due to a lower risk of bleeding, particularly in GI malignancies.

E. AF is frequent in patients with cancer, with a prevalence of 2.4% and a 1.8% increase after a cancer diagnosis. It may develop as a marker of occult cancer or after cancer surgery, direct tumor invasion of the atria, or other factors such as older age, inflammation, hypoxia, paraneoplastic manifestations, and autonomic nervous system imbalance in this population. AF has also been linked to several cancer therapies, such as cisplatin, irinotecan, paclitaxel, thalidomide, 5-FU, and arsenic trioxide. AF occurs in 2% to 16% of patients undergoing cancer therapy as new-onset AF or recurrence of paroxysmal AF. The risk of thromboembolism is 2-fold higher in patients with cancer, with the caveat that anticoagulation increases all-cause mortality in patients with cancer due to major bleeding and intracranial hemorrhage. While the management of AF does not differ from the noncancer population, special precaution must be paid to the interaction of antiarrhythmic therapies with QTc prolonging drugs and cautious use of beta-blockers and calcium channel blockers in patients with CTRCD. The CHA_2DS_2-VASc score has not been extensively validated in patients with cancer, and those with scores of 0 and 1 with cancer have a higher risk of systemic thromboembolism than noncancer controls. The inclusion of cancer in this risk score has been found to improve the accuracy of thromboembolic risk prediction. Considering that this score underestimates the risk of thromboembolic complications in this population, the decision to initiate anticoagulation must be judiciously made when considering thromboembolic risk versus risk of bleeding, which varies with cancer type. Patients with genitourinary and GI malignancies are at higher risk of bleeding, as well as those with thrombocytopenia, renal dysfunction (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m^2), intracranial lesions, active or recent major bleeding, and a high HAS-BLED score. Direct oral anticoagulants should be considered for stroke prevention over LMWH or vitamin K antagonists (except in patients with valvular AF), and LMWH may be used if these are not an option or in the acute hospital setting, although it has not been validated for stroke prevention. In patients with contraindications to anticoagulation, left atrial appendage occlusion devices may be considered for stroke prevention, but prospective data in patients with cancer are lacking and one retrospective study suggested an increased risk of ischemic stroke in patients with active cancer undergoing the procedure.

F. Cancer survivor monitoring. Childhood cancer survivors are at a higher risk of cardiovascular mortality than noncancer controls, with standardized mortality ratios of 3.8 (95% confidence interval [CI], 3.2-4.3) according to the British Childhood Cancer Survivor Study. This risk is also present in adult population, with incidence rate ratios of CVD being 1.1- to 1.7-fold higher in adult (>40 years old) survivors of cancer. This risk is higher in adults with additional cardiovascular risk factors. Cancer survivors should be monitored based on their risk of developing CVD (see **Table 42.5**), with all adults, children, and adolescents who received anthracyclines or RTX to the chest receiving annual screening for cardiovascular risk factors. Cardiovascular surveillance recommendations for child, adolescent, and adult cancer survivors are summarized in **Table 42.8**. Carotid artery ultrasound should be considered every 5 years in asymptomatic patients with a history of head/neck RTX starting 5 years after cancer therapy.

TABLE 42.8 Recommendations for Cardiovascular Surveillance in Cancer Survivors

Population of Cancer Survivors	Recommended Surveillance
All cancer survivors	Annual screening for modifiable cardiovascular risk factors in those treated with cardiotoxic agents or RTX to the heart. Consider annual ECG and serum biomarkers annually.
Moderate-risk childhood and adolescent survivor	Consider echocardiographic surveillance every 5 y.
High-risk childhood and adolescent survivor	Consider echocardiographic surveillance every 2 y.
Asymptomatic moderate-risk adult survivor	Consider echocardiographic surveillance every 5 y.
Asymptomatic high- and very high-risk adult survivor	Consider echocardiography at years 1, 3, and 5 after completion of cardiotoxic therapy and every 5 y thereafter. Consider noninvasive screening for CAD every 5-10 y in those who received >15 Gy MHD starting at 5 y after RTX.

CAD, coronary artery disease; ECG, electrocardiogram; MHD, mean heart dose; RTX, radiation therapy.

VI. FUTURE DIRECTIONS. Cardio-oncology is a growing field, and adverse events of cancer therapies are increasingly recognized. Approval of new cancer therapies has noticeably become a faster process, leading to a growing number of new cancer therapies and, therefore, a wider range of cardiovascular adverse effects stemming from these. Consequently, there is a rising need for active surveillance of cardiac adverse effects related to them. Prospective data on patients undergoing cancer therapies are required to understand the epidemiology of CTRCD, while molecular

research on its mechanisms will open pathways to treat and prevent cardiotoxicity. Ongoing efforts are needed to study the optimal delivery of cancer therapies, aiming to maximize its oncologic effect and decrease its cardiovascular toxicity.

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CHAPTER 43

COVID-19 and the Heart

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I. INTRODUCTION. COVID-19 was declared a global pandemic in March 2020. The early descriptions of clinical characteristics among patient cohorts hospitalized with COVID-19 in China, Europe, and the United States consistently noted a high prevalence of individuals with cardiovascular disease and diabetes. In addition, biomarkers of myocardial injury are frequently elevated in patients with COVID-19 and associated with a worse prognosis. Localized thrombosis is a common finding in the lungs, but systemic thrombotic events can also occur.

II. PATHOGENETIC MECHANISMS OF CARDIOVASCULAR DYSFUNCTION IN PATIENTS WITH COVID-19. The potential pathologic mechanisms of cardiovascular dysfunction in patients infected with COVID-19 are as follows:

A. Cytokine release syndrome. Cytokine release syndrome is a systemic inflammatory response that plays a crucial role in the development of cardiovascular complications and is related to underlying disease severity. This inappropriate immune response to the virus can result in end-organ damage.

B. Plaque destabilization. An increased level of catecholamines in response to systemic inflammation may also lead to plaque rupture and destabilization, resulting in acute coronary syndromes. The rupture of atheromatous plaque leads to the exposure of foamy macrophages to the bloodstream. These macrophages express the tissue factor that initiates the formation of microthrombi. Also, the rupture of the plaque exposes vascular smooth muscle cells to the blood flow, which also expresses tissue factor that facilitates the

process of thrombogenesis. In addition, smooth muscle cells may undergo inflammatory activation, which results in the excessive production of inflammatory cytokines.

C. **Prothrombotic state and coagulation disorders.** The activation of coagulation dysregulation in the setting of systemic inflammation can occur through several mechanisms. Polyphosphates derived from microorganisms activate platelets, mast cells, and factor XII of the coagulation cascade. Moreover, the system of complement and components of neutrophil extracellular traps (NETs), as well as the pathogen-associated molecular mechanisms are involved in the activation of the coagulation pathway. The induction of hypoxia-induced factor and endothelial inflammation during hypoxia and systemic inflammatory response may further contribute to the formation of microthrombi.

D. **COVID-19 pandemic as a cardiovascular risk factor.** The indirect effects such as social isolation, chronic stress, change in eating habits, and, for many, reduced physical activity with stay-at-home measures also contribute to cardiovascular risk in patients with preexisting conditions.

III. ASSOCIATION OF CARDIOVASCULAR RISK FACTORS AND DISEASE WITH COVID-19.

Existing data have demonstrated that the following may increase the risk of severe COVID-19 or COVID-19–associated mortality: increased age; male sex; Black, Hispanic, or minority ethnicity; and underlying health conditions including cardiovascular disease and cardiovascular risk factors (eg, hypertension, obesity, chronic kidney disease, diabetes). Previous systematic reviews have illustrated that the presence of cardiovascular disease is associated with more than 3.5 times higher odds of severe COVID-19 and 2.5 times higher likelihood of mortality in patients with COVID-19.

The increased risk of worse outcomes with COVID-19 for patients with cardiovascular disease or cardiovascular risk factors is likely due to underlying changes these risk factors have on inflammatory pathways, immune function, and/or lung function. Cardiovascular risk factors such as diabetes mellitus may lead to immune function dysregulation, which

may, in turn, increase susceptibility and predispose these patients to a severe presentation of COVID-19. Some cardiovascular risk factors including smoking and obesity may impair pulmonary function, resulting in a higher risk of worse outcomes with COVID-19.

Many of the risk factors identified as significantly associated with adverse outcomes with COVID-19 are potentially modifiable. Therefore, primary and secondary prevention strategies, which target these cardiovascular risk factors and conditions, may improve outcomes for people following COVID-19.

IV. IMPACT OF COVID-19 INFECTION ON CARDIOVASCULAR OUTCOMES AND PROCEDURES

A. Ischemic heart disease/acute myocardial infarction. The COVID-19 pandemic disrupted the care of patients with acute myocardial infarction due to both the direct effect of virus on endothelial cells and the pandemic-related factors, such as delay in symptom to the first medical contact and door-to-balloon time. For ST-elevation myocardial infarction (STEMI), the number of hospitalizations decreased with the incidence rate ratio (IRR) of 0.78 (95% confidence interval [CI], 0.72-0.85). In a nationwide database, patients with STEMI with COVID-19 had significantly higher in-hospital mortality rates (18.1%) as compared with patients with non–COVID-19 STEMI (8.2%) (adjusted odds ratio [aOR]: 2.31 [95% CI, 1.70-3.16], $P < .001$). Further, patients with COVID-19 STEMI were more likely to have cardiac arrest, acute kidney injury, and ischemic stroke during the hospitalization.

Similarly, there was a decline in the number of hospitalizations for non–ST-elevation myocardial infarction (NSTEMI) with an IRR of 0.66 (95% CI, 0.60-0.72). In a nationwide analysis, patients with NSTEMI with COVID-19 had significantly higher adjusted in-hospital mortality (9.2% vs 3.4%; aOR: 2.73 [95% CI, 1.98-3.75], $P < .001$) and cardiac arrest. Patients with NSTEMI with COVID-19 were less likely to receive percutaneous coronary intervention (PCI) (27.9% vs 40.8%, $P < .001$; aOR: 0.59 [95% CI, 0.49-0.71], $P < .001$) and coronary artery bypass graft surgery (CABG) (5.9% vs 10.9%, $P < .001$; aOR: 0.38 [95% CI, 0.26-0.56], $P < .001$).

B. Heart failure. COVID-19 can cause heart failure via direct viral infiltration, inflammation, or cardiac fibrosis; may unmask subclinical heart failure in individuals with underlying risk factors; or may exacerbate preexisting heart failure. A meta-analysis demonstrated that there was a significant decline in hospitalizations for heart failure (IRR: 0.66 [95% CI, 0.59-0.73]) but a significant increase in mortality (RR: 1.11 [95% CI, 1.03-1.20]) during the COVID-19 pandemic. Patients surviving hospitalization for heart failure during the pandemic also had higher all-cause mortality at 1 year compared with patients hospitalized in 2019.

C. Thromboembolism. There was a significant increase in the incidence of pulmonary embolism (PE)-related death in 2020 in the United States during the COVID-19 pandemic (49,243 in 2020, 39,450 in 2019, and 38,215 in 2018). In the nationwide cohort, in-hospital mortality among patients with concomitant COVID-19 and PE was significantly higher as compared with patients with PE without COVID-19 (19.2% vs 7.2%, aOR: 3.1 [95% CI, 3.0-3.2], $P <$ .001). In addition, other outcomes including respiratory failure requiring mechanical ventilation, acute renal failure, and cardiac arrest were also significantly higher in patients with concomitant COVID-19 and PE. Further, the utilization of systemic or catheter-directed thrombolysis and mechanical thrombectomy were also less often utilized in patients with COVID-19.

In a cohort study of 48 million adults in England and Wales, COVID-19 was associated with substantial excess incidence of both arterial thromboses and venous thromboembolism (VTE), which declined with time from COVID-19 diagnosis. Excess incidence was higher, for a greater duration, after hospitalization compared to nonhospitalized patients with COVID-19.

1. **Others**
2. **Takotsubo cardiomyopathy.** There was a significant increase in the incidence of stress-induced cardiomyopathy during the COVID-19 pandemic when compared with prepandemic periods.
3. **Medication interactions.** Many of the studied medications in patients with COVID-19 interact extensively with other

cardiovascular drugs, including antihypertensives, antiarrhythmics, anticoagulants, antiplatelets, and statins. Remdesivir can cause hypertension and arrhythmias. Chloroquine and hydroxychloroquine affect the intracellular pH, which can result in electrolyte abnormalities, cardiotoxicity, and prolonged QT intervals; they may also interact with antiarrhythmic agents. Azithromycin may result in dysrhythmias, prolonged QTc, and torsades de pointes. Steroids can cause fluid retention, hypertension, and electrolyte changes. Tocilizumab can cause hypertension and increase the metabolism of statins.

V. MYOCARDITIS AND PERICARDITIS RELATED TO COVID-19. In the pre–COVID-19 era, viral illness has been commonly described as one of the most common causes of myopericardial disease in the general population. The viruses most commonly involved in myocarditis/pericarditis include coxsackie viruses, influenza viruses, adenovirus, human immunodeficiency virus (HIV), cytomegalovirus, and Epstein-Barr virus. Interestingly, coronavirus is not particularly cardiotropic, but given the scale of the pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been associated with myocarditis and pericarditis. Both direct viral invasion of cardiac cells and maladaptive host immune responses have been proposed to result in cardiac injury.

A. Myocarditis. The incidence of myocarditis following COVID-19 infection varies substantially depending on the criteria used for diagnosis. In an international multicenter study from the United States and Europe, the incidence of clinically relevant myocarditis in hospitalized patients with COVID-19 ranged between 0.24% and 0.41%. In another study where cardiac magnetic resonance imaging (MRI) was used to screen 1,597 athletes following COVID-19 infection, the prevalence of clinically suspected myocarditis was estimated to be 0.56%. Overall, the current data suggest that while the risk of clinically significant myocarditis/pericarditis is increased with COVID-19 infection, the overall event rate remains low.

Clinical presentation of COVID-19–related myocarditis is highly variable and ranges from asymptomatic to fulminant pump failure

and cardiogenic shock. Presenting symptoms for myocarditis are generally nonspecific and may include dyspnea, chest discomfort, fatigue, and peripheral edema. The electrocardiogram (ECG) abnormalities observed in myocarditis might include sinus tachycardia, new-onset bundle branch block, QTc interval prolongation, pseudoinfarction patterns, or increased ectopy. Laboratory testing typically shows elevated inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin. Cardiac biomarkers including troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are generally elevated. Echocardiogram frequently shows evidence of left ventricular (LV) dysfunction and/or wall motion abnormalities that are typically diffuse but can be regional in a noncoronary distribution. Cardiac MRI findings include myocardial edema and nonischemic late gadolinium enhancement. Endomyocardial biopsy with histologic examination of the myocardium remains the gold standard for the diagnosis of myocarditis; however, this invasive procedure is not required to establish the diagnosis in most cases.

The management of SARS-CoV-2 myocarditis is generally tailored to the degree of heart failure and hemodynamic profile of each patient. As data supporting targeted therapies in COVID-19 myocarditis are lacking, therapeutic approaches should focus on guideline recommended for pharmacologic therapy for heart failure, careful fluid management, and advanced therapies in refractory cases. Remdesivir, a direct antiviral therapy, is frequently used despite inconsistent benefit in clinical trials. Dexamethasone is reasonable in patients with hypoxemia with pneumonia and may reduce mortality.

B. Pericarditis. The risk of pericardial involvement appears to be higher in patients with SARS-CoV-2, but the exact incidence of pericarditis in patients with COVID-19 is unknown. Patients with COVID-19–related pericarditis typically present with chest discomfort that is sharp and pleuritic with improvement by sitting up or leaning forward. The common ECG findings in such patients include widespread concave ST-segment elevation or PR-segment depression. Inflammatory markers such as CRP, ESR, and ferritin are typically

elevated with negative cardiac biomarkers, including troponin and NT-proBNP (unless concurrent myocardial damage exists). In some patients with COVID-19, pericarditis may lead to a pericardial effusion, which can be detected on echocardiogram, computed tomography (CT), or cardiac MRI. Asymptomatic pericardial effusions can also occur. Cardiac tamponade may develop in a minority of patients, which necessitates urgent pericardiocentesis.

Although evidence is lacking, treatment for COVID-19–related pericarditis is generally akin to that of other causes. The mainstay of treatment remains nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine. The safety of NSAIDs in patients with COVID-19 was questioned after reports of symptoms getting worse in a small number of patients treated with ibuprofen. Given the lack of high-quality evidence, current guidelines including the World Health Organization (WHO) and Food and Drug Administration (FDA) do not recommend against NSAIDs use in patients with COVID-19 who develop pericarditis. Corticosteroids are reserved for patients with contraindications to first-line therapy or who failed treatment.

C. **COVID-19 vaccination and myopericardial disease.** Although rare, vaccine-related myopericardial disease is a well-described phenomenon in the literature. The first case reports of suspected COVID-19 vaccine-related myocarditis/pericarditis emerged in the spring of 2021, a few months following the introduction of COVID-19 messenger RNA (mRNA) vaccines at the end of 2020. Subsequently, larger nationwide studies replicated this observation in the general population. In a large vaccine safety study from Israel, a 3-fold increase in myocarditis risk was observed with the use BNT162b2 mRNA COVID-19 vaccine (Pfizer-BioNtech) compared to controls. Notably, the incidence of vaccine-related myocarditis in that study was substantially lower than cases attributed directly to COVID-19 infection (3 vs 11 cases per 100,000 persons, respectively). Similarly, a recent cohort study of 23 million residents found a 75% increased risk of myocarditis following BNT162b2 vaccine. Other studies from Canada, France, the United Kingdom, and Hong Kong all suggested similar association. Subsequently, a

Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices identified a likely association between the COVID-19 mRNA vaccines and cases of myocarditis and pericarditis.

Importantly, this potentially serious adverse event mostly occurs in young male individuals. This observation was consistent across several large nationwide studies. Further, most of the vaccine-related myocarditis/pericarditis cases were observed in the first few days following vaccination, with higher risk associated with the second vaccine dose compared to the first dose. It remains controversial, however, whether the risk of myocarditis differs based on the type of mRNA vaccine received (BNT162b2 or Pfizer-BioNtech vs mRNA-1273 or Moderna).

Clinically, COVID-19 vaccine-related myocarditis/pericarditis generally presents in a similar but milder manner compared to viral-triggered myocarditis/pericarditis. Most patients tend to present with chest pain within a few days following vaccination, with or without preceding fever or myalgia. Virtually all patients have increased troponin levels at the time of presentation. CRP levels and ESR are typically elevated. ECG abnormalities are commonly encountered and nonspecific. Echocardiogram is frequently unremarkable but may reveal LV dysfunction in some patients. Cardiac MRI is usually abnormal in affected patients, with findings of late gadolinium enhancement and myocardial edema. Most of the reported cases in the literature were hospitalized for observation and management. Although large randomized clinical trials are lacking, supportive care is usually the mainstay of treatment in patients with myocarditis after COVID-19 vaccination. In patients with LV dysfunction, goal-directed medical therapy such as beta-blockers and angiotensin-converting enzymes may be considered as hemodynamically tolerated. As stated previously, the clinical course of vaccine-related myocarditis/pericarditis appears mild, with the vast majority of patients having a resolution of symptoms within a few days. Further, the current evidence suggests that myocarditis/pericarditis related to COVID-19 vaccine has an overall quick recovery with no long-term

complications. Nonetheless, it is reasonable to restrict physical activity and competitive sports similar to other causes of myocarditis.

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CHAPTER 44

Cardio-Obstetrics

Deirdre J. Mattina and Julia M. Simkowski

I. INTRODUCTION. Cardiovascular disease (CVD) is now the leading cause of pregnancy-related deaths. Substantial progress in the management of congenital heart disease (CHD) has occurred over recent decades, allowing patients born with heart defects to now survive into their reproductive years. Advances in reproductive technology have also enabled pregnancy in older mothers, in whom hypertension (HTN) and acquired heart disease are more prevalent and can pose challenges for the pregnancy. Rheumatic heart disease (RHD) is uncommon in the United States but is still encountered in immigrant and international populations and may manifest clinically for the first time in pregnancy. Cardiac disease has significant bearing on both maternal and fetal outcomes. It is multidisciplinary discussion and planning regarding risks and management strategies begin prior to conception when possible, to mitigate pregnancy risks.

II. NORMAL PHYSIOLOGY OF PREGNANCY. A series of cardiocirculatory changes occur in pregnancy and peripartum. These changes usually begin during the early first trimester (5-8 weeks), peak in the late second trimester, and tend to plateau thereafter until the postpartum period. This second-trimester peak in hemodynamic adaptations tends to correlate with the onset of clinical manifestations of cardiac complications during pregnancy.

A. The **increase in blood volume** during pregnancy is attributed to estrogen-mediated stimulation of the renin-aldosterone system, leading to salt and water retention. **The plasma volume expansion varies from 20% to 100% and averages around 50%**. The relatively greater increase in plasma volume as compared with red

blood cell mass leads to the physiologic anemia of pregnancy, which usually manifests around 30 weeks.

B. Cardiac output, stroke volume, and heart rate. **Table 44.1** summarizes the changes in heart rate, stroke volume, and cardiac output. **The cardiac output is estimated to increase by approximately 30% to 50% above baseline**. The increase is attributed to higher preload as a result of increased blood volume, decreased systemic vascular resistance, and an increase in maternal heart rate by 10 to 15 beats/min. During the third trimester, stroke volume and cardiac output are dependent on body position and increase in the lateral position (particularly left lateral) and decline in the supine position because of compression of the inferior vena cava by the gravid uterus.

TABLE 44.1 Normal Hemodynamic Changes During Pregnancy and Postpartum Period

Changes During Different Phases of Pregnancy					
Hemodynamic Parameter	**First Trimester**	**Second Trimester**	**Third Trimester**	**Labor and Delivery**	**Postpartum**
Heart rate	↑5%-10%	↑10%-15%	↑15%-20%	↑20%-30%	↓
Stroke volume	↑5%-30%	↑30%-40%	↓20%-30%	↑300-500 mL with each contraction	↓
Cardiac output	↑5%-30%	↑30%-40%	↑>40%	↑50%	Initial ↑ then ↓
Systolic BP	↔ to ↓	↓	↔ to ↑	↑	Baseline
Diastolic BP	↔ to ↓	↓	↓ to ↔	↑	Baseline
Systemic vascular resistance	↓10%-30%	↓30%-40%	↓30%-40%	↑	Baseline

BP, blood pressure.

C. Blood pressure and systemic vascular resistance. The decline in systemic vascular resistance causes blood pressure to begin to fall in the first trimester and reach a nadir of about 10 mm Hg below

baseline by the end of the second trimester. The addition of low resistance vessels in the uteroplacental bed also contributes to the decrease in afterload.

D. The pulse pressure widens due to the greater fall in diastolic blood pressure than in systolic pressure. As many as 11% of pregnant patients develop **uterocaval syndrome** of pregnancy, with a significant and symptomatic drop in blood pressure when lying supine because of vena caval compression. **Weakening of the vascular walls** of the medium and large muscular arteries occurs because of estrogen-mediated decreased collagen deposition and the effects of circulating elastase and relaxin. This makes patients more susceptible to aortic dissection in pregnancy, especially in individuals with abnormally weak aortic tissue (ie, Marfan syndrome).

E. A hypercoagulable state with decreased protein S, increased stasis, and venous HTN is also observed.

F. Hemodynamic changes during labor and delivery. Each uterine contraction displaces 300 to 500 mL of blood into maternal circulation (autotransfusion). Cardiac output increases by approximately 75% during contractions because of an increase in stroke volume and heart rate. Blood pressure and oxygen consumption also rise. The magnitude of these changes is influenced by the mode of delivery and the method of anesthesia.

G. Hemodynamic changes postpartum. Despite blood loss during delivery (averaging 300-400 mL for vaginal delivery and 500-800 mL for cesarean section), there is a **temporary increase in effective venous return because of autotransfusion and relief of caval compression**. This may lead to an increase in stroke volume and cardiac output, resulting in augmentation in renal blood flow and a brisk diuresis. In pregnant patients with preexisting cardiac disease, these rapid hemodynamic shifts may cause profound clinical deterioration. The hemodynamic changes associated with pregnancy usually persist for a few weeks postpartum, and it may take up to 12 to 24 weeks for the parameters to return to their prepregnancy baseline.

III. RISK ASSESSMENT AND GENERAL PRINCIPLES OF MANAGEMENT. One of the most important steps in managing patients with heart disease considering pregnancy is to establish the level of maternal and fetal risk. Discussions of contraception and reproductive therapies should occur in all patients of reproductive age during routine clinic visits. Preconception counseling should include an assessment of both maternal and fetal risks, the need for medication changes during pregnancy, and the possible need for procedural intervention of underlying cardiac lesions PRIOR TO pregnancy. In addition, **those patients at highest risk for maternal morbidity and mortality should be advised AGAINST pregnancy** and referred to a reproductive specialist to consider other options for motherhood (ie, surrogacy, adoption).

Multiple risk scores have been developed to identify patients at higher maternal and fetal risk and are used commonly in clinical practice, including **CARPREGII** (CARdiac disease in PREGnancy), **ZAHARA** (Zwangerschap bij Aangeboren HARtAfwijking), and the **mWHO** (modified World Health Organization) criteria. The mWHO is based on expert opinion and is often the initial step in risk assessment, while CARPREGII and ZAHARA scores are used as additive measures of lesion-specific risk (**Tables 44.2** to **44.4**). Importantly, these risk calculators offer guidance to providers but must be incorporated with a full clinical assessment, multidisciplinary evaluation, and patient-centered goals and values. **Table 44.5** delineates a stepwise approach to the management of patients with preexisting cardiac disease.

TABLE 44.2 Risk Predictors for Adverse Maternal Outcomes

Modified WHO Risk Classification				
Modified WHO Risk Classification	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**
WHO Risk Class I (No detectable increased mortality)	Uncomplicated pulmonary stenosis, patient ductus arteriosus, mitral valve prolapse.	Once or twice during pregnancy at local hospital	Local hospital	2.5%-5%

Modified WHO Risk Classification				
Modified WHO Risk Classification	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**
	Successfully repaired simple lesions (ASD, VSD, PDA, anomalous pulmonary venous drainage), isolated atrial or ventricular ectopic beats			
WHO Risk Class II	Unrepaired ASD or VSD. Repaired TOF, Turner syndrome with aortic disease, arrhythmias	Every trimester, local hospital	Local hospital	5.7%-10.5%
WHO Risk Class II-III	Mild LV impairment (EF >54%), hypertrophic cardiomyopathy, native or tissue valvular heart disease (not group I or IV), Marfan syndrome without aortic dilatation, bicuspid aortic valve without aortic dilation, repaired coarctation	Bimonthly in an expert center	Expert center	10%-19%
WHO Risk Class III (Significant increased risk	Mechanical valve, systemic RV (normal or mild dysfunction),	Monthly in an expert center	Expert center	19%-27%

Modified WHO Risk Classification				
Modified WHO Risk Classification	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**
of maternal morbidity or mortality)	uncomplicated Fontan, cyanotic heart disease (unrepaired), moderate aortic dilatation, coarctation with residual gradient, moderate MS, severe asymptomatic AS, Marfan with aorta <45 mm, bicuspid aortic valve with aortic root 45-50 mm			
WHO Risk IV (Pregnancy not recommended)	Pulmonary arterial hypertension, severe systemic ventricular dysfunction (EF <30%), systemic RV with moderate dysfunction, previous peripartum cardiomyopathy with residual impairment of LV function, complicated Fontan, severe symptomatic MS or AS, severe aortic dilatation, severe coarctation,	Monthly in an expert center	Expert center	40%-100%

Modified WHO Risk Classification				
Modified WHO Risk Classification	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**	**Modified WHO Risk Classification**
	vascular Ehlers-Danlos, Marfan with aorta >45 mm, bicuspid aortic valve with aorta >50 mm			

AS, aortic stenosis; ASD, atrial septal defect; LV, left ventricular; MS, mitral stenosis; PDA, patent ductus arteriosus; RV, right ventricular; TOF, tetralogy of Fallot; VSD, ventricular septal defect.
Reprinted from Davis MB, Arendt K, Bello NA, et al. Team-based care of women with cardiovascular disease from pre-conception through pregnancy and postpartum: JACC focus seminar 1/5. *J Am Coll Cardiol*. 2021;77(14):1763-1777. With permission from Elsevier.

TABLE 44.3 Risk Predictors for Adverse Maternal Outcomes

CARPREG II	
Risk Factor	**Points**
Prior cardiac event or arrhythmia	3
NYHA class III-IV or cyanosis	3
Mechanical valve	3
EF <55%	2
High-risk left-sided valve disease/LVOT obstruction	2
RVSP >49 mm Hg	2
Coronary artery disease	2
High-risk aortopathy	2
No prior cardiac intervention	1
Late pregnancy assessment	1

Score = 0-1, 5% risk; score = 2, 10% risk; score = 3, 15% risk; score = 4, 22% risk; score>4 = 41%.

EF, ejection fraction; NYHA, New York Heart Association; RVSP, right ventricular systolic pressure.
Reprinted from Davis MB, Arendt K, Bello NA, et al. Team-based care of women with cardiovascular disease from pre-conception through pregnancy and postpartum: JACC focus seminar 1/5. *J Am Coll Cardiol*. 2021;77(14):1763-1777. With permission from Elsevier.

TABLE 44.4 Risk Predictors for Adverse Maternal Outcomes

ZAHARA	
Risk Factor	**Points**
Prior arrhythmia	1.5
NYHA class III/IV	0.75
Mechanical valve prosthesis	4.25
Cyanotic heart disease (corrected and uncorrected)	1.0
Left heart obstruction (peak LVOT gradient >50 mm Hg or aortic valve area <1 cm^2)	2.5
System atrioventricular or pulmonary atrioventricular valve regurgitation (moderate/severe)	0.75
Cardiac medication before pregnancy	1.5

Score = <0.5, 2.9% risk; score = 0.5-1.5, 7.5% risk; score = 1.51-2.50, 17.5% risk; score = 2.51-3.5, 43.1% risk; score >3.5, 70% risk.
NYHA, New York Heart Association.
Reprinted from Davis MB, Arendt K, Bello NA, et al. Team-based care of women with cardiovascular disease from pre-conception through pregnancy and postpartum: JACC focus seminar 1/5. *J Am Coll Cardiol*. 2021;77(14):1763-1777. With permission from Elsevier.

TABLE 44.5 Basic Management Principles for Pregnant Patients With Heart Disease

Risk Assessment
Preconception
Thorough history of cardiac symptoms and arrhythmias
Baseline exercise tolerance and functional class
Baseline ECG and echocardiography with ventricular/valvular function and pulmonary pressures

Detailed discussion with the patient about the potential risks to self and fetus
During pregnancy
Follow-up evaluation at least once per trimester
Close monitoring of new symptoms or change in functional class
Serial echocardiography for development of any new symptoms or signs
Treatment
Preconception
Effective and safe contraception until pregnancy is desired.
Consider valve repair or replacement; correction of anomaly prior to conception if pregnancy poses significant risk of worsening clinical status.
Adjust medications to prevent adverse fetal side effects.
During pregnancy
Minimize medication use to only those absolutely required and discontinue or replace medications contraindicated in pregnancy.
If symptoms worsen and if indicated, consider correction of anomaly or valve repair or replacement.
Labor and delivery
Invasive monitoring as needed
Cesarean section for obstetric indication
Monitor for decompensated heart failure and pulmonary edema and treat accordingly.
Postpartum
Adjust and optimize medications.
Consider correction of anomaly or valve repair or replacement if indicated.
Treat postpartum anemia.
Counseling and contraception for future pregnancies

ECG, electrocardiogram.
Adapted from Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart*. 2007;93(5):552-558, with permission from BMJ Publishing Group Ltd.

Management of a pregnant patient with heart disease is a team effort involving the patient, primary care physician, high-risk obstetric team,

and cardiologist. **Prophylactic intervention for cardiac lesions that significantly increase the risk of pregnancy should be performed BEFORE pregnancy when appropriate and feasible**. Most patients with relatively low-risk cardiac conditions are successfully managed throughout pregnancy, labor, and delivery, with conservative medical measures designed to optimize intravascular volume and systemic loading conditions. As with all pregnancies, medications should be used judiciously and only when absolutely required. Drugs that are contraindicated in pregnancy should be discontinued before conception if pregnancy is contemplated. The management of specific cardiac conditions in pregnancy is described in detail later.

IV. CARDIOVASCULAR EVALUATION IN PREGNANCY

A. History. Fatigue, dyspnea, ankle swelling, and reduced exertional capacity are common in normal pregnancy and can mimic cardiac disease. Chest pain, orthopnea, or paroxysmal nocturnal dyspnea may represent cardiac pathology.

B. Physical examination. **Table 44.6 highlights the important cardiac findings in normal pregnancy. Examination findings that are not physiologic include an S4**, a loud systolic murmur, a purely diastolic murmur, and fixed splitting of S_2 or pulmonary crackles.

TABLE 44.6 Findings in Normal Pregnancy

Symptoms
Fatigue
Dyspnea
Palpitations
Reduced exercise tolerance
Orthopnea
Lower extremity edema
Physical examination
Hyperventilation

Symptoms
Lower extremity edema
Distended neck veins with prominent *a* and *v* waves and brisk *x* and *y* descents
Increased heart rate and wide pulse pressure
Upward and leftward deviation of point of maximal impulse
“Flow” murmurs (pulmonic and aortic)
Mammary soufflé (left sternal border, continuous murmur)
Increased first heart sound and exaggerated splitting of second heart sound
Third heart sound
Electrocardiographic findings
Sinus tachycardia
Leftward axis deviation
Increased R/S ratio in leads V_1 and V_2
Repolarization changes
Echocardiographic findings
Increased LV diastolic dimension
Increased LV wall thickness
Mild increase in contractility
Moderate increase in size of right atrium, right ventricle, and left atrium
Functional pulmonary, tricuspid, and mitral regurgitation
Small pericardial effusion

LV, left ventricular.

C. Cardiac biomarker testing in pregnancy is not well studied. B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are the biomarkers of choice to diagnose heart failure (HF) in nonpregnant patients; however, the positive predictive value in pregnancy is lower. Despite significant hemodynamic changes and cardiac chamber dilation in pregnancy, BNP and NT-proBNP remain relatively stable throughout each trimester, but levels

can be higher than in the nonpregnant state. In addition, small studies have shown elevated natriuretic peptide levels with preeclampsia and preexisting heart disease. Conversely, NT-proBNP levels are lower in pregnant patients who are overweight. Overall, **the negative predictive value of natriuretic peptides is high, and elevated levels should prompt further clinical assessment** **(Table 44.7)**.

TABLE 44.7 Natriuretic Peptide Levels in Pregnancy

B-Type Natriuretic Peptide (BNP)	N-Terminal Pro–B-Type Natriuretic Peptide (NT-proBNP)
50 pg/mL suggested URL (no trimester difference)	200 pg/mL URL—First and second trimesters 150 pg/mL URL—third trimester and postpartum

URL, upper reference level.

Non–high-sensitivity troponins remain negative in normal pregnancy but may increase in the setting of preeclampsia. The normative values of high-sensitivity troponins in pregnancy are not known. **Elevated troponin levels are extremely rare in healthy pregnant patients and warrant further cardiac assessment**.

D-dimer levels increase in normal pregnancy; therefore, standard cutoff values cannot be used for the diagnosis of pulmonary embolism in the pregnant patient. Clinical signs and symptoms should be used to assess the probability of venous thromboembolism, and low D-dimer levels can help identify patients at low risk for pulmonary embolism. **Elevated D-dimer levels in the pregnant or recently postpartum patient WITH clinical symptoms suspicious for pulmonary embolism merits further investigation**.

D. Noninvasive testing in pregnancy is appropriate when it will alter clinical management. Echocardiography and **non–contrast-enhanced** magnetic resonance imaging (MRI) are the preferred imaging modalities in pregnancy. Theoretically, air microbubbles could travel to the placenta and result in placental infarction; thus, echo enhancement with agitated saline is generally deferred until

postpartum. In animal studies, no evidence of fetal harm exists with the use of left ventricular (LV) contrast-enhancing agents, but their use should only be considered if clinically necessary in pregnant and lactating patients. Chest radiography (CXR) should be performed only when absolutely necessary and with shielding of the pelvic area with protective lead. Computed tomography (CT) and nuclear imaging expose both mother and fetus to ionizing radiation and should be minimized/avoided when feasible.

E. Invasive testing with transesophageal echocardiography beyond the second trimester is considered to be "full stomach" status, regardless of fasting time due to decreased gastric motility during pregnancy. In combination with increased intra-abdominal pressure, the risk of aspiration is high and consideration for endotracheal intubation is recommended. Pulmonary artery catheterization (without fluoroscopy) can be utilized during pregnancy, labor, delivery, and the postpartum period for invasive monitoring and can be very useful for patients with hemodynamic compromise. Cardiac catheterization during pregnancy is rarely needed, except in the setting of acute myocardial infarction (MI) or urgent balloon valvuloplasty. Fluoroscopy and cine time should be minimized and direct radiation to the fetus avoided. Vascular access from the arm rather than the leg is preferred whenever feasible.

There is a 3-fold increased risk for teratogenesis, fetal hypoxia, and miscarriage/preterm birth when anesthetic agents are administered in pregnancy. Fetal exposure to ionizing radiation increases the risk of childhood cancer. Fetal radiation exposure should not exceed 50 mGy. Invasive procedures in pregnancy beyond 22 weeks gestation (viability) should include fetal monitoring.

V. PREGNANCY AND CONGENITAL HEART DISEASE. In general, patients with noncyanotic CHD have better outcomes with pregnancy compared to patients with cyanotic disease. Complex CHD is associated with an increased risk of postpartum hemorrhage, preterm birth, and small for gestational age babies. Where applicable, patients should be made aware of the potential inheritability of the congenital disease and referred to a geneticist for informed decision-making.

A. **Atrial septal defect (ASD) and patent foramen ovale (PFO).** Isolated ASD or PFO is usually well tolerated in pregnancy and is considered low-risk lesions. Paradoxical pulmonary embolism during pregnancy has been reported. Filtered intravenous tubing should be used to minimize the risks of air embolism. Ideally, an ASD with a significant shunt (>1.5:1) should be corrected prior to pregnancy. Secundum ASD that is repaired prior to pregnancy is not associated with an increased risk of complications.

B. **Ventricular septal defect (VSD).** Isolated VSD without pulmonary HTN is usually well tolerated during pregnancy, and correction of VSD prior to pregnancy and before the development of pulmonary HTN eliminates the risk. In pregnant patients with VSD and pulmonary HTN, a drop in blood pressure during or after delivery can result in transient shunt reversal. This may be prevented by close monitoring of blood pressure, volume replacement, and the use of vasopressors, if necessary. VSD is commonly inheritable.

C. **Patent ductus arteriosus** without pulmonary HTN usually has a favorable outcome. In patients with pulmonary HTN, the management principles are similar to those with VSD.

D. **Coarctation of aorta (COA).** Although usually associated with favorable outcomes, coarctation has been associated with severe HTN, congestive HF, and aortic dissection during pregnancy. There is also an association with congenitally bicuspid aortic valve (AV) and Circle of Willis aneurysms. Limiting physical activity and controlling blood pressure may prevent dissection and hemorrhage risks. Beta-blockers are usually the antihypertensive drugs of choice, although care should be taken to avoid hypotension as this may compromise uteroplacental circulation. COA with evidence of systemic HTN, HF, or a peak gradient >20 mm Hg should be corrected prior to pregnancy, although this does not alleviate the risk for dissection. Correction of COA during pregnancy is indicated in patients with severe uncontrollable HTN or HF and may be performed percutaneously.

E. **Congenital aortic stenosis (AS).** A congenitally bicuspid AV is one of the most common causes of AS. These patients should be screened

for other cardiac malformations, including COA. **The details of AS management are described later in Section VI C.*

F. Pulmonic stenosis. Isolated pulmonic stenosis is usually well tolerated in pregnancy. It should be corrected prior to pregnancy if severe (peak gradient >60 mm Hg). Percutaneous balloon valvuloplasty during pregnancy may be required in patients with severe right ventricular failure.

G. Ebstein anomaly. Noncyanotic Ebstein anomaly is usually well tolerated. **Patients who are cyanotic are at very high risk for maternal HF and fetal prematurity or death**. During labor and delivery, care should be taken to prevent a drop in blood pressure, and close hemodynamic monitoring is required along with rest, oxygen, and blood gas monitoring. It is sometimes associated with Wolff-Parkinson-White syndrome, and pregnancy may precipitate supraventricular arrhythmias. Tricuspid regurgitation is usually well tolerated during pregnancy.

H. Tetralogy of Fallot (TOF). Patients with TOF who have undergone successful repair during childhood with little or no residual outflow tract gradient, no pulmonary HTN, and preserved ventricular function usually tolerate pregnancy well. In those with uncorrected or only partially corrected TOF, increased blood volume during pregnancy with increased venous return and decreased systemic vascular resistance may result in right-to-left shunt and cyanosis. A similar process may also occur with a fall in blood pressure during labor and delivery. **The outcome of pregnancy is very poor for both mother and fetus once cyanosis occurs**. It is associated with high rates of premature labor, spontaneous abortion, and fetal growth restriction. The risk of a cardiac defect in the neonate ranges from 3% to 17%; genetic counseling and screening for the 22q11 deletion should be offered to pregnant patients with TOF. Patients with residual lesions after partial correction, such as pulmonic regurgitation, right ventricular outflow obstruction, and right ventricular dysfunction, are at risk for HF and arrhythmia during pregnancy.

I. Eisenmenger syndrome. Pregnancy in patients with Eisenmenger is associated with very high maternal mortality, in the range of

30% to 50%, with a 50% risk of fetal loss if the mother survives. Maternal death occurs mostly between the first few days to the first few weeks following delivery because of rapid hemodynamic deterioration. **Patients with Eisenmenger syndrome should be counseled against pregnancy**. Early therapeutic pregnancy termination may be considered, given the danger to the mother (**Table 44.8**). If pregnancy is continued, close monitoring is necessary. Restricted physical activity, continuous oxygen use for at least the third trimester, and consideration of pulmonary vasodilators are recommended. Because of the increased incidence of thromboembolism, anticoagulant therapy is recommended, starting from the third trimester until 4 weeks postpartum. An attempt to assist the second stage of labor (with the use of forceps or vacuum) should be made; cesarean delivery is associated with significantly higher mortality.

TABLE 44.8 Emergency Contraception to Prevent Pregnancy

1. Types: oral levonorgestrel, oral ulipristal acetate, copper intrauterine device (all methods must be administered within 5 d of intercourse.)
2. Emergency contraception has much lower risk relative to continued pregnancy in high-risk patients and can be used in all forms of cardiovascular disease.
3. Bosentan reduces plasma levonorgestrel levels, which can decrease efficacy.
4. Nausea and vomiting for 24 h are common side effects.

J. Pulmonary arterial hypertension (PAH). This is associated with **very high maternal mortality (30%-40%) and poor fetal outcomes**. Worsening of symptoms occurs in the second and third trimesters, and death is usually from right ventricular failure or arrhythmias. Pregnancy should be strongly discouraged in patients with PAH, and early therapeutic pregnancy termination should be considered for those who become pregnant (**Table 44.8**). Anticoagulation should be continued in those with a history of thromboembolism and strongly considered for primary prophylaxis of thromboembolism. There is no consensus on best method of delivery or anesthesia, but close hemodynamic monitoring during labor,

delivery, and the early postpartum period is advised. Oxygen plus pulmonary vasodilators may be used.

K. Cardiomyopathy. This is discussed separately in Section VII.

L. Aortopathy. Genetic counseling is recommended in patients contemplating pregnancy with a first- or second-degree relative or personal history of aortopathy. Patients with underlying connective tissue disease are more susceptible to aortic dissection as the increase in matrix metalloproteinases during pregnancy can weaken large-vessel walls. **Pregnancy in patients with vascular Ehlers-Danlos is not recommended due to high risk for aortic and uterine rupture**.Aortic complications occur most frequently in the third trimester or postpartum**. Mortality from type A dissection in pregnancy is 70%, while type B aortic dissection is associated with 8.6% maternal mortality and 50% fetal mortality**. Serial imaging in pregnancy through 6 months postpartum with echo or noncontrast magnetic resonance angiography is recommended at 4- to 8-week intervals. Pregnancy is deemed most safe when the aorta measures ≤45 mm, but the risk of dissection increases in the presence of other risk factors (ie, family history, rapid expansion of aortic size, HTN). Blood pressure goal is <120 to 130 mm Hg, and beta-blockers are first-line therapy. Vaginal delivery with adequate pain control and an assisted second stage can be considered, although cesarean section at a hospital with cardiothoracic surgery available should be strongly considered in high-risk patients.

VI. VALVULAR HEART DISEASE AND PREGNANCY.

Valve lesions associated with very high maternal and fetal risks include severe mitral stenosis (MS), severe AS, and mechanical valves requiring anticoagulation. Lesions associated with low maternal and fetal risks include pulmonary stenosis and mitral valve prolapse.

- Comprehensive echo and assessment at a tertiary center with a valve team and maternal-fetal medicine obstetricians with expertise in high-risk pregnancy management are recommended for moderate-severe valvular heart disease (VHD).

- Consider exercise stress testing preconception in asymptomatic patients with severe VHD for further assessment of valve hemodynamics and functional status.
- Patients with severe symptomatic VHD should be assessed for valve intervention prior to pregnancy.
- Patients with mechanical valves contemplating pregnancy should be fully informed of high maternal and fetal risks.

A. MS. MS is the most common rheumatic valvular lesion seen in pregnancy and is poorly tolerated. The physiologic changes in pregnancy with increased blood volume and heart rate can lead to an increased pressure gradient across the valve and decreased diastolic filling time. This leads to increases in left atrial pressure and ensuing symptoms of pulmonary edema with dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Atrial fibrillation with rapid ventricular rate often causes further clinical deterioration. Patients with moderate-to-severe MS are more susceptible to these hemodynamic disturbances. The rapid increase in venous return during labor and delivery may cause significant decompensation and requires close monitoring.

Management depends upon the severity of stenosis, symptoms, and time of diagnosis. If MS is diagnosed prior to pregnancy, patients with severe MS (valve area ≤ 1.5 cm^2) or moderate symptomatic stenosis should be offered percutaneous mitral balloon valvuloplasty (PMBV) or valve repair if PMBV is not feasible, before pregnancy. In patients with moderate asymptomatic stenosis, careful assessment of symptoms and exercise tolerance testing can help guide preconception intervention decisions. Optimal management of an already pregnant patient with MS is aimed at reducing heart rate and left atrial pressure. Beta-blockers are the drug of choice, and selective beta1-adrenergic drugs are preferred to nonselective beta-blockers to avoid beta2-adrenergic–mediated uterine relaxation. In patients with atrial fibrillation, digoxin may also be used for ventricular rate control, and full anticoagulation is indicated to minimize thromboembolism risks. Electrical cardioversion can be performed safely during pregnancy if the hemodynamic status warrants

restoration of sinus rhythm. Left atrial pressure may be controlled by judicious use of diuretics (excessive use can lead to reduced uteroplacental perfusion). In patients with symptoms and signs of clinical deterioration despite optimal medical therapy, PMBV may be necessary during pregnancy. This should be avoided in the first trimester if possible, and proper abdominal and pelvic shielding must be used. Echocardiographic guidance by an experienced operator can limit radiation exposure. In cases with severe MS refractory to medical therapy and not amenable to PMBV, mitral valve repair or replacement may be considered.

Cardiopulmonary bypass during pregnancy carries substantial risk of fetal demise and should be performed with normothermic perfusion and high-flow volumes with the mother in the lateral decubitus position to maximize placental perfusion.

Most women with MS can safely undergo vaginal delivery. Patients with symptomatic moderate and severe MS should have a planned induction with telemetry and arterial line monitoring during labor and delivery as well as the immediate postpartum period (12-24 hours). Hemodynamic optimization guided by pulmonary artery catheterization can be considered in select cases. Epidural anesthesia is usually better tolerated than general anesthesia. Tocolytic agents with beta-mimetic effects should be avoided with MS due to tachycardia-mediated elevations in left atrial pressure. An assisted second stage of labor should be used to reduce hemodynamic fluctuations, and cesarean section is generally performed for obstetric indications only.

Fetal and neonatal complications, including intrauterine growth restriction (IUGR), low birth weight (LBW), and fetal death are increased in mothers with MS.

B. **Mitral regurgitation (MR).** The most common cause of MR during pregnancy is either RHD or mitral valve prolapse. MR is usually well tolerated in pregnancy because the fall in systemic vascular resistance leads to decreased LV afterload. For asymptomatic patients with severe MR, valve repair can be considered prior to pregnancy. **Asymptomatic patients with nonsevere MR are managed**

conservatively without any therapy> Symptomatic decompensation may occur due to atrial fibrillation, HTN, or hemodynamic changes in later stages of pregnancy. Symptomatic MR can be treated with beta-blockers, diuretics, and digoxin. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are contraindicated during pregnancy because of their teratogenic effect. Hydralazine may be used in patients with MR and HTN for afterload reduction. Acute MR due to ruptured chordae is rare in pregnancy and may require intra-aortic balloon pump placement and emergent surgery.

C. **AS.** The most common etiology for AS in childbearing age in developed countries is a congenitally bicuspid valve, whereas rheumatic AS is more common in developing nations. Mild-to-moderate AS with preserved LV function is usually well tolerated during pregnancy. **Severe AS (ie, AV area <1.0 cm2 and mean gradient ≥40 mm Hg or aortic valve area index (AVAi) $0.6_2/m_2$, aortic velocity >4 m/s) significantly increases risks during pregnancy and may lead to significant hemodynamic deterioration and HF**. In a large North American cohort, maternal cardiac complications including stroke, cardiac arrest, or death occurred in 10%, HF in 42%, and arrhythmias in 25% of pregnancies with severe AS. **Patients with severe symptomatic AS should be counseled against pregnancy or undergo valve replacement surgery prior to conception**. Medical management of severe asymptomatic AS (confirmed by normal exercise stress testing and serum BNP levels) may be considered. Symptoms such as chest pain, syncope, or dyspnea usually present late in the second trimester or early in the third trimester. Patients with bicuspid AV and aortic root dilation, especially those with COA, are at increased risk for spontaneous aortic dissection.

When severe symptomatic AS is diagnosed during pregnancy, percutaneous aortic balloon valvuloplasty (PABV) should be performed before labor and delivery. Although PABV may reduce the risk of decompensation in patients with severe AS, it has limited durability and only serves as a temporizing measure until the patient

can safely undergo AV replacement. Aortic insufficiency (AI) that occurs as a postprocedural complication of PABV is usually well tolerated during labor and delivery. AV replacement surgery should only be considered for symptomatic severe AS refractory to medical therapy and valve morphology not amenable to PABV. Feasibility of transcutaneous aortic valve replacement (TAVR) in pregnancy is not yet known but can be considered in expert centers with a high-risk cardio-obstetrics team.

Invasive hemodynamic monitoring, as in patients with MS, may be required during delivery. **Spinal anesthesia and epidural anesthesia are discouraged during labor and delivery because of their vasodilatory effects**. Cautious diuresis can be used to mitigate pulmonary edema, but hypotension should be avoided to preserve placental perfusion. Sinus rhythm should be restored as in MS.

Fetal echocardiography should be offered to women with congenitally bicuspid AV as transmission of left-sided obstructive lesions is 10%. **Risks of prematurity and fetal death are high with severe AS in pregnancy**.

D. Aortic regurgitation/AI. AI is generally well tolerated in pregnancy because of the combination of reduced systemic vascular resistance and shortened diastole with the rise in heart rate. AI may be due to congenitally bicuspid valve, infective endocarditis, autoimmune disorder, or aortopathy. When AI is diagnosed, familial and/or genetic screening for aortopathy should be done to determine the risk for aortic dissection and fetal transmission. In symptomatic patients with decompensated HF, diuretics, digoxin, and hydralazine may be used for afterload reduction.

E. Prosthetic heart valves. The type of prosthetic valve implanted in women of childbearing age is controversial. **Where possible, the patient's own valve should be conserved or repaired**. Although bioprosthetic heart valves (BHVs) and homograft valves have a lower risk of thromboembolism and do not require anticoagulation, valve deterioration can occur within 10 years of implantation. Early valve deterioration almost certainly mandates redo valve replacement surgeries. Patients should be made aware of the possibility of valve

degeneration and should be monitored for signs and symptoms of this throughout pregnancy.

Mechanical heart valves (MHVs) confer increased maternal and fetal mortality and morbidity due to the need for anticoagulation> Maternal mortality with MHV is ~1%. Pregnancy is a hypercoagulable state and valve thrombosis occurs in ~5% of patients with MHV during pregnancy. **Management of anticoagulation in pregnancy is challenging, and no anticoagulation strategy is consistently safe for mother and fetus**> The use of Xa and direct thrombin inhibitors is not recommended in pregnancy. **Patients with MHV-contemplating pregnancy should be fully informed of maternal and fetal risks and managed in tertiary centers skilled in anticoagulation management in pregnancy** (**Table 44.9**).

TABLE 44.9 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients With Mechanical Prosthetic Valves

Class I (Benefits >>>Risk): Procedure/Treatment Should Be Performed/Administered	Level of Evidence
All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring.	B
Women with mechanical heart valves who cannot maintain therapeutic anticoagulation should be counseled against pregnancy.	B
Pregnant women with mechanical valve prosthesis who are on warfarin should switch to twice-daily LMWH (with a target anti-Xa level of 0.8-1.2 U/mL at 4-6 h after dose) or intravenous UFH (with an activated partial thromboplastin time 2 times control) at least 1 wk before planned delivery.	C
Women with mechanical heart valves and their providers should use shared decision-making to choose an anticoagulation strategy for pregnancy. Women should be informed that VKA during pregnancy is associated with the lowest likelihood of maternal complications but the highest likelihood of miscarriage, fetal death, and congenital abnormalities, particularly if taken during the first trimester and if the warfarin dose exceeds 5 mg.	B
Pregnant women with valve prosthesis should stop UFH at least 6 h before planned vaginal delivery.	C

Class I (Benefits >>>Risk): Procedure/Treatment Should Be Performed/Administered	Level of Evidence
Pregnant women with mechanical valve prosthesis who are on LMWH should switch to UFH (with an aPTT 2 times the control) at least 36 h before planned delivery.	C
If labor begins or urgent delivery is required in a women therapeutically anticoagulated with a VKA, cesarean section should be performed after reversal of anticoagulation.	C
Class IIa (Benefits >>Risk): It Is Reasonable to Perform Procedure/Administer Treatment	
For pregnant women with mechanical prostheses who require a dose of warfarin ≤5 mg/d to maintain a therapeutic INR, continuation of warfarin for all three trimesters is reasonable after full discussion with the patient about risks and benefits.	B
For pregnant women with mechanical prostheses who require >5 mg/d of warfarin to achieve a therapeutic INR, dose-adjusted LMHW (with a target anti-Xa level of 0.8-1.2 U/mL at 4-6 h after dose) at least 2 times per day during the first trimester, followed by a warfarin during the second and third trimesters, is reasonable.	B
For pregnant women with mechanical prostheses who require a dose of warfarin >5 mg/d to achieve a therapeutic INR, and for whom dose-adjusted LMWH is unavailable, dose-adjusted continuous intravenous UFH during the first trimester (with aPTT 2 times control), followed by warfarin for the second and third trimesters, is reasonable.	B
For hemodynamically stable pregnant women with obstructive left-sided mechanical valve thrombosis, it is reasonable to manage with slow-infusion, low-dose fibrinolytic therapy.	B
Class IIB	
For pregnant women with mechanical prostheses who require a warfarin dose >5 mg/d to achieve a therapeutic INR, dose-adjusted LMHW (with a target anti-Xa level of 0.8-1.2 U/mL at 4-6 h after dose) at least 2 times per day for all 3 trimesters may be considered.	B
For pregnant women with mechanical prostheses who require a dose of warfarin <5 mg/d to maintain a therapeutic INR, dose-adjusted LMHW at least 2 times a day during the first trimester, followed by warfarin for the second and third trimesters, may be considered.	B
For pregnant women with mechanical prostheses, aspirin 75-100 mg daily may be considered, in addition to anticoagulation, if needed	B

Class I (Benefits >>>Risk): Procedure/Treatment Should Be Performed/Administered	Level of Evidence
for other indications.	
Class III (Risk ≥Benefits): Procedure/Treatment Should Not Be Performed/Administered	
The use of anti-Xa direct oral anticoagulants with mechanical heart valves in pregnancy has not been assessed and is not recommended.	C
For patients with mechanical valve prostheses, anticoagulation with the direct thrombin inhibitor, dabigatran, should not be administered.	B
LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4-6 h after administration	B

Level of evidence: A, multiple population risk strata evaluated; B, limited population risk strata evaluated; C, very limited population risk strata evaluated.

aPTT, activated partial thromboplastin time; ASA, aspirin; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol*. 2014;63(22):e57-e185.

Risks for miscarriage, prematurity, small for gestational age, and fetal death are greater with MHV than BHV.

VII. CARDIOMYOPATHY IN PREGNANCY

A. Peripartum Cardiomyopathy (PPCM). This is defined as an idiopathic cardiomyopathy with an EF <45% presenting toward the end of pregnancy or in the months following delivery, in the absence of other identifiable or preexisting cause of HF. The incidence of PPCM in the United States is estimated to be 1 in 1,000 to 1 in 4,000 live births, and >40% of cases occur in Black mothers. Maternal risk factors for PPCM include **age>30, African American descent, residency in the Southern United States, multifetal pregnancies, diabetes, and hypertensive disorders of pregnancy (HDP)**> Symptoms include fatigue, dyspnea, peripheral edema, and

abdominal discomfort and distention. Because these symptoms are often experienced with normal pregnancy, delays in diagnosis of PPCM are common. Elevated BNP and pulmonary edema are not typically seen in normal pregnancy and should prompt immediate evaluation for cardiac dysfunction.

Our understanding of the pathophysiology of PPCM continues to evolve, but current research suggests that there is an imbalance of placental hormones leading to microvascular dysfunction coupled with a genetic predisposition and other disease-provoking risk factors. Standard management of pregnant patients presenting with decompensated HF includes oxygen, diuretics, digoxin, hydralazine, and nitrates. ACE-Is/ARBs and spironolactone are contraindicated in pregnancy but should be commenced postpartum. Angiotensin receptor blockers/neprilysin inhibitors (ARNIs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), and ivabradine have not been studied in pregnant and lactating people. The hypercoagulable state of pregnancy combined with severe systolic dysfunction increases the risks of thromboembolism, and anticoagulation should be considered with EF <30% to 35%. Very limited data have shown improved LV recovery and reduced HF end points in select populations, given bromocriptine (a prolactin inhibitor). The use of bromocriptine remains experimental in the United States and a class IIb, Level of Evidence B recommendation in the 2018 European Society of Cardiology (ESC) guidelines. Although breastfeeding was initially discouraged in PPCM due to presumed prolactin-driven endothelial dysfunction, a contemporary registry—*Investigations of Pregnancy-Associated Cardiomyopathy (IPAC)*—has shown no association with breastfeeding and persistent LV dysfunction. The decision to breastfeed should remain a personal choice for mothers with PPCM and should not be discouraged by providers. If bromocriptine is used in the management of PPCM, patients should be counseled that breastfeeding will no longer be feasible. Wearable cardiac defibrillators should be considered for patients with PPCM and EF <35%.

Approximately 70% of patients completely recover LV function within 6 months of delivery. The remainder either experience stable

LV dysfunction or continue to experience clinical deterioration, and prognosis is worse in Blacks compared to Whites. Patients with severe LV dysfunction and decompensation should be evaluated for cardiac transplantation or mechanical support after pregnancy. **Patients without recovery of EF >50% have a 50% risk of acute HF or worsening cardiomyopathy in subsequent pregnancies, and mortality is 25% to 50%. Subsequent pregnancy should be discouraged in patients with a history of PPCM WITHOUT recovery of EF >50%**> Those WITH recovery of EF have a 20% risk of worsening HF in subsequent pregnancies and should be managed in experienced centers. Patients with persistent LV dysfunction should avoid estrogen-containing contraceptives postpartum.

Rates of stillbirth, spontaneous abortion, and preterm delivery are more common in women with persistent LV dysfunction.

B. Hypertrophic cardiomyopathy (HCM). Most asymptomatic patients with HCM have a favorable outcome during pregnancy; however, the overall morbidity and mortality with HCM and pregnancy is higher than that in the general population. Symptoms such as chest pain, palpitations, dyspnea, and syncope may occur and are more common in women who were symptomatic prior to pregnancy. Atrial fibrillation with hemodynamic deterioration and ventricular fibrillation (VF) can occur.

Basic tenets of management in the pregnant patient with HCM include maintenance of adequate intravascular volume to maintain appropriate LV end-diastolic volume, as well as avoidance of tachycardia, both of which decrease LV outflow tract gradients. Blood loss, volume depletion, and vasodilators should be avoided. Beta-blockers are usually the drug of choice for symptomatic patients. Patients with a history of syncope, life-threatening arrhythmias, or a family history of sudden cardiac death should be considered for prophylactic implantable defibrillators prior to pregnancy because of the potential arrhythmogenic effect of pregnancy.

Vaginal delivery is considered safe, but tocolytics with beta-adrenergic properties and prostaglandins should be avoided. Epidural

anesthesia is used with caution because of the peripheral vasodilatory effect, and excessive blood loss should be promptly repleted with fluids or blood transfusion. The brisk diuresis immediately postpartum may lead to a rapid decrease in intravascular volume and, therefore, a symptomatic increase in outflow tract gradient. This can be avoided by gentle intravenous hydration decreasing over 24 to 48 hours postpartum.

There is an increased risk of fetal prematurity and fetal inheritability approaches 50% in certain familial forms of HCM.

C. Other cardiomyopathies. Management of cardiomyopathy due to atherosclerosis, spontaneous coronary artery dissection (SCAD), and other nonischemic cardiomyopathies is similar to nonpregnant patients, with the exception of avoidance of medications known to be teratogenic. **See Section II on heart failure and transplant for guideline-directed medical therapy of cardiomyopathy.*

D. Pregnancy after cardiac transplantation. Pregnancy after cardiac transplantation is considered high risk for mother and fetus. Maternal morbidity is increased from HTN, preeclampsia, renal failure, premature rupture of membranes, and infection. Pregnancy care in this high-risk population would require a multidisciplinary team at an expert center.

Fetal growth restriction and preterm labor risks are increased, along with potential adverse fetal effects of immunosuppressive medications.

III. ACUTE CARDIOVASCULAR DISORDERS AND PREGNANCY

A. Coronary artery disease (CAD). MI during pregnancy is rare; **coronary spasm, in situ coronary thrombosis, and SCAD are more frequently the underlying precipitants of MI** rather than obstructive atherosclerosis. Most MIs occur during the third trimester. Risk factors include age >30, smoking, chronic HTN, diabetes mellitus (DM), and multigravida state. **Maternal mortality is 11% and fetal mortality is 9% for MI in pregnancy**> Acute MI may be the initial clinical manifestation of an underlying hypercoagulable state, such as the antiphospholipid antibody syndrome. The diagnosis

of acute MI in the pregnant patient should follow guidelines established for the general population, and coronary angiography should occur without delay. Medical management with aspirin, beta-blockers, and nitrates is considered safe. Short-term heparin administration has not been associated with increased maternal or fetal adverse effects. Clopidogrel, ticagrelor, and prasugrel have no known fetal harm but should be held 5 to 7 days prior to delivery. Thrombolytics are relatively contraindicated and should only be used emergently when primary percutaneous coronary intervention (PCI) is not available. The U.S. Food and Drug Administration (FDA) recently removed its recommendation that statins are contraindicated in pregnancy and use of hydrophilic statins (ie, pravastatin, rosuvastatin) should be considered on an individual basis. **See Section I on ischemic heart disease for the management of acute coronary syndromes.*

B. Aortic dissection. Aortic dissection during pregnancy has been reported in patients with Marfan syndrome, chronic HTN, COA, Turner syndrome, and cocaine use. It occurs most commonly in the third trimester and the peripartum period. Beta-blocker is the preferred medication for the management of HTN and to reduce LV wall stress during pregnancy. Emergent surgical repair is high risk for the mother and fetus but may be necessary to preserve the mother's life.

IX. ARRHYTHMIAS AND PREGNANCY. Synchronized cardioversion is safe during all stages of pregnancy. Antiarrhythmic medications in pregnancy and lactation are reviewed in **Table 44.10**. Catheter ablation during pregnancy should be reserved for arrhythmias refractory to medical management and be performed after the first trimester if feasible. Fetal radiation can be reduced with the use of contemporary three-dimensional (3D) mapping systems and decreased frame rates during fluoroscopy. Implantable cardioverter-defibrillators (ICDs) should be placed when indicated by standard practice guidelines.

TABLE 44.10 Antiarrhythmic Medications in Pregnancy and Lactation

Medication	Previous Categorization	Pregnancy	Lactation
Class Ia			
Quinidine	C	Weigh options, risks, vs benefits	May use while breastfeeding. Excreted in low levels in breast milk; not expected to cause infant harm based on limited excretion into milk
Procainamide	C	Weigh options, risks vs benefits	Caution advised while breastfeeding. Excreted in low levels in breast milk; not expected to cause infant harm based on limited excretion into milk
Disopyramide	C	Weigh options, risks vs benefits Risk of uterine contractions	May use while breastfeeding. Monitor infant for anticholinergic effects; may decrease breast milk production
Class Ib			
Lidocaine	B	Weigh options, risks vs benefits	May use while breastfeeding. No known risk of infant harm based on limited human data and drug properties. May decrease milk production
Mexiletine	C	Weigh options, risks vs benefits	Caution advised while breastfeeding. Excreted in low levels in breast milk; not expected to cause harm in infants older than 2 mo; monitor for infant toxicity
Class Ic			
Flecainide	C	Weigh options, risks vs benefits	May use while breastfeeding. Excreted in low levels in breast milk; not expected to cause harm in infants based on limited excretion in milk
Propafenone	C	Weigh options, risks vs benefits	May use while breastfeeding. Excreted in low levels in breast milk; not expected to

Medication	Previous Categorization	Pregnancy	Lactation
			cause hard in infant harm based on limited excretion in milk
Class II			
Metoprolol	C	Weigh options, risks vs benefits Bradycardia, hypoglycemia	May use while breastfeeding. No known risk of infant harm based on limited human data and limited excretion in milk
Atenolol	D	Use alternative agent IUGR, bradycardia, hypoglycemia	Recommend an alternative beta-blocker. Drug excreted extensively in breast milk; risk of bradycardia in the infant; infants older than 3 mo appear to be at little risk of adverse effects
Propranolol	C	Weigh options, risks vs benefits Bradycardia, hypoglycemia	May use while breastfeeding. No known risk of infant harm based on human studies. Low levels excreted in breastmilk
Class III			
Amiodarone	D	Weigh options, risks vs benefits. Congenital goiter, bradycardia, and QT-interval prolongation risk	**May be unsafe.** Excreted in breast milk in variable amounts for weeks, even after mother discontinues medication. Can reduce milk production if mother develops hypothyroidism. Infant may develop hypothyroidism and requires monitoring. No information on iodine levels excreted into breast milk.
Sotalol	B	Weigh options, risks vs benefits Bradycardia, hypoglycemia	**May be unsafe.** Extensively excreted in breast milk and renal excretion; infants need to be monitored closely if prescribed. No reports of bradycardia in infants whose mothers were on sotalol

Medication	Previous Categorization	Pregnancy	Lactation
Ibutilide	C	Weigh options, risks vs benefits	May use while breastfeeding. No human data available, but infant harm not expected based on drug properties
Dofetilide	C	Weigh options, risks vs benefits Risk of teratogenicity at ≥2 mg/kg/d based on animal studies	Possible excretion in breast milk based on drug properties
Class IV			
Verapamil	C	Weigh options, risks vs benefits	Caution advised while breastfeeding. Excreted in breast milk in low levels; not expected to harm infants, especially if greater 2 mo of age; can cause hyperprolactinemia and galactorrhea
Diltiazem	C	Weigh options, risks vs benefits	Caution advised while breastfeeding. <1%-2% excreted in breast milk. Not expected to cause infant harm based on drug properties
Class V			
Adenosine	C	Weigh options, risks vs benefits	May use while breastfeeding. Has a short half-life; not expected to cause infant harm based on drug properties
Digoxin	C	Weigh options, risks vs benefits	May use while breastfeeding. Excreted in breast milk at low levels; no known risk of infant harm based on limited human data. If given intravenously, avoid breastfeeding for 2 h.

IUGR, intrauterine growth restriction.
From Park K, Bairey Merz CN, Bello NA, et al. Management of women with acquired cardiovascular disease from pre-conception through pregnancy and postpartum: JACC focus seminar 3/5. *J Am Coll Cardiol*. 2021;77(14):1799-1812. Data from LactMed online resource by the National Library of Medicine's TOXNET and epocrates drug database. LactMed is a registered trademark of the U.S. Department of Health and Human Services.

A. Benign ectopy. Premature atrial complexes and premature ventricular complexes are the most frequent rhythm disturbances of pregnancy and are not associated with adverse maternal or fetal outcomes. Beta-blockers can be considered for severe symptoms, with caution to avoid hypotension.

B. Atrioventricular nodal reentrant tachycardia is the most common supraventricular arrhythmia in pregnant and nonpregnant females. Vagal maneuvers are safe in pregnancy. Adenosine may be administered to the pregnant patient for both diagnostic and therapeutic purposes.

C. Atrial fibrillation and atrial flutter. Management of atrial fibrillation in pregnancy is not addressed in the 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines. Rate control may be achieved with digoxin, beta-blockers, and nondihydropyridine calcium channel antagonists. Thromboembolic risk assessment tools have not been validated in pregnant patients, but pregnancy is a known hypercoagulable state. **See Section XIII C for use of anticoagulants in pregnancy.*

D. Congenital long QT syndrome. The risk of sudden death with long QT syndrome can persist as long as 9 months postpartum (highest risk in those with LQT2 genotype). Beta-blockers should be continued during pregnancy and postpartum to mitigate arrhythmogenic risks.

E. Postural orthostatic tachycardia syndrome (POTS). POTS is a challenging condition with limited effective medical therapy. Symptoms can remain unchanged, worsen, or improve in pregnancy. Conservative measures of increased salt and fluid intake, along with compression socks are initial management tools. Data are limited on

the efficacy of propranolol, fludrocortisone, or midodrine in pregnancy, but they can be considered for severe refractory symptoms to prevent syncope.

F. Ventricular tachycardia (VT) and VF are rare during pregnancy. They may, however, be the presenting manifestation of PPCM. VT has also been associated with thyrotoxicosis and hyperemesis gravidarum (due to electrolyte disturbances). Most antiarrhythmic medications used to treat VT/VF are safe during pregnancy, **except for amiodarone**, which should be used with extreme caution after failure of other medications, because it may lead to **neonatal hypothyroidism**. In addition, combined hormonal contraceptives may increase amiodarone levels, and QTc monitoring is warranted.

X. HYPERTENSIVE DISORDERS OF PREGNANCY. Hypertensive disorders are the most common adverse pregnancy outcome (APO) and complicate 5% to 10% of pregnancies. Prevalence is markedly increased in Black and American Indian/Alaskan Native populations. Blood pressure treatment is aimed at minimizing maternal end-organ damage (such as LV hypertrophy, renal failure, or intracerebral hemorrhage), balanced against concerns that excessive pressure lowering may negatively impact fetal growth. The most commonly used antihypertensives and their potential adverse effects during pregnancy are shown in **Table 44.11**. Postpartum blood pressure evaluation is recommended within 72 hours after hospital discharge in patients with HDP. HDPs are associated with increased risks of essential HTN and long-term CVD. **2021 USPSTF guidelines recommend prophylactic aspirin 81 mg/daily after 12 weeks of gestation for pregnant patients at high risk for preeclampsia or with ≥2 moderate-risk factors for preeclampsia**> HDP can be broadly classified into chronic HTN, gestational HTN, and the preeclampsia-eclampsia spectrum.

TABLE 44.11 Cardiovascular Drugs and Pregnancy/Lactation

Drug	Use in Pregnancy	Use in Lactation	Adverse Effects
Aspirin	First choice antiplatelet for	Low-dose used for CVD. Appears in	Safe in doses ≤150 mg. High doses

Drug	Use in Pregnancy	Use in Lactation	Adverse Effects
	CVD, prevention of premature birth and preeclampsia	subclinical amounts in human milk	increase the risk of gastroschisis, premature closure of ductus arteriosus, and fetal bleeding risk.
Clopidogrel	May be used (shortest duration necessary). Must be stopped 5-7 d before regional anesthesia	Weigh risk/benefits. Low risk of infant harm based on limited human data and drug properties	No adverse effects in animal studies. Limited human data
Prasugrel, ticagrelor, cangrelor	May be used (shortest duration necessary). Must be stopped 5-7 d before regional anesthesia	Weigh risk/benefits. No human data, but drug excretion into milk possible based on drug properties	Ticagrelor crosses the placenta. No reported complications with prasugrel
Ranolazine	Unknown	Unknown	Maternal toxicity and osseous deformities seen in animal studies. Limited human data. Current recommendation is use during pregnancy only when potential benefit to patient justifies potential fetal risk.
Tirofiban/eptifibatide	Unknown	Unknown	Not well studied. Case reports indicate may be safe, but data are limited. Eptifibatide’s

Drug	Use in Pregnancy	Use in Lactation	Adverse Effects
			short half-life may allow safe use close to delivery.
Beta-blockers Labetalol Atenolol Metoprolol Carvedilol Propranolol	Labetalol first line for HTN management Metoprolol preferred in ACS and CHF (avoids beta2-mediated uterine relaxation and peripheral vasodilation). Atenolol contraindicated	Weigh risk/benefits Labetalol and metoprolol are safe; carvedilol has unknown risk. Avoid atenolol if possible. Low levels found in breast milk.	Atenolol has been associated with birth defects/IUGR.
Calcium channel blockers Nifedipine Verapamil Diltiazem Amlodipine	Nifedipine is first line for HTN and tocolysis (when used with magnesium). Verapamil fairly safe (second line after beta-blockers for rate control) Amlodipine probably safe for HTN	Nifedipine is safe. Weigh risk/benefits of verapamil and diltiazem. Excreted at low levels in breast milk, but no harm expected based on drug properties	Possible prematurity, IUGR, fetal bradycardia in some CCB No known teratogenicity based on limited human data Tocolytic effects may cause maternal hypotension and placental hypoperfusion.
Vasodilators Nitroprusside Hydralazine Nitroglycerin	May be used for CAD, CHF, and HTN. Concern for fetal cyanide toxicity at high doses of nitroprusside	Weigh risk/benefits. Limited data. Possible harm with nitroprusside	Crosses placenta; potential hypotension
Statins	Weigh risk/benefits Hydrophilic statins (rosuvastatin and pravastatin)	Weigh risk/benefits. Hydrophilic statins (rosuvastatin and	Limited human data. Contemporary studies with no

Drug	Use in Pregnancy	Use in Lactation	Adverse Effects
	may be considered on an individual basis. [a]**No longer contraindicated by the FDA.**	pravastatin) may be considered on an individual basis. [a]**Not recommended by the FDA.**	significant signal of teratogenicity. Use in first trimester correlated with premature birth
Bile acid sequestrants	Considered safe for dyslipidemia management	Considered safe. Limited data	May lower fat-soluble vitamins
ACE-Is/ARBs	Contraindicated	Captopril, benazepril, enalapril, and quinapril are considered safe. No infant harm expected by low levels excreted in breastmilk. Conflicting data for ARBs, currently contraindicated	Fetal renal and cardiac abnormalities
Inotropic agents Dopamine Dobutamine Epinephrine	May be used	Probably safe	No adverse fetal effects. Dopamine may inhibit prolactin release.
Diuretics Hydrochlorothiazide Furosemide Spironolactone	Spironolactone contraindicated in pregnancy	May be used	Possible placental hypoperfusion Risk of fetal antiandrogenic effects at high doses of spironolactone in animal studies
Methyldopa	May be used. Avoid if history of depression.	May be used	Not currently available in the United States

ACE-Is, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CAD, coronary artery

disease; CHF, congestive heart failure; CVD, cardiovascular disease; FDA, Food and Drug Administration; HTN, hypertension; IUGR, intrauterine growth restriction.

[a]Adapted from Park K, Bairey Merz CN, Bello NA, et al; American College of Cardiology Cardiovascular Disease in Women Committee and the Cardio-Obstetrics Work Group. Management of women with acquired cardiovascular disease from pre-conception through pregnancy and postpartum: JACC focus seminar 3/5. *J Am Coll Cardiol*. 2021;77(14):1799-1812. PMID: 33832606.

Fetal complications including preterm birth and IUGR are increased with HDP.

A. Chronic HTN is defined as blood pressure of 140/90 mm Hg before pregnancy, before 20 weeks of gestation, or persisting beyond 3 months postpartum. It is associated with increased maternal and fetal morbidity and elevates the risk of preeclampsia. The recent Chronic Hypertension in Pregnancy Trial (CHAP) showed better pregnancy outcomes without increased fetal risks when targeting a blood pressure <140/90 mm Hg in comparison to treating only severe HTN (≥160/105 mm Hg).

B. Gestational HTN is defined as HTN induced by pregnancy and diagnosed after 20 weeks of gestation, with resolution prior to 3 months postpartum.

C. Preeclampsia is defined as HTN after 20 weeks of gestation with proteinuria OR signs/symptoms of organ dysfunction. Onset of preeclampsia is usually in the third trimester with rapid resolution after delivery, although postpartum cases are reported. Intravenous labetalol and hydralazine along with magnesium should be used to treat acute severe HTN, followed by oral nifedipine (**Tables 44.12** and **44.13**).

TABLE 44.12 Diagnostic Criteria for Preeclampsia/Eclampsia

Blood pressure (after 20 wk of gestation)	≥140/90 mm Hg on two occasions **OR** ≥160/100 mm Hg once (confirmed)
AND	
Proteinuria	• ≥300 mg/24 h urine collection • Protein/creatinine ratio ≥0.3 mg/dL

	• 2+ dipstick
OR	
Thrombocytopenia	<100K
Renal insufficiency	• Creatinine >1.1 mg/dL • 2× baseline creatinine
Liver dysfunction	Transaminases >2× upper normal level
Pulmonary edema	
Neurologic symptoms	New headache or visual disturbances

Adapted from Gestational hypertension and preeclampsia ACOG Practice Bulletin, Number 222. Obstet Gynecol. 2020;135(6):e237-e260.

TABLE 44.13 Risk Factors for Preeclampsia

- Chronic HTN
- Chronic kidney disease
- Autoimmune disorders
- Diabetes mellitus/gestational DM
- First pregnancy
- Multifetal gestation
- Family history of preeclampsia
- BMI >35 kg/m^2
- African-American Ethnicity
- Nulliparity
- Maternal age >40
- Pregnancy interval >10years

BMI, body mass index; DM, diabetes mellitus; HTN, hypertension.

Eclampsia is the development of grand mal seizures in the setting of preeclampsia.

When preeclampsia/eclampsia is accompanied by poor prognostic features—severe HTN, **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets), placental abruption, cerebral hemorrhage, pulmonary edema, or renal failure—the fetus must be delivered immediately to normalize blood pressure.

XI. GESTATIONAL DIABETES. Gestational diabetes mellitus (gDM) affects of pregnancies in the United States. (more updated data suggests 5-14%) Insulin resistance increases in pregnancy. Maternal risk factors for gDM include obesity, advanced maternal age, prior history of gDM, family history of diabetes, and Hispanic, Native American, South Asian, East Asian, or Pacific Islander heritage.

Management of gDM includes:

- Nutrition and exercise counseling: 30 minutes of moderate-intensity aerobic exercise 5 days a week, or 150 minutes per week. Consider referral to a dietician/diabetes educator.
- Insulin is the preferred pharmacotherapy.
- If unable to afford or safely use insulin, metformin is an acceptable alternative.
- There is limited safety data for other oral diabetic agents in pregnancy.

Delivery for well-controlled gDM is recommended at term. Late- or early-term delivery (38-39 weeks of gestation) is suggested if vascular complications are present. A scheduled cesarean delivery should be considered by a multidisciplinary team if the estimated fetal weight is 4,500 g or more.

In large cohort studies, **patients with a history of gDM have up to 20-fold higher risk of type 2 diabetes mellitus (DMII), 2-fold higher risk of chronic HTN, and 2.8-fold higher risk of ischemic heart disease**> They also have a 40% risk of recurrent gDM in subsequent pregnancies. Testing for gDM should occur at 24-28 weeks of gestation in patients without prior known DMII. Patients with gDM should be tested for prediabetes or DMII at 4-12 weeks postpartum and then every

1-3 years thereafter. Cardiology practitioners should routinely screen for a history of gDM to accurately assess future CV risk.

Fetal risks of gDM include fetal macrosomia, large for gestational age, shoulder dystocia, neonatal hypoglycemia, birth injury, and preterm delivery.

XII. DYSLIPIDEMIA AND PREGNANCY. Physiologic changes in glucose and lipid metabolism in pregnancy result in increased total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels, while high-density lipoprotein cholesterol (HDL-C) levels decline. Total cholesterol can increase by 35% and peak near term. Statin therapy is no longer contraindicated during pregnancy. *See Section XIII D. Bile acid sequestrants are safe in pregnancy and can lower LDL-C by 15% to 30%. Limited data are available on the use of statins during breastfeeding; however, bile acid sequestrants are considered safe during breastfeeding.

High triglyceride and low HDL-C levels increase the risk for large of gestational age and macrosomia. There is no data showing an increased risk of fetal complications for patients with familial hypercholesterolemia, however.

XIII. MEDICATION CONSIDERATIONS IN PREGNANCY AND POSTPARTUM

A. CV drugs. The most commonly used CV drugs and potential adverse effects during pregnancy/lactation are shown in **Table 44.11**.

B. Antiarrhythmics. The most commonly used antiarrhythmics and their potential adverse effects during pregnancy/lactation are shown in **Table 44.10**.

C. Anticoagulants. Conditions requiring anticoagulation during pregnancy include mechanical prosthetic heart valves, chronic atrial fibrillation, history of venous thromboembolism, Eisenmenger syndrome, antiphospholipid antibody syndrome, and inherited deficiencies predisposing to thromboembolism (eg, prothrombin gene mutation and factor V Leiden deficiency).

The three most common agents considered for use during pregnancy are **unfractionated heparin (UFH), low-molecular-**

weight heparin (LMWH), and warfarin. The Ninth Edition of the American College of Chest Physician's evidence-based clinical practice guidelines on antithrombotic therapy and prevention of thrombosis recommends LMWH for the prevention and treatment of venous thromboembolism in pregnancy. For pregnant patients with MHVs, warfarin is recommended in the first trimester if the daily dose is <5 mg and for all patients in the second and third trimesters. For those in whom the daily dose of warfarin >5 mg, LMWH twice daily with through anti-Xa levels for monitoring (between 0.7-1.2 and 1.0-1.2 U/mL) or a continuous infusion of UFH with a partial thromboplastin time (PTT) ≥twice the control is recommended during the first trimester. The 2020 AHA/ACC Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves are presented in **Table 44.5**. Ultimately, the choice of anticoagulation regimen depends on the preferences of the patient and physician after consideration of the maternal and fetal risks associated with the use of each drug, and **no anticoagulant therapy is consistently safe in pregnancy**.

The incidence of warfarin embryopathy (fetal bone and cartilage formation abnormalities) has been estimated at 4% to 10%; the risk is highest when warfarin is administered during the 6th through the 12th week of gestation and is dose dependent. When administered during the second and third trimesters, warfarin has been associated with fetal optic atrophy, microcephaly, intellectual disability, spasticity, and hypotonia. Other risks include neonatal intracranial hemorrhage and retroplacental hematoma.

D. Statins. The FDA no longer considers statins contraindicated in pregnancy. The use of hydrophilic statins (ie, pravastatin, rosuvastatin) should be considered on an individual basis.

E. Antibiotics. The 2018 ACC/AHA guidelines on the management of adults with CHD suggest it is reasonable to consider antibiotics at the time of membrane rupture prior to vaginal delivery for patients with prosthetic cardiac material or unrepaired/palliated cyanotic defects.

F. Contraception. Contraceptive counseling and pregnancy planning for female CV patients of reproductive age are critically important for

the health and survival of both mother and baby. The 2021 JACC Focus Seminar on Cardio-Obstetrics by Lindley et al identified lapses in preconception counseling and contraceptive prescribing to CV patients and offers the following recommendations:

- Preconception counseling (including current method of contraception and desire for pregnancy) and sexual health counseling are recommended to begin in pediatric cardiology clinics for teenage patients, and continue into adulthood, at regular intervals.
- The values and preferences of the patient should guide the conversation and subsequent recommendations made with shared decision-making among the patient's cardiologist, obstetrician-gynecologist, and primary care provider.
- Patients who desire a highly effective method of contraception should be promptly referred to an experienced provider.
- It is important to recognize the risk that pregnancy poses for the patient based on their individual condition and assess if the current method of contraception offers appropriate protection. See **Tables 44.2** to **44.4**.
- It is important to recognize social determinants of health that affect access to contraception (Black or Hispanic, low income, lower level of education, insurance status, geographic location, age) and help eliminate barriers to equitable care when feasible.

IV. DISPARITIES IN PREGNANCY CARE. In contrast with every other high-income nation, maternal mortality in the United States has been rising for the past three decades. Eighty percent of pregnancy-related deaths are preventable, and the majority of deaths are due to CV causes. Pregnant patients without medical insurance and those with Medicaid have significantly less access to preventive medical care during and after pregnancy compared with commercially insured patients. **Black mothers are 3 to 4 times more likely to die in childbirth than White mothers**, and they have higher rates of PPCM and preeclampsia. Health care systems should partner with communities to diversify the health care workforce, develop educational tools that are culturally sensitive,

and consider nonhospital-based care delivery using trusted community sources. All clinicians should aim to achieve CV health equity by eliminating barriers caused by systemic racism and unconscious bias.

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SECTION VIII

Preventive Cardiology

EDITOR: **Leslie Cho**

CHAPTER 45

Dyslipidemia

Vincent Chen and Leslie Cho

I. INTRODUCTION. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world. The global burden of death from CVD rose from 12.1 million per year in 1990 to 18.6 million per year in 2019. The annual global prevalence of ischemic heart disease and stroke in 2019 were 197 and 101 million, respectively, and these numbers are projected to increase as age-standardized CVD rates are beginning to rise in countries where they were previously declining. In the United States, **CVD is the number one killer**, accounting for 36% of all deaths. As many as 660,000 Americans have a new myocardial infarction (MI) each year, and 326,200 are victims of sudden cardiac death. The average age at first MI is 65.1 years for men and 70.2 years for women. According to the Centers for Disease Control and Prevention, elimination of all forms of CVD would raise the overall life expectancy by 7 years.

A. Economic consequences of CVD. The economic burden of CVD and stroke in the United States was estimated to be $316.6 billion in 2011 to 2012 and is projected to increase to $918 billion by 2030. In 2010, CVD was the leading cause of hospitalization, contributing to >5.8 million patient discharges and 4.4 million emergency department visits.

B. Prevention of coronary artery disease (CAD). **Table 45.1** shows important targets for secondary prevention among patients with known coronary or noncoronary vascular disease. The goals for primary prevention are similar, but the cost-effectiveness of medical intervention is not so favorable in all populations. The consequences of modest population-wide risk reduction (eg, reduction in fat intake [currently 33% of total calories] and cholesterol levels) and lifesaving technologies (eg, surgery, angioplasty, and coronary care units) have reduced the death rate and possibly contributed to reduced morbidity, but the burden of CVD remains a major challenge.

TABLE 45.1 Goals for Secondary Prevention Among Patients With Known Vascular Disease

Risk Factor	Goal
Hypertension	130/80 mm Hg
Dyslipidemia	LDL <55 mg/dL (<40 mg/dL in those with recurrent CVD events) as recommended by European Society and Canadian Societies of Cardiology, National Lipid Association and International Atherosclerosis Society No goal per the ACC/AHA 2018 guidelines. High-intensity statin therapy is recommended, with non-statin lipid lowering therapies recommended if LDL >70 mg/dL.

Risk Factor	Goal
	Triglycerides <100 mg/dL
Physical activity	30 min, 3 or 4 times per week
Body mass index	≤24.9 kg/m^2
Diabetes mellitus	Near-normal blood sugar (HbA_{1C} <6.5%)
Smoking	Complete cessation

ACC, American College of Cardiology; AHA, American Heart Association; HbA_{1C}, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

II. CLINICAL IMPORTANCE OF HYPERLIPIDEMIA. Hyperlipidemia is an important **correctable predictive factor for CAD**. There is a strong, independent, continuous, and graded relation between total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) level and risk of CAD events. This relation has been clearly demonstrated in men and women in all age groups. More than one-half of U.S. adults (105 million) have TC levels >200 mg/dL, and of these, 37 million have values >240 mg/dL. In general, a 1% increase in LDL-C level leads to a 2% to 3% increase in the risk of CAD.

A. Lipoproteins are large molecular compounds that are essential to the transport of insoluble cholesterol and triglycerides (TGs) within the blood. They contain a lipid core composed of TGs and esterified and unesterified cholesterol and are surrounded by phospholipids and specialized proteins known as **apolipoproteins**. The **six major classes of lipoproteins** are **chylomicrons, very low-density lipoproteins (VLDLs), intermediate-density lipoproteins (IDLs), LDLs, high-density lipoproteins (HDLs), and lipoprotein(a) (Lp(a))**. Chylomicrons are assembled in the intestinal tract and associated with a variety of apolipoproteins; once in circulation, they are metabolized into IDLs. The atherogenicity of chylomicrons is uncertain. LDL-C is the dominant form of atherogenic cholesterol in humans.

B. Apolipoproteins are necessary for the structure and enzymatic processes of lipids. Apolipoprotein A1 (**apo A1**) is a major component of **HDL**, and **apo B** is the main apolipoprotein for the remaining **non-HDLs**. Apolipoprotein(a) (not to be confused with apo A1) is a large glycoprotein that is covalently bound to apo B to constitute Lp(a). Apo C, apo D, and apo E are other clinically important apolipoproteins.

III. LIPID-LOWERING TRIALS. Aggressive lipid-lowering drug treatment of persons at various risk levels reduces CAD morbidity and mortality rates and increases overall survival. Although the association between hyperlipidemia and CAD was established much earlier, the demonstration of a relationship between reduction in serum lipid levels and a reduction in all-cause mortality had to await the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins." Multiple

randomized trials have provided overwhelming evidence of the benefit of statins in both primary and secondary prevention of CV events.

A. Primary prevention statin trials

1. The **West of Scotland Coronary Prevention Study (WOSCOPS) (1995)** demonstrated that treatment of men at relatively high risk with profoundly elevated cholesterol levels significantly reduced the risk of heart attack and death from heart disease. The double-blind study randomized 6,600 healthy men with a baseline mean LDL-C level of 193 mg/dL to pravastatin (40 mg/d) or placebo, for an average of 5 years, and demonstrated a 31% relative reduction in the incidence of nonfatal MI or CAD death. Follow-up of this population published in 2007 showed that the statin group continued to experience lower rates of CV death after a further 10 years, even though only one-third continued to take statins during the additional follow-up period.
2. The **Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (1998)** demonstrated benefit among patients with more typical risk profiles, including lower cholesterol values, than among those in the WOSCOPS. AFCAPS/TexCAPS patients had a baseline mean TC level of 220 mg/dL and LDL of 150 mg/dL. The study randomized 6,600 patients to lovastatin 20 to 40 mg daily or placebo and demonstrated a 36% relative risk reduction (RRR) for the first acute major coronary events in the lovastatin group.
3. The **Heart Protection Study (HPS) (2002)** randomized 20,536 subjects with a mean LDL of 131 mg/dL in a 2 × 2 factorial design to daily simvastatin (40 mg) or placebo and to antioxidants or placebo (the antioxidant arm did not show any benefit or harm). The study focused on patients who were deemed high risk for CVD, but not thought to merit treatment with statins based on the prevalent clinical practice at that time. Increased risk was defined as the presence of or history of CAD, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, or treated hypertension. Simvastatin therapy was associated with a 13% reduction in all-cause mortality, including an 18% reduction in coronary death rate. The beneficial impact of statin therapy was seen with respect to all CV end points, with significant reductions in risk of nonfatal MI, incidence of first stroke, and coronary and noncoronary revascularization. **Treating patients with LDL levels <100 mg/dL was also associated with a beneficial reduction in vascular events**. The benefit was maintained in patients receiving other cardioprotective medications, such as angiotensin-converting enzyme inhibitors, beta-blockers, and aspirin. Although not strictly a primary prevention trial, the HPS provided evidence to support treatment of risk as endorsed by the National Cholesterol Education Program (NCEP) guidelines. However, the HPS results refuted the threshold LDL level (as proposed by NCEP III at that time) below which statins were not previously indicated.
4. **Pravastatin in Elderly Individuals at Risk of Vascular Disease (2002)** randomized 5,804 patients between the ages of 70 and 82 years with mean LDL of

147 mg/dL to placebo or pravastatin. These patients had preexisting coronary, cerebral, or peripheral vascular disease or had a history of smoking, hypertension, or diabetes. The study demonstrated a 15% reduction in the composite of coronary death, nonfatal MI, and stroke over a period of 3 years. The study demonstrated the efficacy of primary and secondary prevention in the older patients.

5. The **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (2002)** randomized 10,355 patients with hypertension with one other coronary risk factor and a baseline mean LDL-C level of 148 mg/dL to pravastatin 20 to 40 mg/d or usual care. The study did not demonstrate a mortality difference in the two arms after a follow-up period of 4.8 years. This lack of observable difference in outcome might have resulted from the relatively modest LDL reduction (17% with pravastatin vs 8% in usual care) or the fact that 26% of the patients in the "usual care" group were taking a statin at the end of the trial.
6. The **Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (2003)** randomized 10,305 patients with hypertension and at least three other CV risk factors and a baseline mean LDL-C level of 133 mg/dL to atorvastatin 10 mg/d or placebo. The study was stopped prematurely after a median follow-up of 3.3 years by the safety monitoring committee because of a significantly higher incidence of the primary end point (nonfatal MI or fatal congenital heart disease [CHD]) in the placebo group. The study demonstrated a 36% RRR for the primary end point in the atorvastatin group compared with the placebo group. Further analysis demonstrated that the benefit of statin therapy started after only 1 year of treatment. There was also a significant reduction (RRR of 27%) in the incidence of fatal and nonfatal stroke in the atorvastatin group. This study, like the HPS, provided further evidence of the benefit of statins in patients at high risk for CVD without regard for baseline TC or LDL levels.
7. The **Collaborative Atorvastatin Diabetes Study (CARDS) (2004)** randomized 2,838 patients with diabetes with one additional CV risk factor, no history of CVD, and an average baseline LDL-C of only 117 mg/dL to atorvastatin 10 mg/d or placebo. This study was also terminated prematurely owing to an excess incidence of the primary end point (a composite of acute coronary events, coronary revascularization, or stroke) in the placebo group after a median follow-up of 3.9 years. Overall, the atorvastatin group had an RRR of 37% for the primary end point and 27% for all-cause mortality. The importance of this trial was its demonstration of the clinical benefit of statin use in patients with diabetes, regardless of baseline LDL-C level, making a compelling case for statin use in all patients with diabetes with at least one additional CV risk factor. According to the NHANES III data, 82% of patients with diabetes in the United States would meet the entry criteria for the CARDS trial.
8. The **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (2008)** focused on patients with normal LDL-C levels but increased levels of high-sensitivity C-

reactive protein (CRP). This was the first clinical trial to demonstrate that statin therapy may benefit patients with low-to-normal LDL levels and no known CVD. The study randomized 17,802 healthy subjects with an LDL-C <130 mg/dL and a CRP ≥2.0 mg/L to daily rosuvastatin of 20 mg or placebo. The trial was stopped early for a mortality benefit after a median follow-up of 1.9 years. The study demonstrated that after 1 year of therapy, there were lower levels of LDL-C (55 vs 110 mg/dL) and lower levels of CRP (2.2 vs 3.5 mg/L) in the rosuvastatin-treated group. There was also a lower incidence of the primary end point of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed death from CV cause (0.77 vs 1.36 events per 100 person-life years) as well as the risk of all-cause mortality (1.00 vs 1.25 deaths per 100 person-life years) in the rosuvastatin-treated group.

B. Secondary prevention statin trials

1. The **Scandinavian Simvastatin Survival Study (4S) (1994)** was the first secondary prevention trial to demonstrate a clear reduction in total mortality. Simvastatin reduced total mortality among patients with CAD by 30%, largely because of a 42% reduction in deaths from CAD. The 4S treated 4,444 men and women with CAD and mean baseline LDL of 188 mg/dL, with a range of 130 to 266 mg/dL.
2. The randomized, controlled **Cholesterol and Recurrent Events Trial (1996)** was designed to evaluate the effects of treatment with pravastatin on 4,159 persons who had experienced acute MI 3 to 20 months before randomization and had moderately elevated TC levels (mean 209 mg/dL) and LDL levels (mean 139 mg/dL). The benefits of pravastatin therapy in preventing recurrent coronary events were similar in the subset analysis of age, sex, ejection fraction, hypertension, diabetes mellitus, and smoking.
3. The **Long-Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) (1998)** was the first to examine the use of a statin for patients with a history of unstable angina. The LIPID study provided new data on noncoronary mortality (ie, stroke) and on other groups, such as women and patients with diabetes, who previously had been underrepresented in clinical trials. LIPID demonstrated improved CAD outcomes among all patients, including those with unstable angina.
4. **Myocardial Ischemia Reduction with Acute Cholesterol-Lowering Trial (2001).** This trial demonstrated CV benefits with initiation of early statin therapy following acute coronary syndrome (ACS). The trial randomized 3,086 adults with unstable angina or non–Q-wave MI to high-dose atorvastatin (80 mg/d) or placebo between 24 and 96 hours after hospital admission. There was a reduction in the primary end point of nonfatal infarction, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring hospitalization in the atorvastatin group (14.8% vs 17.4%, RRR of 16%). The benefit was driven primarily by a 26%

reduction in recurrent symptomatic ischemia. The trial did not show a mortality benefit (death, MI, or need for revascularization).

5. **Pravastatin or Atorvastatin Evaluation and Infection Therapy-TIMI 22 (PROVE-IT-TIMI-22) (2004).** This trial was designed to determine whether intensive lipid-lowering therapy in patients with ACS reduced major coronary events and mortality more than "standard" lipid lowering. A total of 4,162 patients who had been hospitalized for ACS within the preceding 10 days were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d. After 2 years of follow-up, the composite end point (all-cause mortality, MI, unstable angina, coronary revascularization, and stroke) was significantly reduced by 16% with atorvastatin compared with pravastatin. High-dose atorvastatin was well tolerated, with no cases of rhabdomyolysis. Of note, the LDL-C level attained on atorvastatin 80 mg/d was 33 mg/dL lower than on pravastatin with a mean of 62 mg/dL. These results suggested that the use of intensive lipid-lowering therapy to achieve very low LDL-C levels was of benefit in a group of patients at high risk for recurrent coronary events.
6. **A to Z trial: phase Z (2004)—early intensive versus a delayed conservative simvastatin strategy in patients with acute coronary syndromes (2004).** This trial studied whether early initiation of high-dose statin therapy would lead to a reduction in long-term cardiac events compared with a more conservative, delayed low-dose statin strategy in high-risk patients with ACS. The trial enrolled a total of 4,497 patients with a recent ACS, TC level ≤250 mg/dL and median LDL level 111 mg/dL, and at least one additional risk factor who were randomized to either intensive statin therapy strategy (simvastatin 40 mg for 1 month, followed by 80 mg through 2 years) or a conservative strategy (placebo for 4 months followed by simvastatin 20 mg through 2 years). Although the study showed an early and sustained reduction in LDL in the aggressive strategy arm, it did not show a significant reduction in the primary composite end point of CV events (CV death, MI, readmission for ACS, and cardiovascular accident [CVA]) or death from any cause compared with a more conservative strategy. There were also more patients who developed creatine kinase (CK) concentrations more than 10 times the upper limit of normal in the aggressive strategy arm (9 vs 1) and three patients who developed rhabdomyolysis while on simvastatin 80 mg.
7. The **Treating to New Targets (TNT) (2005)** trial sought to demonstrate the benefit of intensive lipid-lowering therapy in patients with stable coronary disease. The trial randomized 10,001 patients with clinically evident CHD and baseline LDL-C levels <130 mg/dL to atorvastatin 80 mg/d or atorvastatin 10 mg/d. After 4.9 years of follow-up, the group receiving atorvastatin 80 mg/d had a 22% RRR in the primary composite end point of death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke compared with the group receiving atorvastatin 10 mg/d. High-dose atorvastatin was remarkably safe, with a 1.2% incidence in elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than 3 times the upper limit of normal, compared

with a 0.2% incidence in the atorvastatin 10 mg group. Rates of myalgias and rhabdomyolysis were similar between the two groups. This study provided compelling evidence that the use of intensive statin therapy to reduce LDL-C to levels below 100 mg/dL had marked clinical benefit in patients with stable CHD.

8. The **Incremental Decrease in End Points through Aggressive Lipid Lowering (2005)** trial randomized 8,888 patients with a prior history of acute MI and baseline LDL level of 122 mg/dL to atorvastatin 80 mg/d or simvastatin 20 mg/d. After 4.8 years of follow-up, there was a nonsignificant difference in the risk of the composite end point of coronary death, acute MI, or cardiac arrest. However, if either stroke or revascularization was added to the primary end point, the results favored the atorvastatin group, and the associated hazard ratios (HRs) were similar to the results of PROVE-IT and TNT. Despite the published negative result of this trial, it provided complementary evidence for the benefit of intensive LDL lowering in patients at high risk for coronary events.

C. Nonstatin lipid-lowering trials

1. **Fibrate trials.** Peroxisome proliferator-activated receptors (PPARs) are nuclear receptor proteins that function as transcription factors when activated. PPARα is the molecular target activated by the fibrate drugs; activation of PPARα leads to decreases in serum TG levels through increased lipoprotein lipase activity and modest increases in HDL-C through increased expression of HDL apolipoproteins.
   a. **The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (1999)** was a multicenter study that randomized patients with known CHD and low HDL-C (≤40 mg/dL) and LDL-C (≤140 mg/dL) levels to gemfibrozil (1,200 mg/d) or placebo with a mean follow-up of 5.1 years. The study showed that gemfibrozil therapy was associated with a significant 22% reduction in the combined incidence of nonfatal MI and CHD death. This was the first lipid intervention trial to show that raising HDL-C concentrations in patients with CHD and low HDL-C and LDL-C levels will reduce the incidence of major coronary events.
   b. The **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (2005)** trial focused on the prevention of CHD in patients with type 2 diabetes using fenofibrates. The study randomized patients with type 2 diabetes diagnosed after 35 years of age with no clear indication for cholesterol-lowering therapy at baseline to fenofibrate (200 mg/d) or placebo. The study failed to show a difference in the primary composite end point of CHD or nonfatal MI between the two groups at 5-year follow-up. However, several secondary end points were lower in the fenofibrate group, including nonfatal MI and coronary revascularization.
   c. The **Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD Lipid) (2010)** was designed to evaluate whether the addition of fenofibrate to statin therapy among patients with type 2 diabetes (baseline LDL 100 mg/dL and median TGs 164 mg/dL) would be effective in preventing CV

events. The study randomized half of the patients within the initial ACCORD trial with type 2 diabetes and treated with a statin medication to fenofibrate (160 mg daily) or placebo. Although a significant reduction in median TG level (164-122 mg/dL) was seen with the addition of fenofibrate to statin therapy, there was no reduction in the primary end point (first occurrence of CV death, nonfatal MI, or nonfatal stroke) when compared with statin therapy alone. In a subgroup analysis, a trend toward benefit of fenofibrate was shown in the group of patients with diabetes that had a significant dyslipidemia (low HDL and high TGs). Additional subgroup analysis showed a trend toward harm in women (but not men) in the fenofibrate group that warrants further investigation in future studies.

d. **PROMINENT (2022)** randomized 10,497 patients with type 2 diabetes, TG levels 200 to 499 mg/dL, and HDL-C below 40 mg/dL to pemafibrate (0.2 mg twice daily) or placebo. Patients either had baseline LDL-C below 100 mg/dL or were on statin therapy. The baseline TG level was 271 mg/dL, and the baseline LDL-C was 78 mg/dL. At 4 months, TGs were reduced by 31% in the pemafibrate group (from 273 to 189 mg/dL), and VLDL-C was reduced by 25% (from 49 to 31 mg/dL). LDL-C and apo B levels were higher in the pemafibrate group. There were no differences in rates of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization between pemafibrate and the placebo group. Results from PROMINENT suggest that while efficacious in reducing TG levels, **enhanced lipolysis from fibrates is unlikely to manifest as improved CV outcomes without concomitant reduction in LDL-C**.

2. Niacin trials

a. The **Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (2011)** was a study that compared the treatment of extended-release niacin versus placebo among statin-treated patients with established heart and vascular disease and baseline LDL 71 mg/dL and HDL 35 mg/dL. The study randomized 3,414 patients with optimally treated LDL-C and low HDL-C with established vascular disease (documented by coronary angiography or by prior MI, carotid angiography or prior ischemic stroke, or peripheral arterial disease) to extended-release niacin (1,500-2,000 mg/d) or placebo. There was no significant difference in the primary composite outcome of CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization (16.4% in the extended-release niacin group vs 16.2% in the placebo group). The study was terminated 18 months early after it was evident that the addition of extended-release niacin would not be beneficial. Furthermore, there was a small (numerical) excess in ischemic strokes and hospitalizations for ACS.

b. **The Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE)** was a trial to assess the effects of adding

extended-release niacin (2 g) in combination with laropiprant (40 mg) to effective statin-based LDL-C–lowering treatment in 25,673 high-risk patients with prior vascular disease (baseline LDL 63 mg/dL and HDL 44 mg/dL). Laropiprant is an antagonist of the prostaglandin D2 receptor DP_1 that has been shown to improve adherence to niacin therapy by reducing flushing in up to two-thirds of patients. The niacin-laropiprant group had a lower LDL by 10 mg/dL and a higher HDL by 6 mg/dL; however, there were no significant differences in the incidence of major adverse vascular events between the treatment group and placebo. There was an increased incidence of worsening of diabetes control in the treatment group. This trial provided evidence that increasing HDL levels did not necessarily improve CV outcomes, which was also later found in cholesteryl ester transfer protein (CETP) inhibitor trials.

3. **The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) (2015)** was a study that compared the effect of adding ezetimibe versus placebo to simvastatin in patients with a recent ACS. The study randomized 18,144 patients who had been hospitalized for ACS within the preceding 10 days and had LDL-C levels of 50 to 100 mg/dL if they were receiving lipid-lowering therapy or 50 to 125 mg/dL if they were not to either ezetimibe (10 mg) and simvastatin (40 mg) versus placebo and simvastatin (40 mg). Over a median follow-up of 6 years, the median LDL level was 53.7 mg/dL in the ezetimibe-simvastatin group versus 69.5 in the simvastatin monotherapy group. There was 6.4% RRR and 2% absolute risk reduction in the primary end point of CV death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke in the ezetimibe-simvastatin group. There were no increased side effects in the ezetimibe-simvastatin group. This trial was the first trial to highlight that more intensive LDL reduction with nonstatin medications (ezetimibe) can reduce the risk of recurrent CVD in a secondary prevention population.
4. **CETP inhibitor trials.** CETP is responsible for transfer of cholesteryl esters from HDL to LDL and VLDL, leading to increased HDL levels and reduced LDL levels if inhibited. Several preclinical studies had shown a significant ability of this class of drugs to increase HDL levels by >50% and reduce LDL levels by >20%, and there was tremendous excitement about its potential. However, randomized trials examining clinical outcomes showed no effect and, possibly, harm of CETP inhibitors when added to a statin therapy background. In ILLUMINATE, torcetrapib was associated with an increased risk of CV events by 25% and mortality risk by 50% despite reducing LDL by 25% and increasing HDL by 72% thought to be due to an off-target effect of increasing blood pressure. The DAL-OUTCOMES study (15,871 patients) and ACCELERATE study (12,000) were terminated because of the lack of efficacy. These trials highlight the importance of approving new drugs based on large trials examining clinical outcomes rather than approving them based on their effect on surrogate markers. More recently, the HPS3/TIMI55-REVEAL trial (30,449 patients) showed that adding anacetrapib to

high-intensity statin therapy (HIST) in patients with CVD resulted in a lower rate of coronary events, but there was no effect on death. Many experts argue that the observed benefit in this trial was mainly related to the magnitude of LDL lowering. Given the inconsistent evidence for clinical benefit from this class of drugs, the exact role of CETP inhibitors in clinical practice needs to be better defined in future studies.

5. **Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.** PCSK-9 is a protease that promotes the binding and degradation of LDL receptors intracellularly. As such, inhibition of PCSK-9 leads to increased LDL receptors on the cell membrane and increased uptake of LDL, leading to a reduction in serum LDL-C. **FOURIER (2017) and ODYSSEY OUTCOMES (2018) evaluated evolocumab and alirocumab, respectively, in patients with high-risk CVD on background statin therapy and demonstrated ~60% reduction in LDL-C for both study medications**, with reductions in rates of major CV events from 11.3% to 9.8% (HR 0.85, 95% confidence interval [CI]: 0.79-0.92) in FOURIER and 11.1% to 9.5% (HR 0.85, 95% CI: 0.78-0.93) in ODYSSEY OUTCOMES. PCSK-9 inhibitors have powerful LDL-C–lowering effects, with LDL-C values of 30 to 50 mg/dL in both trials at 1 year.
6. **Omega-3 fatty acids**
   a. **Japan EPA Lipid Intervention Study (JELIS) (2007).** The goal of this trial was to evaluate treatment with the fish oil supplement eicosapentaenoic acid (EPA) in addition to statin therapy compared with statin therapy alone among patients with hypercholesterolemia (baseline LDL 187 mg/dL and median TGs 151 mg/dL). The study randomized patients in an open-label manner to treatment with EPA (1,800 mg/d) in addition to statin therapy (pravastatin 10 mg/d) or simvastatin (5 mg/d) or to statin therapy alone. At a mean follow-up of 4.6 years, there was a significant reduction in the primary end point of major adverse CV events in the EPA plus statin group (2.8% vs 3.5%). This was driven primarily by a significant reduction in rates of unstable angina and a trend toward lower rates of nonfatal MI and revascularization. No difference was seen in sudden cardiac death or fatal MI.
   b. **REDUCE-IT** and **STRENGTH.** Given the lower rates of major adverse cardiovascular events (MACE) observed with EPA in the JELIS trial, the REDUCE-IT trial (2019) studied **icosapent ethyl**, an EPA ethyl ester, for reducing CVD in high-risk CV patients on background statin therapy (LDL-C 41-100 mg/dL) and with hypertriglyceridemia 135 to 499 mg/dL. After a median follow-up of 4.9 years, the rate of CVD death, nonfatal MI, nonfatal stroke, unstable angina, or coronary revascularization was lower in the icosapent ethyl group (HR 0.75, 95% CI 0.68-0.83) compared with the placebo group, with event rates of 22% in the placebo group and 17% in the treatment group. After publication, concerns arose about whether the placebo in REDUCE-IT—with mineral oil to mimic the consistency of icosapent ethyl—

was a truly neutral comparator. The negative findings in STRENGTH (2020), which examined the use of **omega-3 carboxylic fatty acids EPA and docosahexaenoic acid (DHA)** in patients with high-risk CVD with hypertriglyceridemia on maximally tolerated statin therapy, deepened the debate about the utility of omega-3 fatty acids in CVD prevention. Further studies are needed to clarify the seemingly discordant results from these two trials.

7. **Other novel therapies.** The advent of small molecule therapeutics has led to a revolution in nonstatin adjuncts in reducing LDL-C and preventing CVD.
   a. **Bempedoic acid is a small molecule prodrug that requires activation by very long-chain acyl-CoA synthetase 1, which is expressed in the liver, but not in muscle.** Once activated, it inhibits adenosine triphosphate (ATP) citrate lyase, an enzyme upstream of HMG-CoA reductase in the cholesterol synthesis pathway. The **CLEAR Serenity (2019) and CLEAR Tranquility (2018) trials** assessed the lipid-lowering efficacy of bempedoic acid 180 mg daily in patients with prior atherosclerotic CVD (ASCVD), heterozygous familial hypercholesterolemia (FH), or multiple CV risk factors but intolerant of statin therapy. Reductions in LDL-C of 15% to 18% were observed with bempedoic acid, and when combined with ezetimibe 10 mg, reductions in LCL-C of 38% were observed. The Food and Drug Administration (FDA) approved the fixed-dose combination of bempedoic acid and ezetimibe in 2020 for adults with heterozygous FH or at very high risk for ASCVD who need further LDL-C lowering on maximally tolerated statin therapy. Recently, the CLEAR Outcomes trial showed a benefit in statin-intolerant patients with regard to reduction in MACE with the addition of bempedoic acid. Further understanding of the use of bempedoic acid in the armamentarium against CVD in all populations remains to be seen.
   b. **Inclisiran is a small interfering RNA (siRNA) that inhibits translation of the messenger RNA (mRNA) encoding PCSK-9.** Following the publication of the ORION trials in 2021, inclisiran received approval in the United States for the treatment of heterozygous FH or as adjunctive lipid-lowering therapy for secondary prevention. The ORION-9 trial (2020) enrolled 482 patients with heterozygous FH and observed a reduction in LDL-C by 40%; ORION-10 and ORION-11 each enrolled over 1,500 patients with prior ASCVD and LDL-C >70 mg/dL and also observed LDL-C reductions by ~50%. At twice a year, the low frequency of injections and long-acting effect of the drug is a great advantage. However, data on CV outcomes and cost-effectiveness are still pending; the ORION-4 and VICTORION-2P trials are actively recruiting and will further clarify the role of inclisiran in CVD prevention.

D. Meta-analyses

1. **CTT Collaborators (2005).** A large meta-analysis of 90,056 individuals from 14 randomized trials of statin drugs, this analysis demonstrated an impressive 12%

reduction in all-cause mortality for each 1 mmol/L (39 mg/dL) reduction in LDL. There was a 19% reduction in coronary mortality and 21% reduction in MI, coronary revascularization, and stroke. Statin use showed benefit within the first year of use and was greater in subsequent years. Statins were also remarkably safe, with no increase in cancer seen and a 5-year excess risk of rhabdomyolysis of 0.1%.

2. **Cannon—Intensive Statin Therapy (2006).** A meta-analysis of 27,548 patients from four trials that investigated intensive versus standard lipid-lowering therapy found a significant 16% odds ratio reduction in coronary death or MI in the group that received intensive therapy. There was a nonsignificant trend toward decreased CV mortality.
3. **Boekholdt—Very low levels of atherogenic lipoproteins from statin trials (2014).** This meta-analysis of 38,153 patients from eight statin trials showed that there was significant interindividual variability in response to statins with more than 40% of patients on HIST not reaching LDL <70 mg/dL. Those who achieved very low levels of LDL <50 mg/dL had a lower risk of CV events than those who achieved moderately low levels.

IV. MANAGEMENT OF LIPIDS. The 2013 American College of Cardiology/American Heart Association (ACC/AHA) lipid guidelines abandoned the use of LDL-C treatment target levels in guiding therapies for the primary or secondary prevention of CVD. The most recent 2018 ACC/AHA guidelines for the management of blood cholesterol and the 2022 ACC expert consensus document for nonstatin therapies continue the avoidance of setting LDL-C treatment targets. Instead, various statin intensities are recommended for certain patient populations, and nonstatin adjuncts are advised for patients at higher risk of CVD **if LDL-C remains above a particular threshold** after statin therapy. It is worth mentioning that the European Society of Cardiology (ESC), Canadian Society of Cardiology, National Lipid Association, and the International Atherosclerosis Society continue to recommend LDL and non-HDL treatment targets, with the most recent ESC 2019 guidelines on dyslipidemia management advising an LDL-C goal of <55 mg/dL in secondary prevention patients.

A. The ACC/AHA 2018 lipid guidelines

1. **All adults aged 20 years or above and without a history of CAD or other atherosclerotic disease** should have a nonfasting or fasting lipid panel (ie, TC, LDL-C, HDL-C, and TG levels) every 5 years. If a nonfasting lipid panel is obtained and TG level is >400 mg/dL, a follow-up 8-hour fasting lipid panel is recommended. In patients not taking statins aged 40 to 75 without diabetes or prior ASCVD and with LDL-C <190 mg/dL, calculate the estimated 10-year ASCVD risk using the Pooled Cohort Equation (PCE). A 10-year risk <5% is considered low risk, 5% to 7.5% is considered borderline risk, 7.5% to 20% is considered intermediate risk, and >20% is considered high risk. **Have a clinician-patient discussion about risks, benefits, costs, and patient preferences before initiating statin therapy.**

2. **Consider measurement of Lp(a) in those with a family history of premature CVD or a personal history of CVD without major risk factors.** Lp(a) >50 mg/dL may be considered a risk-enhancing factor in men, or in women who also have hypercholesterolemia.
3. **Heart healthy lifestyle habits are the foundation of ASCVD prevention.** Patients with a 10-year risk <5% (low risk) should have lifestyle therapies emphasized. Primordial prevention delays the onset of CVD risk factors and reduces the cumulative exposure to a given risk factor, thereby delaying or preventing CVD and compressing morbidity toward the end of the life course. Nonlipid risk factors for CVD should be reviewed with the patient as well.
4. **Patients with clinical ASCVD should receive HIST**, which lowers LDL-C by >50%. In comparison, moderate-intensity statin therapy lowers LDL-C by 30% to 50%. Low-intensity statin therapy lowers LDL-C by <30%.
5. **Very high-risk patients include those with multiple ASCVD events or single ASCVD event but multiple high-risk conditions.** In these patients, if LDL-C remains >70 mg/dL despite HIST, consider addition of ezetimibe. If LDL-C remains >70 mg/dL despite statins and ezetimibe, consider the addition of PCSK-9 inhibitor.
6. **Patient groups who are candidates for statin therapy**
   a. **Patients with clinical ASCVD:** Patients should receive HIST unless they are >75 years old or cannot tolerate HIST in case of which moderate-intensity statin is recommended.
   b. **Patients with LDL ≥190 mg/dL:** HIST is recommended, without calculating a 10-year ASCVD risk score.
   c. **Patients with type 1 or 2 diabetes mellitus, age 40 to 75, and with LDL 70 to 189 mg/dL:** Moderate-intensity statin is recommended, without calculating a 10-year ASCVD risk score. If there are multiple risk factors or if the patient is 50 to 75 years of age, use a high-intensity statin.
   d. **Patients aged 40 to 75 years without diabetes mellitus or ASCVD, with LDL 70 to 189 mg/dL, and an estimated 10-year ASCVD risk of ≥7.5%:** Moderate-intensity statin is recommended for those at intermediate risk (7.5%-20%), and high-intensity statin is recommended if 10-year ASCVD risk >20% (high risk).
   e. Patients with a 10-year risk 5% to 7.5% (borderline) but also risk enhancers may benefit from statin therapy. **Risk-enhancing factors** are not individually represented in ASCVD risk estimation using the PCE and include family history of premature ASCVD, metabolic syndrome, persistent LDL-C >160 mg/dL, TG >175 mg/dL, chronic kidney disease, premature menopause (<40 years old), history of preeclampsia, chronic inflammatory disorders (eg, human immunodeficiency virus [HIV], rheumatoid arthritis, psoriasis), high-risk ethnic groups (eg, South Asian), high sensitivity CRP >2.0 mg/dL, ankle-brachial index <0.9, or elevated Lp(a).

f. Among those with intermediate risk, if risk decision is uncertain, consider obtaining coronary artery calcium (CAC) score. Those with CAC zero have reclassified their risk downward and no statin may be considered; those with CAC 1 to 99 favor initiation of statin; and those with CAC >100 are recommended to have a statin prescribed.

B. Types of therapy

1. **Therapeutic lifestyle changes (TLCs)** encompass **increased physical activity, ideal weight maintenance, and a diet** that emphasizes vegetables, fruits, whole grains, and lean protein sources (fish, low-fat dairy, low-fat poultry, nuts) and limits added sugars, sweets, and red meats. Other TLCs are listed in **Table 45.2**. Intake of *trans*-fatty acids should be kept to a minimum as these both drive up LDL-C and decrease HDL-C. For most patients, it is essential to reduce saturated fat intake over total fat intake; for patients with metabolic syndrome, a fat intake of 30% to 35% may be optimal for reducing lipid and nonlipid risk factors. High-carbohydrate diets may worsen hypertriglyceridemia in these patients. Dietary carbohydrates should be derived predominantly from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables. Daily intake of 5 to 10 g of viscous fiber reduces LDL-C levels by approximately 5% and the use of plant stanols and sterols (2-3 g/d) by another 6% to 15%. **TLCs can achieve an almost 30% reduction in LDL-C level in highly motivated individuals and should form the cornerstone of all preventive activity**. Benefits of LDL-C lowering may be evident within 6 to 12 months, although the individual response to a cholesterol-lowering diet depends on many factors. Some of the response is genetically determined, and increased body mass index is associated with less response to dietary change. LDL-C should be measured 6 weeks after initiating optimal diet, and if the goals are not met, intensification of TLCs and use of plant sterols or stanols should be considered. Referral to a dietitian for education and dietary counseling is invaluable at this stage. If, after 3 months of TLCs, adequate control is not achieved, drug therapy should be considered.

TABLE 45.2 Components of Therapeutic Lifestyle

Component	Recommendation	Approximate LDL Reduction
Diet		
Saturated fat	<7% of total calories	8%-10%
Dietary cholesterol	<200 mg/d	3%-5%
Polyunsaturated fat	Up to 10% of total calories	
Monounsaturated fat	Up to 20% of total calories	
Total fat	25%-35% of total calories	
Carbohydrate	50%-60% of total calories	

Component	Recommendation	Approximate LDL Reduction
Dietary fiber	20-30 g/d	
Total protein	15% of total calories	
Therapeutic Options for LDL Lowering		
Plant stanols/sterols	2 g/d	6%-15%
Increased viscous soluble fiber	5-10 g/d (consumption of 10-25 g/d may have added benefit)	3%-5%
Physical activity	Enough moderate activity to expend at least 200 kcal/d	

LDL, low-density lipoprotein.

2. **Pharmacotherapy.** The high efficacy of statins in lowering LDL-C level and their demonstrated mortality benefits make them the agents of first choice for the treatment of most forms of hyperlipidemia. **Table 45.3** summarizes the most commonly used agents affecting lipoprotein metabolism.

TABLE 45.3 Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Lovastatin, 20-80 mg Pravastatin, 20-40 mg Simvastatin, 20-80 mg Fluvastatin, 20-80 mg Atorvastatin, 10-80 mg Rosuvastatin, 10-40 mg	LDL-C ↓ 18%-55% HDL-C ↑ 5%-15% TG ↓ 7%-30%	Gastrointestinal distress Myopathy Increased liver enzymes	Absolute: Active or chronic liver disease Relative: Concomitant use of certain drugs[a]
Bile acid sequestrants	Cholestyramine, 4-16 g Colestipol, 5-20 g Colesevelam, 2.6-3.8 g	LDL-C ↓ 15%-30% HDL-C ↑ 3%-5% TG—no change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: Dysbetalipoproteinemia-TG >400 mg/dL Relative: TG >200 mg/dL
Nicotinic acid	Immediate release, crystalline nicotinic acid, 1.5-3 g Extended release, Niaspan, 1-2 g	LDL-C ↓ 5%-25% HDL-C ↑ 15%-35% TG ↓ 20%-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: Chronic liver disease-severe gout Relative: Diabetes-hyperuricemia-peptic ulcer disease

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
	Sustained release, 1-2 g			
PCSK-9 inhibitors	Evolocumab, 140 mg SC every 2 wk or 420 mg every month Alirocumab, 75 mg SC every 2 wk	LDL-C ↓ 60%	Flulike symptoms Injection site reactions Diarrhea Muscle pain or spasm	Absolute—Patients with serious hypersensitivity to PCSK-9 inhibitors
Fibric acids	Gemfibrozil, 600 mg bid Fenofibrate, 200 mg Clofibrate, 1,000 mg bid	LDL-C ↓ 5%-20% (may be increased in patients with high TG) HDL-C ↑ 10%-20% TG ↓ 20%-50%	Dyspepsia Gallstones Myopathy	Absolute: Severe renal disease-severe hepatic disease

bid, twice daily; GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK-9, proprotein convertase subtilisin/kexin type 9; TG, triglyceride.

[a]Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P450 inhibitors (fibrates and niacin should be used with appropriate caution).

a. Statins. Statins inhibit HMG-CoA reductase in the cholesterol synthesis pathway and are the first-line therapy in the management of hypercholesterolemia. The category includes seven drugs: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin.

(1) Effectiveness. When dietary measures are inadequate, statins effectively **lower TC and LDL-C levels in patients with mixed hyperlipidemias** (ie, elevated cholesterol and TG levels). Statins are **extremely effective in reducing LDL-C levels in most patients with primary hypercholesterolemia**. Statins decrease TC by 15% to 60% and LDL-C by 18% to 55% and increase HDL-C levels by 5% to 15%. Declines in apo B levels commensurate with reductions in LDL-C have been demonstrated. Statins also reduce TG levels by 7% to 30% but have minimal effects on apo A1, apo A2, and Lp(a). **All statin drugs at the starting dose and within one to two dose titrations are well tolerated, efficacious**, and reasonably equivalent with respect to safety profiles.

(2) Adverse effects. Statins are remarkably safe drugs, with a low incidence of side effects. However, **they are contraindicated in pregnancy**. The most common side effects are **mild gastrointestinal disturbances** (eg, nausea, abdominal pain, diarrhea, constipation, and flatulence). Headache, fatigue, pruritus, and myalgias are other minor side effects, but these complaints usually do not warrant discontinuation of therapy.

(a) **Liver function test abnormalities.** Mild, transient elevations in liver enzymes have been reported with all statins. Marked elevation of transaminases is rare, but clinicians should use caution before starting statins in patients with acute or chronic liver disease, though statins are not contraindicated in those with chronic stable liver disease. In the HPS, only 0.5% of patients had to stop treatment because of elevated ALT levels. Even when taking the highest dose of atorvastatin (80 mg), patients in PROVE-IT and TNT had only a 3.3% and 1.1% incidence, respectively, of transaminase elevation more than 3 times the upper limit of normal. In general, for each doubling of a statin dose, there is a 0.6% increase in the risk of elevation of transaminase levels. The transaminase elevation is usually asymptomatic, and there is no recommendation by the ACC or AHA for routine monitoring of liver enzymes for patients on statins. However, if they are checked due to symptoms or physical concerns for liver disease, **statin therapy can be held when transaminase levels increase more than 3 times the upper limit of normal**; transaminase levels typically normalize within 2 weeks and rechallenge with a lower dose of the same statin or with a different statin can be tried.

(b) **Statin-associated muscle symptoms (SAMSs)** describe a spectrum of muscle-related statin-associated side effects, from more common myalgias (5%-10% in observational studies and real-world clinical setting), in which CK is normal, to the rarer entities of myositis, rhabdomyolysis, or autoimmune myopathy. Statin-associated myalgias can appear at any time during statin therapy, even years after initiation of treatment. Muscle symptoms usually resolve with discontinuation of the statin. There is recent evidence that statin inhibition of mitochondrial coenzyme Q10 (CoQ10) may be responsible for statin-induced myalgias, and there are conflicting small studies regarding the benefit of CoQ10 supplementation on statin myalgias. Myositis and rhabdomyolysis are characterized by muscle pain, stiffness, or aching and serum CK elevations, with rhabdomyolysis possessing elevations >10 times the upper limit of normal and associated renal injury. Statin-associated autoimmune myopathy is characterized by the detection of antibodies against HMG-CoA reductase; symptoms may not resolve completely even after drug discontinuation. The risk of myositis may be increased in the older patients, those with a low body mass index, those with multisystem disease such as chronic renal failure, those in the perioperative period, and those on multiple medications. Simvastatin 80 mg has been associated with a slightly higher incidence of myopathy and rhabdomyolysis compared with other statins, especially when combined with gemfibrozil. This could be due to the decreased rate of plasma clearance of simvastatin in older versus

younger patients. Death from statin-induced rhabdomyolysis is exceedingly rare, with an incidence of 1.5 deaths per 10 million prescriptions. Statin-naïve patients should be warned to report symptoms of muscle pain or stiffness immediately if they occur after starting the drug, but routine CK measurements in asymptomatic patients are not warranted.

(c) **Drug interactions.** When statins are used in combination with certain pharmaceutical agents, such as erythromycin, gemfibrozil, azole antifungals, cimetidine, methotrexate, or cyclosporine, the risks of CK elevation and myositis increase. These drug combinations should be avoided or used judiciously with interval measurements of CK levels and liver function. Pravastatin and fluvastatin are safer in combination with other drugs because these two drugs do not use the cytochrome P450 3A4 microsomal pathways for metabolism. Verapamil and amiodarone are two commonly used CV agents that inhibit this pathway, and the concurrent use of simvastatin, atorvastatin, or lovastatin may, therefore, predispose to an increased risk of myositis. The FDA has recommended that simvastatin should not be prescribed at a dose of 80 mg, given the higher rate of myopathy at this dose unless patients have already safely taken this dose for >12 months. Patients requiring this dose to maintain lipid goals should be transferred to another statin drug capable of achieving that goal. Simvastatin dosage in combination with amiodarone, diltiazem, or verapamil should not exceed 10 mg daily and should not exceed 20 mg daily in combination with amlodipine or ranolazine.

b. **Cholesterol absorption inhibitors** such as ezetimibe inhibit cholesterol absorption by the enterocyte. Ezetimibe reduces cholesterol absorption from the small bowel by 23% to 50% and reduces serum LDL level by 14% to 20% when used in combination with a statin. Reduction in clinical end points or surrogate end points has not been demonstrated for this group of drugs in all people. The Study of Heart and Renal Protection trial reported that cholesterol lowering with a combination of simvastatin and ezetimibe in patients with chronic kidney disease significantly reduced the risk of major atherosclerotic events by 17%, including significant reductions in the risk of nonhemorrhagic stroke and revascularizations, when compared with placebo. IMPROVE-IT compared ezetimibe/simvastatin versus simvastatin in subjects with stabilized high-risk ACS and showed that the addition of ezetimibe led to lower LDL levels and lower rates of CV events.

c. **PCSK-9 inhibitors.** The mechanism of action of PCSK-9 inhibitors along with landmark clinical studies was described above. Alirocumab and evolocumab are used for LDL-C lowering after being added to maximally tolerated statin therapies. Both medications are administered as subcutaneous injections every 2 to 4 weeks. Hypersensitivity reactions or injection site reactions are the most

common side affects of these medicines. Cost-effectiveness of PCSK-9 inhibitors may be a concern, with one analysis suggesting incremental cost-effectiveness ratios (ICER) from $141,700 to $450,000 per QALY using mid-2018 list prices (traditionally high-value therapies have ICER <$50,000 per QALY gained and low-value therapies have ICER >$150,000 per QALY gained).

d. **Bile acid sequestrants** lower LDL-C level by interfering with reabsorption of bile acids in the distal ileum, reducing the amount returned to the liver. This causes upregulation of cholesterol conversion into bile acids within the liver, so LDL receptors are increased, and more LDL-C is returned from the bloodstream. The average LDL level decrease is approximately 15% to 30%, with a small rise seen in HDL level (3%-5%). TGs show no change or may rise; therefore, these agents should be avoided in patients with elevated TGs; colesevelam is contraindicated in patients with a history of hypertriglyceridemia-induced pancreatitis. Two small angiographic trials, the NHLBI Type II Coronary Interventional Study and the St Thomas Atherosclerosis Regression Study, have demonstrated reduced progression of CAD on serial angiograms in men with hypercholesterolemia who were taking cholestyramine. These agents may be of particular benefit in patients with minor elevation in LDL-C, for young patients, for women considering pregnancy, and in combination with a statin in those with very high LDL-C levels. In a pregnant patient, additional supplementation of iron and folate may be necessary because resins used over the long term can interfere with their absorption. Overall, bile acid sequestrants are free of systemic side effects as they are not systemically absorbed; however, gastrointestinal side effects such as constipation are common, and compliance is poor as a result. Caution should be used in patients who have gastrointestinal dysmotility.

e. **Nicotinic acid or niacin.** Niacin affects all lipid parameters favorably (ie, LDL reduction of 5%-25%, TG reduction of 20%-50%, and HDL elevation of 15%-35%). It is one of the only agents that reduces Lp(a) significantly (up to 30%). Unfortunately, compliance is poor because of frequent side effects. Flushing and pruritus, gastrointestinal discomfort, glucose intolerance, and hyperuricemia often accompany the use of niacin. Hepatotoxicity is rare but is more commonly seen with the sustained-release preparation. It is often heralded by a dramatic reduction in lipid levels. There are limited data on long-term therapy with this agent. Niacin may be particularly useful for patients who do not have substantial elevations in their LDL-C levels, and low doses may be used to treat diabetic dyslipidemia. High doses should be avoided in patients with diabetes, and the drug should be avoided in those with a history of gout, peptic ulcer disease, or active hepatic disease. In the HPS2-Thrive trial, niacin and laropiprant on a background statin therapy did **not** reduce adverse CV events despite raising HDL concentrations. Taken together, the TG-lowering

effect of niacin is appreciated, but niacin is not currently endorsed by the ACC or AHA as an add-on to statin therapies for LDL-C lowering.

f. **Fibrates are effective at lowering TG levels** by 20% to 50% and raising HDL levels by 10% to 20%. The mechanism of action involves activation of the nuclear transcription factor PPARα, with resultant increases in hepatic synthesis of apo A1 and apo A2 (raising HDL) and increase in lipoprotein lipase–mediated lipolysis, thus lowering TG levels. LDL level reduction varies with the agent used and may range from 5% to 20% in patients who are not hypertriglyceridemic. Fenofibrate appears to lower LDL more effectively than gemfibrozil. Although a higher mortality rate was seen in the clofibrate arm of the World Health Organization (WHO) clofibrate study, such a finding was not seen in subsequent studies of gemfibrozil or fenofibrate. These agents have been demonstrated to impart a reduction in risk of CAD events and are of use in patients with elevated TGs. The VA-HIT (1999) found a reduction in fatal and nonfatal MI with gemfibrozil use in men with CAD who had low HDL levels (mean 32 mg/dL), but the FIELD trial (2005) did not find a significant reduction in the primary end point of CAD death or MI in patients with diabetes. Although fibrates are often used in combination with statin therapy to treat mixed dyslipidemia, there are no studies demonstrating reduction in clinical events with this approach. Even the most recent PROMINENT trial (2022) did not find a difference in CV outcomes between the use of pemafibrate or placebo, despite effective reduction in TG levels of about 31%. The combination of statin and fibrate increases the risk of myopathy, in particular when gemfibrozil is used. However, for patients with very high TG levels (>1,000 mg/dL), fibrate therapy reduces the risk of pancreatitis and should be considered.

g. **CETP inhibitors** such as torcetrapib, dalcetrapib, anacetrapib, and evacetrapib inhibit the process in which TGs from VLDL or LDL are exchanged for cholesteryl esters from HDL, resulting in higher HDL levels and reduction of LDL levels. Results from a torcetrapib study in 2004 demonstrated a significant increase in HDL (61%) and a decrease in LDL (17%) when receiving the drug in addition to atorvastatin and a 46% increase in HDL when receiving the drug alone. However, the phase 3 ILLUMINATE trial was terminated in 2006 after an increase in CV events and mortality was shown to be associated with the drug. As described above, several trials have concluded that CETP inhibitors fail to decrease CV events despite efficient lowering of LDL and raising of HDL levels raising suspicion about whether this class of drugs will continue to be investigated.

h. **Additional nonstatin therapies.** Bempedoic acid is a prodrug that is activated in hepatocytes and inhibits ATP citrate lyase upstream of HMG-CoA reductase activity in cholesterol synthesis. Inclisiran is the only siRNA available to inhibit translation of PSCK-9 mRNA within the hepatocyte. Presently, the administration of inclisiran must be done in the clinic setting. Safety and

efficacy trials of bempedoic acid and inclisiran were described above, and clinical outcomes trials for these medications are still ongoing. Evinacumab is a novel human monoclonal antibody that inhibits angiopoietin-like protein 3 (ANGPTL3) and was FDA approved in 2021 to lower LDL-C in patients greater than 12 years of age with homozygous FH when used in combination with statins. Evinacumab blocks the inhibition of lipoprotein lipase by ANGPTL3 and allows for increased processing and clearance of VLDL particles, resulting in lower serum TGs and LDL-C. In the ELIPSE HoFH trial, patients with homozygous FH on background lipid-lowering therapy saw a mean reduction of LDL-C from 255 to 135 mg/dL.

3. **Choice of an agent and combination therapy.** The use of statin therapy for the treatment of hyperlipidemia should be guided by the expected change in LDL-C levels (**Table 45.4**). Most statins have a log-linear dose-response pattern, with each doubling of dose associated with a further 7% reduction in LDL-C levels. Adverse effects of statins are also dose dependent and rise with the use of higher doses.

TABLE 45.4 Average Reduction in Low-Density Lipoprotein Cholesterol Associated With the Starting Dose of Statin Agents

Agent	Average LDL-C Reduction (%)
Lovastatin (20 mg)	24
Pravastatin (20 mg)	24
Simvastatin (20 mg)	35
Fluvastatin (20 mg)	18
Atorvastatin (10 mg)	37
Rosuvastatin (10 mg)	47

LDL-C, low-density lipoprotein cholesterol.

   a. The combination of a statin plus ezetimibe has been shown to be highly safe and effective at lowering LDL-C levels, with reduction in clinical outcomes in patients at very high risk for ASCVD. The availability of a generic formulation makes ezetimibe an appealing first choice as a nonstatin adjunct for LDL-C lowering.
   b. The combination of statin and PCSK-9 inhibitors is extremely effective at lowering LDL-C levels by ~60% without many side effects. The FDA has approved this approach for patients with residual hypercholesterolemia and known ASCVD and patients with heterozygous or homozygous FH.
   c. **Statins and bile acid sequestrants.** In isolated forms of LDL-C elevation, this combination exhibits highly complementary mechanisms of action. The combination of a statin with a bile acid sequestrant is ideal, owing to the lack of potentiation of side effects. The sequestrant provides little added toxicity, and the LDL-C lowering needed may not necessitate a full sequestrant dosage.

Unfortunately, patient compliance with the combination is poor because of the common gastrointestinal side effects of resins. Although the combination may reduce **LDL level by as much as 70% in some patients**, there appears to be a ceiling effect, with no LDL lowering occurring beyond the original level with an increase in dose of either agent.

Combining a statin with niacin is attractive because it can favorably influence all lipid subfractions. The side effects of the combination are increased, but not synergistic, and the risk of myopathy may be lower than previously believed. The main serious side effect of the combination is hepatotoxicity, which may be reduced by using extended-release niacin. In small studies using this combination, the risk of hepatotoxicity (ie, persistent elevation of AST or ALT of more than 3 times the upper limit of normal) at niacin doses of 2 g/d was about 1%. The HPS2-Thrive showed no clinical benefit in adding niacin and laropiprant to statins.

d. The combination of a **statin plus fibrate** is theoretically appealing for treating mixed hyperlipidemias, but no reduction in clinical events has been demonstrated with this approach. The combination is associated with an increased risk of myopathy, specifically with gemfibrozil. Although earlier work suggested a higher incidence, later studies suggest this complication may be seen in approximately 1% of patients with the currently used agents.

V. THERAPY OF SPECIFIC LIPID DISORDERS

A. Very high LDL-C levels usually result from inherited disorders of lipoprotein metabolism and carry a high risk of premature atherosclerosis with its attendant morbidity and mortality. However, **both hypothyroidism and nephrotic syndrome** may secondarily cause markedly elevated LDL-C and should be ruled out in any patient presenting with hypercholesterolemia. In addition to addressing the underlying cause, most of these patients with secondary hypercholesterolemia will need high-dose statin therapy and dietary restrictions. The addition of ezetimibe with an additional third agent (eg, bile acid sequestrant, bempedoic acid, niacin) is often warranted to achieve target levels. Therapy should be initiated early, and family members should be screened for hyperlipidemia. Patients with homozygous FH are deficient in LDL receptors, and measures that reduce cholesterol absorption (eg, diet, ileal exclusion, bile acid sequestrants, and ezetimibe) or act by LDL receptor upregulation (eg, statins, PCSK-9 inhibition, inclisiran) may not be wholly effective. These patients may be treated with evinacumab, which acts upstream of LDL-C formation, or by LDL apheresis, and should be managed in tertiary care centers only.

B. Elevated TG levels may be caused by many factors, and more than one cause may be active in a given patient. Moderate (175-499 mg/dL) and severe hypertriglyceridemia (>500 mg/dL) are thought to result from elevated VLDL, and in the latter, excess VLDL and chylomicrons. The excess chylomicrons are likely responsible for the increased risk of hypertriglyceridemia-associated pancreatitis in cases of severe hypertriglyceridemia. Milder elevations in TGs are caused by obesity, sedentary

lifestyle, smoking, excess alcohol intake, and high-carbohydrate diets, and TLC is imperative to reducing ASCVD risk, with adherence to very low-fat diets (<15% calories from fat). With more severe hypertriglyceridemia, substitution of medium-chain fatty acids while avoiding very high-carbohydrate intake should be considered, along with dietitian referral. In certain patients, secondary causes such as diabetes, renal failure, Cushing disease, nephrotic syndrome, or medications (eg, protease inhibitors, corticosteroids, retinoids, beta-blockers, and oral estrogens) may be responsible, and genetic abnormalities in TG handling may be pertinent in others. While statins may not be especially effective at reducing TG levels, patients with hypertriglyceridemia often have comorbid metabolic syndrome, hypertension, and diabetes and warrant statins for ASCVD risk reduction. Persistent hypertriglyceridemia despite TLCs can be managed with omega-3 fatty acids, fibrates, and niacin. Data from the REDUCE-IT and STRENGTH trials have been discussed above, and despite the discordant conclusions with respect to reduction of CVD outcomes, significant reductions in serum TG levels were observed with both the icosapent ethyl arm in REDUCE-IT and combination EPA/DHA (omega-3 fatty acids) in STRENGTH.

C. **Low HDL-C** levels often accompany minor or modest elevations in TG levels. Low HDL level has been shown in epidemiologic studies to be an independent risk factor of CVD. However, despite a multitude of research on currently available therapies to raise HDL, there has been no conclusive evidence that raising serum HDL-C levels contributes to lower rates of CVD. In patients who have isolated low HDL levels without any elevation in TG levels, the first goal is to identify and modify lifestyle factors (eg, high-carbohydrate diet, sedentary lifestyle, obesity, and smoking) and medications (eg, progestational agents and anabolic steroids). The next step encompasses calculation of 10-year risk and treating LDL-C with a statin when appropriate. The AFCAPS/TexCAPS study found a clear benefit for statin therapy in patients with low HDL-C levels.

D. **Diabetic dyslipidemia.** Patients with diabetes are at an increased risk for CV events and fare poorly after CAD manifests. Diabetes is associated with an increase in small LDL particles and is often associated with high TG and low HDL levels. As such, it also leads to significant discordance between estimated LDL levels and levels of non-HDL or TC/HDL ratio, which are better predictors of risk in this patient population. Hyperglycemia is an independent risk factor for CAD. Primary prevention is important in this group and was demonstrated to be efficacious in the HPS trial. **All patients with diabetes should be considered for statin therapy and TLCs**. Secondary goals include improved non–HDL-C levels and TC/HDL-C levels and treatment for elevated TG levels. Blood sugar control and insulin therapy often facilitate the former, but fibrates or low-dose niacin may be necessary in some patients. Patients with diabetes also often have coexisting hypertension. Blood pressure control and smoking cessation are essential because both interventions are highly effective at reducing CV events in this population.

VI. SUMMARY. Despite advances in technology to reduce mortality in ASCVD when it occurs, the importance of preventing incident or recurrent ASCVD is also to reduce the attendant morbidity associated with each ASCVD event. The clinical trials in the 1990s to 2000s in primary and secondary ASCVD reduction cemented statins as the central pillar of hypercholesterolemia management. The past decade has seen the rise of numerous adjuncts to statins in the management of hyperlipidemia, including ezetimibe, bempedoic acid, PSCK-9 inhibition, inclisiran, and evinacumab. The emergence of such a multitude of novel therapies requires clinicians specializing in CVD prevention to pay careful attention to not only study design, patient selection, and outcomes analysis but also to cost-effectiveness, medication access, and the patients' own goals for their health care.

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CHAPTER 46

Hypertension and Nonlipid Cardiovascular Risk Factors

Luke J. Laffin and Agam Bansal

I. INTRODUCTION. Beyond hyperlipidemia and dyslipidemia, numerous additional cardiovascular (CV) risk factors are implicated in the incidence of atherosclerotic cardiovascular disease (ASCVD). Hypertension (HTN), obesity, and smoking are examples of risk factors that not only increase the risk for ASCVD but also increase the risk of heart failure and atrial fibrillation. The following sections discuss the management of HTN and other nonlipid risk factors for the prevention of CV disease.

II. HYPERTENSION. Elevated blood pressure (BP) is the **world's foremost cause of CV morbidity and mortality**. HTN control rates within the United States are **worsening**, attributable to a variety of factors, including dietary indiscretion, sedentary lifestyles, and increased rates of obesity. Numerous safe and effective medications are widely available to lower BP, yet lifestyle modification remains the cornerstone for the successful treatment of HTN.

A. Pathogenesis

1. HTN results from a **complex interaction of genetic, environmental, and demographic factors**. A number of pathophysiologic factors are involved in the development of primary HTN (formerly called essential HTN) and include increased sympathetic nervous system activity, autonomic imbalance (increased sympathetic tone, abnormally reduced parasympathetic tone), vascular remodeling, arterial stiffness, and endothelial dysfunction.
2. The renin-angiotensin-aldosterone system plays a major role in vascular remodeling (alterations in structure, mechanical properties, and function of small arteries) and critical target organ damage (myocardial fibrosis, renal injury).

B. Genetics

1. In patients with primary HTN, heritability has been estimated to range from 30% to 50%, indicating that a large proportion of variation in BP can be attributed to additive genetic effects. Variation in BP appears to be the result of the contribution of several different genes. In addition, there are simple Mendelian forms of high BP in which a single-gene defect may be largely responsible for the hypertensive phenotype.
2. Genetic mutations of HTN single-gene forms include glucocorticoid remedial HTN (chimeric gene formation; autosomal dominant), 11-beta-hydroxylase (mutation in gene encoding), 17-alpha-hydroxylase deficiency, Liddle syndrome (mutation in the sodium channel gene), HTN exacerbated by pregnancy, syndrome of apparent mineralocorticoid excess, and pseudohypoaldosteronism.
3. A family history of HTN can be a surrogate marker for undefined, genetically linked risk factors shared by the family. Risk factors such as obesity, dyslipidemia, and insulin resistance are predictive of future HTN.

C. Contribution to CV risk. A shift in diagnostic emphasis from diastolic blood pressure (DBP) to systolic blood pressure (SBP) occurred beginning in the 1990s. SBP, DBP, and pulse pressure are important in staging HTN at different ages. Earlier generations of physicians favored the importance of DBP over SBP. With the aging of the population, HTN has become a disease of older patients, specifically **reflected by isolated systolic hypertension** (ISH). As arteries stiffen and pulse wave amplification decreases with aging, a general shift in elevation occurs from DBP to SBP and, eventually in some, to pulse pressure as the predictors of CV risk.

D. Evaluation of HTN

1. A complete history, physical examination, basic serum chemistries, lipid profile, urinalysis, and electrocardiogram (ECG) are recommended for the initial evaluation of a hypertensive patient. **Urinalysis is especially important because of the impact that kidney disease has on drug treatment selection**.
   a. Optional evaluations include an albuminuria assessment, echocardiogram, and serum uric acid level.
   b. Ambulatory blood pressure monitoring (ABPM) and assessment of plasma renin activity (PRA) (or increasingly direct renin

concentration [DRC]) are not indicated for routine evaluation of most patients with HTN at the first visit.

2. History should include detailed family history, nonprescription medications (nonsteroidal anti-inflammatory drugs, diet pills, decongestants, appetite suppressants, herbal therapy), oral contraceptive use, alcohol intake, illicit drugs, and sleep history. The physician should always be alert to history or physical examination findings that suggest a **secondary cause for a patient's HTN**.
3. The physical examination should include two or more BP measurements separated by 2 minutes.
   a. BP should be obtained seated and, after standing for at least 2 minutes, in accordance with recommended techniques.
   b. BP should be verified in the contralateral arms; if values are different, the higher value should be used.
   c. Special attention should be directed to the funduscopic examination; the presence or absence of carotid bruits or distended neck veins, thyroid enlargements; and examination of the heart, lungs, abdomen, and extremities. Attention should also be directed to peripheral pulses, the presence of abdominal bruits, and the presence or absence of edema.
4. **Out-of-office BP monitoring.** The 2017 American BP guidelines recommend out-of-office BP measurements to confirm the diagnosis of HTN and for titration of BP-lowering medication, in conjunction with telehealth counseling or clinical interventions (**Figure 46.1**).

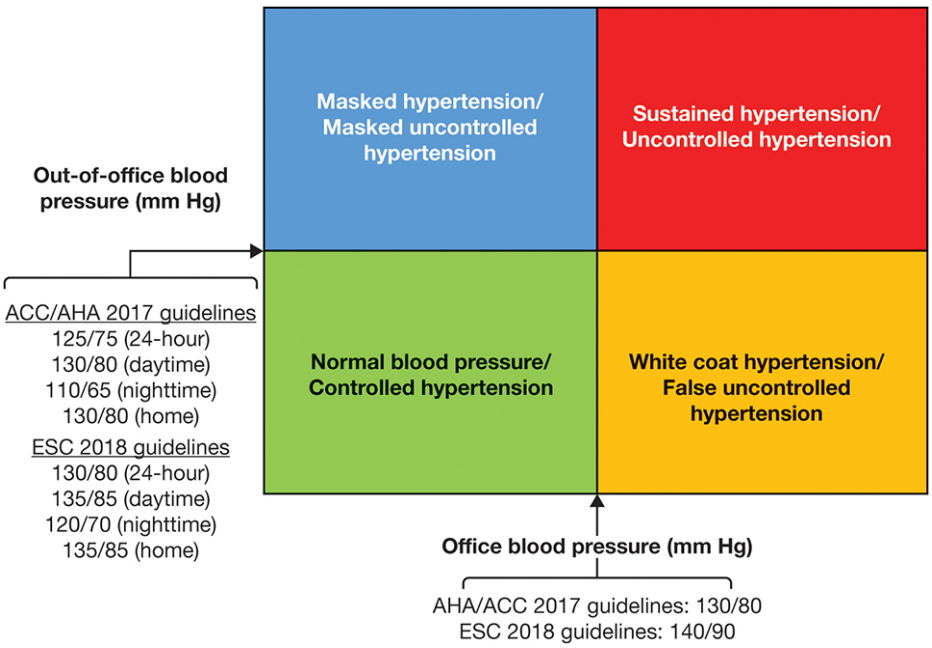

FIGURE 46.1 Office versus out-of-office blood pressures.

a. **ABPM.** Gold standard for measuring BP accurately and differentiating between different forms of HTN, such as **white-coat, masked, and sustained HTN**

   (1) Recent data suggests that **white-coat HTN** is not a benign finding and is associated with an increased risk of future CV disease.

   (2) **Masked HTN** is defined as persistently normal or controlled office BP measurements with elevated outside office BPs.

   (3) Prevalence of masked HTN is unknown but likely ranges from 10% to 40% based on the population sampled.

   (4) Target organ damage (TOD) may be similar to that of patients with primary HTN.

   (5) Nocturnal HTN and nondipping (or reverse dipping) is a subgroup of masked HTN with a high prevalence among African Americans with HTN and chronic kidney disease (CKD).

b. **Self-monitoring of blood pressure (SMBP).** Less expensive alternative and provides similar accuracy to 24-hour ABPM in managing patients with HTN. A major drawback of SMBP when

compared to 24-hour ABPM is the lack of evaluation of BP during sleep.

E. Resistant HTN. Persistence of BP above goal, while being treated with **maximally tolerated triple-drug therapy**, commonly including a blocker of the renin-angiotensin-aldosterone system, a long-acting calcium channel blocker (CCB), and a diuretic appropriate for a patient's renal function

1. In addition, patients with HTN who require **four or more antihypertensive medications and BP is controlled are also deemed to have resistant HTN**.
2. Above goal with five or more medications as "**refractory HTN**" including chlorthalidone and a mineralocorticoid receptor antagonist
3. Prevalence of true resistant HTN is unknown because reports of its prevalence are often missing one of the elements needed to exclude pseudoresistance (**medication dose, adherence, or out-of-office BP**). However, the prevalence of apparent treatment-resistant HTN is between 10% and 20%.
4. More intensive therapy with emphasis on targeted volume control using diuretic therapy can achieve goal BP levels in a significant percentage of patients with apparent resistant HTN.
5. The PATHWAY-2 trial, published in 2015, demonstrates that **spironolactone is the most effective add-on drug** for the treatment of resistant HTN. Subsequent additional pharmacotherapies are based on expert opinion, lacking large-scale clinical trials, and should be individualized for the patient.

F. Secondary HTN. For patients with resistant HTN, or with an early age of HTN onset, several clinical clues can suggest the possible presence of secondary HTN. **Table 46.1** divides the causes of secondary HTN into four broad categories. Secondary hypertensive disorders can be effectively treated or cured, leading to partial or complete normalization of resistant HTN in most patients.

TABLE 46.1 Secondary Causes of Hypertension

Renal
Renal artery stenosis Renal parenchymal obstruction

Polycystic kidney disease
Endocrine
Primary aldosteronism Cushing syndrome Congenital adrenal hyperplasia Pheochromocytoma/paraganglioma
Adrenal and adrenal like
Acromegaly Hypercalcemia Liddle syndrome Gordon syndrome
Other
Coarctation of the aorta Preeclampsia Acute intermittent porphyria Thyroid (hyper-, hypo-) Medications

1. **Primary aldosteronism**. Most common secondary cause of HTN. The most common cause of primary aldosteronism is an aldosterone-producing adenoma (70%-80%). However, glucocorticoid-remediable aldosteronism (GRA), adrenal hyperplasia, and adrenal carcinoma are other considerations.
    a. Although the clinical manifestations of primary aldosteronism are not distinctive, the best clues to the presence of primary aldosteronism include HTN with **spontaneous hypokalemia** (<3.5 mEq/L), **HTN with provoked hypokalemia** (<3.0 mEq/L during diuretic therapy), or simply resistant HTN. One should be especially suspicious of primary aldosteronism if potassium is <3.5 mEq/L despite potassium supplementation, angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy, and/or a potassium-sparing diuretic.
    b. However, **not all patients with primary aldosteronism have hypokalemia**; 7% to 38% of patients with primary aldosteronism may have normal serum potassium.
    c. Best screening tests are the levels of plasma aldosterone (PA) and PRA or DRC. **Current BP medications do not need to be stopped when screening (because screening rates are notoriously low)**. If

renin is suppressed, then further evaluation including 24-hour urine aldosterone following salt loading should be undertaken after holding medications that impact serum aldosterone levels for at least 2 weeks (ideally >4).

d. An adrenal computed tomography (CT) scan is helpful in differentiating between adrenal adenoma, adrenal hyperplasia, and adrenal carcinoma. The overall sensitivity of localizing aldosterone-producing tumors by high-resolution CT scanning exceeds 90%. Adrenal carcinomas are typically large (>5 cm) in comparison to a hypodense unilateral macroadenoma (>1 cm). Normally, abnormalities in both glands represent adrenal hyperplasia.

e. Adrenal vein sampling after administration of adrenocorticotropic hormone (ACTH) is pivotal in the lateralization of excess aldosterone production. The sampling of the adrenal vein is **technically difficult and should be restricted to experienced centers**. Newer nuclear imaging techniques may obviate the need for this invasive procedure in the future.

f. **Medical therapy with eplerenone** (selective aldosterone receptor antagonist) **or spironolactone** can be used in patients with bilateral adrenal adenomas, adenomas that cannot be excised surgically (poor surgical risk), in individuals with adrenal hyperplasia, and in those with significant responses to aldosterone receptor antagonists who do not desire surgery. Adrenal adenomas may be removed laparoscopically. Surgical removal of an aldosterone-producing adenoma (unilateral disease) improves BP and normalizes a patient's biochemical profile. However, **a significant percentage of patients are not cured of HTN even with adrenalectomy**, and the persistence of HTN is usually owing to underlying primary HTN or the development of nephrosclerosis, given a long history of elevated BP.

2. **Renal parenchymal disease. CKD** is defined as the presence of kidney damage or reduced renal function for 3 months or more, irrespective of the cause. Kidney damage is usually detected as albuminuria >300 mg/d, and reduced renal function is defined as an estimated glomerular filtration rate (GFR) <60 mL/min/1.73 m^2. Renal parenchymal disease is a common secondary cause of HTN, although not often reversible.

a. The HOPE study data demonstrated a **continuous relationship between serum creatinine levels and CV outcomes** in patients with HTN who are normotensive. An **additive risk** exists with increased serum creatinine and moderately **increased albuminuria**.

b. The clinical clues are easily detected with a urinalysis and screening tests of renal function (serum creatinine and eGFR). Additional screening studies may include renal duplex ultrasonography.

c. Aggressive treatment and **control of BP can slow the progression of renal function loss**, especially with ACE inhibitors or ARBs as specific additions to the regimen. With advanced renal failure (GFR <30 mL/min/1.73 m^2 corresponding to a serum creatinine of 2.5-3.0 mg/dL), the use of loop diuretics is usually warranted to optimize fluid volume, which is critical for BP control.

3. **Renovascular disease.** Renal artery stenosis that results in renovascular HTN occurs in 1% to 5% of all patients with HTN. The most common causes of renovascular disease are **fibromuscular dysplasia (FMD) and atherosclerosis**.

a. Atherosclerotic renal artery disease (RAD) accounts for 90% of all renovascular lesions, usually occurring at the ostium or within the proximal 2 cm of the renal artery. Patients with atherosclerotic renal artery stenosis may present with HTN, renal failure secondary to ischemia, and/or recurrent episodes of congestive heart failure (CHF), and flash pulmonary edema.

b. FMD is found predominantly in young women. Radiographically, it is characterized by a "**string of beads**" **appearance**, with the beading extending beyond the normal caliber of the artery, located in the middle to the distal portion of the artery. Less common forms of fibrous renal artery stenosis include perimedial fibroplasia, medial hyperplasia, intimal fibroplasia, and adventitial hyperplasia.

c. Clinical clues for renovascular HTN include **abrupt onset of HTN**, age <30 years or >55 years, **accelerated HTN** (grade 3 or 4 retinopathy), HTN refractory to a triple-drug regimen, HTN and diffuse vascular disease (carotid, coronary, peripheral vascular), systolic/diastolic epigastric bruit, HTN and unexplained renal insufficiency, **renal insufficiency induced by ACE inhibitor therapy**, severe HTN, and **recurrent flash pulmonary edema**.

d. Uncontrolled BP and progressive compromise in renal function are the primary **indicators for intervention**. For younger patients with FMD (medial fibroplasia, intimal fibroplasia, periarterial hyperplasia), percutaneous transluminal renal angioplasty (PTRA) is the mainstay of therapy, with surgical revascularization considered a secondary indication. Successful angioplasty results in a reduction of both the disease and HTN.

(1) The primary goal of therapy for patients with hemodynamically significant RAD is control of HTN and preservation of kidney function. The three current therapeutic options available to treat patients with RAD include (a) medical management, (b) surgical revascularization, and (c) percutaneous angioplasty with or without stent placement.

(2) Patients with the following characteristics are more likely to benefit from revascularization: those with a **short duration of elevation of BPs prior to discovery of renovascular disease**, failure or intolerance of optimal medical therapy, and **recurrent heart failure and flash pulmonary edema**. Data suggest that in the absence of one of those factors, medical therapy alone is generally recommended. A 2016 meta-analysis comparing the effectiveness of strategies for managing unilateral renal artery stenosis (including eight randomized controlled trials [RCTs]) found no benefit from intervention (in addition to medical therapy) on mortality, major adverse cardiovascular event (MACE), or BP control.

G. Treatment of outpatient HTN. The 2017 American BP guidelines provided new classifications for the stages of HTN: office BP >130 to 140/80 to 90 mm Hg as stage 1 HTN and >140/90 mm Hg as stage 2 HTN. This contrasts with the prior definition of stage 1 HTN as >140/90 mm Hg. The 2018 European guidelines maintain a threshold of 140/90 mm Hg to classify an individual as having stage 1 HTN and label 130 to 139/85 to 89 mm Hg as "high normal." Several landmark clinical trials have assessed the impact of different therapeutic agents and BP targets on outcomes in the presence of HTN.

1. Lifestyle modification is the cornerstone of any attempts at BP reduction. Healthy dietary patterns, most notably the DASH diet ("dietary approaches to stopping hypertension"), **low daily sodium**

intake, appropriate body weight, regular physical activity, and limiting alcohol intake are the main lifestyle factors that are emphasized. Patients should consume less than 2,300 mg of sodium daily and ideally aim for less than 1,500 mg of sodium daily. The impact of sodium restriction to control HTN cannot be overstated. Multiple historical and contemporary studies in various populations demonstrate this clear benefit.

2. **Pharmacotherapy.** It is generally accepted that **the first-line therapy for the treatment of primary HTN includes either thiazide-type or thiazide-like diuretics, ACE inhibitors/ARBs, or CCBs**, unless compelling indications exist for the use of another category such as beta-blockers in the presence of heart failure with reduced ejection fraction or arrhythmias.
   - **a.** The 2017 American BP guidelines and several meta-analyses conclude that the major determinant of CV risk reduction is not the type of BP-lowering medication but the magnitude of BP reduction.
   - **b.** The Systolic Blood Pressure Intervention Trial (**SPRINT**) published in 2015 was the major impetus for guideline recommendations for more aggressive BP lowering when it demonstrated significant improvement in CV outcomes for patients treated to a goal BP of <120 mm Hg compared with <140 mm Hg systolic.
   - **c. Most patients will need at least two drugs to achieve BP control** and most patients should be started on combination therapy if BP >140/90 mm Hg. Patients should return for follow-up monthly until the BP goal is achieved. Serum potassium and creatinine should be monitored at least twice per year.
     - **(1)** The Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension trial (**ACCOMPLISH**) investigated the ideal initial combination therapy by comparing an ACE inhibitor and diuretic or ACE inhibitor and CCB combination. Benazepril/amlodipine was associated with reduced CV events compared with benazepril/hydrochlorothiazide (9.6% vs 11.8%).
     - **(2)** The **Diuretic Comparison Project (DCP)** investigated whether substituting chlorthalidone for hydrochlorthiazide would result in better CV outcomes among veterans with HTN. There was no difference in MACEs between study participants

randomized to chlorthalidone compared with those kept on hydrochlorothiazide. Thus, if a patient's BP is controlled, there is not necessarily a need to use chlorthalidone, but if BP is not controlled, chlorthalidone more effectively lowers BP.

H. Hypertensive emergencies. Various terms—including *accelerated HTN, hypertensive crisis, malignant HTN, HTN emergencies*, and *hypertensive urgencies*—generally denote severe elevated BPs. Conditions associated with severely elevated SBPs are associated with target organ damage (**papilledema, heart failure, central nervous system dysfunction, aortic dissection**, etc). These emergencies **require immediate BP reduction**, not necessarily to "normal" levels, to prevent or limit ongoing TOD.

1. Defective autoregulation mechanisms of certain vascular beds that lead to arteritis and ischemia. Excessive abrupt increases in BP above an autoregulation range result in target organ damage, especially within the brain and kidney.
2. Because the risk-benefit ratio of immediate therapy for some forms of hypertensive emergencies has not been clearly established, **an individual approach should be invoked to guide therapy** (clinical setting, absolute level of BP increase, potential for worsening target organ perfusion).
3. Elevated BP alone, **in the absence of symptoms or new or progressive target organ damage**, rarely requires emergency therapy and has previously been referred to as hypertensive urgency, although that terminology is falling out of favor. A number of effective agents are available for the management of hypertensive emergencies (**Table 46.2**).

TABLE 46.2 Drugs for the Management of Hypertensive Emergencies

Agent	Dose	Onset/Duration of Action (After Discontinuation)	Precautions/Contraindications
Parenteral Vasodilators			
Nitroprusside	0.25-10.0 mcg/kg/min as IV infusion	Immediate/1-2 min after infusion	Nausea, vomiting, muscle twitching; with prolonged use may cause thiocyanate intoxication,

Agent	Dose	Onset/Duration of Action (After Discontinuation)	Precautions/Contraindications
	maximal dose for 10 min only		methemoglobinemia acidosis, cyanide poisoning
Fenoldopam	0.1-0.3 mcg/kg/min IV infusion, increase every 15 min until BP goal is reached	5-15 min/30-60 min	Headache, tachycardia, flushing, local phlebitis
Nitroglycerin	5-200 mcg/min as IV infusion, 5 mcg/min increase every 5 min	1-5 min/3-5 min	Headache, reflex tachycardia, vomiting, flushing, methemoglobinemia
Nicardipine	5-15 mg/h IV infusion	1-5 min/30-40 min, but may exceed 12 h after prolonged infusion	Reflex tachycardia, nausea, vomiting, headache, increased intracranial pressure; hypotension may be protracted after prolonged infusions
Clevidipine	2 mg/h IV infusion, increase every 2 min with 2 mg/h as IV bolus, repeated, or 15-30 mg/min by IV infusion	2-3 min/5-15 min	Headache and reflex tachycardia
Hydralazine	10-20 mg as IV bolus or 10-40 mg IM, repeat every 4-6 h	10 min IV/>1 h IV; 20-30 min IM/4-6 h IM	Tachycardia, headache, vomiting
Enalaprilat	0.625-1.250 mg every 6 h IV	15-15 min/4-6 h	Renal failure in patients with bilateral renal artery stenosis, hypotension, history of angioedema
Parenteral Adrenergic Inhibitors			

Agent	Dose	Onset/Duration of Action (After Discontinuation)	Precautions/Contraindications
Labetalol	0.25-0.5 mg/kg IV bolus; 2-4 mg/min as IV infusion until BP goal is reached, 5-20 mg/h subsequently	5-10 min/3-6 h	History of second- or third-degree AV block, HFrEF, asthma, bradycardia
Metoprolol	2.5-5 mg IV bolus over 2 min, repeat q5 min to maximum if 15 mg	1-2 min/5-8 h	History of second- or third-degree AV block, HFrEF, asthma, bradycardia
Esmolol	0.5-1 mg/kg IV bolus or 50-300 mcg/kg/min by infusion	1-2/10-30 min	Greater than first-degree heart block, bradycardia, HFrEF, asthma
Phentolamine	0.5-1 mg/kg as IV bolus OR 50-300 mcg/kg/min by infusion	1-2/10-30 min	Tachyarrhythmias, orthostatic hypotension
Clonidine	150-300 mcg IV bolus in 5-10 min	30 min/4-6 h	Sedation and rebound hypertension

AV, atrioventricular; BP, blood pressure; HFrEF, heart failure with reduced ejection fraction; IM, intramuscular; IV, intravenous; q, every.
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4. Hypertensive emergencies **during pregnancy** warrant careful drug selection and hemodynamic monitoring to avoid any increase in fetal risk. Hydralazine, methyldopa, and magnesium sulfate are traditional therapeutic agents in pregnancy; however, labetalol has been used more recently. Bolus injections may achieve therapeutic BP-lowering

goals sooner than continuous infusion. **Consideration of timely delivery of the infant will often help with BP control**.

III. OBESITY. Rates of obesity are rising throughout the world, with large increases in class III obesity (body mass index [BMI] >40 kg/m^2) and among children and adolescents. As of 2020, 71% of U.S. adults are overweight or obese (BMI >25 kg/m^2). Moreover, almost half of Americans are projected to have obesity by 2030 (BMI >30 kg/m^2). This is a critical problem among all races but in particular among for African American women, among whom the prevalence of obesity is >56%. The percentage of children and adolescents with obesity has more than doubled over the past two decades. There are clear links between obesity and the development of cardiac risk factors: HTN, dyslipidemia, and diabetes.

A. Link between obesity and CV disease

1. A positive association among BMI, increased total cholesterol and triglyceride levels, and decreased high-density lipoprotein cholesterol (HDL-C) levels is documented in all age groups.
2. Fat distribution appears to be a more important predictor of ASCVD than the total amount of fat because android fat patterns are more metabolically active and highly associated with dyslipidemia. Although BMI and waist-to-hip ratios indicate a linear association between obesity and ASCVD, the **waist-to-hip ratio**, which accounts for abdominal adiposity, is generally viewed as a more **accurate predictor of ASCVD**.
3. Obesity among adults is associated with **increased left ventricular (LV) mass**, a powerful independent predictor of mortality and morbidity from CV disease. LV mass in persons with obesity but without diabetes depends, at least in part, on the degree of insulin resistance and hyperinsulinemia and not on BMI and BP.
4. Central obesity is part of the **metabolic syndrome**, which is associated with an increased risk for ASCVD in both sexes. This condition is characterized by elevated plasma triglyceride and low plasma HDL-C levels.
   a. An additional feature is the presence of **dense, atherogenic low-density lipoprotein cholesterol (LDL-C)**.
   b. Other features are HTN, impaired glucose intolerance with hyperinsulinemia, and decreased sensitivity to the action of insulin

on peripheral tissues.

c. Hyperinsulinemia is associated with **lipid derangements, increased production of plasminogen activator inhibitor, and enhanced proliferation of cells in atherosclerotic plaque**. Among patients with hyperinsulinemia, an increased prevalence of ASCVD and a relationship between abnormal insulin levels, glucose metabolism, and severity of ASCVD have been reported. The physiologic response to insulin resistance is increased secretion of insulin, which may lead to glucose intolerance or frank diabetes mellitus.

B. Therapy

1. **Caloric restriction, behavior modification, and exercise** are the main treatment modalities for weight loss. The greatest weight losses occur with a combined regimen of diet and exercise rather than diet or exercise alone.
2. Several **medications** can be used for the management of obesity. Although historically long-term pharmacologic agents for weight loss and maintenance of weight loss were cautioned against due to the potential of untoward side effects (particularly adverse CV side effects), this paradigm is shifting.
3. The study of **GLP1 receptor agonists and combined GLP1/GIP receptor agonists** among patients with diabetes demonstrated improved CV outcomes and significant weight loss. This led to their study in patients with obesity but without diabetes and demonstrated between 10% and 25% total body weight loss.
   a. SELECT was the first trial to demonstrate that treatment of obesity reduced the risk of MACEs. Published in 2023, SELECT randomized 17,604 patients with preexisting CV disease, but without diabetes mellitus, to placebo or semaglutide (GLP1 receptor agonist). A 20% reduction in the risk of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke was observed. Additional CV outcome trials of combined GLP1/GIP receptor agonists are ongoing (SURMOUNT-MMO, tirzepatide).
   b. Other weight loss mediations include phentermine/topiramate, orlistat, and bupropion-naltrexone.

c. Among patients who are morbidly obese (BMI >40 kg/m^2) and patients who are obese (BMI between 35 and 40 kg/m^2) with coexisting conditions, **metabolic (bariatric) surgery** can be an effective treatment option for those who have failed noninvasive therapies.

IV. TOBACCO USE. Smoking, the single most preventable cause of death in the United States, is a leading risk factor for ASCVD. Second-hand smoke also increases the risk for ASCVD. The causal role of smoking in CV disease was derived from >20 million person-years of follow-up study. As of 2020, nearly 13% of adults in the United States smoked cigarettes. Rates of smoking are higher among people with lower education level and those living below the poverty level. Exposure to second-hand smoke increases the risk of death from coronary artery disease (CAD) by 30%. More than 90% of current smokers began their habit before reaching 21 years of age.

A. Pathophysiology. Cigarette use activates platelets, increases circulating fibrinogen, increases heart rate, and elevates BP. It also appears to promote atherosclerotic plaque disruption. A strong dose-response relationship exists between smoking and CAD. The number of cigarettes smoked per day is directly proportional to the risk of MI. The adverse effect of smoking is present among men and women (but may be stronger among women) of all ages and ethnic groups with or without prior CAD. Cardiac death is 2 to 4 times greater among current smokers than nonsmokers.

B. Risk reduction and therapy. Risk for CV disease begins to decline soon after smoking cessation. There is a 50% reduction in adverse CV events within the first 2 to 4 years of cigarette cessation; however, increased CV risk still exists 10 years after cessation. It may take as long as 20 years to regain baseline risk. A **combination of behavioral intervention and pharmacologic therapy** is recommended to aid patients with smoking cessation efforts. First-line pharmacologic therapies include **nicotine replacement therapy** (transdermal patch, gum, nasal spray, lozenge, and inhaler), **varenicline, and bupropion**. Extensive materials on smoking cessation for patients and health care providers are provided by the U.S. Department of Health and Human Services and can be found online at www.ahrq.gov.

V. SEDENTARY LIFESTYLE

A. **Pathophysiology.** A sedentary lifestyle is associated with an increased risk for ASCVD. Sedentary persons have almost double the risk for CAD death as that of active persons. In five prospective exercise studies, persons at the lowest levels of exercise conditioning had an age-adjusted CAD mortality risk 2 to 10 times that of the best-conditioned participants. A sedentary lifestyle is also associated with obesity, HTN, type 2 diabetes mellitus, and dyslipidemia. More than 50% of the U.S. population does not exercise at least 20 minutes 3 times a week, and 40% of adults are classified as sedentary.

B. **Risk reduction. Even moderate physical activity provides a reduction in risk.** Regular physical activity prevents obesity, may reduce weight, and promotes positive effects on BP, LDL-C, HDL-C, and triglyceride levels. Independent of other risk factors, physical fitness has a direct protective effect against ASCVD events. Among patients who have had MI, phase 2 cardiac rehabilitation programs significantly reduce CV mortality in the 5 years following completion by up to 40%. Current physical activity guidelines recommend a minimum of 150 minutes per week of moderate-intensity aerobic physical activity (or at least 75 minutes of vigorous-intensity physical activity). Most patients would be well served to also complete at least some strength and resistance training as well.

1. **Mechanism**

   a. Exercise **improves glucose tolerance and insulin sensitivity, increases fibrinolysis, improves oxygen uptake** in the heart, and **increases coronary artery diameter**. Exercise reduces the sensitivity of the myocardium to catecholamines and the risk of ventricular arrhythmias. Exercise lowers LDL-C levels and, as such, reduces cardiac events. Exercise can alter the progression of coronary atherosclerosis. Among patients with angiographically documented CAD, exercise training may increase regression and reduce the progression of coronary lesions.

   b. Studies on the long-term effect of exercise are difficult to conduct and have known difficulties trying to quantify exercise.

2. **Problems with adherence.** Only half of persons who begin an exercise program adhere to it for more than 6 months.

   a. Physicians may need to help **tailor exercise programs for individual patients** to participate in activity that is sustained. The

so-called exercise prescriptions can be helpful in motivating patients and ensuring safe levels of physical activity.

b. In healthy persons, **precautions** must be taken to **prevent injury**. The current guidelines may be **slightly modified for older exercisers** to emphasize a longer warm-up period to enable musculoskeletal and cardiorespiratory readiness for exercise and an adequate cool-down period.

VI. NONTRADITIONAL RISK FACTORS. Many patients with few traditional risk factors experience life-threatening acute coronary syndromes without prior symptoms of disease. Several potential risk factors have been identified that may enhance risk for ASCVD. These include levels of C-reactive protein (CRP), lipoprotein(a) or Lp(a), homocysteine, fibrinogen, and myeloperoxidase (MPO), as well as genetic mutations and single-nucleotide polymorphisms (SNPs) in a number of candidate genes.

A. CRP is a marker of systemic inflammation. Inflammation can initiate and lead to progression of atherosclerosis. CRP continues to gain prominence as an important parameter in the assessment of CV risk. This is particularly true, given residual elevated high-sensitivity CRP (hsCRP) portends higher risk than residual elevated LDL-C when combining data from the PROMINENT, STRENGTH, and REDUCE-IT CV outcomes trials.

1. Pathophysiology

a. CRP is an independent risk factor for the development of adverse CV events in both apparently healthy individuals and patients with established coronary heart disease. CRP binds to oxidized LDL-C, promoting the uptake of LDL-C by macrophage scavenger cells in the arterial wall and enhancing the atherosclerotic process.

b. The degree of associated risk throughout various levels of CRP, often measured as hsCRP, has been evaluated in several studies.

(1) Men in the Physicians' Health Study with the highest quartile CRP had **3 times the risk of MI** and **twice the risk of ischemic stroke** compared with men in the lowest quartile.

(2) In women, the difference is even more pronounced. The relative risk of CV events in the highest quartile of CRP compared with the lowest quartile of CRP in women is **4.4**.

(3) An increased risk of sudden cardiac death has also been seen in patients with elevated CRP levels.

2. Clinical use

a. Standard CRP assays are not sufficiently sensitive to discriminate within the narrow range of CRP values associated with an increase in CV events. The development of hsCRP assays, however, has made this possible. The American Heart Association (AHA)/Centers for Disease Control and Prevention guidelines have established cut-points of risk for hsCRP: a level of <1 mg/L is considered low, 1.0 to 3.0 mg/L is average, and >3.0 mg/L is high and is associated with increased CV risk. Higher levels (>10 mg/L) suggest an alternative cause for inflammation, such as infection or underlying rheumatologic illness.

b. When deciding on whether to initiate statin therapy for the primary prevention of coronary events, hsCRP measurement may prove helpful in patients with a moderate level of CV risk. In the Air Force/Texas Coronary Atherosclerosis Prevention Study, lovastatin reduced the incidence of CV events in patients with low lipid levels if CRP levels were elevated. No improvement was seen in the cohort of patients with low lipid levels and normal CRP values. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin study (JUPITER) targeted individuals with elevated hsCRP levels without hyperlipidemia and showed that statin therapy substantially lowered CV events in this population.

c. The 2018 American College of Cardiology (ACC)/AHA blood cholesterol guidelines note that hsCRP is a risk-enhancing feature in primary prevention patients and should be considered when considering the initiation of lipid-lowering therapy among individuals with intermediated ASCVD risk. Ongoing clinical trials continue to evaluate the role of targeted anti-inflammatory treatments to reduce CV event rates.

d. Canakinumab (monoclonal antibody targeting interleukin-1B) reduced adverse CV events in a high-risk population with residual CV risk attributed to ongoing inflammation. It is not used in this patient population due to excess risk of fatal infection.

e. Colchicine also targets residual inflammation. There are contrasting data suggesting it may have benefit among high-risk patients.

B. Lipoprotein(a) or Lp(a) is apolipoprotein B attached to apolipoprotein A (apoA), a highly glycosylated protein, via a disulfide bond. Although it is a lipoprotein, Lp(a) is often considered a **marker of increased risk of thrombosis**.

1. Pathophysiology

a. There is a striking amino acid sequence homology between apoA and plasminogen, suggesting that Lp(a) may play an important role in the connection between atherosclerosis and thrombosis. **Lp(a) is atherogenic**; it accumulates in atherosclerotic lesions, binds to apoB-containing lipoproteins and proteoglycans, and can be taken up by foam cell precursors. It may also promote thrombosis when it binds to fibrin and blocks the fibrinolytic action of plasmin.

b. Lp(a) is associated with risk of ASCVD and calcific aortic stenosis and may be more predictive of CAD among younger men, women, and persons with hyperlipidemia.

c. It is **90% to 95% genetically determined** and does not change significantly throughout one's lifetime. Widespread Lp(a) screening is not recommended in the United States currently, but is recommended in patients with a early family history of ASCVD. European and Canadian guidance suggests one-time Lp(a) screening in all individuals.

d. Current Food and Drug Administration (FDA)-approved lipid-lowering therapies do not have a major impact on Lp(a) levels. Statins may slightly increase Lp(a), and post hoc analyses of trials of monoclonal antibody PCSK9 inhibitors suggest they may lower Lp(a) by 10% to 30%. This amount of Lp(a) lowering is unlikely to meaningfully reduce the future risk of ASCVD. As such, novel Lp(a)-lowering therapies being studied in ongoing clinical trials reduce Lp(a) by >75%.

e. Pelacarsen (antisense oligonucleotide) and olpasiran (small interfering RNA [siRNA]) are each RNA-based therapeutics that demonstrate effective Lp(a) lowering. Their ability to reduce the incidence of MACEs is being assessed in parallel CV outcome trials.

2. **Therapy.** Statins are the initial preferred therapy for patients who require LDL-C–lowering therapy due to the elevated risk of Lp(a) portends. A PCSK9 inhibitor may be added if further control is needed. Although niacin reduces Lp(a) levels, it is not recommended. In patients with severely elevated Lp(a) and recurrent adverse CV events, apheresis is an option.

C. Homocysteine is a product of folate metabolism. It is derived from the sulfur-containing amino acid methionine and is metabolized through pathways associated with folic acid, vitamin B_6, and vitamin B_{12} as cofactors. Elevated plasma homocysteine levels (>15 mcmol/L) confer an **independent risk for vascular disease**, according to the cross-sectional and prospective case-control studies. The mechanism by which homocysteine appears to promote vascular disease is **unclear**. Elevated homocysteine levels seem to play a role in the production of arterial lesions, but deficiencies of other factors, such as vitamin B_{12} and folic acid, may also be involved, especially in the older patients.

1. **Trials of homocysteine lowering.** The results of three such large, prospective, randomized trials, the Vitamin Intervention for Stroke Prevention (VISP) trial, the Norwegian Vitamin Trial (NORVIT), and the HOPE-2 trial, assessed the role of folic acid, vitamin B_6, and vitamin B_{12} in the prevention of CV events. Overall, there was no convincing benefit; therefore, such therapy is not recommended for this indication.

D. Fibrinogen, a large hepatically synthesized glycoprotein, is a clotting factor that activates thrombin, induces platelet aggregation through the glycoprotein IIb/IIIa receptor, and stimulates smooth muscle proliferation. Several prospective studies, including the Framingham Heart Study, have shown an **impressive relationship between the plasma fibrinogen level and the occurrence of CAD and stroke**. Plasma fibrinogen levels >350 mg/dL are powerful independent risk factors for stroke and MI.

1. **Risk reduction and therapy**. Factors associated with a decrease in fibrinogen level include smoking cessation, physical activity, moderate alcohol intake, normalization of body weight, and postmenopausal hormone replacement. No clinical trial has identified a drug that reduces fibrinogen level safely and selectively.

E. MPO. As discussed previously, inflammation plays a major role in the pathogenesis of ASCVD and the development of MI. MPO is a protein with enzymatic activity that is released during activation and degranulation of neutrophils and monocytes. For patients in the emergency department with chest pain, serum levels of MPO predict risk for MI at 30 days and 6 months, even in the absence of myocardial necrosis. In patients with non-ST-elevation MI, MPO levels predict 30-day risk of recurrent nonfatal MI or hospitalization for acute coronary syndrome.

F. Nonlipid genetic factors. The identification of genetic risk factors/markers for CV disease and the elucidation of their mechanism of risk elevation are an important area of translational research. Polygenic risk scores are increasingly being studied as an adjunct to traditional risk models for incident ASCVD (such as the pooled cohort equation). Unfortunately, at present time in the general population, they do not provide significant risk discrimination beyond traditional models used today.

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CHAPTER 47

Diabetes and the Heart

Nandini Mehra and Dennis Bruemmer

I. INTRODUCTION. The presence of diabetes mellitus, including both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), confers an increased risk for cardiovascular disease (CVD). A diagnosis of T2DM in the fifth decade is associated with a 6- to 7-year decrease in longevity largely because of complications of atherosclerosis. Individuals with T2DM without a history of coronary artery disease (CAD) have an incidence rate of myocardial infarction (MI) approximately similar to that of patients with previous MI and no history of diabetes, suggesting that diabetes confers a CAD risk equivalent. In the United States, the prevalence of T2DM correlates closely with obesity and has shown a sharp rise over recent decades. A similar trend has been noted across the world, with urbanization, adoption of sedentary lifestyle, and changing dietary patterns playing a major contributory role. Consequently, the management of diabetes, along with hypertension, dyslipidemia, and obesity, has become the focus in both the primary and secondary prevention of cardiovascular events. In addition to treating associated cardiovascular risk factors, large cardiovascular outcome trials (CVOTs) have evaluated the impact of newer therapies for hyperglycemia in people with T2DM, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP1-RAs). The findings from these trials have significantly improved cardiovascular outcomes in people with T2DM. The purpose of this chapter is to discuss the current epidemiology and pharmacotherapy of T1DM and T2DM with an emphasis on the latest evidence-based practice for the treatment and prevention of cardiovascular events in individuals with this disease.

II. EPIDEMIOLOGY

A. Epidemiology of diabetes

1. Diabetes is one of the most common chronic diseases in both developed and developing nations. This rise in prevalence is driven partly by rising levels of obesity, physical inactivity, and urbanization, coupled with the aging population and greater longevity. In the United States, approximately 13% of the population has T2DM and 34% has prediabetes, indicating that half of the U.S. population has either T2DM or prediabetes. The International Diabetes Federation most recently reported that 537 million people are currently living with diabetes; many are yet undiagnosed and untreated. By the year 2030, the global population with diabetes is expected to rise to 643 million (**Table 47.1**).

International Diabetes Federation Estimates of Prevalence of Diabetes

TABLE 47.1

Location	Population With Diabetes in Million (2021)	Projected Population With Diabetes in Million (2045)
North America and Caribbean	51	63
Middle East and North Africa	73	136
Europe	61	69
South and Central America	32	49
Southeast Asia	90	151
Africa	24	55
Western Pacific	206	260

2. The greatest burden of diabetes lies in developing countries. India and China are notable for exceptionally high prevalence based on figures from 2021.
3. **T2DM has grown increasingly more prevalent in childhood and in ethnic minorities such as African Americans, Hispanic Americans, and Native Americans.** Approximately, one out of five adolescents in the United States has prediabetes, owing to the increase in the prevalence of overweight and obesity. Up to 45% of diabetes cases in adolescents are now designated T2DM. **Diabetes prevalence is higher in men than in women, but there are more women in total with diabetes**.
4. In the United States, 95% of cases with diabetes are T2DM, but T1DM has also shown increased incidence over recent years. The increase occurs largely in the youngest individuals (<5 years) and those with moderate genetic susceptibility.

B. Spectrum of insulin resistance to T2DM

1. There is a continuum between the early pathologic features of disordered glucose metabolism and T2DM.
2. A **diagnosis of diabetes** can be made on the basis of **HbA1c measurement ≥6.5%, fasting blood glucose ≥126 mg/dL** (7.0 mmol/L), or a **2-hour plasma glucose of ≥200 mg/dL** (11.1 mmol/L) during a 75-g oral glucose tolerance test. In the absence of unequivocal hyperglycemia, a positive result should be confirmed on repeat testing. In the setting of classic hyperglycemic symptoms, a single random glucose ≥200 mg/dL is considered diagnostic. These diagnostic criteria are summarized in **Table 47.2**.

TABLE 47.2 Criteria for the Diagnosis of Diabetes

Diabetes
• **HbA1c** ≥6.5% (48 mmol/mol)[a]

Diabetes
Or • **Fasting plasma glucose** ≥126 mg/dL (7.0 mmol/L)[a] Or • **2-H plasma glucose** ≥200 mg/dL (11.1 mmol/L) in 75-g oral glucose tolerance test[a] Or • **In a patient with classic symptoms of hyperglycemia** or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL
Prediabetes
• **HbA1c** 5.7%-6.4% (39-46 mmol/mol) Or • **Fasting plasma glucose** 100-125 mg/dL (5.6-6.9 mmol/L) = IFG Or • **2-H plasma glucose** 140-199 mg/dL (7.8-11.0 mmol/L) in 75-g oral glucose tolerance test = IGT

HbA1c, glycosylated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.
[a]In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

3. It is now recognized that the microvascular and macrovascular complications are not limited only to individuals meeting the diagnostic criteria for established diabetes. The progression from normal glucose tolerance to T2DM involves intermediate stages of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), also collectively termed "prediabetes." Importantly, a diagnosis of prediabetes is associated with a 2-fold increase in cardiovascular risk.
   a. There is usually a **long latent asymptomatic phase** prior to the development of overt T2DM. Longitudinal studies suggest that insulin resistance onset occurs 10 to 20 years prior to the diagnosis of diabetes and is the best predictor of whether an individual will develop T2DM in the future. Insulin resistance places pressure on the pancreatic beta cells to augment secretion of insulin and, therefore, promotes beta-cell dysfunction. Once the beta cell is unable to compensate sufficiently for the peripheral insulin resistance state, progression to T2DM will ensue. The underlying etiology of T2DM is complex, with both environmental and genetic predisposing factors promoting insulin resistance and beta-cell dysfunction.
   b. **Epidemiologic evidence** regarding the impact of prediabetes states comes from the Diabetes Epidemiology: COllaborative analysis of Diagnostic criteria in Europe (DECODE) group. The relationship between 2-hour postload glucose and cardiovascular mortality was linear, with a continuum of risk extending into

and below the prediabetes glucose range. In subjects without a diagnosis of diabetes, the investigators observed no threshold level of fasting or 2-hour postload glucose concentration above which the risk of all-cause or cardiovascular mortality death increased sharply.

c. There is evidence that the **pathogenic effect of hyperglycemia on the endothelial cells already exists in the prediabetes stage**. The full transition from the early metabolic abnormalities of prediabetes to established diabetes probably occurs in about two-thirds of individuals.

d. There is interest in determining **interventions that may decrease the likelihood of progression to diabetes**. The Diabetes Prevention Program Research Group randomly assigned 3,234 participants without diabetes, but with elevated fasting and postload glucose concentrations, to placebo, metformin (850 mg twice daily), or intensive lifestyle intervention. The incidence of diabetes over an average follow-up of 2.8 years was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. **The lifestyle intervention was significantly more successful in preventing diabetes than the metformin strategy**. However, the addition of metformin reduced the risk for progression to T2DM compared to placebo.

III. DIABETES AND ATHEROSCLEROSIS

A. ***Diabetes accelerates the atherosclerotic process.*** Autopsy series have revealed more diffuse coronary involvement, greater severity of vessel stenosis, and more severe left main disease in persons with diabetes, compared with those without. Similarly, adverse coronary anatomy findings have been observed in autopsy studies of patients with a history of childhood onset of T1DM who died before the age of 40 years. The pathophysiology of atherosclerosis in diabetes remains incompletely understood but is thought to involve hyperglycemia, lipid abnormalities, and dysfunctional endothelial and vascular smooth muscle function, coupled with a propensity for inflammation, thrombosis, and platelet activation.

B. It is recognized that the **synthesis of nitric oxide (NO) by the vascular endothelium is reduced in subjects with diabetes**. NO is among several key substances that maintain healthy endothelial function, which includes freedom from adhesion molecule activation, leukocyte diapedesis, platelet aggregation, and activation of thrombosis. However, the bioavailability of NO is adversely affected by hyperglycemia, high levels of free fatty acids, and insulin resistance. Current research reveals the impact of excessive oxidative stress (which can be induced by hyperglycemia, fatty acids, or insulin resistance) on NO production and also on the generation of advanced glycation end products, which are suspected to mediate various negative cellular effects in diabetes. Reactive oxygen species also activate protein kinase C with wide-ranging effects on cellular metabolism, including activation of the phosphoinositide 3-kinase (PI3K) pathway, which has a role in mediating cell adhesion and migration. The ability of NO to act on vascular smooth muscle and cause vasodilation is reduced; endothelial cell dysfunction in diabetes is

coupled with increased production of vasoconstrictors, such as prostanoids and endothelin.

C. Another key pathogenic feature of atherosclerosis in diabetes is the PI3K- and nuclear factor κB–stimulated **alterations in adhesion molecule expression on the endothelial surface**. This causes the endothelium to become more adherent to passing cells, and selectins on the surface of leukocytes attach to receptors such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1 and migrate into the intima. Here monocytes take on oxidized low-density lipoprotein (LDL) and become macrophage foam cells, which are instrumental in the development of an atherosclerotic plaque. The tendency toward small, dense LDL particles in diabetes is another factor contributing to atherosclerosis. Smooth muscle cell proliferation ensues, leading to the deposition of collagen and other extracellular matrix proteins into the plaque.

D. Platelet function is also abnormal in diabetes, with overexpression of the glycoprotein IIb/IIIa receptor promoting inappropriate platelet adhesion and activation. Upregulation of multiple coagulation factors such as factor VII, thrombin, tissue factor, and plasminogen activator inhibitor-1 increases the tendency toward clotting, therefore contributing to the risk of thrombosis at the site of a plaque rupture or stent placement.

IV. IMPACT OF DIABETES ON HEART DISEASE

A. Both ***T1DM and T2DM confer significantly elevated risks of CAD, acute coronary syndrome (ACS), post-MI complications, heart failure, and sudden cardiac death***. In addition, the incidence of peripheral arterial disease, stroke, and end-stage renal failure is elevated in individuals with diabetes. The cardiovascular complications of T2DM account for the majority of the socioeconomic burden of this chronic disease on both individuals and society.

1. **As many as 80% of individuals with diabetes will die from cardiovascular causes.** Per the Framingham Heart Study, the **risk** of CAD is ***doubled*** in men and ***tripled*** in women with diabetes, compared with age-matched subjects without diabetes.
2. The Emerging Risk Factors Collaboration undertook a large meta-analysis that demonstrated a **2-fold excess risk of outcomes** such as coronary heart disease, coronary death, and nonfatal MI among individuals with established diabetes. They also found diabetes to be even more strongly related to fatal than to nonfatal MI, possibly suggesting more severe manifestations of coronary disease in those with diabetes. Hazard ratios (HRs) were particularly elevated for CVD among individuals with diabetes who were female, younger, and nonsmokers or had lower than average blood pressure (BP).
3. **Patients with diabetes are much more likely to present with atypical symptoms in the setting of ACS and experience more silent MI.**

4. Various angiographic trials have demonstrated that patients with **diabetes undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) tend to have significantly more severe CAD**, with a preponderance of multivessel disease and greater severity of lesions than those without diabetes. Despite the more severe plaque burden, diabetes correlates with lesser collateral vessel formation.
5. The residual **risk** in individuals with T2DM following their **first cardiovascular event is significantly greater** than that noted in the nondiabetic group even after revascularization.
6. Post-MI complications and mortality in patients with diabetes correlate with post-MI ejection fraction and the presence of multivessel coronary disease. **Cardiogenic shock is more common and more severe in post-MI patients with diabetes**. The higher in-hospital mortality among the post-ACS population with diabetes is largely related to the greater incidence of acute decompensated heart failure and, to a lesser extent, the increased risk of reinfarction and infarct extension.
7. The CAD mortality arising from T1DM has also been studied. Laing et al reported a prospective study of 23,751 individuals with T1DM, where subjects were followed for up to 29 years. As is typical of a T1DM cohort, the relatively young age correlated with a low event rate. However, their **CAD risk was several times higher** than that of a matched population without diabetes.

V. CARDIOVASCULAR RISK FACTOR MODIFICATION IN PEOPLE WITH DIABETES

A. The risk factors that predispose individuals with diabetes to develop CVD are the same as those that raise cardiovascular risk in people without diabetes. However, the prevalence of all major risk factors for CAD is increased in individuals with diabetes, including overweight and obesity (89%), dyslipidemia (44%), hypertension (69%), and smoking (19%). Given the overall higher cardiovascular risk conferred and the frequent combination of multiple risk factors, comprehensive management of cardiovascular risk is important to improve adverse cardiovascular outcomes. The landmark Steno-2 trial evaluated the effect of multifactorial intervention comprising of behavior modification and pharmacologic therapy of cardiovascular risk factors in patients with T2DM and microalbuminuria on cardiovascular outcomes. The intensive management regimen included dietary fat restriction, 30 minutes of exercise 3 to 5 times per week, smoking cessation, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) administration irrespective of BP, additional agents to target BP <130/80 mm Hg, 150 mg aspirin, stepwise glycemic management to target A1c <6.5%, statin therapy for LDL cholesterol reduction, and fibrate treatment for isolated hypertriglyceridemia. Compared to conventional treatment, the intensive group achieved significantly lower HbA1c, LDL cholesterol, BP, and triglycerides (TGs). There was an absolute risk reduction of 20% in cardiovascular events with multifactorial intervention cardiovascular events. The subjects were then followed up for a further mean of 5.5 years, at which point the primary end point of

all-cause mortality was assessed. Significant differences in BP, HbA1c, LDL, and TGs were absent by this later follow-up point. The primary end point at 13.3 years was time to all-cause death, and an absolute risk reduction of 29% was evident in the group assigned to intensive, multifactorial intervention. This study established that there were long-term benefits of aggressive multifaceted risk factor management and that tight glycemic control and treatment with aspirin, antihypertensives, and lipid-lowering drugs appeared to be additive. Therefore, current society and national guidelines highlight the importance of a broad approach to targeting multiple cardiovascular risk parameters and supporting the use of medications with proven cardiovascular benefit (**Table 47.3**).

TABLE 47.3 Summary of Comprehensive Treatment Goals and Pharmacologic Management of Cardiovascular Risk

	People With Diabetes
Blood pressure goal	<130/80 mm Hg
A1c goal	<7%
LDL cholesterol goal in people with diabetes and one or more cardiovascular risk factors	<70 mg/dL[a]
LDL cholesterol goal in people with diabetes and established atherosclerotic cardiovascular disease	<55 mg/dL[a]
Coexisting atherosclerotic disease or risk factors for atherosclerotic CVD	SGLT2 inhibitor and/or GLP1 agonist
Coexisting heart failure with preserved or reduced ejection fraction	Addition of SGLT2 inhibitor
Coexisting diabetic kidney disease	**1.** Addition of ACE inhibitor or angiotensin receptor blocker **2.** Addition of SGLT2 inhibitor **3.** Addition of finerenone in patients with albuminuria on maximum ACE inhibitor/ARB therapy
Coexisting atherosclerotic disease	Daily aspirin for secondary prevention. May use clopidogrel if allergic to aspirin

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CVD, cardiovascular disease; GLP1, glucagon-like peptide-1; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose cotransporter-2.

[a]Consider the addition of ezetimibe or PCSK9 inhibitor to maximum tolerated statin therapy to achieve the recommended LDL cholesterol goal.

B. While compelling evidence supports multifactorial intervention to treat hyperglycemia, hypercholesterolemia, hypertension, and smoking cessation, current guideline recommendations for HbA1c, LDL cholesterol reduction, BP target, and smoking cessation are only achieved in one out of five patients with diabetes. Furthermore, evidence-based, combined pharmacologic treatment with high-intensity

statin therapy, ACE inhibitors or ARBs, and SGLT2 inhibitors or GLP1-RA for the reduction in cardiovascular event rates is achieved in less than 5% of patients with T2DM. In the following section, we discuss guideline-recommended treatment of cardiovascular risk factors in people with diabetes.

1. **Dyslipidemia.** Diabetic dyslipidemia is a major risk factor among individuals with diabetes. Diabetes is associated **with small, dense LDL** particle composition, increased levels of apolipoproteins B and E, low levels of high-density lipoprotein (HDL) cholesterol, and high TG levels. These lipid composition abnormalities cluster with insulin resistance and abdominal adiposity and appear to induce endothelial dysfunction and an increased susceptibility to thrombosis.
   a. **LDL cholesterol reduction** for both primary and secondary prevention is a cornerstone of T2DM management. The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend primary prevention treatment with moderate-intensity statin therapy in all people with diabetes ages 40 to 75 years and an LDL cholesterol of 70 to 189 mg/dL and high-intensity statin therapy in people with diabetes if multiple cardiovascular risk factors are present. The updated 2023 American Diabetes Association (ADA) guidelines, endorsed by the ACC/AHA, recommend **moderate statin therapy for people with diabetes aged 40 to 75 years without CVD, high-intensity statin therapy to achieve an LDL cholesterol of <70 mg/dL for people with diabetes aged 40 to 75 years without CVD but one or more cardiovascular risk factors, and high-intensity statin therapy to achieve an LDL cholesterol of <55 mg/dL for people with diabetes and atherosclerotic CVD** (secondary prevention). Addition of ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy is recommended if the respective LDL cholesterol target is not achieved on maximum tolerated statin therapy.

      Some of the factors that may influence decision-making for more aggressive LDL cholesterol reduction in patients with diabetes and no history of CAD may include a duration of diabetes of more than 10 years, patients with diabetes and target organ damage including chronic kidney disease (CKD), family history of premature atherosclerosis, lifetime atherosclerosis risk, abnormal coronary artery calcium score or ankle-brachial index, lipoprotein(a) [Lp(a)] elevation, or high-sensitive C-reactive protein ≥2 mg/L. For secondary prevention in people with diabetes, guidelines now include a lower LDL cholesterol target of <55 mg/dL and the addition of ezetimibe and/or PCSK9 inhibitors if this LDL cholesterol target cannot be achieved on maximum tolerated statin therapy. The evidence to support lower LDL cholesterol targets and the addition of non–statin therapy in patients with diabetes derives from three different trials. In the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), the addition of ezetimibe to simvastatin reduced cardiovascular events, and the mean LDL cholesterol achieved was 54 mg/dL in patients receiving simvastatin and ezetimibe. Twenty-seven percent of patients

had diabetes, and in this patient group, combination of ezetimibe with statin therapy resulted in an absolute risk reduction of cardiovascular event by 5%. In the two PCSK9 inhibitor trials, namely, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER) and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab), 40% and 29% of patients had diabetes, and the achieved LDL cholesterol levels were 30 and 40 mg/dL, respectively. The composite primary cardiovascular outcomes were reduced by 15% in both trials with the addition of a PCSK9 inhibitor in addition to statin therapy. As a result, more aggressive LDL cholesterol lowering is now recommended in current guidelines for people with diabetes and established CVD.

b. **Elevated TG levels** are characteristic of the lipid panel in diabetes and constitute an independent cardiovascular risk factor. Fibrates have traditionally been considered an appropriate therapy to target hypertriglyceridemia and have often been added to statin therapy for this indication. However, the Fenofibrate Intervention and Event Lowering in Diabetes trial, however, showed no benefit with fenofibrate therapy, and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial did not demonstrate any cardiovascular benefit of adding fenofibrate for the treatment of hypertriglyceridemia. Similarly, treatment with niacin has been evaluated in the Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) and Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) and failed to demonstrate cardiovascular benefit in addition to statin therapy. Finally, multiple outcome trials have assessed whether various formulations of omega-3 fatty acids to reduce hypertriglyceridemia improve cardiovascular outcomes. The Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT) enrolled patients with established CVD or diabetes and elevated TGs of 135 to 499 mg/dL and revealed a 25% relative risk reduction of the primary end point composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina with the addition of icosapent ethyl. A similar cardiovascular benefit has not been seen with other formulations of omega-3 fatty acids. For example, the Long-Term Outcomes Study to Assess Statin Residual Risk with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia (STRENGTH) trial did not show cardiovascular benefit of a carboxylic acid formulation of the n-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (n-3 carboxylic acid) to statin therapy in patients at increased cardiovascular risk. Current guidelines recommend primarily lifestyle modification for the treatment of hypertriglyceridemia and consideration of additional medical therapy with fibrates or omega-3 fatty acids to reduce the risk of pancreatitis in patients with TG levels above 500 mg/dL. **In patients with established CVD on statin**

therapy, the addition of icosapent ethyl can be considered to reduce cardiovascular risk.

c. **Low HDL levels** predict poor cardiovascular outcomes in a number of epidemiologic studies and are commonly present in patients with diabetes. However, multiple large CVOTs using various approaches to pharmacologically raise HDL cholesterol, including fibrates, cholesteryl-ester transfer protein inhibitors, and nicotinic acid have failed to show a favorable impact on cardiovascular outcomes. Therefore, **guidelines do not recommend specific treatment for raising HDL cholesterol**.

2. **Hypertension.** Multiple large trials have shown the benefit of improved BP control in patients with diabetes. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, a fixed dosage combination of perindopril-indapamide was tested against matching placebo. The intervention resulted in a 5.6 and 2.2 mm Hg reduction in systolic (SBP) and diastolic BP, respectively, which translated to a 14% reduction in mortality, 14% reduction in coronary events, and a 21% reduction in renal events over 4.3 years of follow-up. Subsequently, the ACCORD trial randomized subjects with diabetes to a target SBP of <120 or <140 mm Hg. The lower target group showed no difference in the primary cardiovascular outcomes end point but did have a significantly lower stroke rate; however, this was at the expense of significantly more adverse drug events and an increased risk of a creatinine rise of >1.5 mg/dL. Following the ACCORD trial, the Systolic Blood Pressure Intervention Trial (SPRINT) examined patients randomized to intensive BP control (SBP <120) versus standard of care (SBP <140) and showed a significant reduction in the primary composite outcome of MI, ACS, stroke, heart failure, and/or death in patients with intensive BP control. However, this trial specifically excluded patients with diabetes. Most recently, the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial randomized patients aged 60 to 80 years to either intensive BP control (SBP target 110-130 mm Hg) or liberal BP control (SBP 130-150 mm Hg). Patients treated with more intensive BP control had improved composite cardiovascular outcomes. Approximately 19% of the patients had diabetes in this trial. Based on this evidence, current 2017 AHA/ACC BP guidelines and the 2023 ADA guidelines recommend initiation of treatment in patients with hypertension with diabetes if their BP is 130/80 mm Hg or higher. **The treatment goal for hypertension in patients with diabetes is <130/80 mm Hg**, if this can be safely achieved.

3. **Obesity.** The prevalence of obesity has more than doubled in the United States since 1980. Currently, more than 70% of the U.S. population is considered overweight or obese. Obesity and being overweight are defined by body mass index (BMI), "overweight" being 25 to 30 kg/m^2, class I obesity 30 to 35 kg/m^2, class II obesity 35 to 40 kg/m^2, and class III obesity >40 kg/m^2. Waist circumference and waist-to-hip ratio better reflect abdominal adiposity and are more reliable predictors of CAD outcomes than BMI. Obesity is associated with an

in increased risk for CVD, including CAD and heart failure. Because insulin sensitivity is inversely correlated with visceral adiposity, obesity is major risk factor for the development of T2DM. For patients with diabetes, weight management is recommended to improve hyperglycemia and cardiovascular risk factors. Key strategies for weight management include lifestyle change, medical weight loss therapy, and metabolic surgery.

a. **Lifestyle modification.** Lifestyle modification includes nutrition change and physical activity. Dietary recommendations for patients with diabetes include a diet enriched in fruits, vegetables, and lean and plant-based sources of protein. Interventions to support lifestyle modification through supervised weight management programs are more effective in achieving weight loss than nutritional counseling alone. Physical activity of 150 minutes or more of moderate- to vigorous-intensity aerobic activity per week, spread over at least 3 days/wk, is recommended. In the Look AHEAD trial, patients who are overweight or obese with type 2 diabetes were randomized to intensive lifestyle modification to promote weight loss through reduced caloric intake and physical activity, compared to diabetes education and support only. Although cardiovascular event rates were not reduced, intensive lifestyle reduced HbA1c and essentially all cardiovascular risk factors. People with diabetes are encouraged to attempt at least 5% body weight loss to improve HbA1c levels and cardiovascular risk factors. Although the benefit of lifestyle modification is proven, only a few patients with diabetes are able to achieve and sustain weight loss.

b. **Medical weight loss.** Medical weight loss is indicated in patients with diabetes and a BMI of 27 kg/m^2 or higher, as T2DM is considered a weight-related complication. GLP1-RAs are the preferred pharmacologic therapy for medical weight loss, due to their glucose-lowering efficacy and the improvement in cardiovascular outcomes (discussed further later).

   (1) **Liraglutide and semaglutide** are the two GLP1-RAs U.S. Food and Drug Administration (FDA) approved specifically for medical weight loss therapy in people with and without diabetes. Liraglutide is administered by subcutaneous injection daily and started at 0.6 mg followed by titration to a final dose of 3 mg daily. Semaglutide is a long-acting GLP1-RA and administered at a starting dose of 0.25 mg by subcutaneous injection once per week. The dose is then titrated every 4 weeks to a final dose of 2.4 mg weekly. More than 70% and 85% of people treated with liraglutide or semaglutide loose more than 5% of body weight, respectively. Adverse side effects including nausea, diarrhea, and vomiting are common. These agents are contraindicated in the presence of multiple endocrine neoplasia (MEN) syndrome, and if patients have medullary thyroid cancer (MTC).

   (2) **Tirzepatide** is a dual GLP1 and glucose-dependent insulinotropic protein (GIP) agonist currently approved in the United States for the treatment of

T2DM and being evaluated by FDA also for the specific treatment of obesity. In the SURMOUNT-1 trial, once-weekly injection of tirzepatide at 5, 10, and 15 mg was associated with 16%, 22%, and 23% weight loss after 72 weeks of treatment, respectively.

(3) **Orlistat** reduces fat digestion by inhibiting gastric and pancreatic lipases. The recommended prescription dose is 120 mg 3 times daily. Major side effects include abdominal cramps, flatus, fecal incontinence, diarrhea, and oily stools; there is a rare association with severe liver injury. Multiple trials have demonstrated a greater initial weight loss (approximately 3%) with orlistat, compared with placebo, and also slower weight regain in the longer term. In individuals who are obese with diabetes, orlistat not only promotes weight loss but also decreases HbA1c at 1 year in comparison with placebo. Vitamin supplementation is warranted because of the lack of absorption of fat-soluble agents.

(4) **Phentermine/topiramate** is a schedule intravenous (IV) controlled substance and acts through norepinephrine release and gamma-aminobutyric acid receptor modulation. It is initiated as a 3.75/23-mg extended-release tablet and then titrated up to a maximum dose of 15/92 mg. It is associated with an 8% to 10% weight loss compared with placebo. Sympathomimetic side effects are common, and phentermine/topiramate or phentermine monotherapy is not recommended in patients with CVD or uncontrolled hypertension. Phentermine/topiramate is contraindicated in pregnancy. Providers are encouraged to enroll in the FDA Risk Evaluation and Mitigation Strategy (REMS) program when prescribing this medication.

(5) **Naltrexone/bupropion** is an opioid receptor antagonist that was approved in 2014. It is formulated as naltrexone (32 mg) and bupropion (360 mg) twice daily. The main limiting side effect is nausea, and, in randomized controlled trial (RCT), the use of this agent resulted in a 3.3% to 4.8% weight loss compared with placebo.

c. Metabolic surgery. Compared to behavioral lifestyle change and medical weight loss therapy, metabolic surgery leads to the most effective and sustained weight loss. Bariatric surgery is indicated in adults with a BMI $\geq$40 kg/m^2 with or without associated comorbidities, in adults with a BMI of 35 to 39.9 kg/m^2 with at least one comorbidity, or in adults with a BMI of 30 to 34.9 kg/m^2 and uncontrolled type 2 diabetes. Surgical options include malabsorptive procedures including Roux-en-Y gastric bypass and restrictive procedures such as laparoscopic adjustable gastric bands and sleeve gastrectomy. Weight loss after malabsorptive bariatric surgery tends to reach a nadir at 12 to 18 months with an average of 70% excess body weight loss and a 35% decrease in BMI, followed by an average 10% weight regain in the following 10 years. Metabolic complications after weight loss surgery are notably improved; between 50%

and 70% of patients achieve complete remission of T2DM. Hypertensive medications are frequently reduced, and approximately 40% of patients with hypertension are in remission after metabolic surgery. Similarly, lipid profiles improve after surgery, primarily TG levels and low HDL cholesterol levels, but also LDL cholesterol levels are reduced to normal levels in about 20% of patients. In retrospective analyses, **cardiovascular mortality, coronary event rates, incidence of heart failure, stroke, and atrial fibrillation, as well as long-term all-cause mortality are all reduced in patients undergoing bariatric surgery**. However, it is important to note that vitamin supplementation is necessary in malabsorptive surgeries as well.

4. **Tobacco.** Approximately 13% to 20% of patients with diabetes smoke tobacco. Continued tobacco use in patients with diabetes is associated with a **markedly increased risk of MI and peripheral arterial disease**. Lipid abnormalities, in particular LDL cholesterol oxidation, and the development of atherosclerotic plaques are enhanced in the presence of smoking and diabetes. Conversely, cardiovascular risk significantly declines with smoking cessation. Therefore, smoking cessation and referral to smoking cessation programs should be strongly encouraged.

VI. PHARMACOLOGIC MANAGEMENT OF DIABETES

A. CVD is the major cause of mortality in patients with diabetes. About 60% of patients seen by the practicing cardiologist have diabetes. Seventy percent of patients presenting with an MI have prediabetes or diabetes, which is undiagnosed in about half of the patients. Therefore, the cardiologist will need to actively participate in the diagnosis and treatment of people with diabetes, not only for cardiovascular risk factor management but also to support pharmacologic treatment strategies with proven cardiovascular benefit, particularly SGLT2 inhibitors and GLP1-RAs. Both medication classes reduced cardiovascular events rates in patients with diabetes, and SGLT2 inhibitors reduce cardiovascular mortality in patients with both systolic and diastolic heart failure with and without T2DM. Historically, approaches have been focused on improving primarily HbA1c levels, assuming this would translate to improved cardiovascular outcomes. However, in 2008, the FDA mandated CVOTs of new agents brought to market, which has provided important data on cardiovascular outcomes in people with diabetes. In the following section, we briefly review key pharmacologic approaches to the treatment of diabetes.

1. **Benefit of intensive versus standard glucose control.** The early Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) trial were among the first randomized trials to confirm the cardiovascular and microvascular benefit of more intensive glucose control in people with diabetes.
   a. The **UKPDS** study randomized patients with newly diagnosed T2DM from 1977 to 1991 with a median baseline HbA1c of 9.1% to receive either intensive therapy with sulfonylurea and insulin versus conventional therapy with diet and

treatment only for notably elevated glucose levels. The median HbA1c achieved was 7.0% in the tight control group versus 7.9% in the conventional group. The composite of any diabetes-related end points was significantly reduced by 12%, driven primarily by a 25% reduction in microvascular end points, including renal failure or death from renal failure, vitreous hemorrhage, or photocoagulation. The risk for MI was reduced by 16%, but this difference did not reach significance. In a subgroup of 753 patients who are overweight with newly diagnosed T2DM, patients were randomized to metformin versus dietary modification. The risks for any diabetes-related end point, all-cause mortality, and MI were reduced by 32%, 36% and 39%, respectively. These observations, albeit in a small subgroup of patients, have ultimately led to the previous treatment recommendation of metformin as first-line therapy for T2DM.

b. The **DCCT** study tested whether early intensive intervention in subjects with T1DM improves microvascular complication and long-term CVD. The intervention arm included multiple-daily insulin injections or insulin pump therapy, whereas the standard treatment included only a few injections per day and less frequent follow-up. The achieved HbA1c levels were 7.4% in the intensive arm and 9.1% in the standard treatment arm. After 6.5 years of follow-up, intensive insulin therapy was associated with a significant 76% reduction in retinopathy, 39% reduction in microalbuminuria, and 60% reduction in neuropathy. Cardiovascular and peripheral artery outcomes were reduced, but not statistically significant.

c. There is long-term cardiovascular benefit following early intensive glycemic control. Both intervention trials UKPDS and DCCT confirmed significant improvements in microvascular outcomes with tighter glycemic control in both T1DM and T2DM. However, a clear benefit of intensive glycemic control on macrovascular cardiovascular end points was only observed after long-term follow-up. During the follow-up observational Epidemiology of Diabetes Interventions and Complications (EDIC) of the initial DCCT cohort, 93% of subjects were followed for a mean of 17 years of follow-up in both DCCT/EDIC combined. Despite the loss of metabolic separation between previous intensive and standard treatment, there was macrovascular risk reduction in the intensive treatment group, resulting in a 42% risk reduction for all cardiovascular events. Similar to DCCT, UKPDS trial subjects were followed up for 10 years and differences in glycemic dissipated within 1 year after follow-up. However, a 24% risk reduction in microvascular events, a 15% risk reduction in the risk for MI, and a 13% risk reduction in mortality persisted after 10 years of follow-up in the intensive treatment cohort. The long-term cardiovascular benefit seen a decade after a follow-up of DCCT/EDIC and UKPDS provided a key rationale to support early intensive treatment of hyperglycemia and tighter HbA1c levels.

2. **Intensive therapy to target HbA1c levels of ≤6.5% does not confer cardiovascular benefit but reduces microvascular complications.** In the initial DCCT and UKPDS intervention trials, cardiovascular outcomes were reduced, but the reduction in HRs did not reach statistical significance and was only confirmed after long-term follow-up, likely owing to the low event rates in these patient cohorts. Therefore, three large randomized controlled CVOTs followed to address whether more intensive lowering of hyperglycemia in patients at increased cardiovascular risk improves cardiovascular outcomes.
   a. The **ADVANCE** trial randomized 11,140 patients with T2DM to standard versus intensive glucose control. Intensive control was achieved with the use of the sulfonylurea gliclazide plus other agents as necessary to achieve an HbA1c ≤6.5%. After 5 years of follow-up, the mean A1c was 7.3% in the standard group and 6.5% in the intensive group. Insulin was prescribed for 40.5% and 24.1% of patients in the intensive group and the standard control group, respectively. The combined primary outcome of microvascular events (nephropathy and retinopathy) and major adverse cardiovascular events (MI, stroke, and cardiovascular death) was decreased with intensive therapy (18.1% vs 20.0%; HR 0.90, 95% confidence interval [CI] 0.82-0.98). The risk reduction for the primary outcome was primarily driven by a reduction in the risk for nephropathy as there was a benefit of further intensive glycemic control for the risk of retinopathy or cardiovascular events.
   b. **The ACCORD** trial randomized 10,251 people with T2DM and a prior cardiovascular event or at least two additional risk factors for CVD to target either an HbA1c of <6% versus 7.0% to 7.9%. ACCORD was discontinued after 3.5 years of follow-up due to an increased risk for all-cause mortality in the intensive treatment arm. The primary outcome of nonfatal MI, nonfatal stroke, and cardiovascular mortality occurred in 352 patients in the intensive group versus 371 in the standard group (HR 0.90, 95% CI 0.78-1.04, $P = .16$). Hypoglycemia requiring medical attention was more common in the intensive therapy group. The increased mortality risk represented an unexpected observation and may have been related to adverse effects of hypoglycemia, particularly in people with a longer history of T2DM and increased cardiovascular risk—19 of the 41 cardiovascular deaths were attributed to "unexpected or presumed CVD" and may have been hypoglycemia related. It has also been noted that 91.2% of intensive therapy patients were receiving rosiglitazone, which was subsequently associated with an excess cardiovascular mortality, as discussed further later.
   c. The **Veterans Affairs Diabetes Trial (VADT)** randomly assigned 1,791 predominantly male military veterans who had a suboptimal response to therapy for T2DM to receive either intensive or standard glucose control. The mean age was 60 years, 40% had already experienced a cardiovascular event, 52% were receiving insulin, and the mean baseline HbA1c was 9.4%. This high-risk cohort was followed for a mean of 5.6 years, during which time the

mean A1c was 6.9% in the intensive group and 8.4% with standard care. However, there was no significant difference observed between the two groups in any component of the primary outcome or in all-cause mortality (HR 1.07, 95% CI 0.81-1.42; $P = .62$).

3. **Current treatment guidelines recommend an HbA1c target of <7.0% for glycemic control.** Duration of therapy, lack of significant separation in glycemic control between the treatment and control groups, aggressive polypharmacy to lower HbA1c levels, and increased risk for hypoglycemia in people with diabetes and associated comorbidities may all have contributed to the findings in these three glycemic-control outcomes trials. The observation that lower than previously recommended glycemic control does not provide cardiovascular benefit but may be associated with harm in certain groups of patients was an important observation. The outcomes of these glucose interventions provided the rationale for current treatment guidelines to recommend an HbA1c target for most individuals with diabetes of <7.0%. However, **glycemic targets should be individualized**. In selected people with diabetes, an HbA1c target lower than that recommended may be appropriate, if this can be safely achieved without increasing the risk for hypoglycemia, particularly to prevent microvascular complications. These include primarily people with diabetes at a younger age and shorter disease duration, few associated comorbidities, and low risk for hypoglycemia. Conversely, in people with long-standing disease duration, limited life expectancy, increased risk for hypoglycemia (particularly hypoglycemia unawareness), multiple comorbidities, and established vascular complication less stringent HbA1c targets may be appropriate.

While newer pharmacologic agents for the treatment of hyperglycemia were being developed, the FDA issued a guidance in 2008 that mandated industry to complete large CVOTs in patients with established/high-risk CVD to document cardiovascular safety, beyond only providing efficacy data for the improvement in glycemic control. These trials were large in number, had longer term follow-up, utilized standard definitions of adverse cardiovascular outcomes, and had central adjudication of all clinical events. The results of completed trials are summarized in **Table 47.4**.

TABLE 47.4 Characteristics of the Major Randomized Controlled Trials of Intensive Glucose Control in Type 2 Diabetes

	UKPDS 33	ACCORD	ADVANCE	VADT	DCCT
Participants (n)	3,867	10,251	11,140	1,791	1,441
Diabetes duration (y)	0	10	7.9	11.5	2.6
Mean age (y)	53	62	66	60	27
History of CV	Not reported	35	32	40	Not reported

	UKPDS 33	ACCORD	ADVANCE	VADT	DCCT
disease (%)					
Duration of intervention (y)	10.0	3.5	5.0	5.6	6.5
Intensive group treatment	Sulfonylurea or insulin	Any oral drugs, insulin (91% rosiglitazone)	Gliclazide, other drugs including insulin	Glimepiride or metformin, plus rosiglitazone, or insulin	Insulin administration ≥3 times daily
Standard group treatment	Diet	Any oral drugs, insulin (57% rosiglitazone)	Any oral drugs, insulin	Glimepiride or metformin, plus rosiglitazone, or insulin	Insulin administration 1-2 times daily
Intensive group goal	FPG <6.0 mmol/L	A1c <6.0%	A1c ≤6.5%	1.5% absolute A1c reduction, cf. standard group	Preprandial glucose 70-120, postprandial glucose <180, A1c <6.05%
Standard group goal	FPG 6.1-15.0 mmol/L	A1c 7.0%-7.9%	Local standards	Local standards	Absence of symptoms secondary to hyperglycemia
Baseline median A1c (%)	7.1	8.1	7.5	9.4	8.8
Achieved median A1c (%)	7.0 vs 7.9	6.4 vs 7.5	6.5 vs 7.3 (mean)	6.9 vs 8.4	7.4 vs 9.1
Primary CV outcome	MI and sudden cardiac death	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, CV mortality, heart failure, vascular surgery, inoperable CAD, amputation	CV and vascular outcomes
HR for primary outcome	16% risk reduction (*P* = .052)	0.90 (95% CI 0.78-1.04)	Macrovascular 0.94 (95% CI 0.84-1.06)	0.88 (95% CI 0.74-1.05)	41% reduction
HR for death	0.87 (*P* = .006)	1.22 (95% CI 1.01-1.46)	0.93 (95% CI 0.83-1.06)	1.07 (95% CI 0.80-1.42)	Not reported

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; CAD, coronary artery disease; CI, confidence interval; DCCT, Diabetes Control and Complications Trial Research Group; CI,

confidence interval; CV, cardiovascular; FPG, fasting plasma glucose; HR, hazards ratio; MI, myocardial infarction; UKPDS, UK Prospective Diabetes Study; VADT, Veterans Affairs Diabetes Trial.

Data from Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med*. 2009;151(6):394-403. Copyright © 2009 American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.

4. **Glucose-lowering therapies with established cardiovascular benefit.** Only two classes of pharmacologic agents for the treatment of hyperglycemia of T2DM have unequivocal benefit on adverse outcomes of people with diabetes: SGLT2 inhibitors and GLP1-RAs. The introduction of these agents has certainly provided important opportunities for the improvement in outcomes for people with T2DM. Based on the results of the CVOTs discussed in **Table 47.5**, the most recent **2023 ADA Standard of Medical Care guidelines recommend**:

TABLE 47.5 Completed Randomized, Double-Blind, Placebo-Controlled CV Outcome Trials in Type 2 Diabetes Mellitus

Trial	Drug	*N*	Primary CV Outcome	HR	*P*-Value
DPP-4 Inhibitors					
EXAMINE	Alogliptin	5,380	Composite: CV death, nonfatal MI, or nonfatal stroke	0.96	0.32
TECOS	Sitagliptin	14,671	Composite: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA	0.98	0.65
SAVOR	Saxagliptin	16,492	Composite: CV death, MI, stroke	1.00	0.99
GLP1 Agonists					
ELIXA	Lixisenatide	6,068	Composite: CV death, MI, stroke, hospitalization for UA	1.02	0.81
LEADER	Liraglutide	9,340	Composite: CV death, nonfatal MI, or nonfatal stroke	0.87	0.01 (for drug superiority)
SUSTAIN-6	Semaglutide	3,297	Composite: CV death, nonfatal MI, nonfatal stroke	0.74	<0.001 for noninferiority
EXSCEL	Exenatide	14,752	Composite: CV death, nonfatal MI, nonfatal stroke	0.91	<0.001 for noninferiority
REWIND	Dulaglutide	9,901	Composite: CV death, nonfatal MI, nonfatal stroke	0.88	0.026
PIONEER 6	Semaglutide	3,183	Composite: CV death, nonfatal MI, nonfatal stroke	0.79	<0.001
SGLT2 Inhibitors					
EMPA-REG Outcome	Empagliflozin	7,020	Composite: CV death, nonfatal MI, nonfatal stroke	0.86	0.04 (for drug superiority)
CANVAS	Canagliflozin	10,142	Composite: CV death, nonfatal MI, nonfatal stroke	0.86	0.02 (for drug superiority)

Trial	Drug	*N*	Primary CV Outcome	HR	*P*-Value
DELARE-TIMI 58	Dapagliflozin	17,160	Composite: CV death, MI, ischemic stroke	0.93	0.17
			CV death, HF exacerbations	0.83	0.005
CREDENCE	Canagliflozin	4,401	Composite: ESRD requiring IHD, transplant, GFR <15; doubling of Cr; CV death, renal death	0.70	0.00001
DAPA-CKD	Dapagliflozin	4,304	Composite: GFR decrease of ≥50%, ESRD, CV death, renal death	0.61	<0.001
DAPA-HF	Dapagliflozin	4,744	Composite: HF hospitalization, IV treatment for HF, CV death	0.74	<0.001
EMPEROR-Reduced	Empagliflozin	3,730	Composite: CV death, HF hospitalization	0.75	<0.001
EMPEROR-Preserved	Empagliflozin	5,988	Composite: CV death, HF hospitalization	0.79	<0.001
DELIVER	Dapagliflozin	6,263	Composite: HF hospitalization, urgent HF visit, CV death	0.82	<0.001

CANVAS, The Canagliflozin Cardiovascular Assessment Study; Cr, creatine; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EMPA-REG, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose; ESRD, end-stage renal disease; EXAMINE, Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care; GFR, glomerular filtration rate; GLP1, glucagon-like peptide-1; HF, heart failure; HR, hazards ratio; IHD, intermittent hemodialysis; IV, intravenous; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MI, myocardial infarction; SAVOR, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus; SGLT2, sodium-glucose cotransport-2; SUSTAIN-6, The preapproval Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; TECOS, Trial Evaluating Cardiovascular Outcomes with Sitagliptin; UA, unstable angina.

- **Treatment with an SGLT2 inhibitor or GLP1-RA with proven cardiovascular benefit is recommended in patients with T2DM and established atherosclerotic CVD or multiple atherosclerotic CVD risk factors to reduce the risk of major adverse cardiovascular events.**
- **Treatment with an SGLT2 inhibitor with proven benefit is recommended in people with T2DM and established heart failure with either preserved or reduced ejection fraction to reduce symptoms, the risk of worsening heart failure, and cardiovascular death.**
- **Treatment with an SGLT2 inhibitor is recommended in patients with T2DM and diabetic kidney disease (DKD) to reduce CKD progression and cardiovascular events.**
- **Combined therapy with an SGLT2 inhibitor and GLP1-RA may be considered for additive reduction in the risk of adverse cardiovascular and**

kidney events in people with T2DM.

a. **SGLT2 inhibitors.** SGLT2 inhibitors, including canagliflozin, dapagliflozin, and empagliflozin, function by inhibiting the SGLT2, resulting in decreased renal proximal tubular glucose and sodium reabsorption. Since SGLT2 inhibitors only block the reabsorption of filtered glucose, they do not usually cause hypoglycemia. Additional beneficial effects include natriuresis, reduced BP, and weight loss. The **Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose (EMPA-REG)** Outcomes trial randomized 7,028 patients with T2DM at high risk for cardiovascular events on standards of care to either empagliflozin or placebo. Over a median follow-up of 3.1 years, treatment with empagliflozin reduced the primary composite outcome (death from cardiovascular causes, nonfatal MI, or nonfatal stroke) from 12.1% to 10.5% (HR 0.86, $P = .04$). A significant decrease in all-cause (5.7% vs 8.3%) and cardiovascular mortality (3.7% vs 5.9%) was noted in the treatment group along with a remarkable 35% relative risk reduction in hospitalization for heart failure. The SGLT2 inhibitor canagliflozin was evaluated in The **Canagliflozin Cardiovascular Assessment Study (CANVAS)** program that enrolled 10,142 patients at high cardiovascular risk, randomized to canagliflozin or placebo, both in addition to standard of care. Utilizing similar end points as with empagliflozin, canagliflozin resulted in a reduced cardiovascular event rate (26.9 vs 31.5 participants per 1,000 patient-years; HR 0.86; $P = .02$ for superiority), over a mean 188 weeks of follow-up. An increased risk of amputation (6.3 vs 3.4 participants per 1,000 patient-years; HR 1.97) was associated with canagliflozin. Finally, the **Dapagliflozin Effect on Cardiovascular Events-Thrombosis in Myocardial Infarction 58 (DECLARE-TIMI 58)** trial randomized 17,160 people with type 2 diabetes and established CVD or multiple risk factors to either dapagliflozin or placebo. Dapagliflozin had no effect on the risk for cardiovascular events (8.8% in the dapagliflozin group and 9.4% in the placebo group; HR 0.93, 95% CI 0.84-1.03; $P = .17$) but did reduce the risk for cardiovascular death and hospitalization for heart failure (4.9% vs 5.8%; HR 0.83, 95% CI 0.73-0.95; $P = .005$).

The benefit to reduce heart failure hospitalization and cardiovascular mortality led to multiple trials confirming this observation SGLT2 inhibitors in different study cohorts, including patients with reduced and preserved heat failure. In the **EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Reduced Ejection Fraction (EMPEROR-Reduced)**, patients with a left ventricular ejection fraction of 40% or less and heart failure New York Heart Association (NYHA) class II to IV were randomized to receive either empagliflozin 10 mg or placebo. Approximately half of the patients had a history of diabetes. The primary composite outcome of cardiovascular death or hospitalization for worsening heart failure in a population was reduced by 25% (HR 0.75, 95% CI 0.65-0.86; $P < .001$). Similarly, in the **Dapagliflozin in**

Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) treatment with dapagliflozin 10 mg reduced the risk for the composite of worsening heart failure or cardiovascular death in patients with a left ventricular ejection fraction of 40% or less and NYHA class II to IV heart failure (HR 0.74, 95% CI 0.65-0.85).

The spectrum of patients with heart failure to have hospitalization and mortality benefit following treatment with SGLT2 inhibitors was next extended to patients with heart failure with preserved ejection fraction. In the **EMPagliflozin outcomE tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction (EMPEROR-Preserved)** trial, empagliflozin 10 mg led to decreased cardiovascular mortality and/or heart failure hospitalizations (13.8%) compared with placebo (17.1%) (HR 0.79, 95% CI 0.69-0.90; $P < .001$). Finally, in the **Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER)** trial, patients with heart failure and a left ventricular ejection fraction of more than 40% were randomized to receive 10 mg dapagliflozin or placebo. After 2.3 years of follow-up, the primary outcomes of worsening heart failure or cardiovascular death occurred at an incidence of 16.4% in the dapagliflozin group and 19.5% in the placebo group (HR 0.82, 95% CI 0.73-0.92; $P < .001$). Because of these observations in large randomized CVOT, SGLT2 inhibitors with proven benefits are now recommended to reduce the risk of heart failure worsening and cardiovascular mortality in patients with heart failure with either preserved of reduced ejection fraction.

b. **GLP1-RAs.** GLP-1 RAs activate the GLP1 receptor in the pancreas. GLP1 is an incretin hormone, which reduces postprandial glycemic excursion by stimulating insulin release and inhibiting glucagon secretion. In addition, GLP1 delays gastric emptying and enhances satiety. Therefore, GLP-RAs reduce hyperglycemia and stimulate weight loss. The main side effects are gastrointestinal side effects, including nausea, less frequent vomiting, and diarrhea. In animal studies, GLP1-RAs have been associated with MTC and are contraindicated in patients with a personal or family history of MTC. **The three GLP1-RAs with confirmed benefit in large, randomized CVOTs include subcutaneously injected liraglutide, semaglutide, and dulaglutide. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)** evaluated daily subcutaneously injected liraglutide compared with placebo in 9,340 patients over 3.8 years of clinical follow-up. The event rate for the composite end point of cardiovascular death, nonfatal MI, and nonfatal stroke was significantly reduced (HR 0.87, 95% CI 0.78-0.97; $P < .001$ for noninferiority; $P = .01$ for superiority). Microvascular outcomes were also improved with liraglutide as a composite outcome of renal or retinal microvascular events was lower in the liraglutide group than in the placebo group (HR 0.84, 95% CI 0.73-0.97; $P = .02$). The long-acting, once-weekly injected GLP1-RA semaglutide was evaluated for cardiovascular

outcomes in the **Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes (SUSTAIN-6)**. After 2 years of follow-up the HR for the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke was significantly reduced in patients receiving semaglutide (HR 0.74, 95% CI 0.58-0.95; $P < .001$). The third GLP1-RA with confirmed cardiovascular benefit is once-weekly injected liraglutide. The **Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND)** confirmed that once-weekly injected liraglutide trial reduced the HR for the primary outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes compared to placebo occurred (HR 0.88, 95% CI 0.79-0.99; $P = .026$).

The two weekly injectable GLP-1RAs exenatide (The Exenatide Study of Cardiovascular Event Lowering [EXSCEL]) and lixisenatide (The Evaluation of Lixisenatide in Acute Coronary Syndrome [ELIXA]) have been evaluated for superiority in outcome trials but did not show a significant reduction in the primary cardiovascular outcome. In a preapproval cardiovascular outcomes safety trial of an oral formulation of semaglutide in patients with type 2 diabetes (A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes [PIONEER 6]), semaglutide did not significantly reduce cardiovascular outcomes after 15 months of follow-up (HR 0.79, 95% CI 0.57-1.11; $P < .001$ for noninferiority). A long-term CVOT with the oral formulation of semaglutide is currently ongoing. Finally, a long-term CVOT with GLP1-RA/GIP co-agonist tirzepatide is currently ongoing.

5. **Glucose-lowering therapies without proven cardiovascular benefit in large, randomized trials**

   a. **Metformin.** Metformin remains the most widely prescribed medication for the treatment of T2DM, mostly based on the glucose-lowering efficacy and low cost. While previous guideline recommendations have favored metformin as first-line therapy in all patients with T2DM and without contraindications, SGLT2 and GLP1-RAs are now favored as first-line therapy for patients with established atherosclerotic CVD. SGLT2 inhibitors are the preferred first-line therapy for patients with CKD or heart failure. Metformin and other agents should be added to the comprehensive treatment regimen to achieve glycemic control and HbA1c targets.

   As detailed, metformin reduced the risk for diabetes-related end points, including diabetes-related end point, all-cause mortality, and MI, only in a subgroup of 753 patients who are overweight with newly diagnosed T2DM in the UKPDS trial. No additional CVOTs have been performed to support cardiovascular benefit of metformin. In several large meta-analyses including patients from recent CVOTs, metformin treatment was not associated with a decreased risk of cardiovascular death, MI, or stroke.

   Metformin reduces hepatic gluconeogenesis by inhibiting glucose-6-phosphate dehydrogenase and enhances peripheral insulin sensitivity. Because

it does not stimulate insulin release, there is minimal hypoglycemic risk. Metformin insulin-sensitizing mechanism may also provide benefit in the treatment of prediabetes, polycystic ovarian syndrome, and nonalcoholic fatty liver disease, each of which is associated with insulin resistance. Side effects of metformin are usually gastrointestinal in nature and include diarrhea, nausea, early satiety, and abdominal pain. The adverse effect of lactic acidosis is rare, and the risk is increased in patients with renal impairment. Based on newer evidence, the FDA has revised recommendations and advises that metformin is contraindicated in patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. Administration of intravascular iodinated contrast agents increases the risk of renal failure and has been associated with an increased risk of lactic acidosis. The FDA advises that metformin treatment should be held prior to an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; in patients with a history of hepatic impairment, alcoholism, or acute heart failure; or in patients who will be administered intra-arterial iodinated contrast. Metformin is associated with vitamin B_{12} deficiency, and monitoring is recommended.

b. **Sulfonylureas** are insulin-stimulating oral agents, which inhibit the adenosine triphosphate (ATP)-sensitive potassium channels (K) on the pancreatic beta cells. Binding of a sulfonylurea causes a decrease in potassium efflux through the $K+_{ATP}$ channel, inducing membrane depolarization that leads to calcium influx into the beta cell, and insulin release from secretory granules. The main side effects of sulfonylurea treatment include the risk for hypoglycemia, fluid retention, and weight gain. The glycemic efficacy of sulfonylurea is frequently lost after 4 to 5 years of treatment, and additional therapy is required to maintain glycemic targets. There are no long-term outcome trials, which have assessed cardiovascular safety. Conversely, some meta-analyses have raised the concern of adverse cardiovascular outcomes associated with sulfonylureas, including increased risk of cardiovascular events and mortality. The commonly used second-generation sulfonylureas glipizide, glimepiride, and glyburide (also known as glibenclamide outside the United States) are largely metabolized by the liver and excreted renally. Glyburide is not recommended as first line for patients with heart failure, given that it has active metabolites in patients with renal dysfunction.

c. **Dipeptidyl peptidase-4 (DPP-4) inhibitors.** The DPP-4 inhibitors lower plasma glucose by inhibiting DPP-4 activity, which prevents the enzymatic inactivation of GLP1 in the peripheral circulation. The HbA1c-lowering efficacy is modest with an average reduction of HbA1c levels by 0.6% to 0.8%. These agents held much promise to improve macrovascular outcomes as a number of favorable mechanisms were identified in early animal and human studies. Three large CVOTs with sitagliptin (Trial Evaluating Cardiovascular Outcomes with Sitagliptin, n = 14,671), alogliptin (Examination of

Cardiovascular Outcomes with Alogliptin Versus Standard of Care, *n* = 5,380), and saxagliptin (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus, *n* = 16,492) have been conducted. In all of these trials, neither of the DPP-4 inhibitors reduced the composite cardiovascular end point. An increased risk of heart failure was noted with saxagliptin, which should not be used in patients with heart failure.

d. **Thiazolidinediones** include rosiglitazone and pioglitazone, which act by increasing insulin sensitivity in target peripheral tissues via activation of the peroxisome proliferator–activated receptor (PPAR)-gamma nuclear receptor in myocytes and adipocytes, supporting insulin-stimulated glucose transport into the cell. Rosiglitazone has been associated with an excess risk of MI and cardiovascular mortality in a meta-analysis and is rarely prescribed today. Pioglitazone has been evaluated for cardiovascular outcomes in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial, which demonstrated that pioglitazone decreased a primary composite cardiovascular outcome, but this difference did not reach statistical compared to placebo (HR 0.90, 95% CI 0.80-1.02; *P* = .095). Conversely, the Insulin Resistance Intervention after Stroke (IRIS) study revealed a decreased risk for fatal or nonfatal stroke or MI in patients with a history of ischemic stroke or transient ischemic attack (TIA) and insulin resistance treated with pioglitazone, compared to placebo (HR 0.76, 95% CI 0.62-0.93; *P* = .007). Peripheral edema is a noted side effect, and this class of drugs should *not* be used in patients with NYHA class III to IV heart failure because of concerns for sodium and water retention and possible precipitation of heart failure decompensation. Weight gain, by expansion of subcutaneous adipose tissues, is another significant side effect. Another side effect is an increased risk for fracture, predominantly hip and wrist fractures.

e. **Meglitinides,** including repaglinide and nateglinide, are relatively short-acting oral insulin secretagogues. These medications are taken just prior to a meal and promote a reduction in postprandial glucose levels. Because of their short duration of action, meglitinides are useful in the older patients and individuals with erratic eating habits.

f. **Alpha-glucosidase inhibitors** are rarely prescribed in the United States to reduce hyperglycemia. This class of medications includes acarbose and miglitol, which delay the absorption of complex carbohydrates via their action on the glycosidase enzymes in the brush border of the small intestine. They are generally used as an adjunctive therapy and can be useful in controlling postprandial hyperglycemia. The major side effects are flatulence and abdominal pain.

g. **Amylin** is also an adjunctive agent and can be combined with prandial insulin therapy in patients with T1DM or T2DM not meeting glucose targets. Pramlintide is a synthetic version of endogenous amylin, which is synthesized

by beta cells and secreted with insulin in response to a carbohydrate load. The major effects are the inhibition of gastric emptying and suppression of glucagon release. Insulin doses should be reduced on initiation of pramlintide injections to avoid potential hypoglycemia. This agent may also assist in reducing body weight.

h. **Insulin** therapy will ultimately be required in a large proportion of people with diabetes. Insulin therapy includes basal therapy only, multiple-daily injections combining basal/bolus therapy, and continuous insulin therapy using insulin pump devices. Glucose monitoring is pertinent in patients treated with insulin therapy. Continued glucose monitoring devices have facilitated monitoring and provide important information to modify insulin treatment. In patients using insulin pump therapy, continuous glucose monitoring is now frequently integrated into pump management and automated algorithms to adjust basal rates and prevent hypoglycemia. Insulin is available in **ultra-rapid-acting (faster acting insulin aspart, lispro-aabc), rapid-acting (lispro, aspart, glulisine), short-acting (regular insulin), intermediate-acting (neutral protamine Hagedorn or NPH), and long-acting (glargine, detemir, degludec) formulations with** differences in their rates of absorption and durations of action. Mixtures of rapid short- and intermediate-acting insulin are also available. Insulin can cause weight gain and carries a risk of severe hypoglycemia. The hypoglycemic risk is increased in patients with renal and/or hepatic dysfunction, because the liver and kidneys are responsible for the majority of gluconeogenesis and glycogenolysis; in addition, insulin is renally excreted. The associated weight gain and hypoglycemia raised questions when the ACCORD trial revealed higher mortality in the intense therapy arm, where 77% of subjects were using insulin (vs 55% in the standard care arm). The Outcome Reduction With Initial Glargine Intervention trial was a 6.2-year dedicated CVOT of glargine, which demonstrated no increased cardiovascular risk. Endocrinology consultation is recommended in patients with uncontrolled diabetes and insulin therapy, particularly if using multiple-daily injections or if patients are at increased risk for hypoglycemia.

6. **Additional treatment and approach to prevent microvascular disease**

a. **SGLT2 inhibitors.** The EMPA-REG and CAMVAS trials both included prespecified renal end points to assess whether SGLT2 inhibitors may prevent the development and progression of DKD. In EMPA-REG, treatment with empagliflozin reduced the risk for incident or worsening nephropathy compared to placebo (HR 0.61, 95% CI 0.53-0.70; $P < .001$). Similarly, in CANVAS, canagliflozin reduced the risk for adverse renal outcomes, including progression of albuminuria (HR 0.73, 95% CI 0.67-0.79), the composite of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal replacement therapy, or death from renal causes (HR 0.60, 95% CI 0.47-0.77). Therefore, two follow-up studies investigated renal outcomes with SGLT2 inhibitors in primary outcome trials. **The Canagliflozin and Renal**

Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE) trial randomized people with T2DM and related kidney disease (urine albumin/creatinine ratio >300 mg/g and eGFR 30-<90 mL/min/1.73 m^2) to either canagliflozin or placebo. The primary outcome of end-stage kidney disease, doubling of serum creatinine, or death from renal or cardiovascular causes was significantly reduced (HR 0.70, 95% CI 0.59-0.82). Second, **the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD)** trial followed individuals with CKD (urine albumin/creatinine ratio of 200-5,000 mg/g and eGFR 25-75 mL/min/1.73 m^2) with or without diabetes. Dapagliflozin significantly reduced the risk for the primary outcome of a sustained decline in eGFR, end-stage kidney disease, or death from renal or cardiovascular causes (HR 0.61, 95% CI 0.510.72). Because of the notable benefit of SGLT2 inhibitors in patients with DKD, current guidelines **recommend the use of SGLT2 inhibitors in patients with T2DM and DKD with an eGFR ≥25 mL/min/1.73 m_2 and urinary albumin ≥300 mg/g creatinine to reduce CKD progression and cardiovascular events**.

b. **ACE inhibitors or ARBs.** ACE inhibitors or ARBs are indicated the majority of patients with established CVD for secondary prevention, including those with hypertension, history of MI, and the presence of heart failure. In patients with diabetes, hypertension, and DKD, ACE inhibitors or ARBs are recommended treatments. In the 1990s, the benefit of ACE inhibitor use in patients with diabetes and DKD was demonstrated in two key trials. The Collaborative Study group examined the effect of captopril on patients with insulin-dependent diabetic nephropathy and revealed that captopril decreased progression of renal disease as well as mortality in these patients. Similarly, the Captopril Study corroborated the renal benefit of ACE inhibitor therapy in people with T1DM and DKD. Similar observations have been extended to ARBs in patients with diabetic nephropathy secondary to type 2 diabetes. **Therefore, current guidelines recommend treatment with an ACE inhibitor or ARB in patients with albuminuria to reduce the risk of diabetic CKD**.

c. **Finerenone** is a nonsteroidal, selective mineralocorticoid antagonist, which has been evaluated in patients with type 2 diabetes and DKD. The Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease (FIDELIO-DKD) trial in 2020 revealed that treatment with finerenone reduced the risk for the primary composite end point of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes (HR 0.82, 95% CI 0.73-0.93; $P = .001$). The Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease (FIGARO-DKD) trial confirmed further that addition of finerenone decreased the risk of death from cardiovascular causes, nonfatal MI, nonfatal stroke, or hospitalization for heart failure (HR 0.87, 95% CI 0.76-0.98; $P = .03$) in patients with stage 3 or 4 CKD with severely elevated albuminuria and type 2

diabetes. Therefore, guidelines recommend that **in people with type 2 diabetes and CKD with albuminuria treated with maximum tolerated doses of ACE inhibitor or ARB, the addition of finerenone is recommended to improve cardiovascular outcomes and reduce the risk of CKD progression**.

7. **Summary of guideline-recommended approach to reduce hyperglycemia and CVD**
   - **a.** For patients with T2DM and established CVD or increased cardiovascular risk, treatment with an SGLT2 inhibitor or GLP1-RA with proven cardiovascular benefit is the first-line therapy to reduce hyperglycemia and cardiovascular risk.
   - **b.** For patients with T2DM and heart failure with preserved or reduced ejection fraction or DKD, treatment with an SGLT2 inhibitor is recommended.
   - **c.** Medication regimens and glycemic control should be reviewed every 3 months by repeated measurement of HbA1c. If a patient remains below the recommended HbA1c target, early combination therapy of SGLT2 inhibitors and GLP1-RA should be considered to reduce the risk for cardiovascular events. In most patients with an HbA1c >8.5%, dual combination therapy will be required.
   - **d.** Additional pharmacologic approaches that achieve the recommended HbA1c goal should be considered, including treatment with metformin or other therapies.
   - **e.** Comprehensive cardiovascular risk factor reduction is recommended.

VII. REVASCULARIZATION IN PATIENTS WITH DIABETES

A. The cardiovascular management of patients with diabetes incorporates not only careful consideration of medical regimens but also a review of the available literature with regard to revascularization strategies. There have been many advances in evidence-based management of obstructive coronary lesions over recent decades, and many of the trials have identified strategies that confer particular benefit in individuals with diabetes. The choice of CABG versus PCI applies when the coronary anatomy and patient characteristics are amenable to both modalities of revascularization. In practice, there are significant proportions of patients in whom only one modality is realistic. A heart team approach involving a clinician, surgeon, and interventionalist should be utilized to make treatment decisions for this set of patients.

1. **CABG versus PCI.** A series of landmark trials in patients with obstructive CAD have defined current practice with regard to the decision between CABG and PCI. The finding in 1997 that **the Bypass Angioplasty Revascularization Investigation (BARI) subgroup with diabetes had a significant survival benefit in favor of CABG heralded the onset of specific coronary strategies for patients with diabetes**. The subgroup was not prespecified, but the survival benefit was considerable: In subjects receiving insulin or oral agents for diabetes (347 of the total cohort of 1,829), those randomized to CABG had an 80.6% 5-year

survival, whereas balloon angioplasty was associated with 65.5% survival. This was in the interventional era prior to coronary stenting, and the explanation for the poor PCI outcomes in BARI subjects with diabetes is a presumed high rate of vessel restenosis. In addition, patients with diabetes tend to have more diffuse CAD, and lesions distant from the angioplasty site are left unprotected by a PCI strategy.

2. **CABG versus PCI with bare-metal stents (BMSs) and glycoprotein IIb/IIIa inhibitors.** The widespread adoption of coronary stenting—at this stage with BMS—was successful in reducing restenosis rates. Sustained angiographic coronary patency also correlated with superior survival outcomes, symptom scores, and improved regional left ventricular systolic function. The randomized Arterial Revascularization Therapy Study of CABG versus PCI in multivessel disease showed equivalence of major outcomes for CABG and PCI strategies, with the caveat that the incidence of repeat revascularization was higher in the PCI group. This trial was also notable for its diabetes subgroup results; **there was a benefit in terms of 1-year repeat revascularization and major cardiovascular events in patients with diabetes who underwent CABG, as compared with stenting**. Other studies of this era, including the Stent or Surgery trial published in 2002, demonstrated superiority of CABG over PCI in patients with multivessel disease in general.
3. **CABG versus drug-eluting stents (DESs).** The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial investigated the strategies of PCI with DES versus CABG in patients with triple-vessel or left main disease; approximately 26% of SYNTAX participants had diabetes. An evaluation of the 452 SYNTAX subjects with diabetes, 40% of whom received insulin, showed that mortality was significantly higher among subjects with diabetes compared with those without, regardless of the revascularization strategy. At 1 year, the only outcome difference between PCI and CABG in patients with diabetes was the excess of repeat revascularization in the PCI arm. Patients with diabetes had significantly increased repeat revascularization rates compared with those without diabetes when treated with DES, but not after CABG. Stroke was nonsignificantly higher in the SYNTAX CABG arm. The Optimal Management of Multivessel Disease (FREEDOM) trial, completed in 2010, is the largest randomized trial of patients with diabetes undergoing multivessel CABG. The T2DM had to have at least three-vessel coronary disease and one-third had a recent ACS. The study found that FREEDOM patients had significantly improved survival free of death, MI, or stroke and increased overall survival after CABG compared with percutaneous intervention. The rate of the composite outcome in the CABG group compared with PCI was 18.7% versus 26.6% ($P = .005$). However, the stroke rate was greater following CABG than PCI (5.2% for CABG vs 2.4% for PCI; $P = .03$).
4. **CABG outcomes. Bypass conduit attrition rates are known to be higher in patients with diabetes.** As in patients without diabetes, the use of the internal

mammary arteries (IMAs) offers higher long-term patency (in the region of 90% at 10 years) compared with reversed saphenous veins (long-term patency varying between 40% and 75%). Therefore, IMAs are particularly attractive in patients with diabetes, although the practice of using bilateral IMA grafts is controversial because of the potential for sternal wound infections. In addition to wound infections, patients with diabetes have an elevated risk of perioperative stroke with CABG surgery as shown in the FREEDOM trial.

5. **Revascularization versus optimal medical therapy.** The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial raised questions regarding the relative merits of a purely medical versus medical and PCI strategy in patients with obstructive CAD and stable symptoms. This somewhat controversial study concluded that PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal MI or reduce major cardiovascular events over a 2.5- to 7.0-year period. One-third of the participants had diabetes. The 1,605 patients with diabetes enrolled in the PCI versus optimal medical therapy stratum of BARI-2D did not show any difference in cardiovascular outcomes. However, both of these trials randomized patients after an initial angiogram that defined anatomy, and the decision to enroll in the PCI arm of BARI-2D (as opposed to the CABG arm) was made once anatomy was known and at the discretion of the investigators.
6. **Screening asymptomatic patients with diabetes for CAD.** Given the elevated risk of CAD in patients with diabetes, investigators have attempted to determine whether the identification of asymptomatic CAD can improve future outcomes for patients with diabetes. The Detection of Ischemia in Asymptomatic Diabetes study used a nuclear cardiac stress imaging protocol to identify patients likely to have CAD. At 5 years, there was no difference in nonfatal MI or mortality between the nuclear screening and standard care groups. However, the screening arm was notable for a very low rate of significant ischemia detection, and there was a very successful protocol of optimal medication therapy among trial participants.
7. **Screening patients for heart failure.** In patients with diabetes, the current recommendation is to screen patients yearly with a troponin for the development of heart failure. Similarly, N-terminal pro–B-type natriuretic peptide (NT-proBNP) has been utilized as a marker for early detection of heart failure. The STOP-HF investigators used brain natriuretic peptide (BNP) levels (>50) to screen for early development of heart failure. In the group with elevated BNP who were randomized to intensive therapy, the rate of major cardiovascular events was decreased. Nearly concurrently, in the PONTIAC trial, the investigators found that patients with diabetes and elevated BNP (>125 pg/mL) who were treated with intensive therapy (beta-blockers and renin-angiotensin system antagonists) had a decreased risk of cardiovascular death or heart failure hospitalization. As such, the ADA has recommended screening diabetic patients with a yearly troponin and/or yearly BNP to identify heart failure earlier.

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SECTION IX

Noninvasive Assessment

EDITOR: **Brian P. Griffin**

CHAPTER 48

Exercise Electrocardiographic Testing

Arsalan Derakhshan and Tamanna K. Singh

I. INTRODUCTION

A. Exercise electrocardiographic testing is the most accessible and least expensive modality for stress testing, albeit with limitations. In the past decade, it has become clear that ST-segment changes during exercise have low sensitivity and specificity in the evaluation of coronary artery disease (CAD) and are poor predictors of risk. This may be partially due to the fact that stable obstructive plaques, which typically result in exercise-mediated ischemia, are less relevant to myocardial infarction (MI) and sudden cardiac death than unstable nonobstructive plaques. Although the bulk of obstructive CAD screening has now shifted toward various stress imaging modalities, many of the physiologic parameters measured during exercise have emerged as powerful prognostic indicators. As such, the main uses of exercise electrocardiographic testing should be **evaluation of prognosis** and as **a gateway to other imaging modalities**. Stand-alone testing for CAD diagnosis is reserved for patients with **intermediate risk for CAD** and should be ordered with a careful understanding of the limitations of the test for this purpose.

1. The **advantages** of exercise electrocardiographic testing are its ability to assess a variety of prognostic markers, most importantly **functional capacity**, which is a powerful predictor of mortality and other physiologic responses to exercise (chronotropic response, heart rate [HR] recovery, etc). Practical advantages of exercise electrocardiographic testing include widespread availability, safety, ease of administration, and relatively low cost.

2. **Disadvantages.** As a screening test for CAD in persons without symptoms, exercise electrocardiography is generally not helpful or indicated. It has a relatively **low sensitivity and specificity**, which can be improved with careful selection of the patient population undergoing testing.

B. Patient selection is discussed in reviewing indications and contraindications for exercise stress testing. However, as an overview, this modality can be used **diagnostically** (1) to assess chest pain in patients with intermediate risk of CAD, (2) to assess arrhythmia provocation, and (3) to assess exertional symptoms (presyncope, palpitations) and **prognostically** (1) to risk-stratify patients with hypertrophic cardiomyopathy, valvular heart disease, and congenital heart disease; (2) to evaluate patients with known CAD and a change in clinical status; (3) to evaluate response to treatment with regard to angina and exercise-induced arrhythmias; and (4) to assess a limited role in risk stratification after MI.

II. LIMITATIONS OF EXERCISE ELECTROCARDIOGRAPHIC TESTING

A. Before ordering an exercise electrocardiography test, the physician should have an understanding of pretest probability and the limitations of the test.

B. Bayes theorem states that the probability of a positive test result is affected by the likelihood (ie, conditional probability) of a positive test result among the population who has undergone the test (ie, pretest probability). The higher the probability that a disease is present in a given individual before a test is ordered, the higher the probability that a positive test result is a true-positive test result. Pretest probability is determined on the basis of symptoms, age, sex, and risk factors and can be divided into very low, low, intermediate, and high (**Table 48.1**).

TABLE 48.1 Pretest Probability of CAD According to Age, Sex, and Symptoms

Age (y)	Sex	Typical/Definite Angina Pectoris	Atypical/Probable Angina Pectoris	Nonanginal Chest Pain	Asymptomatic
30-39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40-49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50-59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60-69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

CAD, coronary artery disease.
Reprinted from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 1997;30(1):260-315. Copyright © 1997 Elsevier. With permission.

C. **Sensitivity and specificity.** The likelihood that an abnormal electrocardiographic finding indicates CAD is much higher for an older person with multiple risk factors than for a young person with no risk factors. Sensitivity and specificity vary with the population being tested.

1. Exercise electrocardiographic testing is **best used** in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history.
2. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.
3. Exercise electrocardiographic testing has a higher sensitivity and specificity for **persons at high risk**. For most of these patients, however, invasive testing is preferred for a more definitive diagnosis and possible intervention. Excluding patients with *left*

ventricular hypertrophy or *resting ST depression* and those *taking digoxin* also improves sensitivity and specificity.

D. Positive predictive value (PPV)

1. PPV is defined as the probability that an individual with a positive test result will truly have that disease.
2. PPV is highly dependent on pretest probability (ie, prevalence of disease) in the population being tested. For example, in a population at low risk, the PPV of electrocardiographic exercise testing is only 21%, but in a population at high risk, PPV rises to 83%.

III. PHYSIOLOGY

A. Exercise requires energy expenditure, which is largely attained from oxidative metabolism. As a result, a natural relationship is created between oxygen consumption and metabolic demand such that the total body oxygen uptake can be expressed as metabolic equivalents (METS)

B. 1 MET is set as the resting energy expenditure and is defined as roughly 3.5 mL O_2/kg body weight/min.

C. An activity that is 10 METs by definition would consume 10 times the amount of oxygen compared to resting state (35 mL O_2/kg/min).

D. During exercise testing, an individual is asked to exert themself until a peak total body oxygen uptake (PVO_2) is reached, that is the point of maximally tolerated exercise that is otherwise limited by exertional symptoms.

E. In order to meet the metabolic demands of exercise, cardiac output is augmented by increases in HR as well as increases in stroke volume all while oxygen extraction is increased at a tissue level.

F. This increased myocardial oxygen demand can be used to test the adequacy of myocardial oxygen supply.

G. Myocardial blood flow can be compromised by coronary artery narrowing as well as endothelial dysfunction resulting in impaired autoregulation.

H. The supply-demand mismatch of coronary blood flow during exercise stress electrocardiography can be ascertained by symptoms, ischemic

changes on electrocardiogram (ECG), abnormal blood pressure (BP) response, and ischemia-driven arrhythmias.

IV. INDICATIONS

A. Much has changed in the landscape of exercise stress testing since its early description in the 1950s and 1960s. Our understanding of exercise and coronary physiology has allowed for more precise exercise protocols, and the advancement of technology has allowed for more elegant assessment of coronary perfusion beyond symptoms and ischemic changes on ECG. Although clinical practice has changed some since the American College of Cardiology/American Heart Association (ACC/AHA) last update for Exercise Testing in 2002, exercise stress electrocardiography's role remains steadfast by offering an affordable modality, free of radiation that has powerful prognostic value, especially with respect to exercise capacity.

B. Exercise stress electrocardiography can be used diagnostically and prognostically as well as in the evaluation of atherosclerotic and nonatherosclerotic disease. Although not an exhaustive list of indications, the list below is meant to serve as a framework for potential indications.

1. Atherosclerotic disease

a. Symptoms suggesting myocardial ischemia

b. Acute chest pain in patients excluded from acute coronary symptom (ACS)

c. Known CAD with worsening symptoms

d. Post-MI without in patients who did not receive coronary revascularization and have left ventricular ejection fraction (LVEF) > 40% and otherwise no other high-risk feature

e. Assessment of antianginal therapy

2. Nonatherosclerotic disease

a. Valvular disease

(1) Asymptomatic severe aortic stenosis—to elicit symptoms or abnormal BP response

b. Adult congenital disease

c. Arrhythmias
   (1) Elicit exercise-induced arrhythmia.
   (2) Risk-stratify ventricular preexcitation.
   (3) Assess response of antiarrhythmic or ablation.

V. **CONTRAINDICATIONS.** Contraindications to exercise testing are divided into absolute and relative categories (**Table 48.2**).

TABLE 48.2 Contraindications to Exercise Testing

Absolute Contraindications
Acute MI (within 2 d)
Ongoing unstable angina
Uncontrolled cardiac arrhythmias with hemodynamic compromise
Active endocarditis
Symptomatic severe aortic stenosis
Decompensated heart failure
Acute pulmonary embolism, pulmonary infarction, or deep vein thrombosis
Suspected or known dissecting aneurysm
Acute myocarditis or pericarditis
Acute aortic dissection
Physical disability that precludes safe and adequate testing
Relative Contraindications
Known obstructive left main coronary artery stenosis
Moderate-to-severe aortic stenosis with uncertain relation to symptoms
Tachyarrhythmias with uncontrolled ventricular rates
Acquired advanced or complete heart block
HOCM with severe resting gradient
Recent stroke or transient ischemic attack
Mental impairment with limited ability to cooperate
Resting hypertension with systolic or diastolic blood pressure >200/100 mm Hg

Uncorrected medical conditions, such as significant anemia, important electrolyte imbalance, and hyperthyroidism

HOCM, hypertrophic obstructive cardiomyopathy; MI, myocardial infarction.
Reprinted with permission from Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128(8):873-934. Copyright © 2013 American Heart Association, Inc.

VI. PATIENT PREPARATION

A. Instructions. Table 48.3 provides a typical list of instructions given to patients before testing.

TABLE 48.3 Patient Preparation

Patients should refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 h of testing.
Patients should be rested for the assessment, avoiding significant exertion or exercise on the day of the assessment.
Patients should wear clothing that allows freedom of movement, including walking or running shoes, and a loose-fitting shirt with short sleeves that buttons down the front. They should not wear restrictive undergarments during the test.
Outpatients should be warned that the evaluation may be fatiguing and that they may wish to have someone available to drive them home afterward.
If the test is for diagnostic purposes, it may be helpful for patients to discontinue prescribed cardiovascular medication after discussion with their physician. Antianginal agents alter the hemodynamic response to exercise and significantly reduce the sensitivity of electrocardiographic changes for ischemia. Patients taking intermediate- or high-dose beta-blockers should taper their medication over a 2-4-d period to minimize hyperadrenergic withdrawal responses.
If the test is for functional purposes, patients should continue their medication regimen on their usual schedule so that the exercise responses will be consistent with responses expected during exercise training.
Patients should bring a list of their medications with them to the assessment.

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B. Medications

1. Before diagnostic testing, **cardiovascular drugs are withheld** at the discretion of and under the guidance of the supervising physician. This greatly increases the sensitivity of the test.
   a. Beta-blockers pose a special challenge. Patients taking beta-blockers are often unable to mount an adequate increase in HR to achieve the level of stress needed for the test. Abrupt withdrawal of beta-blockers is discouraged due to consequential reflex tachycardia. The best possible solution is to withdraw the beta-blocker over several days before an exercise test if the test is for diagnostic purposes. This is not always possible, however, because of time constraints or the necessity of drug therapy. In these cases, the records should reflect beta-blocker use at the time of testing.
   b. **Digoxin** may impact test interpretability. To avoid a reading that cannot be used to confirm a diagnosis, digoxin should be withheld for 2 weeks before testing.
2. Alternatively, if evaluation of symptoms with exertion is the primary goal, cardiovascular medicines should be continued.
3. Patients undergoing diagnostic testing should take their **other usual medications** on the day of the test to reproduce more closely the conditions outside the exercise laboratory.

III. EXERCISE PROTOCOLS. There are advantages and disadvantages to each exercise protocol (**Table 48.4**). Selection depends on the patient characteristics, the equipment available, and the familiarity and comfort of the testing personnel with the protocol.

TABLE 48.4 Common Exercise Protocols

Functional Class	O_2 cost (mL/kg/min)	MET	Treadmill Protocol									
			Bruce (3-min Stages mph/grade)		Cornell (2-min Stages mph/grade)		Balke (2-min Stages mph/grade)		Naughton (2-min Stages mph/grade)		Jogger (2-min Stages mph/grade)	
World-class athlete	70.0	20	–	–	–	–	–	–	–	–	–	–
	66.5	19	6.0	22	–	–	–	–	–	–	–	–
	63.0	18	–	–	–	–	–	–	–	–	6.0	20.0
	59.5	17	5.5	20	–	–	–	–	–	–	6.0	17.5
Athlete	56.0	16	5.0	18	5.0	18	–	–	–	–	6.0	15.0
	52.5	15	–	–	–	–	4.0	20	–	–	6.0	12.5
	49.0	14	–	–	4.6	17	–	–	–	–	6.0	10.0
Fit	45.5	13	4.2	16	4.2	16	3.5	20	–	–	6.0	7.5
	42.0	12	–	–	–	–	–	–	–	–	6.0	5.0
	38.5	11	–	–	3.8	15	3.0	20.0	–	–	5.5	2.5
Normal and 1	35.0	10	3.4	14	3.4	14	3.0	17.5	–	–	5.0	2.5
	31.5	9	–	–	–	–	3.0	15.0	–	–	–	–
	28.0	8	–	–	3.0	13	3.0	12.5	2.0	21.0	–	–
	24.5	7	2.5	12	2.5	12	3.0	10.0	–	7.5	–	–
2	21.0	6	–	–	2.1	11	3.0	7.5	2.0	14.0	–	–
	17.5	5	1.7	10	1.7	10	3.0	5.0	2.0	10.5	–	–
	14.0	4	–	–	–	–	3.0	2.5	2.0	7.0	–	–
3	10.5	3	1.7	5	1.7	5	3.0	0	2.0	3.5	–	–
	7.0	2	1.7	0	1.7	0	–	–	2.0	0	–	–
4	3.5	1	–	–	–	–	–	–	1.0	0	–	–

MET, metabolic equivalent.

A. An **optimal protocol** achieves peak workload and maximizes the sensitivity and specificity of the test.

1. **Workload.** An optimal protocol incorporates a **gradual increase** in the level of work so that the patient's true peak workload can be determined. If there are large increases in workload, maximum oxygen consumption (MVO_2 max) may fall between two levels. The test is also more comfortable for the patient if the increases in workload are not large.
2. **Duration.** The optimal duration for an exercise test is **8 to 12 minutes**. Periods longer than this measure muscular endurance rather than cardiovascular fitness. Periods shorter than this do not allow adequate time for the patient to warm up and achieve maximum workloads.
3. **Stage length.** Steady-state oxygen consumption is reached after about 2 minutes of exercise at a given workload. The optimal protocol would have stage lengths of **2 to 3 minutes**.
4. **Exercise method.** Both **bicycle riding** and **treadmill testing** are used; the latter is more commonly used in the United States.
   a. The primary physiologic **advantage of bicycle riding** is the ability to take **direct measurements** of workload in watts, which

has a direct linear relation to $M\dot{V}O_2$. With a **treadmill**, the examiner can only **estimate workload** because workload depends on the efficiency of walking, the weight of the patient, and the change in energy expenditure between walking and running.

B. Protocol options

1. Bruce protocol

a. Advantages. The Bruce protocol has been widely used in the past and is often the basis of older studies; therefore, **comparisons are easier**. Because the Bruce protocol has a final stage that cannot be completed, it is a good protocol for a highly fit person.

b. Disadvantages

(1) The main disadvantage of the Bruce protocol is the **large increments of change in workload between stages**. These large increases mean that peak workload falls somewhere between stages for many people. This is a problem in evaluating functional capacity and may result in a lower sensitivity for the test.

(2) The fourth stage of the Bruce protocol is an awkward stage that can be run or walked, resulting in divergent oxygen costs and workloads.

2. Modified Bruce protocol. Developed for less fit persons, the modified Bruce protocol adds additional stages 0 and 1/2. These stages, at 1.7 mph (2.7 km/h) with 0% and 5% grades, respectively, provide a **lower workload for persons with poor cardiovascular fitness**. However, even these workloads may be too heavy for some debilitated patients and may result in premature fatigue.

3. Other protocols. Protocols superior to the Bruce protocol have been developed. These protocols have more gradual increases in workload and can be modified to suit the individual.

a. The **Naughton protocol** is optimal for older or debilitated persons and allows for a gradual increase in workload.

b. The **Balke protocol** is adequate for younger, fit persons. It maintains a speed of 3, 3.5, or 4 mph (4.8, 5.6, or 6.4 km/h, respectively) and increases the grade every 2 minutes.

c. The **Cornell protocol** is useful for a wider range of fitness levels depending on the starting grade. It allows for a gradual increase in grade and speed and may be started at 0%, 5%, or 10% grade, depending on fitness level.

d. **Ramp protocols** are computer-driven protocols that continuously increase workload until maximum exertion is reached. This is the ultimate in continuous advancement, but steady state may not be reached at any given workload.

III. DATA

A. Electrocardiographic data. Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The **portion of the ECG most sensitive to ischemia** is the ST segment. The pathophysiologic mechanism of the ST change is net depression caused by a current of ischemia from the affected myocardial cells. The TP segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST changes are listed in **Table 48.5**.

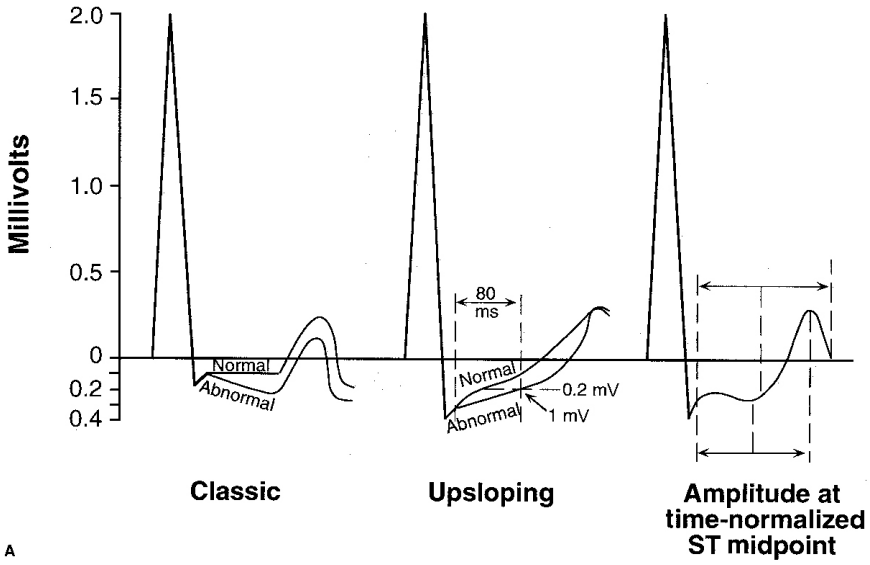
TABLE 48.5 Baseline Abnormalities That May Obscure Electrocardiographic Changes During Exercise

Left bundle branch block
Left ventricular hypertrophy with repolarization abnormality
Digitalis therapy
Ventricular paced rhythm
Wolff-Parkinson-White syndrome
ST abnormality associated with supraventricular tachycardia or atrial fibrillation
ST abnormalities with mitral valve prolapse and severe anemia

1. ST-segment changes

a. **Measurement of the ST segment.** To date, there is no clear consensus as to where to measure the ST segment. Traditionally, it is measured 80 ms immediately beyond the J point, but some investigators suggest measuring at the J point or at the midpoint of the ST segment (using the end of the T wave or the peak of the T wave to determine the end of the segment; **Figure 48.1A**).

b. **ST-segment changes** are measured from the isoelectric baseline, which can be determined from the PR interval. If the ST segment is elevated at rest, any depression that occurs with exercise is still measured from the isoelectric line; early repolarization of the ST segment at rest is normal. If, however, the ST segment is depressed at rest, any further depression should be measured from the baseline ST segment (**Figure 48.1B**).



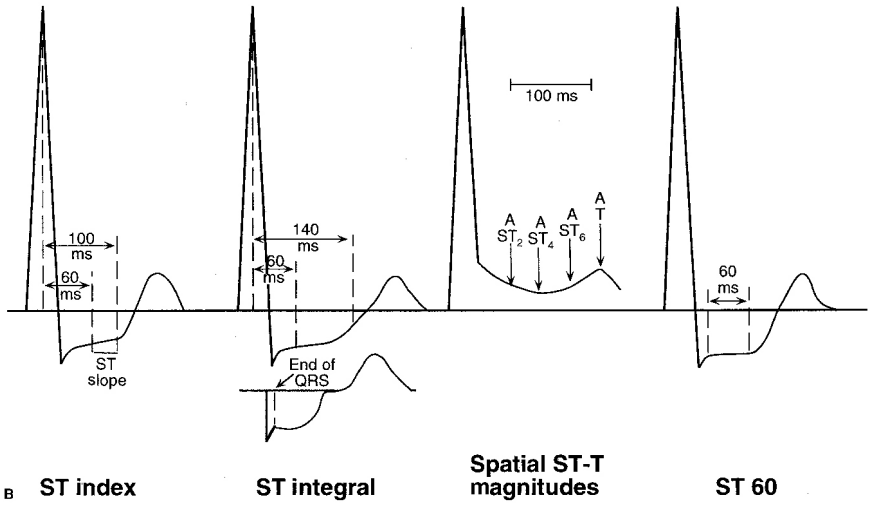


FIGURE 48.1 **A.** Blomqvist recommended using the end of the T wave for measuring the midpoint of the ST segment, but Simons used the peak of the T wave. This change was made to have a more stable end point, because the end of the T wave is much more difficult to find than the peak of the T wave. **B.** The ST integral, as defined by Sheffield, required that the end of the QRS complex, or J junction, be found and that the area measurement stop as soon as the ST segment crossed the isoelectric line or as the T wave began. The ST integral used by most commercial systems initiates the area at a fixed period after the R wave and then ends 80 ms thereafter.

c. Normal response. During exercise, there is depression of the J junction that is maximal at peak exercise and returns to baseline during recovery. This normal depression is upsloping and typically <1 mm below the isoelectric line 80 ms after the J point.

d. ST depression does **not** localize the area of ischemia.

(1) ST depression of at least 1 mm that is horizontal or downsloping is abnormal, as is upsloping ST depression of at least 2.0 mm.

(2) Baseline ST abnormalities are less likely to represent exercise-induced myocardial ischemia, and the baseline ST depression should be subtracted from the peak ST depression.

(3) Criteria that increase the probability of ischemia are the **number of leads** involved (ie, more leads increase the

probability of ischemia), the **workload** at which the ST depression occurs (ie, lower workload increases the probability), the **angle of the slope** (ie, a downsloping angle has a higher probability than a horizontal one), **ST-segment adjustment relative to heart rate (ST/HR index)**, the **amount of time in recovery** before normalization of the ST segment (ie, longer recovery increases the probability), and, possibly, the **magnitude of the depression**. Changes in the lateral leads, particularly V_5, are more specific than in any of the other leads. Changes in the **inferior leads alone are likely to be a false-positive** result.

e. The **meaning of ST elevation** depends on the presence or absence of Q waves of prior MI.

(1) ST-segment elevation **with Q waves of prior MI** is a common finding among patients who have had MI. It occurs among up to 50% of patients with anterior MI and 15% of patients with prior inferior MI, and it is not caused by ischemia. The mechanism is thought to be dyskinetic myocardium or ventricular aneurysms. There may even be reciprocal ST-segment depression. Patients with more extensive Q waves have more pronounced ST elevation. These patients typically have a lower ejection fraction than those without elevated ST segment with a Q wave. These changes do not imply ischemia (although they may imply viability) and should be interpreted as normal.

(2) ST-segment elevation **without Q waves of prior MI** represents marked transmural myocardial ischemia. ST elevation may also indicate the location of the ischemia. This finding should be interpreted as abnormal.

f. ST normalization, or the lack of ST changes during exercise, **may be a sign of ischemia**. This phenomenon occurs when ischemic ST depression and ST elevation cancel one another. This effect is rare, but it should be considered in tests of patients with no electrocardiographic changes but with a high likelihood of CAD.

2. **R waves may change in amplitude** during exercise. There is no diagnostic value in these changes.
3. **T-wave and U-wave changes**
   a. The **T wave** normally decreases gradually in early exercise and begins to increase in amplitude at maximal exercise. One minute into recovery, the T wave should be back to baseline. T-wave **inversion is not a specific marker of ischemia** and may occur normally.
   b. If the U wave is upright at baseline, **U-wave inversion** may be associated with ischemia, left ventricular hypertrophy, and valvular disease.
4. **Arrhythmias.** **Table 48.6** lists abnormal arrhythmias that may occur during exercise. Ectopic atrial and ventricular beats during exercise are not predictive of outcome, but ventricular ectopy during recovery may be associated with worse outcome. Sustained ventricular tachycardia and ventricular fibrillation are abnormal but occur rarely.

TABLE 48.6 Absolute and Relative Indications for Termination of an Exercise Test

Absolute Indications
Acute MI or suspicion of MI
Onset of moderate-to-severe angina or increasing anginal pain
Drop in SBP >10 mm Hg, despite an increase in workload, when accompanied by any other evidence of ischemia
Serious arrhythmias (eg, second- or third-degree atrioventricular block, sustained ventricular tachycardia or increasing premature ventricular contractions, and atrial fibrillation with fast ventricular response)
Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
Unusual or severe shortness of breath
Central nervous system symptoms, including ataxia, vertigo, visual or gait problems, or confusion
Technical inability to monitor the ECG
Patient's request

Relative Indications
Pronounced electrocardiographic changes from baseline >2 mm of horizontal or downsloping ST-segment depression or >2 mm of ST-segment elevation, except in aVR, measured 60-80 ms after the J point in a patient with suspected ischemia
Drop in SBP >10 mm Hg (persistently below baseline) despite an increase in workload, in the absence of other evidence of ischemia
Any chest pain that is increasing
Physical or oral manifestations of severe fatigue or shortness of breath, wheezing
Leg cramps or intermittent claudication (grade 3 on 4-point scale)
Hypertensive response (SBP > 250 mm Hg and diastolic blood pressure > 115 mm Hg)
Less serious arrhythmias such as supraventricular tachycardia
Exercise-induced bundle branch block that cannot be differentiated from ventricular tachycardia
General appearance

ECG, electrocardiogram; MI, myocardial infarction; SBP, systolic blood pressure. Adapted from Swain DP, Brawner CA, Chambliss, HO, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. Williams & Wilkins; 2013 and from Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation*. 2013;128(8):873-934.

5. **Time to resolution of changes.** The longer into recovery that it takes for electrocardiographic changes to resolve, the higher is the probability that they are important. Rapid recovery (<1 minute) indicates less likelihood of disease and that disease if present is less severe.
6. Bundle branch block or conduction delay. Exercise-induced left bundle branch block (LBBB) is predictive of a worse outcome.

B. Age-predicted maximum heart rate (APMHR). The two most common formulas are as follows:

APMHR = 220 − age

APMHR = 200 − ½ age

The APMHR may be much lower or much higher than a person's actual measured MHR. **HR should not be used as an indicator of**

maximal exertion or in the decision to terminate testing. If MHR does not exceed 85% of APMHR during testing and there are no substantial electrocardiographic changes, the test is usually read as nondiagnostic. If there are substantial electrocardiographic changes, the test is read as abnormal, regardless of the HR achieved.

C. Rating of perceived exertion (RPE) is a better marker of maximal level of exertion.

1. A useful indicator of percentage of maximum workload achieved is the **RPE scale**. This is a subjective scale used to rate how much effort the subject feels they are expending during an exercise test. The subject should be advised to rate how they feel overall and not according to an individual element, such as leg fatigue. Although subjective, the scale has been shown to be reproducible, and maximum ratings correspond well with maximum exertion.
   a. The **Borg scale** is used most often. The original scale ranges from 6 to 20, which is meant to correspond to an HR increase from 60 to 200 beats/min during exercise.
   b. The **modified Borg scale** ranges from 0 to 10. The scale includes word anchors, which are important for an accurate assessment of work level. The scales are not linear, and at higher workloads, the changes in RPE are closer together.
2. A maximal level of exertion is marked by a score >18 (Borg scale) or 9 (modified Borg scale), respiratory quotient >1.1 (if carbon dioxide exchange is monitored), and overall patient appearance.

D. In addition to electrocardiographic monitoring, **BP monitoring** is an important aspect of the exercise test for safety and for the diagnosis of CAD. It should be checked in each walking stage. It may not be practical to check BP while the subject is running.

1. **Systolic blood pressure** (SBP) normally rises during exercise. A **failure of SBP to rise** with increasing workload or a drop in SBP usually indicates the presence of CAD and is an indication to **terminate testing**.
2. **Diastolic BP** decreases with exercise and may be audible down to 0 during vigorous activity. Unlike SBP, diastolic BP is not useful in diagnosis or safety monitoring.

E. Symptoms. The presence or absence of symptoms and their change over time are included in the final report.

F. Functional capacity. Functional testing is a powerful marker for prognosis. Persons who achieve >6 METs of workload have a significantly lower mortality rate than those who do not achieve this workload, regardless of electrocardiographic changes. On the basis of age and workload achieved, functional capacity can be divided into five classifications (**Table 48.7**). Among 3,400 patients with no history of diagnosed CAD undergoing exercise testing at the Cleveland Clinic, those with average or better classifications had a 2.5-year mortality of <2% compared with 6% and 14% for those who were in the fair and poor groups, respectively. The adjusted relative risk for fair or poor functional capacity in this population was almost 4.

TABLE 48.7 Functional Capacity Classifications by Age and Sex

Age (y)	Low[a]	Fair	Average	Good	High
Women					
20-29	<7.5	8-10.3	10.3-12.5	12.5-16	>16
30-39	<7	7-9	9-11	11-15	>15
40-49	<6	6-8	8-10	10-14	>14
50-59	<5	5-7	7-9	9-13	>13
60-69	<4.5	4.5-6	6-8	8-11.5	>11.5
Men					
20-29	<8	8-11	11-14	14-17	>17
30-39	<7.5	7.5-10	10-12.5	12.5-16	>16
40-49	<7	7-8.5	8.5-11.5	11.5-15	>15
50-59	<6	6-8	8-11	11-14	>14
60-69	<5.5	5.5-7	7-9.5	9.5-13	>13

[a]Functional capacities are given in metabolic equivalents.

IX. TERMINATION OF EXERCISE TESTING.

The AHA and American College of Sports Medicine (ACSM) have developed very similar indications for

exercise termination (**Table 48.6**). The decision when to terminate a test ultimately relies on the expertise and judgment of those performing the test.

A. **Absolute indications** are all serious findings. A drop in SBP with increasing workload is a particularly ominous sign and usually, but not always, indicates the presence of severe CAD.

B. **Relative indications** for termination of testing are findings that should increase the level of concern and vigilance among those administering the test and possibly cause cessation of testing. Relative indications for termination rely heavily on the judgment of the personnel performing the test, and the decision to continue the test should not be made lightly (**Table 48.6**).

C. **Postexercise recovery**

1. In **all routine exercise tests, a cool-down period** adds safety to the test. The length of the cool-down period may vary from 30 seconds to several minutes, depending on the person. A general rule is to allow enough time for the HR to drop to <110 beats/min. A shorter cool-down period increases the sensitivity of exercise ECG because of increased venous return; resuming the supine position leads to increased wall stress. This same mechanism also increases the risk of testing.
2. The exception to observing a cool-down period may be made for exercise echocardiography, in which it is important to image the subject when they are as close as possible to MHR.

X. **INTERPRETATION OF DATA.** An experienced clinician must interpret an exercise electrocardiographic test. Although the terms *positive* and *negative* are often used, these terms do not accurately describe the results of an exercise electrocardiographic test and should be avoided. The information to include in an exercise electrocardiographic report is listed in **Table 48.8**.

TABLE 48.8 Elements of Conclusion Section of a Modern Exercise Test Report

Exercise protocol used, duration of exercise, peak treadmill speed and grade, maximum heart rate and percentage of APMHR achieved, resting and peak blood pressure, and

symptoms
Negative/positive/equivocal standard ST-segment response to exercise
"The ST/HR index of ≤1.6 mcV/beats/min is consistent with the absence of obstructive coronary disease and makes anatomically, functionally, and prognostically important coronary disease unlikely"; "The ST/HR index >1.6 mcV/beats/min is consistent with the presence of obstructive coronary disease and predicts increased cardiovascular risk."
The estimated functional capacity of (*x* METs) predicts (high/low) risk of all-cause mortality
The Duke treadmill score of (*x*) predicts a cardiac mortality of (*x*%) per year over the next 5 y. This implies a (low/intermediate/high) risk.
The chronotropic response index of (0.*xx*) predicts an (increased/decreased) risk of death compared with the Duke treadmill score. For patients not on beta-blockers, a value ≤0.80 raises concerns; for patients on beta-blockers, a value ≤0.62 is abnormal.
The heart rate recovery of (*x* beats/min) further predicts an (increased/decreased) risk of death.
The presence/absence of frequent ventricular ectopy during recovery further increases/decreases predicted risk of death.

APMHR, age-predicted maximum heart rate; HR, heart rate; MET, metabolic equivalent. Adapted with permission from Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation*. 2006;114(19);2070-2082.

A. Exercise electrocardiographic test results can be normal, abnormal, normal except for, or nondiagnostic (**Table 48.9**). Nondiagnostic tests are those in which the subject does not achieve 85% of APMHR and has no abnormal electrocardiographic changes or in which baseline electrocardiographic changes are present that obscure ST changes (**Table 48.5**).

TABLE 48.9 Guidelines for Interpretation of Results of Exercise Electrocardiography

Variable	Normal	Normal Except for	Abnormal
Symptoms	Neuromuscular chest pain	Angina as an isolated finding	Syncope
	Fatigue, shortness of breath, and leg or joint pain	Atypical angina	Angina when associated with ST- or T-wave changes,

Variable	Normal	Normal Except for	Abnormal
			including borderline
		Chest discomfort of questionable causation	Angina when associated with exercise hypotension
		Claudication	
		Dizziness and lightheadedness	
		Other noteworthy symptoms	
Blood pressure response (mm Hg)	SBP increases >10 but is <230 at peak.	SBP ≥230 at peak exercise	Any drop in SBP as exercise intensity increases
	DBP increases ≤10 but is <120 at peak.	DBP ≥120 at peak exercise	
	DBP stays the same or decreases.	DBP increases ≥12 from rest if peak is ≥100.	
	DBP increases ≥12 from rest but peak is <100.		
Arrhythmias	Occasional PVCs	Paroxysmal SVT	Sustained SVTs, AF, atrial flutter, or junctional rhythm
	PACs	Increased frequency of PVCs or couplets during exercise	Nonsustained VT
	Frequent PACs or PVCs at rest that abate during exercise	Isolated run of nonsustained VT	Second- or third-degree AV block
	Chronic AF, atrial flutter	Ventricular couplets	AV dissociation
		Paroxysmal escape rhythms	Exercise induced before excitation

Variable	Normal	Normal Except for	Abnormal
			Idioventricular rhythm
			Very abnormal
			Sustained VT (≥30 s)
			VF/cardiac arrest
			Asystole
ST segments	≥1.0 mm ST depression or elevation	Borderline ST changes (0.5-0.9 mm ST depression)	≥1.0 mm H or D ST depression
		ST elevation in leads in area of prior MI	≥1.5 mm U ST depression
		T-wave inversion	≥1.0 mm U ST depression if associated with anginal symptoms
		Pseudonormalization of resting T-wave abnormalities	≥1.0 mm ST elevation in leads without Q waves or not over a prior MI
			Very abnormal
			≥2.0 mm H or D ST depression
			≥2.5 mm U ST depression
			≥2.0 mm ST elevation in leads without Q waves or not over a prior MI
Functional capacity	Normal or mildly impaired exercise tolerance	Low exercise tolerance	Inability to achieve 3-MET workload

AF, atrial fibrillation; AV, atrioventricular; D, downsloping; DBP, diastolic blood pressure; H, horizontal; MET, metabolic equivalent; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction; SBP, systolic blood pressure; SVT, supraventricular tachycardia; U, upsloping; VF, ventricular fibrillation; VT, ventricular tachycardia.

B. Prognosis

1. The **Duke nomogram** (**Figure 48.2**) is a simple chart that factors in ST-segment deviation, amount of angina during exercise, and exercise capacity to give an estimate of a 5-year survival and average annual mortality. This nomogram was derived by means of regression analysis and can be a useful tool in determining prognosis and the degree of aggressiveness needed in treating a patient. The **Duke treadmill score (DTS)** is a numeric form of the nomogram and has been validated in several studies as an important predictor of mortality:

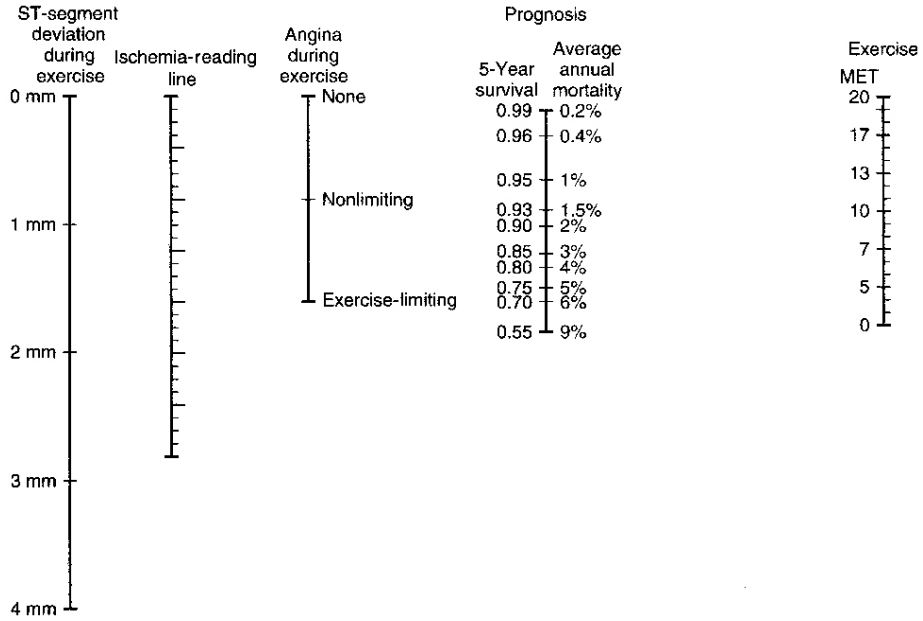


FIGURE 48.2 Duke nomogram for estimation of the prognosis. MET, metabolic equivalent.

DTS = duration of exercise (in minutes) − (5 × maximal ST-segment deviation)

In the previous equation, 0 = no angina, 1 = non–test-limiting angina, and 2 = exercise-limiting angina.

Low risk: DTS ≥ +5

Intermediate risk: DTS = −10 to <+5

High risk: DTS < −10

2. The **HR recovery**, defined as the difference in HR at peak exercise and at 1 minute after cessation of exercise, has important prognostic significance. An HR recovery of 12 beats/min or less is considered abnormal during an upright cool-down period. For patients assuming an immediate supine position, such as during exercise echocardiography, a value of <18 beats/min is considered abnormal.
3. The **chronotropic response index (CRI)** is a measure of MHR in relation to chronotropic reserve. A normal response is defined as a CRI of >0.8 (0.62 for patients on beta-blockers):

$$\text{CRI} = \frac{\text{peak HR} - \text{resting HR}}{\text{APM HR} - \text{resting HR}}$$

4. **Ventricular ectopy in recovery** from exercise, including frequent ventricular ectopics (>7/min), couplets, bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation, has been shown to be predictive of all-cause mortality. These findings in recovery are a better predictor of death than ventricular ectopy during exercise.
5. A published nomogram (1) for patients with suspected CAD and a normal ECG undergoing exercise treadmill testing demonstrates how a simple combination of clinical and stress testing variables can be used to predict mortality.

XI. POTENTIAL COMPLICATIONS. Complications of exercise electrocardiographic testing are rare, but they do occur (**Table 48.10**). Exercise testing of healthy persons without CAD rarely results in cardiac complications, which are most likely to occur among persons with underlying CAD. Several researchers have looked at large numbers of unselected persons involved in various activities to determine risk.

TABLE 48.10 Potential Medical Complications of Exercise Electrocardiographic Testing

Cardiovascular Complications
Cardiac arrest
Ischemia
Angina MI
Arrhythmias
Supraventricular tachycardia Atrial fibrillation Ventricular tachycardia Ventricular fibrillation
Bradyarrhythmias
Bundle branch blocks Atrioventricular nodal blocks
Congestive heart failure
Hypertension
Hypotension
Aneurysm rupture
Underlying Medical Conditions Predisposing to Increased Complications
Hypertrophic cardiomyopathy
Coronary artery anomalies
Idiopathic left ventricular hypertrophy
Marfan syndrome
Aortic stenosis
Right ventricular dysplasia
Congenital heart defects
Myocarditis
Pericarditis
Amyloidosis
Sarcoidosis

Long QT syndrome
Sickle cell trait
Sudden death
Pulmonary Complications
Exercise-induced asthma
Bronchospasm
Pneumothorax
Exercise-induced anaphylaxis
Exacerbation of underlying pulmonary disease
Gastrointestinal Complications
Vomiting
Cramps
Diarrhea
Neurologic Complications
Dizziness
Syncope (fainting)
Cerebrovascular accident (stroke)
Musculoskeletal Complications
Mechanical injuries
Back injuries
Joint pain or injury
Muscle cramps or spasms
Exacerbation of musculoskeletal disease

MI, myocardial infarction.

A. Cardiac arrest

1. For the **general population**, there is approximately 1 cardiac arrest per 565,000 person-hours of exercise.
2. Among **persons with known CAD**, there is an estimated 1 arrest per 59,000 person-hours of vigorous activity. Exercise testing may

precipitate ACSs. Acute MI has been reported in approximately 1.4 per 10,000 exercise tests.

3. Among **persons at low risk** for CAD, however, the risk for cardiac arrest during exercise testing is much lower. In one study, no complications occurred in 380,000 exercise tests of young persons with presumably no heart disease.

B. Conduction abnormalities

1. Transient LBBB, right bundle branch block (RBBB), or hemiblocks can rarely be seen as a result of ischemia of ischemia- or rate-dependent–refractory periods of the fascicles.
2. **Atrioventricular (AV) nodal block** can be divided into two categories based on the location of disease: intranodal or infranodal.
   a. Given the autonomic nervous system regulation of the AV node over the His-Purkinje system, response to exercise can help localize the conduction disease. If the heart block improves with exercise, the pathology is likely to be within the AV node, and if the block worsens, the pathology is likely infranodal.

C. Arrhythmic complications are a potential hazard of exercise testing (**Table 48.9**). Arrhythmias are more likely among persons with a history of arrhythmia. In this population, they occur in 9% of tests compared with an overall incidence of 0.1%.

1. **Atrial fibrillation** is the most common arrhythmia that occurs during testing, occurring in 9.5 per 10,000 tests.
2. **Ventricular tachycardia** is less common, occurring in 5.8 per 10,000 tests.
3. **Ventricular fibrillation** is even less common, occurring 0.67 times per 10,000 tests.

D. Deaths during exercise testing are exceedingly rare among well-monitored patients but may occur in 1 of 25,000 tests. If death occurs, it is usually caused by sudden cardiac death or MI.

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CHAPTER 49

Nuclear Cardiac Imaging

Gary Parizher and Wael A. Jaber

I. INTRODUCTION.

Nuclear cardiology has an integral role in the noninvasive detection of coronary artery disease (CAD), assessment of myocardial viability, and stratification of risk. In addition, novel imaging protocols have been instituted to detect and risk stratify patients with certain cardiomyopathies. With respect to CAD, nuclear stress testing imparts improved sensitivity and specificity over standard exercise stress testing as supported by recent American College of Cardiology/American Heart Association and European Society of Cardiology guidelines. For example, the average sensitivity and specificity of single-photon emission computed tomography (SPECT) with technetium-99m (^{99m}Tc) have been reported to be 90% and 74%, respectively—although the exact performance characteristics depend on the prevalence of the disease in the population being studied as well as the sex and body habitus of the patient. Nuclear imaging can provide functional and prognostic information that is quantifiable, reproducible, and readily obtainable in diverse patient populations. Importantly, this imaging modality has an excellent performance record in patients with and without CAD, in males and females, with and without prior revascularization, and with various degrees of left ventricular (LV) dysfunction.

II. INDICATIONS (Table 49.1)

TABLE 49.1 Appropriate Indications for Myocardial Perfusion Imaging[a]

Patient Group	Condition	Imaging Technique
ED patient with chest pain	For risk stratification in patients with *possible* ACS. Negative initial serum markers and enzymes. ECG is nondiagnostic.	Rest perfusion imaging (with ECG gating, if possible)
	For CAD diagnosis in patients with *possible* ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan	Same-day rest/stress (ECG-gated) myocardial perfusion imaging
Acute MI/unstable angina	Assessment of LV function	Rest myocardial perfusion imaging with ECG gating (rest gated radionuclide angiography is an alternative option)
ST-elevation MI	Measurement of infarct size and residual viable myocardium, in an unrevascularized asymptomatic stable patient after completion of the infarct	Rest myocardial perfusion imaging with ECG gating or with stress perfusion imaging with ECG gating, as well as metabolic imaging.
	Thrombolysis without coronary angiogram, to identify inducible	Rest and stress myocardial perfusion imaging, with ECG gating whenever

Patient Group	Condition	Imaging Technique
	ischemia and myocardium at risk	possible
Non–ST-elevation MI/unstable angina	In an unrevascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the “culprit” vessel or in remote myocardium	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible
	In individuals whose angina is stabilized on medical therapy or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible
	To assess the functional significance of a coronary stenosis on angiography	Rest and stress myocardial perfusion imaging
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* able to exercise to 85% MPHR or more	Individuals with preexcitation, LVH, on digoxin, or >1 mm ST-segment depression on resting ECG	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible
	Individuals with left bundle branch block or ventricular-paced rhythm	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	Patients with an intermediate—or high-risk Duke treadmill score	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible
	In an individual with a prior abnormal myocardial perfusion scan and new or worsening symptoms	Repeat rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease *and* not able to exercise	To identify the extent, severity, and location of inducible ischemia	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible
Detection of CAD in patients with syncope	Patients with intermediate and high risk for CHD and no ischemic equivalent	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible

Patient Group	Condition	Imaging Technique
	CV events, and poor (<4 METs) or unknown functional capacity	*or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	In individuals with established or suspected CAD and poor (<4 METs) or unknown functional capacity	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible *or* In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	Diagnosis of CAD in patients with left bundle branch block or ventricular-paced rhythm and at least one risk factor for adverse perioperative CV events	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	In suspected or established CAD, prognostic assessment of those with left bundle branch block or ventricular-paced rhythm on rest ECG	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes	Rest and adenosine or dipyridamole stress PET-myocardial perfusion study
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging *or* Rest/redistribution SPECT perfusion imaging *or* Myocardial perfusion plus FDG-PET metabolic imaging *or* Resting sestamibi SPECT perfusion imaging
	Prediction of improvement in natural history following revascularization	Stress/redistribution/reinjection thallium-201 SPECT perfusion imaging *or* Rest/redistribution thallium-201 SPECT perfusion imaging *or* Myocardial perfusion plus FDG-PET metabolic imaging

ACCF, American College of Cardiology Foundation; ACR, American College of Radiology; ACS, acute coronary syndrome; AHA, American Heart Association; ASE, American Society of Echocardiography; ASNC, American Society of Nuclear Cardiology; CAD, coronary artery disease; CHD, congenital heart disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ED, emergency department; FDG, [18F]fluoro-2-deoxyglucose; LV, left ventricular; LVH, left ventricular hypertrophy; METs, metabolic equivalents; MI, myocardial

infarction; MPHR, maximal age-predicted heart rate; PET, positron emission tomography; SCCT, Society of Cardiovascular Computed Tomography; SCMR, Society for Cardiovascular Magnetic Resonance; SNM, Society of Nuclear Medicine; SPECT, single-photon emission computed tomography.

[a]Based on the ACCF/ASNC/ACR/AHA/ASE/SCCT/SCMR/SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging.

A. Coronary artery disease

1. **Diagnosis.** Nuclear perfusion studies are performed to establish noninvasively the diagnosis of CAD in the following situations: history of **stable angina; chest pain of unclear causation; unstable angina** after stabilization; **abnormal exercise test result** without symptoms; **risk stratification** in the setting of multiple factors thought to confer a high likelihood of subclinical CAD; scheduled standard exercise testing in the setting of an **abnormal electrocardiogram** (ECG; because of LV hypertrophy with associated repolarization changes, ST depression >1 mm, manifest preexcitation pattern on ECG, digoxin use, left bundle branch block, or ventricular-paced rhythm); and previously **nondiagnostic graded exercise test**. Multi-society guidelines for the management of chest pain, published in 2021, corroborate the use of nuclear myocardial perfusion imaging (MPI) for patients with intermediate-high pretest probability of CAD, provided acute coronary syndrome has been ruled out. Given the limited sensitivity and specificity of stand-alone ECG treadmill testing, this technique was relegated to a class IIa recommendation, and stress testing with imaging is the preferred modality with a class I indication.
2. **Assessment of the physiologic importance of known coronary lesions.** MPI can assist in the determination of the functional significance of a coronary stenosis that is in the "moderate-to-severe" (50%-70%) range on angiographic evaluation. It can, therefore, be useful to evaluate a specific coronary lesion before proceeding to revascularization. Also, in patients with multivessel disease of unclear severity, MPI can be used to assess the most significant lesion and its contribution to myocardial ischemia and symptoms. These remain accepted indications for nuclear perfusion imaging, although its use for this purpose is being supplanted by other modalities that can assess the functional significance of coronary lesions at the time of angiography (eg, fractional flow reserve).
3. **Assessment after therapeutic intervention.** In the past, MPI was often performed as a routine follow-up procedure after percutaneous intervention and coronary artery bypass grafting (CABG). More recent recommendations on the appropriate use of this modality suggest that routine screening in **asymptomatic** patients who have been successfully revascularized by either method is **not** necessarily warranted, except in the evaluation of patients more than 5 years after CABG. In 2022, the results of the POST-PCI randomized trial were published, demonstrating that, among high-risk patients who had undergone percutaneous coronary intervention (PCI), a follow-up strategy of routine stress testing did not improve clinical outcomes at 2 years compared to standard care alone. On the other hand, MPI is certainly appropriate in patients who have undergone prior revascularization and are presenting with **recurrent symptoms** consistent with coronary ischemia, or when there is uncertainty regarding complete revascularization.

4. **Risk stratification.** With MPI, it is possible to stratify risk among patients with stable angina or unstable angina, those who have had myocardial infarction (MI), and those about to undergo noncardiac operations.
5. **Identification of prior MI**, particularly among patients with angiographically normal coronary arteries when thrombolysis or coronary vasospasm is suspected; visualization and quantification of ischemia and scar can be well delineated on MPI.

B. **Assessment of LV function.** Although nuclear imaging is used less often for this purpose than in the past because of the desire to reduce patients' radiation exposure when possible, gated blood pool imaging remains an accurate method of determining the ejection fraction. In addition, MPI provides a "bonus" evaluation of LV function at rest and poststress, which can identify a marker of risk if LV ejection fraction (LVEF) drops poststress. Furthermore, LV function on MPI is accurate when compared to cardiac magnetic resonance imaging (MRI).

C. **Diagnosis of cardiomyopathy.** Nuclear imaging studies with novel protocols have been used to detect infiltrative cardiomyopathies such as amyloidosis and sarcoidosis. In addition, if an ischemic cardiomyopathy is suspected in the setting of reduced LV function, nuclear imaging is sometimes used, particularly if coronary angiography is not feasible or desired (body habitus or advanced renal disease).

III. **CONTRAINDICATIONS**. In addition to standard contraindications to exercise stress testing, specific considerations apply uniquely to nuclear imaging in general and the subgroup of pharmacologic/vasodilator stress perfusion studies.

A. **General contraindications to nuclear studies.** Due to "crosstalk" from radioisotopes with similar energy windows, MPI is contraindicated for patients who have had **iodine-131 therapy** within 12 weeks; ^{99m}**Tc studies** within 48 hours, including bone, lung, multigated acquisition (MUGA), liver, tagged red blood cell (to evaluate gastrointestinal bleeding), and renal scans; **indium-111 scans** within 30 days; **gallium-67 scans** within 30 days; and **oral intake** within 4 hours (except for water).

B. **Contraindications to dipyridamole, adenosine, or regadenoson** administration include allergy to any of these agents, allergy to aminophylline, ongoing theophylline therapy (must be discontinued for 36 hours), history of uncontrolled asthma or reactive airway disease, significant atrioventricular nodal block, and caffeine (an adenosine antagonist) consumption within 12 to 24 hours. A relative contraindication is a recent use of vasodilator medications (within 12-24 hours depending upon the medication), which will render the vasodilator stress agent ineffective in further dilating the coronary vasculature. In addition, resting vasoplegia exhibited by patients with advanced liver cirrhosis may blunt or eliminate the incremental vasodilatory effect of pharmacologic stressors used in cardiac testing.

IV. **EQUIPMENT**. The most basic tool in nuclear imaging is the **gamma camera**, which is used to detect gamma rays (ie, x-ray photons) produced by the chosen radionuclide. There are two types of gamma cameras commonly utilized in nuclear cardiology.

A. **A single-crystal camera** consists of one large sodium iodide crystal. Other essential elements of this camera include the **collimator**, a lead device that screens out the

background or scattered photons, and the **photomultiplier**, an electronic processor that translates photon interactions with the crystal into electric energy.

1. Electric signals from the photomultiplier are processed by the **pulse height analyzer** before reaching a final form. Only signals in a specified energy range are incorporated into the interpreted images. The range recognized by the pulse height analyzer is adjustable and is established on the basis of the radiopharmaceutical used.
2. **Digitalization** of the single-crystal camera has greatly enhanced its performance.

B. A **multicrystal camera** works with an array of crystals with increased count detection capability. Because of the availability of an individual crystal to detect scintillation at any given time, this type of camera can be used to detect many more counts than do a single-crystal camera.

Specially dedicated gamma cameras are the foundation of nuclear imaging in cardiology.

C. SPECT cameras utilize a single crystal to acquire multiple two-dimensional (2D) images, which are reconstructed to generate a 3D image.

1. Innovations in cardiac imaging have produced **ultrafast SPECT** cameras. These cameras are able to decrease scan time and radiation dose by constraining all available cameras to image only the cardiac field of view. There is a resulting increase in count sensitivity at no loss of, or even a gain in, resolution.

D. Cadmium zinc telluride (CZT) cameras, such as the D-SPECT camera (Spectrum Dynamics), use semiconductor-based solid-state detectors for image acquisition. These cameras are capable of dynamic acquisition, which allows for the calculation of absolute myocardial blood flow (see **Section VII.D**). While there is potential for CZT cameras to improve the diagnostic capability of SPECT, they have not been widely deployed in the United States and their incremental utility compared to conventional SPECT remains to be determined.

E. In the case of **PET** scanning, a **positron camera** is used to detect the photon products of positron annihilation. Interaction between a positron and an electron causes annihilation, with the generation of two high energy photons (511 keV) that travel in opposite directions.

1. A multicrystal camera is used and oriented in multiple concentric rings. Each crystal is linked optically to multiple photomultipliers. The crystals are oriented in diametric pairs positioned exactly 180° apart such that each pair of crystals must be struck simultaneously by annihilation photons to record activity. Background interference and stray photon energy are automatically accounted for, and artifact is limited.
2. Most positron cameras contain **bismuth germanate** for annihilation photon detection.
3. PET cameras can also be operated in 2D and 3D modes. The 3D mode of operation requires significant computational power for accurate geometric reconstruction but comes with improved resolution and sensitivity.
4. Most PET/CT equipment installed in the United States are analog systems. Newer digital PET cameras record individual photons using one-to-one coupling between the scintillation crystals and the digital sensors. This results in improved count rate performance and supports enhanced spatial resolution.

F. A CT scanner can be paired with the gamma camera. This allows for concomitant acquisition of a low-dose chest CT, facilitating quantification and characterization of the amount of tissue between the heart and the gamma camera. This information can be used to compensate for artifactual attenuation of the radionuclide signal (see **Section VIII**).

G. Continuous electrocardiographic monitoring is also important during nuclear imaging. Thickening of a segment of the myocardial wall with systolic contraction results in a corresponding "brightening" of the radionuclide signal from that segment. Using the ECG to synchronize image acquisition over multiple points in the cardiac cycle, known as "gating," enables the digital reconstruction of an animation portraying this systolic brightening (a gated image). This is important for evaluating systolic function as well as artifacts.

V. STRESS PROTOCOLS

A. Exercise stress testing. Standard exercise testing is frequently complemented with nuclear imaging. The radioisotope is injected at peak exercise, and time is allowed for circulation of the agents while exercising (usually at least 1 minute before termination of exercise).

B. For patients who are unable to exercise, **pharmacologic stress testing** is used in concert with nuclear imaging. Adenosine, regadenoson, and dipyridamole are vasodilators that are useful in noninvasive testing because of differences in coronary flow reserve. In the presence of marked coronary stenosis, the distal vessel is maximally dilated and, therefore, possesses little flow reserve.

1. Adenosine acts at several different receptors (A_1, A_{2A}, A_{2B}, and A_3) and thus has several physiologic effects. Its desired effect for the purpose of pharmacologic stress is to substantially enhance coronary flow in normal beds (ie, those with normal flow reserve), although much less so in distributions supplied by a stenotic artery. The resultant disproportionate flow allows for utilization or heterogeneous radiotracer uptake.

a. Administration. Adenosine is infused at 140 mcg/kg/min for 6 minutes. The radiotracer is then injected after 3 minutes of the start of adenosine infusion.

b. Side effects commonly experienced include chest pain, headache, nausea, and flushing, which typically resolve in 2 to 5 minutes. Atrioventricular block and bronchoconstriction are the result of effects on the A_1 and A_3 receptors, respectively. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.

2. Dipyridamole is an adenosine reuptake inhibitor, leading to increased extracellular concentrations of adenosine, and thus has very similar effects. It has a longer distribution half-life than adenosine, however, of approximately 25 minutes.

a. Administration. Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min). The maximum vasodilatory effect is achieved 4 minutes after completion of the infusion, and the radiotracer is injected at this point. A slight increase in heart rate (10 beats/min) and a decrease in blood pressure (10 mm Hg) are frequently observed.

b. Side effects. Headache, nausea, chest pain, hypotension, dizziness, and flushing have been reported. Severe side effects may necessitate reversal of the dipyridamole effect with aminophylline, given as a 50- to 100-mg intravenous bolus.

3. Regadenoson is a selective A_{2A} receptor agonist that has been Food and Drug Administration approved for clinical use in MPI since 2008. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and ADVANCE-MPI 2—have demonstrated the safety of this agent in a total of 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.

a. Administration. Regadenoson is given as a single 0.4-mg (in 5-mL) intravenous bolus and does not require adjustment for body mass index or renal or hepatic function. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes.

b. Side effects of chest pain, headache, nausea, and flushing do occur with regadenoson and typically resolve within 2 to 5 minutes. However, atrioventricular block and bronchoconstriction are far less common than with adenosine or dipyridamole, because of the lack of agonism of the A_1 and A_3 receptors with this A_{2A}-selective agent. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.

4. Dobutamine is an agonist of the beta1 and beta2 receptors and thus increases both heart rate and contractility (with a mild reduction in systemic vascular resistance).

a. Administration. Infusion is begun at 5 mcg/kg/min and increased every 3 minutes to a maximum dose of 40 mcg/kg/min. The radiotracer is injected at a maximum dose (or at 85% of age-predicted maximum heart rate), and the infusion is continued for 2 to 3 minutes.

b. Side effects associated with dobutamine include ectopy, headache, flushing, dyspnea, paresthesias, and hypotension.

VI. MECHANICS AND TECHNIQUES

A. Image acquisition. Fundamentally, nuclear imaging consists of three steps: intravenous injection of a radiotracer under prespecified conditions; distribution and tissue accumulation of the radiotracer depending on its specific characteristics and patient physiology; and, finally, anatomic localization of the tracer signal using the gamma camera along with image processing software. Often, nuclear imaging for the assessment of CAD consists of at least two image acquisitions, one at rest and one with stress, with additional acquisitions based on the clinical question at hand. Basic perfusion imaging can be performed by means of **planar** and **tomographic** techniques. The tomographic, or SPECT, method is most commonly used today; in the current era, SPECT images are preferred for the assessment of normal versus abnormal myocardial perfusion.

1. Planar images are acquired in three views: **anterior, left anterior oblique (LAO)**, and **steep LAO** or **left lateral (LLAT) orientation** (**Figure 49.1**). Planar imaging alone is currently rarely done in the United States because of its susceptibility to artifacts, inadequate definition of vascular territories, and poor sensitivity relative to SPECT.

Planar images remain important for the assessment of cardiac position in the chest, extracardiac activity, patient motion, potential attenuators, and presence of pericardial effusion, among other findings.

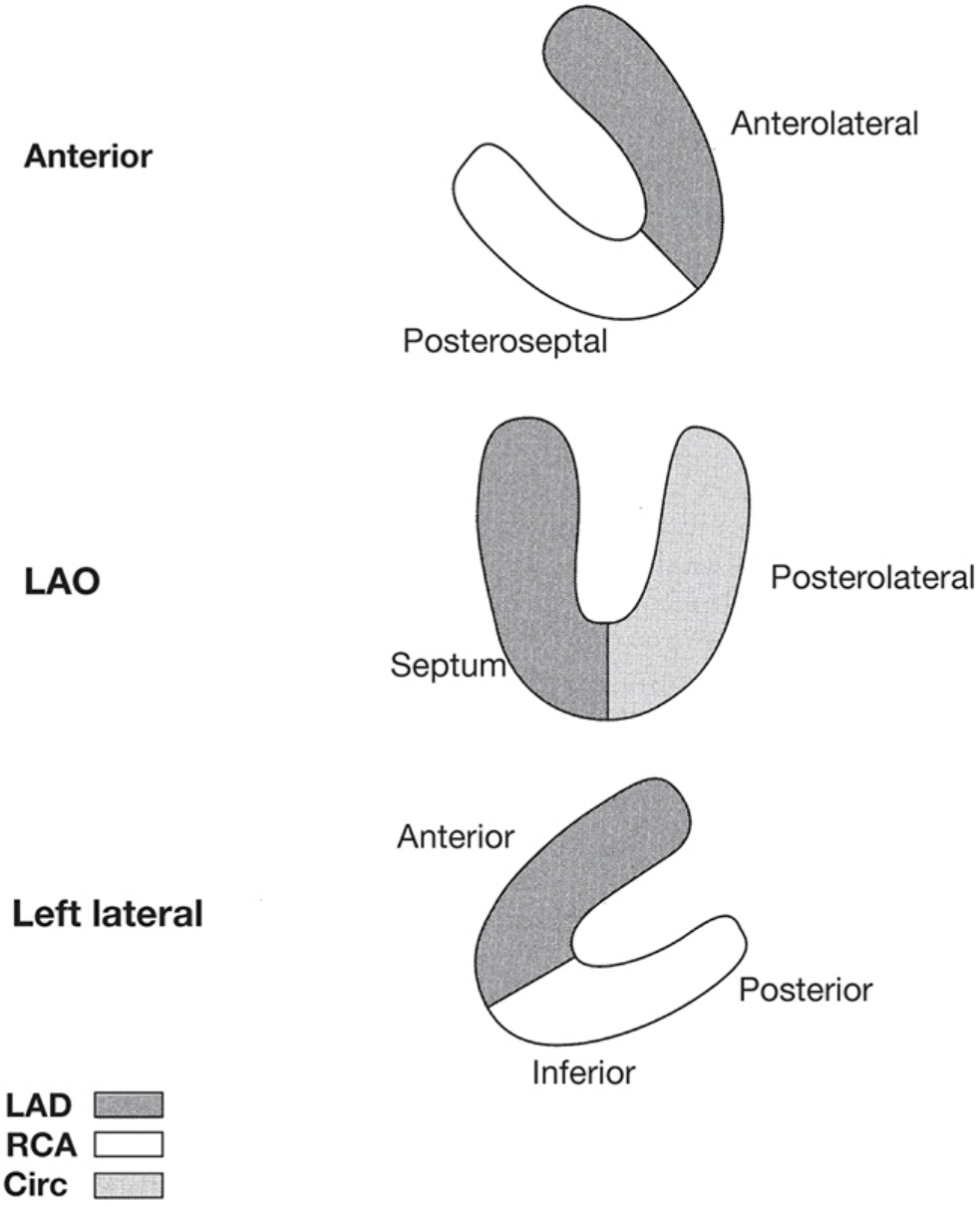

FIGURE 49.1 Standard planar views and vascular territories. Circ, circumflex artery; LAD, left anterior descending artery; LAO, left anterior oblique; RCA, right coronary artery.

2. Using **SPECT**, a series of planar images are usually obtained over a 180° arc to reconstruct a 3D representation of the heart. The arc typically extends from the 45° right anterior oblique plane to the 45° left posterior oblique plane, with the patient in the supine position.
   a. Three orientations are analyzed in the final representation: **short axis, vertical long axis**, and **horizontal long axis**. A computer-generated display, the **polar map**, is

also analyzed as a quantifiable representation of count density.

b. Unlike planar imaging, **SPECT and PET** can be used to **separate vascular territories** and improve image interpretation. These modalities, however, also **increase the time needed** for image acquisition and require close attention to quality control issues.

B. Radiopharmaceuticals available for nuclear imaging include thallium-201, ^{99m}Tc, and several positron imaging agents. Each possesses specific energy characteristics, kinetic profiles, and biodistribution (see below as well as **Table 49.2**). Different agents have different clinical indications depending on their pharmacokinetic and imaging characteristics.

TABLE 49.2 Characteristics of Common Perfusion Agents

Attribute	Thallium-201	Technetium-99m Sestamibi/Tetrofosmin	Rubidium-82	Nitrogen-13 Ammonia	^{18}F-Fluorodeoxyglucose (FDG)
Energy (keV)	69-83	140	511	511	511
Dose (mCi)	2.5-3.5	20-30	30-60	10-20	10-20
Half-life	74 h	6 h	76 s	10 min	110 min
Cyclotron required	Yes	No	No	Yes	Yes
Perfusion imaging	Yes	Yes	Yes	Yes	No
Viability evaluation	Yes	Yes	No	No	Yes
Redistribution	Yes	Minimal	No	No	No
Gating (electrocardiogram)	No	Yes	Yes	Yes	No

1. Thallium-201

a. General characteristics. Although the use of this agent has fallen out of favor due to its long half-life and low energy window, thallium is still in use in some centers, given its inherently efficient imaging protocol, often in dual-isotope imaging settings. Thallium-201 (ie, thallous chloride) is a metallic element in group IIIA of the periodic table; it is produced in a cyclotron. Thallium emits gamma rays at an energy range of 69 to 83 keV and has a **half-life of 73 hours**. The biologic activity of this element is very similar to that of potassium; the ionic radii of the two elements are virtually identical. Thallium is actively transported into cells by the sodium-potassium adenosine triphosphatase (Na-K ATPase) pump.

b. Kinetics. Approximately 5% of the administered dose of thallium-201 is distributed to the myocardium, proportionate to the blood flow delivered to the coronary circulation.

(1) The **initial uptake** of thallium-201 by the myocardium is directly related to regional blood flow. The myocardial extraction of thallium-201, however, increases at low-flow rates (<10% of basal) and decreases at high-flow rates (more than twice the basal rate).

(2) **Washout.** Almost 85% of the thallium-201 is extracted by myocytes in the first pass. After initial uptake into myocytes, a state of continuous exchange across the cell membrane occurs. The distribution of this radiotracer changes after administration, and thallium-201 washes out from the myocytes, a process called **redistribution**. Thallium-201 washout generally approaches 30% at 2 to 2.5 hours after injection.

(3) **Ischemic myocardium.** Uptake of thallium-201 in ischemic myocardium is lower than uptake in nonischemic segments, and washout time is slower than that from nonischemic zones.

(4) Over time, counts become equal in the ischemic and nonischemic regions (or thallium-201 concentration may increase in ischemic regions) so that thallium-201 concentrations in these disparate areas approach one another. This disparity is taken advantage of during thallium-201 viability imaging.

(5) Because of its susceptibility to artifacts, along with the prolonged radiation exposure resulting from a thallium-201 dose, the American Society of Nuclear Cardiology (ASNC) recommends using ^{99m}Tc-labeled agents instead. Thallium-201 use is on the decline in the United States.

2. **^{99m}Tc-labeled agents**

a. **General characteristics.** ^{99m}Tc is a radiopharmaceutical that can be produced on-site in molybdenum-99/^{99m}Tc generators. It possesses several ideal imaging characteristics, making it the de facto agent of choice for SPECT in the current era.

(1) ^{99m}Tc has a **half-life of 6 hours** and emits gamma rays with a single photopeak of 140 keV. Thus, radiation exposure is decreased as compared to thallium because of the shorter half-life.

(2) ^{99m}Tc-labeled **perfusion agents** include **^{99m}Tc-sestamibi**, **^{99m}Tc-tetrofosmin**, and **^{99m}Tc-teboroxime**. Some studies suggest that ^{99m}Tc-tetrofosmin has more rapid hepatobiliary clearance than sestamibi, which reduces the impact of liver uptake and allows for imaging sooner after injection.

b. **Kinetics.** After administration of ^{99m}Tc-sestamibi, approximately 40% to 60% of the agent is extracted by the myocardium. Initial uptake of the agent is proportional to regional myocardial blood flow, and it is bound to the inner mitochondrial membrane. ^{99m}Tc-tetrofosmin has similar pharmacokinetics to ^{99m}Tc-sestamibi. **Myocardial washout** of ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin is very slow, and little redistribution occurs. The absence of redistribution requires two separate injections of the agent, at **rest** and at **peak stress** (either exercise or pharmacologic). This can be performed with a same-day or 2-day protocol.

c. **^{99m}Tc-pyrophosphate (PYP)**, used in the evaluation of cardiac transthyretin amyloidosis (ATTR), is discussed below in Section **IX.C**.

3. **PET perfusion agents** require a positron camera. Costly equipment, such as a cyclotron or rubidium generator, is necessary to manufacture these radiopharmaceuticals, which has limited their adoption to a few high-volume centers. Nonetheless, the improvement in imaging quality and the ability to quantify myocardial

blood flow make them valuable in the assessment of CAD. PET, unlike SPECT, is universally done with attenuation correction.

a. Perfusion (blood flow) tracers. A number of radiopharmaceuticals exist for the assessment of myocardial blood flow. They can be produced by a cyclotron or generator.

(1) Rubidium-82, the most readily used blood flow tracer, can be generated on-site without the use of a cyclotron. Much like thallium-201, rubidium-82 is a potassium analog that is actively transported into myocytes through the Na-K pump. **Uptake into the myocardium** is proportionate to regional blood flow. Approximately 65% of the radiotracer is extracted at first pass. Because of a short half-life (76 seconds), rubidium-82–based imaging protocols can be used to assess myocardial blood flow rapidly (within 1 hour). However, the short half-life also precludes exercise stress PET imaging with this tracer. The short half-life of rubidium-82 requires injection to be done "under the camera," that is, with the patient already positioned for optimal imaging within the hybrid CT/PET scanner. Rubidium imaging protocols use rapid serial acquisitions following injection to directly visualize the uptake of tracer into the myocardium, and radioactive decay, in real time. Quantitative analysis allows for the measurement of absolute myocardial blood flow, measured in mL/g/min. This can be done at rest and with stress to calculate coronary flow reserve (see **Section VIII**).

(2) Other perfusion agents include the cyclotron-produced **nitrogen-13 ammonia** (half-life 10 minutes) and **oxygen-15 water** (half-life 123 seconds). Image quality with **oxygen-15 water** is poor and requires extensive processing to subtract the blood pool, thus is rarely used in current practice. ^{82}Rb and ^{13}N-ammonia are the perfusion tracers that are used in clinical practice, with ^{82}Rb carrying the distinct advantage of requiring only a generator instead of a cyclotron. The image quality of ^{13}N-ammonia is excellent, although the impracticality of cyclotron production in most facilities is a limiting factor for this agent. For those facilities capable of ^{13}N-ammonia generation, however, it has the "upside" of a longer half-life than rubidium-82; thus, exercise stress cardiac PET imaging could be performed if desired.

b. Metabolic radiopharmaceuticals. Metabolic imaging with PET depends on the use of radiolabeled substrates of cardiac metabolism, largely in the form of [^{18}F]fluoro-2-deoxyglucose (FDG), carbon-11 palmitate, and carbon-11 acetate.

(1) FDG is a glucose analog used by ischemic and hibernating myocardium because of a transition to alternative fuel sources in the hypoxic state. There is diminished oxidation of long-chain fatty acids and increased use of glucose as a secondary fuel source during ischemia or hibernation. FDG is phosphorylated to FDG-6-phosphate after transport across the cell membrane. FDG imaging, therefore, reflects myocardial use of exogenous glucose, and FDG is a widely used metabolic radiopharmaceutical. It has a half-life of 1.83 hours, which means it can be ordered on a daily basis by institutions that do not have an on-site cyclotron—making it the most commonly used metabolic PET imaging

agent. FDG is also used to image cardiac inflammation and aid in the diagnosis of cardiac sarcoidosis (see **Section VIII**).

(2) [^{11}C]Palmitate is taken up by myocytes, converted to acyl-CoA, and relegated to triglyceride stores or beta oxidized to produce [^{11}C]carbon dioxide. The release of this product of beta-oxidation is reflective of long-chain fatty acid oxidation in the myocardium.

(3) [^{11}C]Acetate is metabolized to [^{11}C]carbon dioxide after entering the tricarboxylic acid cycle. Measuring the production of [^{11}C]carbon dioxide in this setting correlates with myocardial oxygen consumption.

II. IMAGING PROTOCOLS

A. ^{99m}Tc SPECT. The relative lack of redistribution requires **two injections** of ^{99m}Tc to obtain rest and stress images.

1. Basic protocols

a. Same-day protocol. Rest images are obtained first, and stress imaging follows to minimize residual scintigraphic activity caused by the higher dose stress injection. This is the opposite order of thallium imaging.

(1) **Rest images** are obtained with injection of 7 to 10 mCi of ^{99m}Tc and image acquisition up to 1 to 1.5 hours later. Imaging is delayed because of slower liver clearance with rest injection.

(2) At peak exercise, ^{99m}Tc is injected at typically 3 times the dose of the resting images (25-30 mCi), a dose high enough to deliberately overshadow any interference from residual tracer remaining after rest injection. **Stress images** are obtained approximately 45 to 60 minutes after injection. Hepatic uptake of ^{99m}Tc occurs within 15 to 30 minutes of injection, and the tracer is excreted into the gastrointestinal tract through the biliary system. Appearance of the tracer in the gastrointestinal tract can interfere with imaging of the inferior wall of the LV.

b. The **separate-day protocol** allows time for decay of activity. Larger doses of ^{99m}Tc can be administered for rest and stress images, and there is minimal interference between the images.

(1) Between 22 and 30 mCi of ^{99m}Tc is injected for stress and rest imaging, separated by 1 to 2 days.

(2) The higher doses possible with the 2-day protocol produce increased count density and better image quality at the cost of inconvenience.

2. Factors that affect image quality. Consumption of a **fatty meal** can enhance biliary excretion of ^{99m}Tc and improve image quality. Because of possible interference from noncardiac uptake, image processing with ^{99m}Tc relies on normalization to the brightest cardiac pixel. Additional artifacts are discussed later.

B. Dual-isotope imaging. The use of both thallium-201 and ^{99m}Tc substantially reduces the time required to obtain stress and rest images. However, dual-isotope imaging is rarely done in practice.

1. The patient receives thallium-201 at rest (3.5 mCi) and, immediately after rest imaging, undergoes stress. At peak stress, the patient is given an injection of 25 mCi of ^{99m}Tc. Stress images are obtained 15 minutes later.
2. This technique makes use of the dissimilar energy levels of the two radionuclides to shorten the protocol while still allowing acquisition of ECG-gated images (because of the use of ^{99m}Tc).
3. The sensitivity (91%) and specificity (75%) of this combination protocol are comparable to the values for conventional ^{99m}Tc SPECT.

C. The disadvantages of the dual-isotope protocols revolve around comparing images obtained with isotopes with different characteristics. There may be more Compton scatter of thallium-201 than of ^{99m}Tc and thus greater myocardial wall thickness and inability to assess transient ischemic dilatation of the LV.

D. PET protocols. Image acquisition with PET is similar to that with SPECT in that tomographic images are obtained in short-axis, horizontal long-axis (sagittal), and vertical long-axis (coronal) views. A positron camera consists of an array of crystals arranged in a circle. Unlike in SPECT, the camera remains stationary in PET.

1. The heart is localized with the patient's arms extended above the head. An **attenuation CT scan** is performed that allows the density of the surrounding thoracic structures to be subtracted to leave only cardiac count activity. This performance of attenuation correction avoids noncardiac interference, which adds a great deal to the accuracy of PET.
2. After the attenuation scan, the **positron-emitting radiopharmaceutical is injected**, and **images are obtained** 2 to 5 minutes later. As mentioned earlier, two photons are created by the annihilation of the emitted positron colliding with the nearest electron it meets in the tissue surrounding it. These two photons travel *exactly 180° apart* while the patient is lying in the circular scanner. This is an important concept because it means there is **no need for collimation**. The detector/analyzer merely has to "accept" the signal it receives only if a simultaneous signal strikes the detector directly across from it in the scanner. This *dramatically* improves the signal-to-noise ratio that can be achieved during imaging.
3. A second perfusion tracer injection takes place at peak stress. If rubidium-82 is the tracer in use, exercise stress is impossible due to the radiopharmaceutical's short half-life.
4. Metabolic imaging can be done after perfusion imaging with the administration of 5 to 10 mCi of FDG. Tomographic images are typically obtained 30 to 50 minutes after FDG injection.

III. IMAGE INTERPRETATION

A. Standard view of normal anatomy. The uptake of radiotracer is homogeneous in persons with normal myocardial perfusion. The tracer is predominantly distributed to the LV myocardium; the right ventricle (RV) usually appears as a faint, thin structure, given that its wall thickness (5 mm) is usually well below the spatial resolution of most SPECT systems and thus subject to partial volume effects. Understanding and interpreting these images, however, requires an understanding of standard planar and SPECT views of LV

anatomic features. In addition, imaging interpretation requires a synthesis of the characteristics of the radiopharmaceutical in use, the conditions under which injection took place, and the clinical context in which the patient presents.

1. **Planar images** are represented as LAO, anteroposterior (AP), and LLAT views.
2. Standard **SPECT views** include the short axis, vertical long axis, and horizontal long axis. The short-axis view is further divided into apical, mid-ventricular, and basal views.

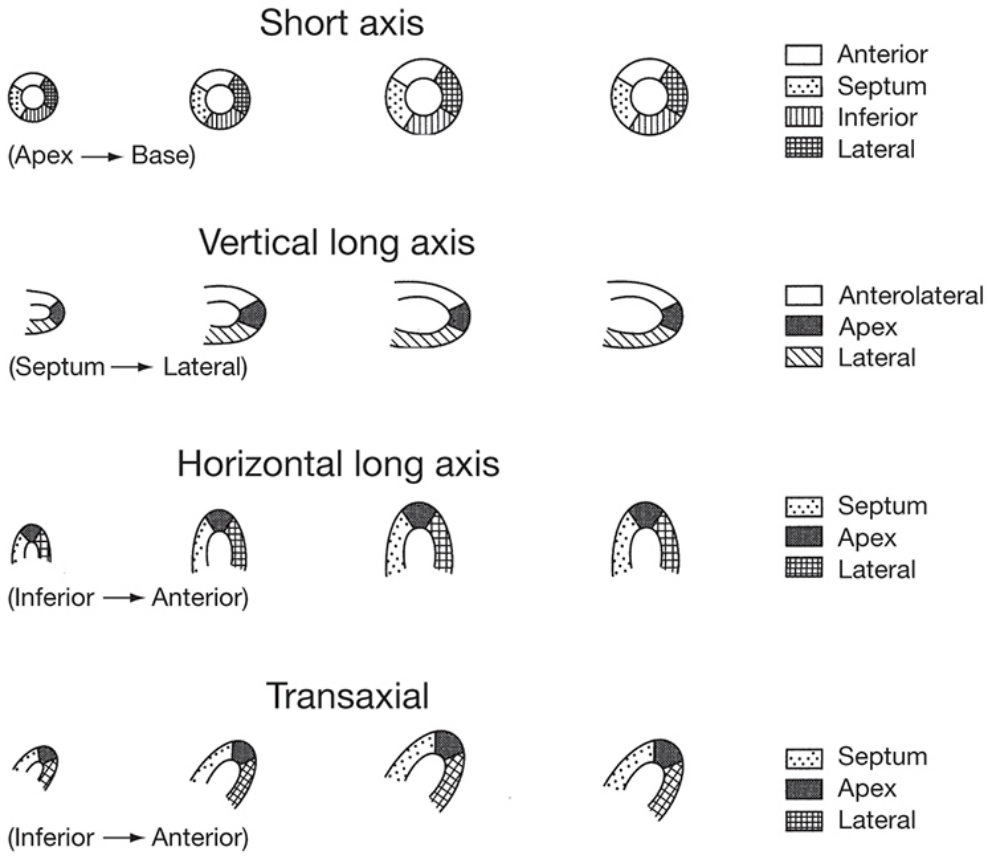

FIGURE 49.2 Standard tomographic projections and myocardial segments.

   a. As with planar views, SPECT images in various projections **correspond with specific myocardial segments** (**Figure 49.2**).
   b. In addition to the standard SPECT sections, short-axis sections can be compiled into a **polar map** (the so-called bull's-eye display). This computer-generated polar map arranges short-axis tomographic images such that the central portion represents apical slices and the periphery consists of the basal segments.

B. Reviewing sequence. Review of nuclear images follows an organized sequence.

1. **Examine unprocessed images** for artifact, extracardiac uptake, and evidence of increased lung uptake.
2. **Examine rest images.** Document defects and their extent and severity.

3. **Examine stress images.** Document defects and their extent and severity.
4. **Evaluate the polar map** in comparison with pooled normal images (derived from a database of patients with low probability of having CAD).
5. **Compare rest and stress images** for enlargement of the LV cavity.
6. **Incorporate the gated SPECT images** to establish overall ventricular function, volumes, and wall function in areas of questionable perfusion defects. Segmental defects that demonstrate normal motion on gated SPECT images may represent artifact.
7. **Examine RV size and function.**
8. In PET cases, examine **myocardial blood flow and coronary flow reserve.**

C. **Characterization of defects.** Given that perfusion images represent regional myocardial blood flow, defects in these images represent an area of myocardium with relatively less uptake and diminished regional blood flow. Defects can be characterized as **fixed (present at rest and with stress) or reversible (present with stress, but not at rest)**. In addition, **artifacts** can occur and usually mimic fixed defects.

1. **Fixed defects.** Fixed (ie, nonreversible) defects are areas of decreased tracer uptake that appear unchanged on both rest and stress images. Fixed defects can **represent scar or viable myocardium**. With thallium-201 imaging, nonreversibility suggests similar rates of clearance from the two regions.
   a. **Differentiating scar from viable myocardium** in the setting of a nonreversible defect can be accomplished through the use of **metabolic radiopharmaceuticals and PET**, or with alternative imaging modalities such as cardiac magnetic resonance. SPECT with ^{99m}Tc is unable to distinguish hibernating myocardium from scar.
   b. Differentiating viable myocardium from scar is paramount because there is clinical and experimental evidence of improved LV function after revascularization of such hibernating regions (see Chapter 50). As methods of revascularization become increasingly applicable in an arena of increasingly complex patient problems, fully defining the so-called fixed defect through metabolic imaging assumes greater importance. Combined imaging protocols with a blood flow agent and a metabolic agent (usually FDG) are used to evaluate viability. In a segment manifesting a fixed perfusion defect, presence of FDG uptake suggests hibernating myocardium, while absent FDG uptake suggests scar. Notably, positive FDG uptake can indicate fibroblast activity in a myocardial segment that was subject to infarction within the previous 12 weeks, which could potentially yield a false interpretation of hibernation.
2. **Reversible defects** are myocardial segments with normal perfusion at rest but decreased relative perfusion on stress images. This pattern is consistent with the presence of **ischemic myocardium** in the region of reversibility.
3. **Artifacts.** Apparent perfusion defects may be artifactual and attributed to soft tissue attenuation, a problem that occurs more often with thallium-201 imaging than when a higher energy agent (^{99m}Tc) is used, though ^{99m}Tc is still subject to these artifacts. Since soft tissue distribution does not change at rest versus with stress, most artifacts present as **fixed defects**.

a. Common causes of the presence of artifacts include **breast attenuation** in women (affecting the anterolateral, septal, anteroseptal, and posterolateral walls of the ventricle) and **diaphragmatic attenuation** in men (predominantly altering the inferior and posterior walls).

b. SPECT artifacts may be more elusive because of processing and reconstruction of tomographic images. **Attenuation correction**, which is built into commercially available software packages, leverages the power of combined SPECT and CT imaging. Using the depth of soft tissue between the myocardium and the gamma camera as visualized on a low-dose CT acquisition, the software can apply a compensation factor to boost counts in myocardial territories that are most subject to soft tissue attenuation. Because of the need for combined imaging, attenuation correction is not used universally in the United States, but when available, it can serve as a valuable tool to avoid artifact misinterpretation.

c. If attenuation correction is unavailable, artifacts can also be assessed using gated imaging. Most attenuation artifacts result in fixed defects. A true fixed perfusion defect should represent scar or hibernating myocardium, which should not be contractile and, therefore, should not brighten on gated imaging. A fixed defect that does exhibit brightening on gated imaging should raise suspicion for an attenuation artifact.

4. **Risk assessment.** Identifying the **extent and severity** of perfusion defects is paramount to quantifying risk. Extent refers to the number of segments affected using the 17-segment model. Severity refers to the degree of decreased radiotracer uptake in each segment. Severity is typically graded on a 0 to 4 scale, with 0 being normal radiotracer uptake and 4 being absent radiotracer uptake. A **summed score** is calculated by adding all scores for the given study. A summed score is calculated at rest and at stress, and the difference between these scores is termed the summed difference score.

a. Specific patterns of perfusion imaging that suggest high-risk coronary anatomic features include perfusion **defects in more than one vascular distribution and transient ischemic LV dilatation (ie, transient ischemic dilation)**. The extent and severity of defects also predict risk. More is discussed regarding risk assessment in subsequent sections.

D. **Quantitative analysis.** The principles of image analysis rely on visual inspection, which is fraught with observer variability.

1. **Computer-aided analysis** of planar data involves comparison of regional radionuclide activity on stress and rest images; count discordance coincides with reversibility. **SPECT** data are quantitatively analyzed by means of comparing count densities on short-axis images (displayed as a polar map) with normal age- and sex-adjusted count profiles. Although they improve sensitivity, these methods are **used in concert with visual analysis**.

2. **PET imaging**, although evaluated in large part in a visual manner, also possesses great clinical utility with the application of **quantitative analysis of myocardial perfusion, myocardial blood flow, and coronary flow reserve.** Moreover, significant advances have been made in the ability to quantify ***absolute***—and not just relative—blood flow in different coronary vascular territories using PET imaging. On the basis of analysis of

baseline blood flow and flow during vasodilator stress, this technique is useful in revealing functionally important coronary lesions even in the presence of multivessel coronary disease or ischemia with no obstructive coronary artery disease/myocardial infarction with no obstructive coronary artery disease (INOCA/MINOCA).

a. The administration of adenosine, dipyridamole, or regadenoson should induce at least a 2- to 3-fold increase in coronary blood flow over baseline in a normal coronary vascular bed. This "flow reserve" is not present in the setting of functionally significant epicardial coronary artery stenosis supplying this myocardial bed (as discussed earlier in the chapter). Thus, relative differences in myocardial perfusion during hyperemia (which may not be appreciated on visual inspection) may be more precisely demonstrated with quantitative analysis of flow reserve.

b. Furthermore, the ability to quantitate absolute myocardial blood flow regionally and globally may help surmount the difficulty in noninvasively diagnosing CAD in the setting of "balanced ischemia" from severe left main or triple-vessel CAD. In addition, abnormally low coronary flow reserve may represent **microvascular dysfunction** in cases where significant macrovascular CAD has been ruled out.

IX. CLINICAL APPLICATIONS

A. Coronary artery disease

1. Detection of CAD. The ability to detect CAD in a noninvasive manner offers numerous additional applications in risk stratification, prognosis, and imaging of acute infarction.

Sensitivity and specificity. Since the introduction of thallium-201 imaging in 1975, the utility of perfusion agents in the diagnosis of CAD has been well established. Quantitative planar imaging and SPECT demonstrate 90% or greater sensitivity.

a. Sensitivity is affected by the number of vessels involved. Single-vessel disease is most likely to produce a false-negative finding. Multivessel CAD rarely produces a normal perfusion scan result. The **specificity** of planar imaging is 83% and that of SPECT is ~70%.

b. In general, radionuclide imaging is best used to evaluate a population at intermediate risk for CAD. The choice of radionuclide agent seemingly has little effect on the accuracy of these techniques.

c. The introduction of **PET**, however, has brought with it **advanced diagnostic accuracy**, with approximately 10% to 15% improvement over SPECT.

(1) Causes of **false-positive** perfusion study results include attenuation defect, technical inadequacies, coronary vasospasm, anomalous coronary circulation, cardiomyopathy, conduction defects such as left bundle branch block, and recanalization of a thrombosed coronary artery.

(2) Causes of **false-negative** perfusion study results include a submaximal exercise stress test, anti-ischemic medical therapy, collateral or overlap circulation, inaccurate interpretation of perfusion images or angiograms, acquisition of suboptimal images, presence of balanced coronary stenosis, and delay in stress imaging.

d. **Risk stratification.** In addition to indicators of higher risk taken from perfusion images, such as increased lung uptake, drop in LVEF poststress, or transient ischemic dilation, determinants in the assessment of risk are as follows:

   a. **Presence of reversible as opposed to fixed defects** is associated with greater likelihood of cardiac events related to acute coronary syndrome at follow-up evaluation. This relation has clinical utility in a number of settings, including risk stratification after MI or in the preoperative setting. In one study involving patients who had had MI without complications, patients with single, fixed defects on thallium-201 images had a 6% cardiac event rate, compared with a rate of 51% for those with thallium-201 scans that indicated high risk of such an event.

   b. Radionuclide **imaging abnormalities** have been identified as **independent predictors of subsequent infarction or death**. In general, the extent and severity of abnormal segments identified on nuclear images can be seen as inversely proportional to the survival rate. Normal findings on a nuclear perfusion study, however, suggest an excellent prognosis, with a yearly mortality rate <1% (in patients with a normal ejection fraction). The application of such prognostic information to the care of patients preparing for noncardiac operations reflects significantly on the patient's surgical risk and has an established role in preoperative evaluation and clearance. For this population, evidence of ischemia on perfusion images portends a higher risk of a perioperative cardiac event.

e. MPI may aid in the diagnosis and risk stratification of patients with **acute coronary syndromes**.

   a. Patients with **chest pain of ill-defined origin** can be given an injection at rest of thallium-201 or ^{99m}Tc. In the presence of true ischemia, a rest defect may be documented, and insight into regional distribution of ischemia and extent of myocardium involved is gained. The **absence of any perfusion defect with ongoing chest pain makes a diagnosis of angina less likely**.

      In the setting of **thrombolysis**, imaging with ^{99m}Tc can provide important information about reperfusion or lack thereof. Injection of ^{99m}Tc before initiation of thrombolysis captures a picture of hypoperfusion, which can, because of the extensive half-life, be imaged at a later time. Subsequent injections reveal the status of perfusion as the period after thrombolysis proceeds (ie, persistent, large defect that represents failed reperfusion). Such applications in the setting of thrombolysis and in acute coronary syndromes have limited clinical utility because of the logistics of staffing and availability of radiopharmaceuticals.

f. **Assessment of ventricular function.** In addition to its use in perfusion analysis in CAD, radionuclide imaging can establish cardiac performance. Radionuclide-based assessment of ventricular function includes first-pass radionuclide angiocardiography and gated blood pool imaging.

   1. **First-pass radionuclide angiocardiography** involves injection of a radionuclide and analysis as the agent passes through the central circulation.

      a. ^{99m}Tc-labeled agents are typically administered in bolus form, and scintigraphic data are recorded for 15 to 30 seconds after injection.

Multicrystal cameras oriented in a straight anterior projection are used for the detection of count rates.

b. This method of ventricular function analysis is more useful in evaluating **RV function** than is gated blood imaging. In patients with **severe LV dysfunction**, transit time through the heart may be slowed; thus, proximal venous access and rapid administration may be necessary.

2. **MUGA scans** are an example of gated blood pool imaging or radionuclide angiography. This relies on ECG gating to correlate multiple individual images of the cardiac blood pool to specific phases of the cardiac cycle.

   a. For the in vivo method, the patient is administered intravenous stannous chloride. Then, a 2- to 3-mL sample of the patient's blood is retrieved and bounded with ^{99m}Tc pertechnetate. This sample is then reinjected into the patient intravenously. The stannous ions reduce the technetium, so they will not leak out of the tagged cells. The in vitro method binds the patient's blood with the stannous ion and technetium prior to reinjection into the patient.

   b. A single-crystal gamma camera is used in the LAO, AP, LLAT, and, sometimes, left posterior oblique projections to obtain serial static images of the cardiac blood pool gated to the R-R interval.

   c. Because multiple cardiac cycles are averaged to obtain the final images, this technique is not optimal for evaluating regional wall motion. For many years, though, MUGA was considered a "gold standard" technique for the assessment of overall LVEF. Radionuclide angiography remains a well-validated and highly reproducible method of assessment of overall LVEF (and importantly, retains this quality especially well at low ejection fractions). The use of this technique is diminishing in the current era of echocardiography and cardiac MRI. However, MUGA is still in use in oncologic clinical trials to accurately and cost-effectively assess changes in LVEF during potentially cardiotoxic antineoplastic treatments.

3. **ECG-gated perfusion imaging.** Perfusion imaging with ^{99m}Tc-labeled tracers during standard nuclear stress testing produces gated images where LV volumes and LVEF may be calculated. The standard injection of 20 to 30 mCi of ^{99m}Tc allows evaluation of **perfusion and function in a single study**.

   a. The *greatest* utility of ECG-gated perfusion imaging may be in elucidating perceived artifacts on perfusion images. For example, if a region has a perceived fixed perfusion defect, yet wall motion is normal in the same region, artifact becomes a more likely consideration as the cause of the filling defect. However, wall motion abnormalities are typically not seen in ischemic segments after exercise nuclear testing because of the delay between peak stress and image acquisition.

   b. Comparison of this method with 2D echocardiography in the evaluation of regional wall motion has shown good correlation between the two.

g. **Cardiac amyloidosis.** Nuclear scintigraphy with ^{99m}Tc-PYP is used in the diagnosis of cardiac amyloidosis. Historically, this agent was used in cardiac disease after MI to assess infarct size but has been repurposed for use in cardiac amyloidosis.

Technetium PYP is a bone tracer that binds to the calcium in amyloid deposits, particularly in transthyretin amyloidosis; uptake is usually absent in light-chain amyloid heart disease. Thus, this test is commonly used to **diagnose ATTR amyloidosis and differentiate it from light-chain disease**. Uptake is graded based upon visual assessment as well as comparing uptake in the heart versus the contralateral lung on planar images.

h. Myocardial innervation imaging. Radiotracer analogs of sympathetic nervous system factors have been used to assess myocardial innervation and predict risk in certain conditions. **Iodine-123 meta-iodobenzylguanidine (MIBG)** is a radiotracer that acts as a false neurotransmitter analog of norepinephrine and is the most frequently used radiotracer for this indication. It is utilized in both adrenal and cardiac imaging, and images are acquired using standard techniques with planar followed by SPECT images.

1. **Heart failure.** In clinical trials, decreasing MIBG uptake was found to be associated with worsening disease status and mortality. The most striking finding was the greater than 99% negative predictive value; patients with normal uptake had very few cardiac events. This tracer may be able to identify a subset of patients who do not meet implantable cardioverter defibrillator (ICD) criteria and who are at high risk for cardiac events. In addition, MIBG uptake was shown to improve after heart failure medical therapy.

i. Clinical applications of PET

1. **Diagnosis of CAD.** Flow imaging with PET is highly sensitive and highly specific for the detection of coronary stenosis, approaching 93% for both.
   a. Higher energy photons (511 keV), higher count densities, shorter half-life, and "built-in" attenuation correction place PET substantially ahead of SPECT in the accurate detection of CAD.
   b. As mentioned before, the ability to quantitate absolute blood flow regionally and globally may help improve the diagnosis of coronary ischemia in the setting of severe multivessel disease and balanced ischemia.
   c. In cardiac transplant recipients, PET with coronary flow reserve is an emerging strategy for evaluation of **cardiac allograft vasculopathy**. At our center, a normal PET can obviate the need for invasive angiographic surveillance in these patients.
2. **Assessment of myocardial viability** (see Chapter 50). The use of **PET with metabolic radiotracers is the standard for identifying viable myocardium**. The presence of a flow-metabolism mismatch, which indicates underperfusion in the presence of metabolically active myocytes, suggests hibernating myocardium. Revascularization of these zones as identified with PET has been shown to result in improvement in wall motion and LVEF. This utility of nuclear imaging has found increasing application in the selection of patients for revascularization who have ischemic cardiomyopathy and heart failure with low ejection fraction, especially in cases with chronic total coronary occlusions.
3. **Cardiac sarcoidosis.** FDG-PET imaging is useful in the detection and prognosis of patients suspected of having cardiac sarcoidosis. Normal myocardium utilizes

glucose and fatty acids for metabolism. Under fasting conditions, myocardial cells shift to utilizing predominantly fatty acids. Inflammatory cells in cardiac sarcoidosis utilize glucose because of high metabolic demands, even during fasting.

a. Sarcoidosis nuclear protocols vary among institutions but attempt to **minimize physiologic glucose uptake** in normal myocardial tissue. Patients are advised to prepare for the examination with a prolonged fast (12-18 hours) and high-protein, low-carbohydrate diet the day before the examination. Rubidium-82 is injected at rest to evaluate for perfusion defects. FDG is injected and a prolonged delay is utilized (usually 60 minutes) prior to image acquisition. However, due to the abovementioned tendency for ischemic myocardium to switch to predominantly glucose metabolism, CAD should be ruled out as part of the clinical evaluation of cardiac sarcoidosis.

b. FDG-PET demonstrating areas of decreased perfusion with increased FDG in the absence of obstructive CAD is suggestive of active cardiac sarcoidosis. In these instances, it is essential to rule out obstructive CAD before referring patients for FDG-PET, given the nonspecificity of FDG uptake and the challenges in myocardial glucose suppression. The ASNC has published specific practice points on how to perform PET-FDG studies with guidance on how to prepare patients for the test as well as on how to interpret the test results.

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SUGGESTED READINGS

LANDMARK ARTICLES

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CHAPTER 50

Stress Echocardiography

Bryan Q. Abadie and Zoran B. Popovic'

I. INTRODUCTION. Stress echocardiography (SE) is an **effective method of evaluating for myocardial ischemia**, based on the detection of **stress-induced regional wall motion abnormalities** (WMAs). Stressors include exercise, pharmacologic agents, and pacing. SE is used to **screen for coronary artery disease** (CAD), and it can help **identify the coronary vessels involved**. The accuracy of SE in the detection of significant coronary artery stenosis is 80% to 90%, which is superior to that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging. In patients with left ventricular (LV) dysfunction and documented CAD, SE can **differentiate viable myocardium from scarred myocardium**, which may help predict whether LV function will improve after revascularization. As a diagnostic test for CAD, **SE is safe and relatively inexpensive** and **can be rapidly performed**. However, interpretation of SE images remains primarily subjective and requires a considerable learning curve. SE can also be used to **assess the severity of valvular disease, hypertrophic cardiomyopathy, and exercise-induced pulmonary hypertension**. In addition, it provides important prognostic information after myocardial infarction (MI) and prior to noncardiac surgery.

II. PATHOPHYSIOLOGY

A. Exercise stress testing. Exercise stress testing is used to either diagnose myocardial ischemia or unmask hemodynamic abnormalities. Myocardial ischemia results from a mismatch between oxygen supply and demand. The ischemic cascade is illustrated in **Figure 50.1**. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than is detected by the

electrocardiogram (ECG) or the onset of symptoms. Exercise-induced non–ischemia-related hemodynamic abnormalities are various and include pulmonary hypertension, dynamic LV tract obstruction, and stenotic valve disease. Exercise can be performed with a treadmill or a bicycle.

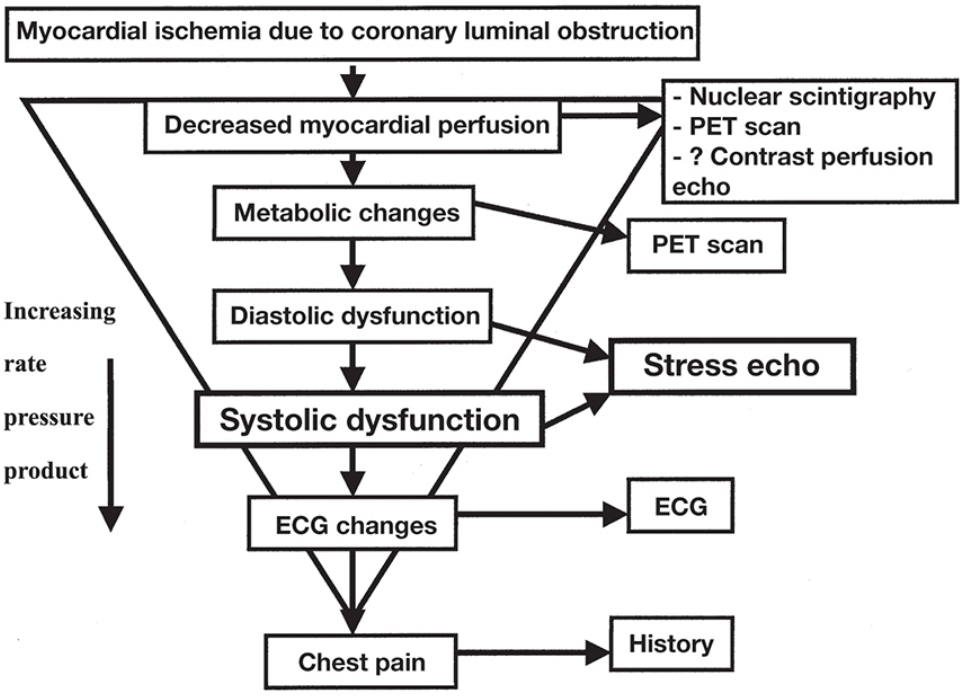

FIGURE 50.1 Ischemic cascade. ECG, electrocardiogram; PET, positron emission tomography.

B. Pharmacologic stress testing. In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.

1. **Sympathomimetic agents.** Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an **increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload)**. Although a number of agents have been evaluated in combination with echocardiography, **dobutamine** is the most widely used. Low-dose dobutamine has

positive inotropic effects mediated through cardiac alpha1 and beta1 receptors. At higher doses, it has positive chronotropic effects mediated through beta2 receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic wall motion, with only minimal effect on end-diastolic LV volume. It can be **combined with atropine** to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR = 220 minus patient's age).

2. A **vasodilator stress test** is performed with **dipyridamole** or **adenosine** infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (ie, coronary steal) and into more normal coronary vessels. This may lead to WMA in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE.
3. **The American Society of Echocardiography (ASE) guidelines recommend dobutamine as the first-line agent for pharmacologic SE.** In addition, much of the data for preoperative risk stratification and viability assessment using SE were derived from pharmacologic studies using dobutamine.

C. Atrial pacing. Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients who cannot exercise and in whom pharmacologic agents are contraindicated.

III. INDICATIONS AND CHOICE OF STRESSOR

A. The **indications and contraindications** for SE testing are similar to those used for exercise electrocardiographic stress testing. The addition of an imaging modality improves the sensitivity and specificity of exercise electrocardiographic stress testing. **Table 50.1** lists factors that may limit the sensitivity of electrocardiographic stress testing to detect CAD; patients with these factors would benefit from a stress test utilizing an imaging modality (ie, echocardiography, nuclear scintigraphy, or positron emission tomography [PET]).

TABLE 50.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary Artery Disease
Left bundle branch block or other intraventricular conduction delay abnormalities
Paced rhythms
Abnormal ST segments at baseline
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

B. **Additional contraindications** to SE occur **with pharmacologic stress** and depend on the underlying pharmacologic stressor. Patients with severe bronchospastic obstructive lung disease or high-grade atrioventricular (AV) block should avoid dipyridamole and adenosine. Patients with unstable ventricular arrhythmias should avoid dobutamine infusion. **Relative contraindications to SE** include unstable angina, severe baseline hypertension, uncontrolled arrhythmias, mobile LV thrombus, critical symptomatic aortic stenosis (AS), and decompensated heart failure.

C. Exercise stress is preferred to nonexercise stress because it more closely reproduces daily activity and is more sensitive in the detection of ischemia, provided the patient is able to achieve an adequate level of stress. No single **exercise modality** has been shown to have superior sensitivity, although the **treadmill** is more widely accepted among patients and physicians. **Bicycle ergometry** can be performed in the upright and supine positions. Images with treadmill stress testing must be obtained after exercise, whereas images may be obtained at peak exercise with bicycle ergometry while the patient continues to exercise. The sensitivity of treadmill testing to detect ischemia is reduced if images are not rapidly obtained (within 90 seconds) after exercise. However, the treadmill usually results in a

greater level of stress than is associated with bicycle ergometry, which is more dependent on patient effort.

D. Up to **30% of patients referred for exercise echocardiography may not be able to achieve an adequate level of exercise stress** because of peripheral vascular disease, chronic obstructive pulmonary disease, or musculoskeletal problems. **Pharmacologic stress testing is usually indicated** in these patients.

IV. METHODOLOGY

A. Patient preparation

1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly beta-blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of dobutamine SE results. With exercise stress testing, these agents should be withheld before the test only if the aim is to detect ischemia. In contrast, if the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia or assess the treatment response and functional capacity in diseases such as hypertrophic cardiomyopathy, mitral regurgitation (MR), or mitral stenosis, stopping these agents renders the stress test futile.
3. The **standard connections for a 12-lead ECG** may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results.

B. **Equipment.** All SE studies are conducted with **exercise electrocardiographic testing and standard hemodynamic monitoring equipment**. An SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of prestress images with peak stress or post–peak stress images. Resuscitation equipment and a defibrillator should be readily available.

C. Performing the test

1. **Exercise SE.** Regardless of the exercise modality, a complete **baseline** echocardiographic scan is obtained for all patients. Resting images are obtained in the parasternal long- and short-axis (papillary muscle and apical views) and apical two-, three-, and four-chamber views. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.
    a. **Treadmill exercise** is performed with standard protocols according to the functional status of the patient. While at least 85% of the APMHR needs to be reached in order to exclude ischemia, exercise is continued to the level of maximum exertion, development of symptoms, or detection of objective signs of cardiac dysfunction (eg, BP or a heart rate drop, appearance of arrhythmias) to maximize test sensitivity. **Post–peak stress images** are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images are obtained in the same views as the baseline study. All critical post–peak stress images should be **obtained within 90 seconds of completing exercise** to maximize test sensitivity.
    b. During **upright bicycle echocardiography**, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches their level of perceived maximal effort. During upright bicycle echocardiography, **images are obtained at rest, before peak, at peak, and after peak exercise**.
    c. With **supine bicycle exercise**, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are obtained **at rest, before peak, at peak, and after exercise**. This exercise modality is not widely used.

d. **Study end points** for exercise SE include **target heart rate** (85% APMHR), **severe electrocardiographic ischemia** (ST-segment depression >5 mm), **intolerable symptoms** (chest pain and dyspnea), **severe hypertension** (systolic BP >220 mm Hg or diastolic BP >110 mm Hg), **hypotension** (systolic BP <90 mm Hg or a fall in systolic BP >20 mm Hg from baseline), **ventricular tachycardia** or **sustained supraventricular tachycardia,** and the **development of new WMAs in at least two contiguous segments**.

2. Pharmacologic SE

a. Dobutamine SE

(1) Dobutamine infusion is started at 10 mcg/kg/min and increased every 3 minutes to 20, 30, and 40 mcg/kg/min, if the objective of the test is ischemia detection. If the patient has not reached 85% of APMHR by the end of the 40 mcg/kg/min dose, a 3-minute dosage of 50 mcg/kg/min may be used. Infusion is begun at lower doses (5 mcg/kg/min) if baseline LV function is abnormal and myocardial viability is being sought or if assessment of valvular lesions is being pursued. Images are obtained at rest and at low dosage (10 mcg/kg/min), pre–peak dosage (30 mcg/kg/min), and peak dosage. Lower initial (5 mcg/kg/min) and final dose (20 mcg/kg/min) are used if the objective is detection of viability and/or AS severity.

(2) Atropine can be used as needed to reach the target heart rate >85% of APMHR if dobutamine alone is not effective. Atropine (0.25-0.5 mg) is given intravenously every minute, starting at the 40 mcg/kg/min dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients who have glaucoma or benign prostatic hypertrophy. Isometric handgrip may also be performed at the peak infusion rate to help achieve the target heart rate.

(3) Study end points for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved

without any other end points, it is preferable to complete the protocol to the end of the 40 mcg/kg/min infusion to increase the sensitivity of the test.

(4) **Side effects.** The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (eg, arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of >5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.

(5) **If angina or severe side effects develop**, the effects of dobutamine may be **reversed with intravenous beta-blockade** (0.5-1 mg/kg esmolol given over 1 minute or 2-5 mg/kg metoprolol given every 2-5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be the preferred agent.

b. Dipyridamole or adenosine SE

(1) Patients with hypotension, AV block, or a history of severe bronchospasm **should not undergo** testing with these agents.

(2) Different protocols of **dipyridamole infusion** have been studied. The protocol recommended by the ASE is a low-dose, two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. **A high-dose** regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.

(3) **Adenosine** is given as a continuous infusion because of its very short half-life and is typically infused at a maximum dose of 140 mcg/kg/min over 6 minutes.

(4) **Regadenoson** is an adenosine receptor agonist with a 2- to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.

(5) **Study end points** for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (eg, bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.

(6) **If hypotension, bradycardia, or bronchospasm occurs**, the effects of dipyridamole, adenosine, and regadenoson can be **reversed with intravenous aminophylline** 50 mg over 60 seconds.

D. Imaging techniques. Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame-by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor-quality images. **Harmonic imaging** has improved endocardial definition, which can be further optimized with **microbubble contrast agents**.

1. Contrast echocardiography. Microbubble contrast agents provide **improved echocardiographic resolution** and allow **real-time assessment of intracardiac blood flow**. These agents are helpful when baseline SE images are suboptimal.

a. Intravenous agitated saline improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. Intravenous agitated saline is not able to cross the pulmonary circulation.

b. **Second-generation microbubble contrast agents**, such as **Optison** and **Definity**, incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable and are able to cross the pulmonary circulation and thus opacify the LV.

c. **These agents are well tolerated and have a low complication rate**. **Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts.** Intra-arterial injection is contraindicated. Administration is relatively contraindicated in patients who are pregnant or nursing, although data are limited in these populations, and guidelines indicate that contrast should be given if needed.

2. **Real-time three-dimensional (3D) echocardiography.** Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. 3D imaging may shorten the acquisition period of postexercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. Limitations include lower spatial resolution and lower frame rates; at this time, 3D SE is not routine in clinical use and remains under investigation.

V. IMAGE INTERPRETATION

A. Qualitative versus quantitative approach

1. **Interpretation of SE findings is predominantly qualitative.** Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is **subject to interobserver and interinstitutional variability**. Suggestions to optimize interpretation of SE images are outlined in **Table 50.2**. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress-induced

myocardial ischemia. SE responses and interpretation are summarized in **Table 50.3**.

TABLE 50.2 Suggestions to Optimize Interpretation of Stress Echocardiographic Images

1. Ensure that prestress and poststress images are comparable views.
2. Ensure that the apex is not foreshortened, especially in two-chamber views.
3. True two-chamber views should not show any of the right ventricle.
4. Use ultrasound microbubble contrast agents when resting images are suboptimal.
5. Check that digital images are timed to begin at systole. If digital clips include diastole, there is an increased likelihood of calling a false-positive wall motion abnormality.
6. Check the heart rate for each poststress image. If images are obtained after the heart rate has returned toward normal, the sensitivity of the test will be reduced.
7. Compare the wall motion of individual segments from rest to stress in the four-screen display to define ischemia and infarction. Then compare segments in the poststress images to identify differences in contraction and in the development of "hinge points."
8. Confirm any wall motion abnormality in a second view if possible.
9. Avoid overcalling ischemia in the basal inferior or basal septal segments.
10. Avoid calling a new wall motion abnormality if it is limited to only one myocardial segment; the abnormality should involve at least two contiguous segments.

TABLE 50.3 Stress Echocardiographic Responses and Interpretation

Resting or Baseline Function	Response to Low-Dose Pharmacologic Stress	Peak Stress and Poststress Function	Interpretation
Normal	Normal	Hyperdynamic	Normal myocardium
Normal	Normal or new WMA	New WMA or lack of hyperdynamic	Ischemic myocardium

Resting or Baseline Function	Response to Low-Dose Pharmacologic Stress	Peak Stress and Poststress Function	Interpretation
		response; LV dilation or decreased EF (with exercise only)	
WMA	No change	No change	Infarcted myocardium
WMA	Improved	Decreased (biphasic response)	Viable (hibernating) myocardium
WMA	No change	Improved	Nonspecific

EF, ejection fraction; LV, left ventricular; WMA, wall motion abnormality.

2. **Quantitative methods** of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, **the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use**. Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.
   a. **Tissue Doppler assessment** along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments. However, tissue Doppler currently lacks segment-specific normal values, limiting its widespread applicability.
   b. **Speckle-tracking echocardiography** (STE) is a recent quantitative technique used to assess strain and strain rate. Speckle patterns unique to a region of the myocardium are tracked throughout the cardiac cycle, quantifying systolic shortening and diastolic lengthening. While LV strain can

measure deformation along LV long, short, and radial axes, long-axis (longitudinal) strain is almost exclusively used in clinical practice. Longitudinal strain is expressed as percent change in length, with more negative values representing normal strain. Strain rate measures the change in strain over time and is expressed as positive (for diastolic component) or negative (for systolic component) values. In a normal heart, both strain and strain rate should improve with stress. Studies of STE using pharmacologic stress agents have found decreases in global longitudinal strain in the setting of ischemia. However, like tissue Doppler, optimal cutoffs remain uncertain. STE has not yet shown an incremental increase in accuracy compared to qualitative assessment.

B. 17-Segment model. Regional wall motion is assessed using a 17-segment model (**Figure 50.2**), with results geographically represented on a circumferential polar plot (**Figure 50.3**).

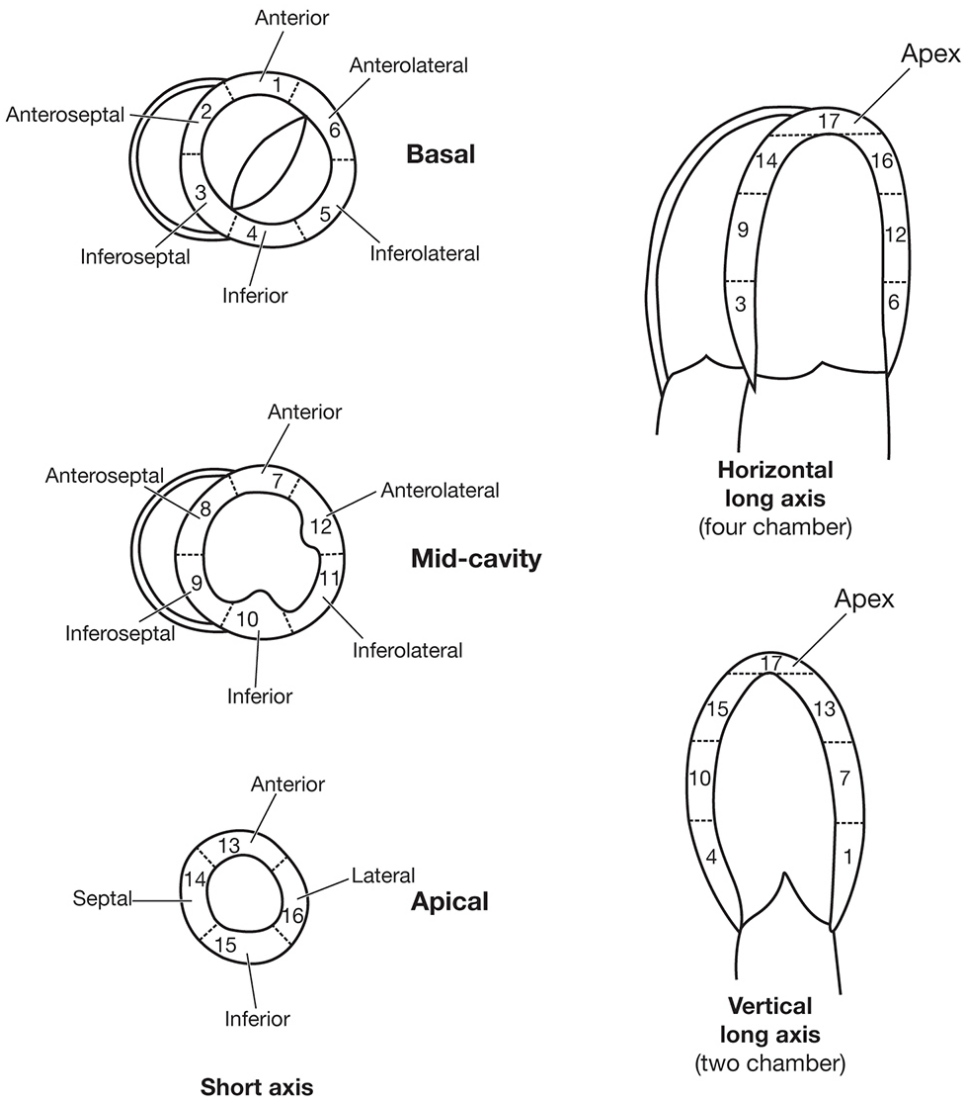

FIGURE 50.2 Diagram of vertical long-axis, horizontal long-axis, and short-axis planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the 17-segment system. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539-542.)

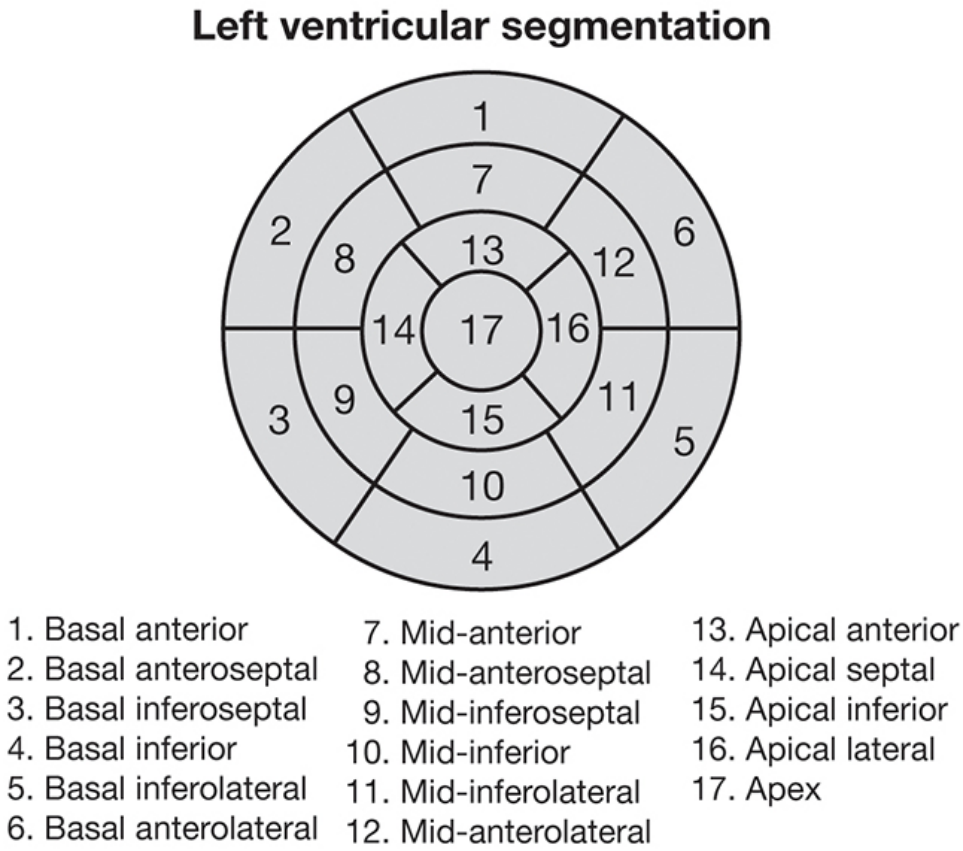

FIGURE 50.3 Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539-542.)

1. The individual **myocardial segments can be assigned to coronary artery territories**, as illustrated in **Figure 50.4**. Of note, this approach is not always correct because of the anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex, and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent.

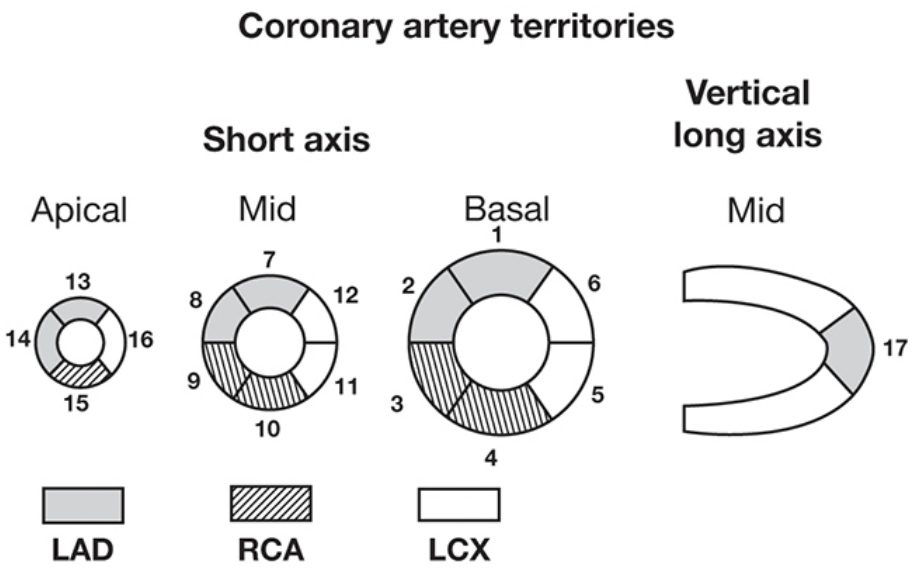

FIGURE 50.4 Assignment of the 17 myocardial segments to coronary artery territories. LAD, left anterior descending; LCX, left circumflex coronary artery; RCA, right coronary artery. (Reprinted with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105(4):539-542.)

2. Wall motion is **subjectively graded** as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, or dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

C. Exercise SE

1. A **normal response** to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, a decrease in LV size, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. **Resting WMAs** usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction,

whereas hypokinetic segments may be partially infarcted and/or viable.

3. An **abnormal response to exercise is defined by the development of worsening of regional myocardial function**. Regional myocardial dysfunction, as **manifested by decreased endocardial excursion and wall thickening**, is **specific for myocardial ischemia**. Decreased excursion with preserved thickening is less specific and can occur with conduction abnormalities, with paced rhythms, and in the normal basal inferior myocardial segments.
4. **Adjunctive diagnostic criteria** for a positive SE examination include **LV cavity dilation, a decrease in global systolic function, worsening diastolic function, and new or worsening MR**. However, these adjunctive diagnostic criteria are **more specific for detecting severe CAD and may not be sensitive** for detecting the presence of mild or moderate CAD.
5. **False-positive findings** may occur with left bundle branch block (septal WMA) and right ventricular (RV) pacing (apical WMA). A pathologic hypertensive response to exercise may also cause LV dilation and systolic dysfunction as can afterload mismatch in the setting of severe valvular lesions such as AS, MR, or aortic regurgitation (AR).
6. **False-negative findings** may occur with a delay in capturing postexercise images, low workload, or inadequate heart rate response (ie, with inadequate stress or the presence of beta-blockers). Additional causes of false-positive and false-negative findings are outlined in **Table 50.4**.

TABLE 50.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of Incorrect Stress Echocardiographic Interpretation	Factors Reducing Specificity or Sensitivity
False-Positive Results	
LBBB, prior cardiac surgery (eg, myectomy)	Reduced or abnormal septal excursion with normal septal thickness

Causes of Incorrect Stress Echocardiographic Interpretation	Factors Reducing Specificity or Sensitivity
Right ventricular pacing	Apical WMA
Nonischemic cardiomyopathy	Regional WMAs (exact cause unknown)
Hypertensive response to exercise (SBP >220 mm Hg, DBP >110 mm Hg)	Nonischemic WMAs and/or LV dilation
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; it is important to be blinded.
Basal inferior or septal WMA	Areas most likely to be overcalled because of reduced excursion because of annular tethering effects
Poor image quality	
False-Negative Results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with beta-blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Left circumflex disease	Lateral wall dropout; more likely to miss ischemia
Delay in capturing images after maximal stress	
Poor image quality	

DBP, diastolic blood pressure; LBBB, left bundle branch block; LV, left ventricular; SBP, systolic blood pressure; WMA, wall motion abnormality.

D. Pharmacologic SE. With a few exceptions, the principles of interpretation of pharmacologic and exercise SE are similar.

1. The **typical ischemic response to dobutamine** is characterized by normal resting wall motion and an initial **hyperdynamic response at low doses followed by a decline in function at higher doses**.

Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.

2. **LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE**. The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs because of severe CAD.
3. Interpretation of results obtained from **dipyridamole or adenosine SE** requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress.

E. Reproducibility. The reader must be well trained in order to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be <80%, particularly with technically difficult studies and studies of patients with mild CAD.

F. Limitations. The ability to interpret stress echocardiograms is mitigated by image quality, the presence of arrhythmias, conduction abnormalities, respiratory interference from hyperventilation, and difficulty in reproducing the translational and rotational motion of the heart.

VI. DIAGNOSTIC ACCURACY. The **diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques**. Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, **sensitivity ranges from 75% to 92%, depending on lesion severity**, and **specificity ranges from 64% to 100%**. As with other

imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease.

A. Exercise SE

1. Comparison with exercise electrocardiographic testing.

Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, **SE has greater diagnostic sensitivity and specificity**, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade (see **Figure 50.1**). Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD (see **Table 50.1**), and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.

2. Comparison with myocardial perfusion scintigraphy

a. Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (>50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should, theoretically, have a higher sensitivity than SE for CAD.

b. Studies using **single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of >90%, slightly higher than that for SE.** However, the **specificity of SE is superior to that of SPECT**, especially in patients with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses.

c. SE is **convenient** and **provides information on cardiac structure and function**, and **the results can be interpreted immediately**, with rapid feedback to the patient and referring physician. SE also **avoids exposure to radioactive tracers** and is substantially **less expensive than SPECT**.

d. SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients who have poor acoustic windows, for example, those with chronic obstructive pulmonary disease. **Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use**.

B. Pharmacologic SE

1. **Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%**, similar to the values for exercise SE. **Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%**. In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.
2. **Myocardial perfusion scintigraphy.** Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT.

III. ASSESSMENT OF VIABILITY

A. Myocardial stunning after MI is common, and it is characterized by viable, nonischemic, and noncontracting myocardium. Patients with **chronic ischemia** may experience **myocardial hibernation**. Hibernating myocardium is characterized by viable, chronically ischemic, and noncontracting myocardium. Dobutamine SE can be used to detect **viable myocardium**, whether stunned or hibernating.

B. Dobutamine infusion may result in augmentation of regional myocardial contractility. Observational studies have suggested that revascularization of hyperperfused, but viable, myocardium can improve recovery of function and survival. A contractile response to dobutamine requires that at least 50% of the myocytes in a given segment are viable.

C. Demonstration of a **biphasic response** to low-dose (5-10 mcg/kg/min) dobutamine strongly suggests viable myocardium. A biphasic response is present when a **resting WMA improves in response to low-dose dobutamine and decreases in function at peak stress or poststress**. The initial improvement reflects recruitment of contractile reserve and hence viability. Higher doses lead to subendocardial ischemia and worsened WMA. A uniphasic response is less predictive of recovery, and a classic ischemic response is not predictive of the recovery of resting function. Because the biphasic response is the most reliable finding, the preference is to induce ischemia whenever possible by proceeding to maximal stress (40 mcg/kg/min).

D. **Myocardial wall thickness** is also an important marker of myocardial viability. When the wall thickness is <**6 mm**, there is **a low likelihood of recovery of function**.

E. **The negative predictive value of dobutamine SE for determining viability is lower than that of thallium stress redistribution reinjection SPECT and fluorodeoxyglucose-PET scanning**. However, **the positive predictive value is greater**. Concurrent use of beta-blockers can reduce the number of viable segments detected and the sensitivity of testing.

F. **Assessment of myocardial perfusion with echocardiography.** Second-generation microbubble contrast agents are small in diameter and reliably traverse the myocardial microvasculature. The microbubbles are destroyed with ultrasound energy, and the rate of microbubble replenishment represents mean red blood cell velocity and myocardial perfusion. Although subject to extensive research, this technology has had limited utilization in clinical practice and is not used routinely in most echocardiography laboratories.

III. PROGNOSTIC ROLE OF STRESS ECHOCARDIOGRAPHY

A. Suspected or known chronic CAD. The **major determinants of prognosis** in patients with chronic CAD are **LV function and the anatomic extent and severity of myocardial ischemia**. SE is an excellent modality for the evaluation of both.

1. **Negative test result.** Perhaps the most important aspect of the prognostic literature is that **a negative test result portends an extremely low risk of subsequent cardiovascular events, as evidenced by an event rate of <1% per year for the subsequent 4 to 5 years**. However, the risk is slightly higher in patients with diabetes or chronic kidney disease.
2. **Presence of ischemia.** Abnormal findings during SE indicate elevated risk for future cardiac events. Patients at intermediate risk for CAD who have abnormal SE findings have a 1-year cardiac event (ie, MI, percutaneous coronary intervention, coronary artery bypass grafting, or death) rate of 10% to 30%. However, this information needs to be integrated with other stress data (ie, exercise capacity, hemodynamic response to exercise, heart rate recovery, chronotropic index, Duke treadmill score, and the type and extent of WMA). Electrocardiographic changes and hypotension are relatively insensitive measures of ischemia during dobutamine SE. However, from the prognostic standpoint, the development of echocardiographic evidence of ischemia with dobutamine is analogous to its development during exercise.
3. **Presence of nonviable myocardium.** In patients with the same pretest probability of disease, those with evidence of nonviable myocardium during SE have higher rates of cardiac events than those with normal SE findings, but they have fewer events than those with evidence of ischemia during SE. Heart failure is a more common end point among the group of patients with nonviable myocardium.

B. Post-MI. High-risk patients after acute MI are routinely identified by age, recurrent angina, LV failure, and shock. In addition, echocardiographic features predicting outcome after MI include LV ejection fraction (LVEF), the extent of resting WMAs, inducible

ischemia (detected as stress-induced WMA), and the amount of viable myocardium. All of these may be identified using SE, and several large studies (most with pharmacologic stressors) have gathered prognostic data using SE in patients post-MI.

C. Noncardiac surgery

1. Preoperative evaluation studies have been predominantly conducted with pharmacologic stress agents, primarily dobutamine. However, exercise SE should be considered if possible. A low ischemic threshold during stress (ischemia at heart rate <70% APMHR) is the strongest predictor of perioperative cardiac events.
2. The predictive value of a positive test ranges from 7% to 25% for hard events (ie, MI or death). The negative predictive value ranges from 93% to 100%. Only a few studies have compared SE and SPECT for the prediction of perioperative cardiac events. A meta-analysis concluded that the tests had comparable levels of accuracy, but the cost features weighted in favor of SE.

D. Cardiac transplantation. Transplant vasculopathy is a major cause of mortality after cardiac transplantation. SE appears to lack both sufficient sensitivity and specificity to be a viable alternative to routine angiography as a screening method for vasculopathy.

E. Reading beyond wall motion. Important prognostic information can be obtained beyond traditional wall motion analysis. Ischemic heart disease may cause subclinical **diastolic dysfunction**. **Left atrial enlargement** correlates with the chronicity and severity of diastolic dysfunction. A normal resting left atrial volume index (<35 mL/m^2) is strongly predictive of a normal stress echocardiogram. **RV dysfunction** is a significant predictor of events, independent of LV ischemia or LVEF.

IX. DIASTOLIC STRESS ECHOCARDIOGRAPHY

A. In many patients, heart failure with preserved ejection fraction ("diastolic") is the dominant form of dysfunction, without any detectable systolic dysfunction at rest or during stress. The **transmitral peak early diastolic velocity (E)** and the **mitral**

annulus early diastolic velocity (é) are used to assess the diastolic dysfunction. In the presence of normal LV systolic function and volumes, an **E/é ratio >14 suggests elevated LV filling pressure and diastolic dysfunction**, whereas a ratio <9 excludes diastolic dysfunction. The primary utility of diastolic SE is to evaluate patients in whom diastolic dysfunction is suspected but the resting echocardiogram is indeterminate (ie, *E*/*é* 9-14). Assessment for diastolic dysfunction should be completed during routine SE, because its presence and severity add to the negative prognostic value of resting or stress-induced systolic dysfunction.

B. Exercise or adrenergic stress normally results in improved myocardial lusitropy (relaxation) to allow for better filling in a shorter amount of time. The tachycardia associated with exercise results in an abbreviated diastolic filling period and an increase in the transmitral peak *E* velocity. In healthy patients, both the transmitral peak *E* velocity and the mitral annulus early diastolic velocity increase with exercise, and the *E*/*é* ratio is not changed. However, **in patients with diastolic dysfunction, the mitral annulus early diastolic velocity is less affected by the change in preload caused by exercise and the E/é ratio increases**.

C. Assessment of diastolic dysfunction can be difficult at rest and is even more so with stress. When diastolic function is the major indication for testing, exercise SE is optimally performed using **supine bicycle ergometry**, because it allows for the acquisition of Doppler recordings during exercise. However, evaluation is routinely performed using treadmill exercise or dobutamine. Tachycardia may result in fusion of the transmitral *E* and *A* velocities at peak stress, making the tracings impossible to interpret. Therefore, Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery, if possible.

X. STRESS ECHOCARDIOGRAPHY IN NONISCHEMIC CARDIAC DISEASE. SE can be used to evaluate the functional significance of a variety of valvular lesions as well as hypertrophic cardiomyopathy. SE is especially helpful when there is a discrepancy between clinical symptoms and the

assessment of valve severity at rest. In addition to the effect of exercise on wall motion and ventricular size and function, other parameters are assessed when valve disease or hypertrophic cardiomyopathy is the prime focus of the stress echocardiogram. Functional capacity, change in pressure gradients across individual stenotic valves of the LV outflow tract (LVOT), change in severity of regurgitation, and the effect of exercise on estimated RV systolic pressure may all be important in understanding the hemodynamic consequences of the lesion under study. It is important to discuss with the sonographer performing the test in what order individual valve or myocardial parameters should be assessed at peak stress to optimize the value of the study. Thus, in mitral stenosis, for instance, peak mitral gradient followed by peak tricuspid regurgitant (TR) velocity and then wall motion and LV size is the appropriate order of peak acquisition of data.

A. Aortic stenosis

1. In patients with symptomatic AS exercise testing is both meaningless and potentially harmful (American College of Cardiology/American Heart Association [ACC/AHA] class III, level of evidence [LOE] B recommendation). In contrast, in asymptomatic patients with a calcified aortic valve and a peak aortic velocity over 4 m/s or a mean pressure gradient over 40 mm Hg, exercise testing may be considered (ACC/AHA class IIa, LOE B recommendation) to elicit exercise-induced symptoms and abnormal BP responses. Reduced functional capacity for age and gender is associated with worse outcomes in severe AS, especially if valve replacement is not promptly performed. While exercise aortic valve hemodynamics has not shown additive value for predicting clinical outcome, RV systolic pressure may offer additional information.
2. Dobutamine stress echo can be used to assess both the **severity of AS and the presence of contractile reserve** in patients with low-flow/low-gradient AS, defined as Doppler-derived aortic valve area <1 cm^2, LVEF <50%, and mean pressure gradient <40 mm Hg or peak aortic velocity <4 m/s. Dobutamine SE remains a reasonable (ACC/AHA class IIa, LOE B recommendation) test in

these patients in the most recent valve guidelines despite emerging evidence that questions its significance (discussed below).

3. In severe AS, low-dose (20 mcg/kg/min) dobutamine infusion results in increased cardiac output with a parallel rise in the mean transvalvular gradient. Provided the calculated aortic valve area remains <1 cm^2, **an increase in the mean transvalvular gradient to a value >40 mm Hg or velocity >4 m/s is consistent with severe AS**. If dobutamine infusion results in an increase in the valve area (typically to >1 cm^2) with little change in the gradient, this is termed *pseudo-severe AS and LV dysfunction* rather than AS, which may be the primary problem. However, recent studies have shown that patient survival is higher with aortic valve replacement versus conservative therapy, even in patients with pseudo-severe AS.
4. Dobutamine SE has been used to assess for contractile reserve, defined as >20% increase in stroke volume with dobutamine infusion. Early studies suggested high mortality in patients who undergo surgical aortic valve replacement (SAVR) who lack contractile reserve. However, with both improvements in surgical technique and the development of transcatheter aortic valve replacement (TAVR), the relevance of contractile reserve has been questioned. More recent studies have found no association between contractile reserve on preprocedural dobutamine SE and mortality in patients treated with SAVR or TAVR.

B. AR. In asymptomatic patients with severe AR, exercise SE is reasonable to assess functional capacity and ventricular response to exercise. Ejection fraction should improve, and the LV size should decrease in a normal response to exercise in the setting of severe AR. An abnormal response to exercise can predict LV dysfunction at follow-up and need for earlier surgery. Exercise SE can also be considered in patients with a discrepancy between symptoms and severity of AR.

C. MR. In asymptomatic patients with severe MR, exercise SE is reasonable (AHA/ACC class IIa, LOE B recommendation) to assess exercise tolerance and the effects of exercise on pulmonary artery

pressure and severity of MR. SE can help predict latent LV dysfunction in patients with normal baseline LV systolic function, severe MR, and minimal or no symptoms. An increase in the LV cavity size or decrease in LVEF at peak stress suggests latent LV dysfunction and an increased risk of LV dysfunction after valve repair. Inability to achieve a functional response expected for age and gender is indicative of poorer outcomes in those not undergoing early surgical intervention for severe MR. Exercise testing is also reasonable in patients for whom there is a discrepancy between symptom severity and severity of MR. (AHA/ACC class IIa, LOE B recommendation)

D. **Mitral stenosis.** Exercise SE should be performed (ACC/AHA class I, LOE C recommendation) to assess the hemodynamic response of the mean gradient and pulmonary artery pressure in patients with mitral stenosis when there is a discrepancy among resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. An increase in the mean transmitral pressure gradient >15 mm Hg or pulmonary artery systolic pressure >60 mm Hg may be indications to consider percutaneous or surgical intervention.

E. **STE in valve disease.** Observational studies have shown that worse preoperative strain in patients with AS, AR, and MR are associated with worse outcomes. A lack of improvement in strain with exercise may be a sign of myocardial dysfunction in these patients, although no large studies have been published demonstrating optimal cutoffs for worse outcomes in this patient population. Reliable tracking of myocardial segments also be challenging at peak stress, limiting its interpretation.

F. **Hypertrophic cardiomyopathy.** In symptomatic patients with hypertrophic cardiomyopathy and high resting LVOT gradients, routine exercise testing is not performed owing to increased risks of arrhythmias and hypotension. Exercise SE provides valuable information, including exercise hemodynamics, exercise capacity, worsening of MR, and provocable gradients in patients who are asymptomatic at rest. Although these patients may have only mild to moderately elevated resting LVOT gradients, using SE to identify

elevated provocable gradients may help explain their exertional symptoms and quantify their exercise tolerance. In addition, more recent data indicate that patients with asymptomatic or minimally symptomatic hypertrophic cardiomyopathy may be accurately risk stratified by their exercise capacity, regardless of their gradients with exercise.

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CHAPTER 51

Cardiovascular Computed Tomography, Including Calcium Scoring

Bryan Q. Abadie and Christine Jellis

I. INTRODUCTION.

Cardiovascular computed tomography (CT) continues to rapidly evolve, with new and expanded indications for noninvasive assessment of the heart, great vessels, and peripheral vasculature. Technological improvements, including increasing numbers of detectors, improved temporal and spatial resolution, and advanced postprocessing techniques, have broadened the clinical utility of this imaging modality. Multidetector computed tomography (MDCT) scanners and new scanning protocols have significantly reduced the required radiation and contrast dosages. Numerous considerations are involved in the proper selection of cardiovascular CT protocols, and skilled operators are required to plan and interpret these examinations.

II. BASICS OF CARDIAC COMPUTED TOMOGRAPHY

A. CT physics. In CT, images are created by rotating an x-ray source emitting a fan-shaped beam of x-rays, which then pass through the body. Some x-rays are absorbed or scattered, but others are transmitted and subsequently sensed by detectors located directly across the x-ray source. In MDCT, the x-ray tube and detectors are mounted on a gantry that rotates rapidly around the patient as they pass through the scanner. As in traditional x-ray radiography, different structures **attenuate** the x-ray beam to differing extents depending on their atomic composition and density, as well as the energy of the incident photons. The data collected by the detectors then go through a complex set of mathematical reconstruction algorithms that create a set of axial images through the technique of

back projection. Each voxel in the resulting axial image is ascribed a specific attenuation value, which is expressed in **Hounsfield units (HU)**. Using a reference of 0 HU for water, −1,000 HU for air, and +1,000 HU for bony cortex, different points are assigned their respective attenuation values. This information is then converted into a grayscale image that can be manipulated by the interpreting physician.

B. Technical challenges for cardiac imaging

1. The fast cyclical motion of the heart requires high **temporal resolution** to avoid blurring or degradation of images because of cardiac motion artifact. In cardiac CT, image acquisition is additionally referenced, or **gated**, to the cardiac cycle. Although data can be acquired throughout the cardiac cycle, most image data sets are reconstructed during periods of minimal cardiac motion, typically a brief 100- to 300-ms interval in late diastole (60%-75% of the R-R interval).
2. High **spatial resolution** is required to image relatively small vessels, such as the coronary arteries. Current MDCT scanners provide a spatial resolution of 0.3 to 0.5 mm, compared with a spatial resolution of 0.1 to 0.2 mm for invasive angiography and intravascular ultrasound.
3. Respiratory motion artifact can be minimized by having the patient hold their breath during image acquisition. Most of the prior generations of clinically available scanners can cover the entire heart in 10 to 12 seconds, whereas the current 320-detector, wide-volume MDCT scanner, as well as the current dual-source MDCT scanner (with high-pitch spiral acquisition—see subsequent text), can image the entire heart in just one heartbeat.
4. Rapid improvements in CT technology and protocoling have outpaced research in the field. However, we are now finally seeing more updated publications and resultant guideline recommendations based on the diagnostic and prognostic yield of information gained from dual-source MDCT as opposed to the older out-single-beam or MDCT detector systems with fewer detectors (eg, 16- to 64-detector MDCT scanners).

C. Current CT hardware

1. **MDCT** involves using an x-ray tube mounted opposite multiple detector rows on a gantry, which is then rotated around the patient at a rapid rate (220-400 ms/rotation). The patient is moved at either a fixed or variable speed, or **pitch**, through the scanner. An increasing number of detectors allows for an increased *z*-axis (cranial-caudal) coverage, permitting faster scans with improved image quality, because of less cardiac and respiratory motion artifact. Temporal resolution is improved by faster gantry rotation, the use of **two x-ray tubes** and detector arrays mounted at 90° angles to each other (dual-source MDCT), and special reconstruction techniques. Dual-source/dual-energy scanners provide substantial improvements by utilizing dual-source MDCT technology as well as dual-energy sources to improve temporal resolution and decrease scatter. The latest generation dual-source MDCT scanners provide a temporal resolution of 66 ms. Spatial resolution is largely determined by detector architecture (typically 0.4-mm isotropic resolution), although thicker slices (1-5 mm) can be acquired to reduce radiation dose according to the study indication. MDCT can be used for both cardiac and noncardiac studies, and it is now the most widely used type of CT hardware for cardiac imaging.
2. **Electron beam computed tomography (EBCT),** although rarely used today, was specifically developed for cardiac imaging. It involves the use of a rapidly oscillating electron beam reflected onto a stationary tungsten target. Because there is no mechanical motion within the gantry, EBCT is capable of very high temporal resolution (50-100 ms). EBCT was used primarily for the quantitative detection of coronary artery calcification (CAC).

D. Image acquisition techniques

1. **Acquisition modes.** Both prospectively triggered axial acquisition and spiral (helical) retrospectively gated acquisition are available for most MDCT scanners. High-pitch spiral acquisition (“Flash” mode) is unique to current generation dual-source MDCT scanners.

2. **Prospectively electrocardiogram (ECG)-triggered sequential (axial, "step-and-shoot") mode.** Single transaxial slices are sequentially acquired while the patient table is incrementally advanced between successive rotations of the gantry. For patients with adequate heart rate control, this mode is most typically the acquisition mode of choice for CT coronary angiography. With prospective ECG triggering, image acquisition occurs only during a prespecified part of the R-R interval. Significant reductions in radiation exposure (up to 90%) are obtained with this mode of image acquisition, compared with retrospective ECG gating.
3. **Retrospectively ECG-gated spiral (helical) mode.** Data are continuously acquired during constant rotation of the gantry with simultaneous, constant (*z*-axis) movement of the patient through the scanner. Because the tube does not perform a complete rotation in any plane, x-ray data are interpolated from a series of sequential frames to create a single tomographic image. This mode of image acquisition should be considered in situations where patients have arrhythmias and/or tachycardia.
4. **High-pitch spiral acquisition ("flash" mode)**. This is the newest MDCT acquisition mode, available on the current generation dual-source MDCT scanners. The latest generation dual-source scanners enable continuous sampling of the *z*-axis at a pitch value of 3.4, by interleaving data acquired from two detector systems. For a CT coronary angiography study, scan acquisition is most commonly triggered in early diastole (60% of the R-R interval) and completed in one cardiac cycle. The strength of this mode of acquisition is the low radiation dose (often <2 mSv).
5. **ECG gating**
    a. **Prospective triggering.** The trigger signal is derived from the patient's ECG based on a prospective estimation of the R-R interval. The scan is usually triggered to begin at a defined point after the R wave, usually allowing image acquisition to occur during diastole. Prospective ECG triggering is one of the most dose-efficient ways of cardiac scanning, because only the very minimum scan data needed for image reconstruction are

acquired. Limitations of prospective triggering (or **"gating"**) include the fact that the acquired data set will be of a limited portion (or phase) of the cardiac cycle only, limiting the opportunity for evaluating image data sets from other cardiac phases. In addition, prospective triggering depends greatly on the regularity of the patient's heart rate and can result in serious misregistration artifact in the setting of arrhythmia.

b. **Retrospective gating.** Unlike prospective triggering, retrospective ECG gating collects data during the entire cardiac cycle. Once the scan is complete, data from specific periods of the cardiac cycle are used for image reconstruction by retrospective referencing to the ECG signal. This approach allows reconstructions to be made from multiple segments of the cardiac cycle and allows assessment of ventricular function via dynamic four-dimensional (4D) imaging. However, retrospective gating results in significantly higher radiation dose exposure, although this can be somewhat mitigated by **dose modulation** (see subsequent text).

E. Other imaging considerations

1. **Segmented reconstruction** refers to image acquisition algorithms that use scan data from more than one cardiac cycle for image reconstruction. This can improve the effective temporal resolution of the scan at the cost of a slight increase in radiation dose.
2. **Dose (or tube current) modulation.** MDCT scanners may operate with fluctuating tube currents that increase radiation dose during portions of diastole (when diagnostic images are most likely to be obtained) and decrease during systole. Dose modulation typically reduces effective radiation dose by approximately 33%, and it is most effective at lower heart rates.

a. **Image reconstruction and interpretation.** Images are most frequently viewed from axial and double oblique planes, in which the 3D data set is manipulated by the interpreting physician so that multiple planes can be viewed to assess cardiac morphology and coronary anatomy. Additional postprocessing techniques can be performed to provide further

diagnostic information or, more frequently, to present to the referring physician.

b. **Multiplanar reformation (MPR)** involves creating straight or curved image planes by cutting orthogonally or obliquely through the 3D acquisition. This aids in evaluating complex 3D structures, such as the coronary arteries.

c. **Maximal-intensity projections** are created by compressing a predetermined volume of image data into a 2D projection of the brightest voxels. This is similar in principle to the 2D images created by typical invasive angiography.

d. **3D or volume rendering** is an advanced image processing approach that uses semitransparent visualization of the outer contours of volumetric data, giving the appearance of a 3D structure. Although often not as useful for assessing smaller structures, these reconstructions can be very helpful for understanding complex spatial relationships between major intrathoracic structures.

e. **4D or cine imaging** from retrospectively ECG-gated spiral data acquisition generates cine images of the CT data for evaluating ventricular and valvular function.

3. **Contrast-enhanced imaging.** Administration of iodinated contrast media increases the attenuation of the blood pool, improving vessel delineation and tissue characterization. When using contrast, image acquisition must be timed such that images are acquired when the blood pool saturation in the target structure is maximal. Various techniques exist to time the arrival of the contrast bolus in the arterial tree and initiate imaging. The specific risks of contrast media are discussed in Section **IV**.

III. INDICATIONS. The roles of cardiac CT in evaluating patients with cardiovascular disease are diverse and continue to evolve. Generally accepted indications for cardiac CT are listed in **Table 51.1** and are discussed in the context of specific clinical situations in Section **VI**. Appropriate-use criteria (AUC) for the use of cardiac CT have also been

published and are discussed at the end of the chapter. The following is a brief listing of the more common indications for MDCT:

TABLE 51.1 Selected Appropriate Indications for Cardiac Computed Tomography

Category	Specific Appropriate Indications
Suspected CAD with symptoms	Intermediate pretest probability of CAD in patients <65 y
	Acute chest pain with intermediate pretest probability of CAD and no ECG changes and negative serial enzymes
	Evaluation of suspected anomalous coronary artery anatomy
	Evaluation of left main disease in patients with moderate-severe ischemia by stress testing
Coronary artery calcium scoring	Asymptomatic patients at intermediate CAD risk Asymptomatic patients with low CAD risk, with risk enhancers[a]
Evaluation of intra- and extracardiac structures	Evaluation of a cardiac mass (suspected tumor or thrombus) in patients with suboptimal/limited images from other noninvasive imaging modalities (eg, TTE, TEE)
Pericardial disease	Evaluation of pericardial anatomy
Congenital heart disease	Assessment of complex congenital heart disease including anomalies of great vessels
Pulmonary vein anatomy	Evaluation of pulmonary vein anatomy prior to invasive radiofrequency ablation for atrial fibrillation
Biventricular pacing	Mapping of the coronary vein anatomy prior to placement of biventricular pacemaker
Assessment of cardiac structure	Assessment of right ventricular morphology and suspected arrhythmogenic right ventricular dysplasia
Planning for structural interventions	Assessment of LVOT size for TAVR, annulus and neo-LVOT size for transcatheter mitral valve replacement, and left atrial appendage size for left atrial appendage occluding devices

CAD, coronary artery disease; ECG, electrocardiogram; LVOT, left ventricular outflow tract; TAVR, transcatheter aortic valve replacement; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

[a]See 2019 ACC/AHA Guidelines on the Primary Prevention of Cardiovascular Disease for a list of risk enhancers.

Adapted from the Taylor AJ, Cerqueira M, Hodgson J, et al. ACCF/SCCT/ACR/AHA/ASE/ASNC/SCMR 2010 appropriate use criteria for cardiac computed tomography. *J Am Coll Cardiol*. 2010;56:1864.

A. **Evaluation of chest pain** in younger (<65 years) patients with low to intermediate pretest probability of obstructive disease and symptoms (eg, chest pain, dyspnea). CT coronary angiography is now recommended by current guidelines over stress testing for this patient population.

B. **Anomalous coronary arteries.** Because of the high spatial resolution and the ability to create 3D reconstructions of the vasculature, MDCT has very high sensitivity and specificity for detection of anomalous origins and courses of the coronary arteries.

C. **Pulmonary vein/left atrial appendage evaluation** is often performed before or after pulmonary vein isolation (PVI) for atrial fibrillation/flutter. This is helpful for the mapping of pulmonary venous anatomy preprocedurally and to exclude pulmonary vein stenosis postprocedurally. The pulmonary vein protocol is being increasingly used in patients with atrial fibrillation to determine anatomic suitability and sizing of the left atrial appendage for closure with percutaneous devices, such as the Watchman or Amulet devices.

D. **Evaluation of cardiac masses** in conjunction with or when other noninvasive imaging modalities, such as transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), are limited/unrevealing or when cardiac magnetic resonance (CMR) imaging is contraindicated.

E. **Evaluation of pericardial disease** in conjunction with or when other noninvasive imaging modalities, such as TTE and TEE, are not able to provide the complete set of diagnostic data (eg, suboptimal/limited images) or when CMR is contraindicated.

F. **Assessment of anatomy in complex congenital heart disease.** MDCT is particularly useful in patients with non–CMR-compatible devices to assess anatomy, prior surgical interventions, and for calculation of volumes via 4D CT imaging in selected cases.

G. **Presurgical evaluation, particularly before redo open heart surgery.** Noncontrast MDCT can be used to assess for the presence of significant calcification of the ascending aorta prior to aortic cannulation, as well as to assess proximity of cardiovascular structures to the sternum prior to redo sternotomy.

H. **Assessment of graft patency after prior bypass surgery** may be feasible in select cases, although the study can be limited by artifacts related to calcification and surgical clips.

I. **Evaluation of aortic disease.** MDCT is the test of choice for evaluation of patients with suspected acute aortic syndrome. It is also valuable for the diagnosis and serial monitoring of thoracoabdominal aortic aneurysms, along with the long-term monitoring of patients who have undergone prior aortic surgery or endovascular stenting.

IV. **CONTRAINDICATIONS.** In comparison to CMR, few absolute contraindications exist for cardiac CT. However, there are important risks associated with radiation and/or contrast exposure that must be weighed against the benefits of the study. **Relative contraindications** to CT scanning are listed below.

A. **Renal insufficiency.** Given the potential for contrast-induced nephropathy, patients with significant renal insufficiency (ie, estimated glomerular filtration rate <30 mL/min/1.73 m^2) should not undergo contrast-enhanced CT, unless the information from the scan is critical and the risks/benefits are thoroughly discussed with the patient and ideally their treating nephrologist.

B. **Contrast (iodine) allergy.** Patients with allergic reactions to contrast should be pretreated with diphenhydramine and steroids before contrast administration. A prior anaphylactic response to contrast is generally felt to be an absolute contraindication for intravenous iodinated contrast administration by many institutions.

C. **Recent intravenous iodinated contrast administration.** Patients who have received an intravenous dose of iodinated contrast should avoid contrast-enhanced CT scanning for 24 hours to reduce the risk of contrast-induced nephropathy. For younger patients with normal renal function without risk factors for contrast-induced nephropathy,

contrast doses of up to 150 to 200 mL per 24 hours are generally well tolerated.

D. **Hyperthyroidism.** Iodinated contrast is contraindicated in the setting of uncontrolled hyperthyroidism because of possible precipitation of thyrotoxicosis.

E. **Atrial fibrillation**, or any significant arrhythmia, is a relative contraindication to CT coronary angiography because of image degradation from suboptimal ECG gating.

F. **Inability to breath-hold for at least 10 seconds.** Image quality will be significantly reduced because of respiratory motion artifact, if the patient cannot comply with breath-hold instructions.

V. SAFETY

A. **Radiation exposure** is an important consideration in various cardiac imaging modalities, including CT. Radiation doses of cardiac CT scans vary greatly, depending on the scan parameter settings, scan range (cranial-caudal length of the scan), gender (women receive more radiation because of breast tissue), and patient's body habitus (obesity increases exposure).

1. **Estimates of radiation dose from MDCT** have varied widely in the literature. **Effective dose** is an estimate of the dose to patients during an ionizing radiation procedure and is expressed in **millisieverts**. For reference, the estimated dose from a chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv. Invasive diagnostic coronary angiography provides effective doses of 2.1 to 4 mSv. In comparison, CT coronary angiography studies have reported doses ranging from 3 to as high as 16 mSv, depending on the scan parameters, with most estimates ranging from roughly 4 to 8 mSv.
2. **Table 51.2** lists radiation dose ranges for the most commonly used cardiac imaging modalities.

TABLE 51.2 Estimated Radiation Exposure From Cardiac Imaging Procedures

Diagnostic Procedure	Typical Effective Dose (mSv)	Equivalent Period of Natural Background Radiation
Natural background radiation	3-4 (range 1.5-7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (Kr-81m)	0.1	2-4 wk
Lung perfusion study (Tc-99m)	1	4-6 mo
Calcium scoring	0.8-2	3-6 mo
CT head	2	6 mo
Cardiac catheterization (diagnostic)	3-4	1 y
64-Slice MDCT (with dose modulation)	8-12	2-3 y
Second-generation, wide-volume 320-detector row MDCT Latest generation, dual-source MDCT (high-pitch spiral/flash mode)	1-2	3-6 mo
Myocardial perfusion (Tc-99)	14	3-4 y
CT of the abdomen/pelvis	10-20	3-6 y
Cardiac PET	4-12	1-3 y

CT, computed tomography; MDCT, multidetector computed tomography; PA, posterolateral; PET, positron emission tomography; R, Roentgen units.

3. **Feasibility of low-dose CT coronary angiography.** With the use of prospective ECG triggering, axial imaging modes, dose reduction, and software adaptations, studies have reported the feasibility of CT coronary angiography with comparable image quality and substantially reduced radiation doses (ie, 1.1-3.0 mSv). For second-generation, wide-volume 320-detector row MDCT scanners, submillisievert radiation dose has been reported for CT coronary angiography studies. With the current generation, dual-source MDCT scanners utilizing the high-pitch spiral acquisition

(Flash mode), many CT coronary angiographic studies can be performed with less than 2 mSv of radiation dose.

B. Contrast-induced nephropathy. Iodinated contrast media can cause renal ischemia by reducing renal blood flow or increasing oxygen demand and may also have a direct toxic effect on tubular epithelial cells. If a contrast-enhanced CT study is necessary in patients with significant renal insufficiency, prophylactic measures should be taken to reduce the risk of renal damage. Most cardiac CT studies require between 80 and 100 mL of contrast.

1. **Risk factors**
   - **a.** Preexisting renal insufficiency
   - **b.** Diabetes mellitus
   - **c.** Increased volume of contrast media
2. **Prophylactic measures** include saline hydration, use of low-osmolar agents, and sodium bicarbonate infusion, although the data for each of these measures remain somewhat controversial.

VI. CLINICAL APPLICATIONS

A. Coronary artery calcium (CAC) scoring uses the observation that coronary calcium is a surrogate marker for coronary atherosclerotic plaque. Studies have shown that the complete absence of CAC makes the presence of significant coronary luminal obstruction highly unlikely and indicates a very low risk of future coronary events. Men tend to have higher calcium scores, and individuals of either gender with renal insufficiency or diabetes mellitus tend to have higher coronary calcium scores. Coronary calcium scoring is considered an appropriate test to better stratify cardiovascular risk in patients with an intermediate probability of future events or in those patients at a low probability with risk enhancers, such as a family history of early atherosclerotic coronary disease.

1. Either noncontrast EBCT or MDCT can be used (typically with a 3.0-mm slice thickness). Contrast is not necessary because calcium is readily identified secondary to its very high x-ray attenuation coefficient (high HU score).

2. The **Agatston CAC volume score** is the most frequently used scoring system. It is derived by measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4, depending on the maximum CT attenuation within that lesion. It is important to note that interobserver variability exists in Agatston scores, as high as 3%. However, with very low and very high scores, such interobserver variability has little clinical meaning.
    a. The **CAC score** can be classified into five groups: (1) 0, no coronary calcification; (2) 1 to 100, mild coronary calcification; (3) >100 to 399, moderate calcification; (4) 400 to 999, severe calcification; and (5) ≥1,000, extensive calcification.
    b. The **CAC score is age and gender specific**. Therefore, there has to be a comparison of the individual data with a "normal" cohort in order to produce meaningful data for risk stratification, usually presented as a percentile distribution (eg, Multi-Ethic Study of Atherosclerosis Risk Score). In general, CAC develops 10 to 15 years later in life in women than in men. Similarly, CAC is generally 5 to 7 times lower at any given age in women than in men.
    c. In a typical cohort of patients with coronary artery disease (CAD), the median CAC score is 975 for men and 370 for women. In comparison with a CAC score of 0, the presence of any CAC is associated with a 4-fold risk of coronary events over 3 to 5 years.
    d. In patients at intermediate clinical risk for coronary events (eg, by the Pooled Cohort Equation), the **CAC score can help reclassify patients to a higher or lower risk group**. For instance, a patient with a CAC score of 0 is at significantly less risk of cardiovascular events as predicted by the Pooled Cohort Equation. Conversely, patients with a CAC score of >0 had a rate of cardiovascular events greater than predicted by the Pooled Cohort Equation.

e. Because statins have no documented effect on CAC progression, **there is no value in repeating CAC in persons with a score of >100 or the 75th percentile**. Alternatively, about 20% of patients with a score of 0 will progress to >0 within 4 to 5 years, and repeat CAC could be considered in this population to guide management of statin therapy.

f. Observational studies have suggested an increase in both initiation and adherence of preventive medications in patients who have undergone CAC.

3. However, not every atherosclerotic plaque is calcified, and even the detection of a large amount of calcium does not directly translate into the presence of significant obstructive coronary artery lesions. Therefore, CAC adds incrementally to traditional risk factor assessment and should not be used in isolation. The test is most useful in intermediate-risk populations, in which a high or low score may reclassify individuals to a higher or lower risk group, respectively. Unselected screening is not recommended.

4. Calcium scoring, with the Agatston score, has also been found to aid grading the severity of aortic stenosis in patients with equivocal echocardiography. Calcium score thresholds of 2,000 AU in men and 1,300 AU in women are suggestive of severe aortic stenosis.

B. **CT coronary angiography** has been shown to be an accurate noninvasive modality for visualizing the coronary arteries, with high sensitivity (85%-95%) and specificity (95%-98%), compared with invasive coronary angiography.

1. CT coronary angiography for evaluating CAD is most useful in low- to intermediate-risk patients with angina or anginal equivalent symptoms. The **negative predictive value** of CT coronary angiography is uniformly high in clinical studies, approaching 95% to 100%; in other words, CT coronary angiography is an excellent modality for ruling out coronary disease.

2. Patients who are generally poor candidates for CT coronary angiography include those who are likely to have heavily calcified

coronary arteries (older than 75 years, end-stage renal disease, and Paget disease), atrial fibrillation/flutter, frequent ventricular ectopic beats, or uncontrolled tachycardia. Quantification of stenosis severity is often impossible in densely calcified arteries due to calcium blooming artifact, whereas image quality is significantly degraded in patients with arrhythmias or tachycardia. The negative predictive value dropped to 83% in one study, where patients with Agatston CAC score of <600 were included.

3. Known severe CAD is generally a contraindication to CT coronary angiography, although can be used in select patients (see below). However, cardiac CT has been shown to have high sensitivity and specificity for the assessment of bypass graft patency in patients with previous coronary artery bypass grafting (see subsequent text).
4. **Stent patency.** Patients with prior coronary artery stents are generally poor candidates for CAC and CT angiography, although selected patients with larger stents in the proximal left anterior descending or left main may be successfully imaged. Current CT technology does not allow for the accurate quantification of in-stent restenosis severity, because of blooming artifact from the metallic struts of the stent.
5. When assessing the coronary arteries, **noncalcified plaque** appears as a low to intermediate attenuation irregularity in the vessel wall. **Calcified plaques** are bright, high-attenuation lesions in the vessel wall and may be associated with positive remodeling of the vessel. Densely calcified plaques are often associated with **calcium blooming artifact**, which can lead to overestimation of luminal stenosis severity.
6. Certain characteristics of noncalcified plaque, such as positive remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign, have been reported to predict atherosclerotic lesions at higher risk of developing subsequent acute coronary syndromes.
7. The accuracy of CT coronary angiography is highest in the larger proximal to medium vessels, which are more likely to benefit from

an invasive management strategy. Coronary stenoses are generally categorized as mild (<50% diameter stenosis), moderate (50%-70% diameter stenosis), or severe (>70% diameter stenosis).

8. Hemodynamic assessment of stenotic lesions, such as CT fractional flow reserve, has shown promise to help guide the use of invasive angiography and to predict revascularization. However, the current technology is proprietary, limiting its widespread utilization.

C. CT coronary angiography in stable chest pain

1. In the PROMISE study, 10,003 patients were randomized to comparing anatomic (with CT coronary angiography) versus functional testing (exercise ECG, nuclear stress testing, or stress echocardiography) for the assessment of symptoms suggestive of CAD. Over a median follow-up of 25 months, the investigators found that long-term patient outcomes were equivalent with both strategies. CT coronary angiography was associated with fewer catheterizations showing no obstructive CAD than functional testing, although more patients in the anatomic testing group underwent subsequent catheterization.
2. In a prospective, open-label, multicenter trial, 4,146 patients with stable chest pain were randomly assigned to either standard care alone or standard care plus CT coronary angiography (SCOT-HEART). CT coronary angiography helped clarify the diagnosis of angina: At 6 weeks, CT coronary angiography reclassified the diagnosis of CAD in 558 (27%) patients and the diagnosis of angina because of CAD in 481 (23%) patients. This led to decreased functional testing, increased invasive angiography, and more focused treatment regimens for patients. After 1.7 years, CT coronary angiography was associated with statistically nonsignificant trend toward reduction in fatal and nonfatal myocardial infarction.
3. CT coronary angiography was widely used in the recently published ISCHEMIA trial where patients with moderate or severe ischemia by stress testing were randomly assigned to an early invasive strategy versus medical therapy alone. There was no

difference in death from CAD or nonfatal myocardial infarction at a median follow-up of 3.2 years. CT coronary angiography was used to evaluate for left main disease and nonobstructive CAD prior to enrollment. Based on this study, CT coronary angiography is a reasonable test in conjunction with stress testing to help guide referral for angiography.

4. The 2021 American College of Cardiology/American Heart Association (ACC/AHA) chest pain guidelines now recommend CT coronary angiography as the initial test of choice in low- or intermediate- risk patients <65 years with cardiac or possibly cardiac chest pain.

D. CT coronary angiography in acute chest pain

1. In a multicenter study of 1,000 patients presenting to the emergency department with suspected acute coronary syndrome (ROMICAT-II), early CT coronary angiography, compared with standard evaluation, reduced the mean length of stay in hospital by 7.6 hours ($P < .001$), and more patients were discharged directly from the emergency department (47% vs 12%, $P < .001$). CT coronary angiography resulted in more downstream testing and higher radiation exposure, without a significant increase in overall costs of care.
2. Another multicenter study enrolled 1,370 patients presenting to the emergency department with a suspected acute coronary syndrome: 908 patients in the CT coronary angiography group and 462 patients in the conventional care group. Compared with conventional care, CT coronary angiography was found to be safe and enabled early discharge from the emergency department (49.6% vs 22.7%). Of 640 patients with a negative CT coronary angiography, none died or had a myocardial infarction within 30 days.

E. Bypass graft imaging

1. **Graft location.** MDCT can accurately characterize the origin, course, and touchdown of prior bypass grafts using intermediate slice thickness (eg, 1.5 mm). This can be important for surgical planning (see subsequent text).

2. **Graft patency.** Using a protocol similar to that used for coronary artery assessment (>1-mm slice thickness), the patency of both arterial and venous bypass grafts can be assessed. Studies have suggested that the sensitivity and specificity of MDCT for detecting stenosis or occlusion of bypass grafts, when compared with invasive angiography, are excellent (97%). Occasionally, artifacts related to metallic clips can interfere with the assessment of distal anastomosis of an arterial graft (internal mammary or radial artery graft).

F. **Anomalous coronary arteries.** Because of the 3D data acquisition, MDCT is an excellent modality for assessing patients with known or suspected anomalous coronary arteries. MDCT can accurately assess the origin and course of anomalous coronaries and can delineate the relationship of the coronary artery to neighboring structures. Although CMR can also be used to assess for the origins of anomalous coronaries, without the need for radiation exposure, the spatial resolution, ease of data acquisition, and reliable image quality of MDCT make it a reasonable first choice (**Figure 51.1**). Intramyocardial **bridging** can also be detected on CT coronary angiography with high sensitivity, although the hemodynamic clinical significance of this relatively common finding cannot be determined by CT.

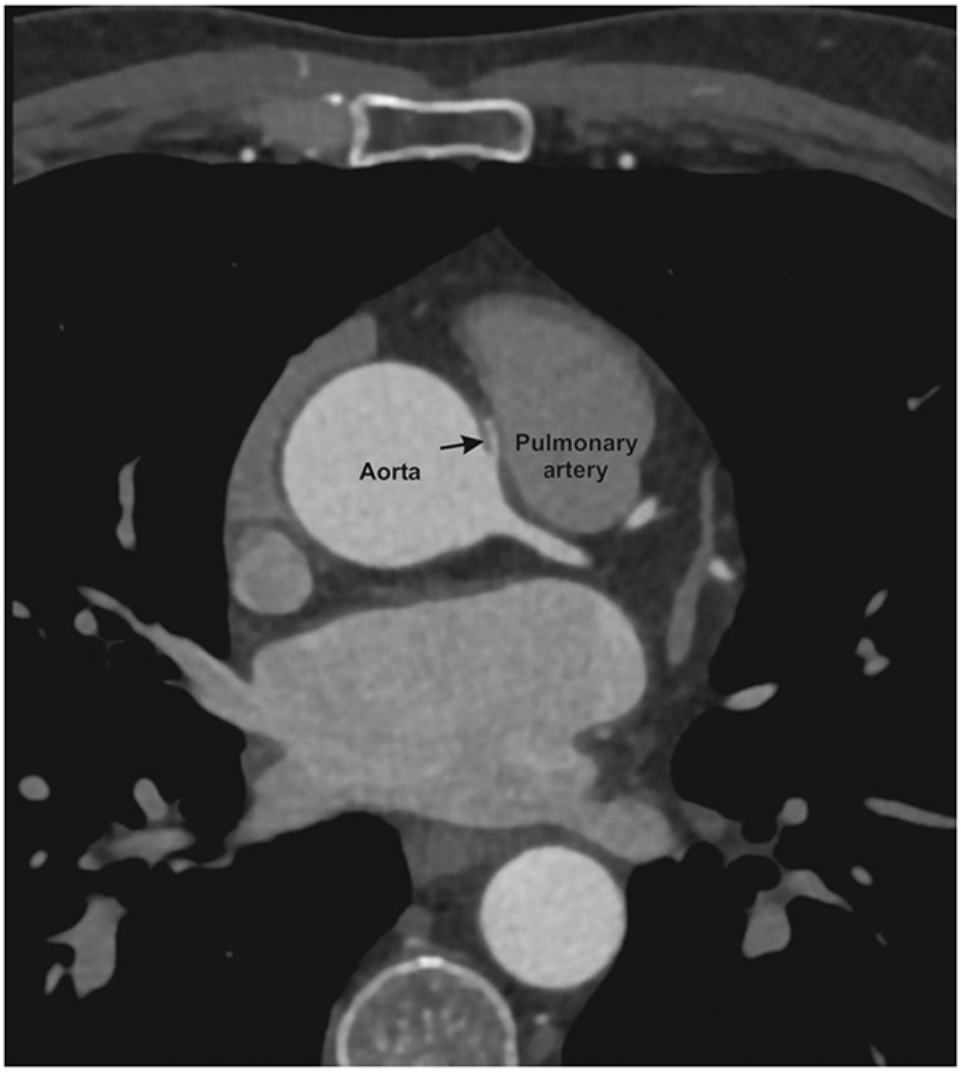

FIGURE 51.1 Axial multidetector computed tomography reconstruction demonstrating anomalous origin of the right coronary artery (RCA; arrow) from the left coronary cusp, with an intramural course, and compression of the ostium of the vessel between the ascending aorta and the pulmonary artery. Note that the ostium of the RCA has a slitlike appearance. This image is from a 68-year-old male, with recurrent chest pain, who is being considered for surgical intervention.

G. Cardiac morphology/function. Contrast-enhanced MDCT can provide high-resolution morphologic images of the cardiac chambers as well as accurate assessment of right and left ventricular systolic function. Other imaging modalities such as echocardiography or CMR, which do not require radiation exposure, are generally preferred for the initial assessment of ventricular function. However,

in patients for whom CMR is contraindicated and accurate chamber volume and function is needed, CT is a reasonable alternative test.

1. Patients with prior **myocardial infarction** can have fibrous replacement of myocardium with or without calcification, ventricular wall thinning, aneurysm formation, and intracavitary thrombus. Cardiac CT is rarely used as the primary imaging investigation to assess for prior ischemic damage. Delayed-enhancement imaging with CMR remains the most widely accepted imaging modality of choice for this indication.
2. **Ventricular dysplasia** is characterized by fibrous and/or fatty replacement of myocardium, ventricular wall thinning and/or focal aneurysm formation, and ventricular cavity dilation with regional or global wall motion abnormalities. Evaluation of these abnormities can be performed on cardiac CT with contrast to assess myocardial structure, tissue characterization, and function using 4D image acquisition.
3. **Mass.** Compared with CMR, cardiac CT provides less comprehensive tissue characterization, although the attenuation of a mass on CT (in HU) can be helpful. For instance, lipomas have low HU numbers, cysts have water density (ie, 0-10 HU), and thrombi have low to intermediate HU numbers. Atrial myxomas can be visualized easily in the left atrium, although right atrial masses may be more difficult to assess, because of contrast mixing at the junction of the right atrium and inferior vena cava (IVC).

H. **Pericardial diseases.** The pericardium appears as a thin structure (1-2 mm) surrounding the heart, usually visible with a small amount of adjacent epicardial/pericardial fat.

1. Findings of pericardial **constriction** on CT include irregular pericardial thickening and calcification, conical or tubular deformities of one or both ventricles, enlargement of one or both atria, dilation of the IVC, and a characteristic diastolic bounce of the interventricular septum.
2. Pericardial effusions can be reliably detected by CT, with the presence of a trivial to small amount of pericardial fluid considered physiologic. Cardiac tamponade is better evaluated by

echocardiography, because of its ability to provide hemodynamic assessment.

3. A pericardial **cyst** will appear as a well-circumscribed paracardiac mass with characteristic water attenuation (HU = 0), usually in the right costophrenic angle.
4. Both primary **neoplasms** and, more commonly, metastatic neoplasms can be visualized in the pericardium.
5. Rare pericardial disorders such as partial or complete **congenital absence of the pericardium** can be diagnosed by CT, with the demonstration of posterolateral displacement of the left ventricular apex and interposition of lung tissue between the aorta and the pulmonary artery.

I. **Congenital heart disease.** MDCT may be useful in select patients in whom echocardiography is nondiagnostic or inadequate and CMR is not available or contraindicated. The ability to evaluate cardiovascular anatomy in multiple planes is often helpful for delineating cardiac morphology in congenital heart disease, particularly with regard to the relationship of the great vessels, pulmonary veins, and coronary arteries. Specific situations in which MDCT can be helpful include the detection of shunts (eg, sinus venosus atrial septal defect, unroofed coronary sinus, patent ductus arteriosus), visualization of pulmonary arteries in cyanotic congenital heart disease, precise definition of aortic anatomy in Marfan syndrome or coarctation, and delineation of partial or total anomalous pulmonary venous drainage. In addition, CT can be useful as the follow-up imaging modality in patients with congenital heart disease, such as L-transposition of the great arteries or patients with Fontan circulations, who have had a prior pacemaker or implantable cardioverter-defibrillator (ICD) implantation, contraindicating CMR.

J. **Diseases of the aorta** constitute a common and important indication for CT examinations. Contrast-enhanced MDCT is nearly 100% sensitive and specific for evaluating acute aortic syndromes. ECG gating is critically important for studies of the aortic root and ascending aorta, given the propensity for motion artifacts to mimic dissection flaps on nongated studies.

1. **Acute aortic dissection** (see Chapter 26) is characterized on CT by visualization of a dissection flap (ie, separation of the intima from the media) that forms true and false lumens. The CT study can characterize the origin and extent of the dissection, classify it as type A or B, assess for concomitant aneurysmal aortic dilation, and identify branch vessel involvement.
2. **Aortic intramural hematomas** are believed to be caused by spontaneous hemorrhage of the vasa vasorum of the medial layer. They appear as crescent-shaped areas of increased attenuation with eccentric aortic wall thickening. Unlike dissections, hematomas do not spiral around the aorta.
3. **Aortic aneurysm** occurs when there is enlargement (≥150%) of the normal aortic caliber (usually >5 cm in the thoracic aorta and >3 cm in the abdominal aorta). Given the often tortuous course of a dilated aorta, it is important that these measurements be made in the true short axis of the aorta, because oblique cuts can result in erroneous overestimation. MPR by cardiac CT allows for precise measurements, enabling accurate initial diagnosis and reliable ongoing monitoring for interval change. Quantitative measurements of an aortic aneurysm can be made for planning endovascular repair with a **stent graft**. The durability of prior thoracic and abdominal aortic interventions can be evaluated by MDCT angiography. In particular, the assessment for endoleaks after endovascular stenting and graft anastomosis complications after surgical graft replacement are well delineated by CT.
4. **Penetrating atherosclerotic ulcer.** These tend to be focal lesions of the descending thoracic aorta that appear as contrast-filled irregular outpouchings of the aortic wall.

K. **Evaluation of pulmonary veins.** In the context of electrophysiologic interventions such as PVI, preprocedural MDCT can be used to define pulmonary venous anatomy and identify supernumerary veins. Postprocedural MDCT can be used to evaluate for pulmonary vein stenosis. In addition, in the setting of congenital heart disease, CT can be used to identify the anomalous pulmonary venous return.

L. **Evaluation of pulmonary embolism (PE).** MDCT is highly accurate in detecting incidental PE, which appears as a filling defect in the pulmonary arteries. This modality is most sensitive for proximal (main through segmental branches) thrombi. Small, more distal emboli may be missed. If pulmonary emboli are clinically suspected, a dedicated computed tomography pulmonary angiogram (CTPE) should be protocoled in preference to a cardiac CT, to optimize the timing of contrast for opacification of the right heart and pulmonary vasculature.

M. **Native valvular heart disease.** Visualization of the valve leaflets, particularly the aortic valve, is feasible with newer generation scanners because of their improved temporal resolution. Dynamic 4D MDCT imaging is particularly useful for the assessment of surgical prosthetic valves for suspected thrombus, as well as infective endocarditis. **Surgical planning**. The utility of MDCT in surgical planning before cardiothoracic surgery, particularly for reoperations, is increasingly recognized. Preoperative scans can evaluate the proximity of mediastinal structures to the sternum (ie, aorta, right ventricle, and bypass grafts) and the degree of aortic calcification (ie, to guide cannulation sites) and concomitantly provide information about cardiac morphology (eg, presence of a ventricular aneurysm).

N. **Peripheral arteries.** MDCT can be used to evaluate peripheral arteries, including the carotid, renal, visceral, and lower extremity vessels. Indeed, imaging these vessels is generally more straightforward than coronary imaging, because of their large caliber and minimal motion. CT can be used for planning and follow-up of vascular disease in these peripheral vascular beds. Given the larger caliber of these vessels, assessment of stent patency is often quite feasible.

O. **Structural cardiac interventions.** MDCT is now the accepted gold standard imaging investigation for the assessment of the aortic annulus size, as well as iliac-femoral anatomy and distance to coronary artery ostia for the purpose of planning for transcatheter aortic valve replacement (TAVR). In addition to the aortic valve calcium score (as noted above), 4D cardiac CT imaging can be useful

for the measurement of aortic valve area and confirmation of severe aortic valve stenosis. Post-TAVR, 4D cardiac CT is increasingly being used to visualize valve leaflets when there is concern for valve dysfunction, including hypoattenuated leaflet thickening (HALT), an increasingly recognized finding that has been associated with elevated gradients and worse long-term mortality (**Figure 51.2**). MDCT is also being increasingly used for the assessment and sizing of the mitral valve annulus and neo-left ventricular outflow tract, to guide transcatheter mitral valve replacement. Recent data have also emerged that MDCT assessment of the left atrial appendage ostium is superior to TEE for sizing the Watchman device for left atrial appendage occlusion. MDCT is also an alternative to TEE for evaluating the presence of left atrial appendage thrombus.

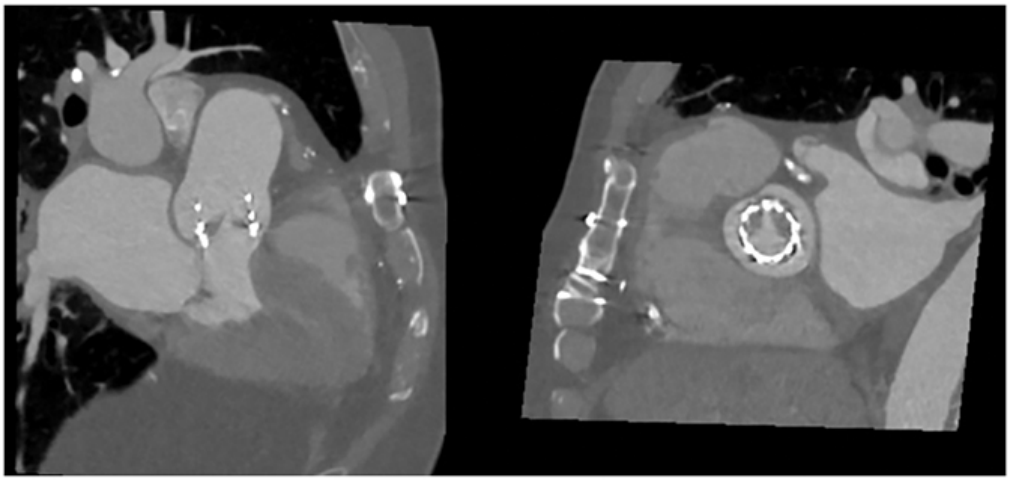

FIGURE 51.2 Multiplanar reconstruction images of a bioprosthetic transcatheter aortic valve within a bioprosthetic surgical valve ("valve-in-valve"), with moderate, hypoattenuated leaflet thickening. 4D cine imaging showed associated restriction of the prosthetic leaflets, particularly those in the right and left sinus positions.

III. APPROPRIATENESS CRITERIA. AUC for the appropriate use of cardiac CT, endorsed by multiple societies and led by the ACC, have been published. The current iteration of AUC for cardiac CT was published in 2010. They serve as guidelines, helping clinicians with the appropriate use of cardiac CT in the context of different clinical situations. Each clinical

situation is designated appropriate (A), uncertain (U), or inappropriate (I) for the use of cardiac CT. For instance, cardiac MDCT is considered an *appropriate* (A) investigation for intermediate-risk patients with suspected CAD and chest pain, but with negative ECG and biomarkers; it is considered an *uncertain* (U) indication to use cardiac MDCT for routine evaluation of coronary arteries following heart transplantation. Based on these guidelines, it is considered an *inappropriate* (I) indication to use cardiac CT to investigate patients with documented moderate or severe ischemia on functional testing; however, this recommendation will likely be updated in future guidelines, given the findings of the ISCHEMIA trial.

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SUGGESTED READINGS

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RELEVANT GUIDELINES

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CHAPTER 52

Cardiovascular Magnetic Resonance Imaging

Megan K. Covington and Deborah Kwon

I. INTRODUCTION

A. Magnetic resonance imaging (MRI) has become more widely available as a diagnostic technique for cardiovascular imaging, and its clinical indications continue to expand. **Advantages of cardiovascular MR (CMR) include its ability to produce high-resolution and three-dimensional (3D) images of the cardiac chambers and thoracic vessels without ionizing radiation (unlike nuclear imaging and cardiac computed tomography [CT]) and its ability to provide comprehensive tissue characterization to further evaluate potential underlying myocardial disease. In contrast to echocardiography, MRI is less operator dependent and is not limited by interferences from adjacent bone or air.** Clinical applications of CMR include imaging of the myocardium and large-vessel vasculature, including ischemic heart disease, valves, pericardium, aorta, peripheral artery, congenital heart disease, and intracardiac masses. Common indications and components of the CMR evaluation are listed in **Table 52.1**.

TABLE 52.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications

Indication	Applications
Aortic disease	Aortic aneurysm morphology and size; acute aortic pathology (dissection, intramural hematoma, penetrating ulcer); coarctation of the aorta; branch vessel disease; evidence of vasculitis; postoperative graft complication including infection or leak; assessment for aortic regurgitation or other associated pathologies

Indication	Applications
Ischemic heart disease	Ventricular volumes and function; myocardial perfusion, myocardial scar and viability; quantification of mitral regurgitation; assessment for LV aneurysm, thrombus, VSD, and other complications
Nonischemic cardiomyopathies	Ventricular volumes and function; myocardial wall thickness; LV outflow tract obstruction in hypertrophic cardiomyopathy; presence and patterns of myocardial scar/fibrosis; myocardial infiltration (amyloidosis, Fabry, sarcoidosis), assessment for myocardial iron deposition in suspected hemochromatosis; quantification of mitral regurgitation; evaluation for ARVD in patients with ventricular arrhythmias or syncope
Pericardial disease	Pericardial effusion; pericardial thickening with or without calcification; pericardial tethering; signs of constrictive physiology including conical/tubular deformity of the ventricles, ventricular interdependence, diastolic septal bounce, and early cessation of diastolic filling
Congenital heart disease	Anatomic definition; ventricular volume and function; valve morphology and function; shunt calculation; assessment for anomalous origin of the coronary arteries; anomalies of the aorta, pulmonary arteries, and systemic and pulmonary veins
Valvular heart disease	Valve morphology; regurgitation and/or stenosis etiology and severity; ventricular size and function
Cardiac masses	Size and extent of mass; tissue characterization
Pulmonary veins	Pulmonary vein anatomy and stenosis; cardiac anatomy and function

ARVD, arrhythmogenic right ventricular dysplasia; LV, left ventricular; VSD, ventricular septal defect.

II. CONTRAINDICATIONS. Contraindications to CMR imaging (CMRI) are listed in **Table 52.2**.

TABLE 52.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

Specific Devices	Special Issues
Cerebral aneurysm clips	Certain cerebral aneurysm clips pose a danger because of the potential for displacement when exposed to a magnetic field.

Specific Devices	Special Issues
	Aneurysm clips classified as “nonferromagnetic” or “weakly ferromagnetic” are safe.
Cardiac pacemakers and ICDs	Patients with MR-conditional CIEDs are able to undergo MRI. While the presence of nonconditional CIED is not a complete contraindication to CMR, a dedicated MR physician and CIED physician should be involved in the study. If there are fractures, MR is not advised. In addition, artifact from the ICD generators will often cause significant image degradation, and image optimization techniques should be employed (ie, wideband phase-sensitive inversion recovery (PSIR), gradient echo cine imaging, etc).
Cardiovascular catheters	Catheters with conductive metallic components (eg, pulmonary artery catheters) have the potential for excessive heating. Hence, patients with such devices should not undergo CMR.
Cochlear implants and hearing aids	Most types of implants employ a strong magnet or are electronically activated. Consequently, MRI is contraindicated because of potential injury or damage to the function of these implants. External hearing aids should be removed before the MRI procedure.
Intravascular coils, stents, and filters	These devices typically become incorporated securely into the vessel wall within 6-8 wk after implantation; hence, most are considered MRI safe. However, specific information on the type of device should be obtained before MRI is planned (mrisafety.com). Intracoronary stents have been shown to be safe during MRI, even when performed on the day of implantation, although many stent manufacturers recommend waiting 6-8 wk.
ECG electrodes	MR-safe ECG electrodes are strongly recommended to ensure patient safety and proper ECG recording.
Foley catheters	Certain Foley catheters with temperature sensors have the potential for excessive heating. They are generally safe if positioned properly and disconnected from the temperature monitor during MRI.
Heart valve prostheses	Most prosthetic heart valves and annuloplasty rings have been labeled MR safe and should not be considered a contraindication to MR examination at ≤3 T any time after implantation.
Metallic foreign bodies	All patients with a history of injury with metallic foreign bodies such as a bullet or shrapnel should be thoroughly evaluated,

Specific Devices	Special Issues
	as serious injury may result from movement or dislodgement of the foreign body.
Metallic cardiac occluders (eg, management of PDA, ASD, or VSD)	MRI is safe for nonferromagnetic devices immediately after implant. Weakly ferromagnetic devices are generally safe approximately 6-8 wk after placement.
Retained epicardial pacing wires	MRI in patients with retained epicardial pacing wires after cardiac surgery is safe. However, retained transvenous pacing wires are usually a contraindication to CMR.

ASD, atrial septal defect; CIED, cardiovascular implantable electronic device; CMR, cardiac magnetic resonance; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; MR, magnetic resonance; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

III. BASICS OF CARDIAC MRI

A. MRI physics. Hydrogen is the most abundant atom in the body, and it is the excitation of the hydrogen nuclei, often referred to as protons, that forms the basis for clinical MRI. The nucleus has an inherent property called "spin," giving it a small magnetic moment. When these spins are placed in a magnetic field, they align parallel to the magnetic field and process at a certain frequency (resonant or precessional frequency), creating a longitudinal magnetization. Application of a radiofrequency (RF) pulse with the same precessional frequency will cause excitation or resonance of the nucleus, temporarily changing its alignment within the magnetic field and resulting in synchronization of the phase of the spins (transverse magnetization). However, this is an unstable state of higher energy. As the RF pulse is switched off, the spins quickly return to their resting state, aligned with the field. The newly established transverse magnetization starts to decay (a process called transversal relaxation), and the longitudinal magnetization recovers back to its original magnitude (a process called longitudinal relaxation). During this process, an RF signal is generated, which can be captured by the receiving coil and readily measured. This process constitutes the underlying principle of MRI.

The signal generated by an excited proton is dependent on its molecular environment, such that the MR signal from a hydrogen atom in blood can be discriminated from the MR signal from a hydrogen atom in fat or other tissue types. An MRI machine, therefore, includes a strong magnet that creates a continuous magnetic field and RF coils for transmitting the excitation pulses and receiving the radio signals generated by the excited protons. Application of predictable variations or "gradients" in the magnetic field, using gradient coils within the magnetic bore, allows 3D spatial localization of each signal. The raw data are initially mapped in "k-space," then a Fourier transformation is performed to generate the final MRI.

B. T1, T2, and image contrast. The rate of relaxation of an excited proton along the longitudinal axis (ie, the direction of the external magnetic field) is described by its T1 time, whereas the transverse axis is described by its T2 time. T1 and T2 times depend on the molecular environment of the protons (intrinsic to the tissue characteristics) and the magnetic field strength. T1 and T2 relaxation times of different tissues are important determinants of image contrast, and although not measured directly, images can be either T1 or T2 "weighted" to facilitate tissue characterization.

C. Issues specific to CMR. Cardiac and respiratory motion poses significant challenges to CMR. In contrast to echocardiography, which is based on real-time imaging, CMRI sequences usually acquire a single image over several heartbeats to optimize the spatial and temporal resolution. It is, therefore, necessary to gate images to the cardiac cycle with either an electrocardiographic or peripheral pulse signal. Respiratory motion is typically countered by performing breath-holds during the examination. In patients who are unable to maintain a breath-hold, averaging multiple MR signals may help decrease the noise created by respiratory motion, at the expense of increasing the examination time by a factor of the number of signals averaged. Respiratory navigator sequences that coordinate imaging with a particular phase of diaphragmatic and hence respiratory motion are also effective, and they are typically used for pulse

sequences that are too long for a single breath-hold, such as free-breathing whole-heart 3D magnetic resonance angiography (MRA) sequences to image the coronary arteries or aorta. Finally, real-time imaging features newer ultra-fast pulse sequences that can be used in the absence of electrocardiographic or respiratory gating, at the expense of a significant decrease in temporal and spatial resolution.

D. CMR pulse sequences and applications

1. **Parallel imaging.** A number of parallel imaging techniques can be applied to all pulse sequences to shorten acquisition times; which is necessary to limit motion artifacts with cardiac imaging. This improves temporal resolution but at the cost of a small decrease in the signal-to-noise ratio (SNR).
2. **Spin echo.** Spin-echo sequences are characterized by a refocusing RF pulse after delivery of the initial excitation pulse. Rapidly flowing blood appears dark as associated protons are no longer in the imaging plane when the refocusing pulse is applied; hence, they are also known as "black-blood" sequences. Spin-echo sequences provide still images, which are typically used for anatomic delineation of the heart and great vessels owing to their excellent tissue contrast and high SNR. They are relatively insensitive to magnetic field inhomogeneities and artifacts related to ferromagnetic objects, such as sternal wires and prosthetic heart valves. The main disadvantage of spin-echo sequences is the relatively longer time it takes to acquire an image, making them more susceptible to motion artifacts and unsuitable for cine imaging. Turbo spin echo is a technique that provides faster acquisition times than does standard spin echo.
3. **Gradient echo.** Gradient echo sequences are characterized by the delivery of one initial excitation pulse with relatively a low flip angle, which enables fast imaging. Rapidly flowing blood appears bright; hence, they are also known as "bright blood" sequences. Gradient echo is a fast imaging technique that is relatively insensitive to motion artifacts, making it ideal for cine imaging. However, it has less tissue contrast and increased susceptibility to magnetic field inhomogeneities and ferromagnetic-related

artifacts. A variety of gradient echo sequences are widely used in CMR for cine imaging, myocardial perfusion and scar assessment, coronary imaging, and MRA.

4. **Cine imaging.** The most widely used pulse sequence for cine imaging is a gradient echo sequence called balanced steady-state free precession (B-SSFP) that "recycles" residual transverse magnetization with each subsequent sequence until a steady-state equilibrium is achieved. B-SSFP is characterized by high SNR and high image contrast between blood and myocardium. However, B-SSFP is relatively insensitive to blood flow and, therefore, can be suboptimal for imaging of valve dysfunction or intracardiac shunts, which can usually be better illustrated using other gradient echo pulse sequences, such as echo planar imaging or phase velocity mapping. In addition, B-SSFP is also more susceptible to magnetic field inhomogeneities, which can be problematic in patients with mechanical valves or other cardiac implants.
5. **Myocardial tagging.** RF pulses can be applied before the excitation pulse to generate dark saturation lines or grids on cine images, which are then tagged to the myocardium and further used to assess myocardial deformation. The tags can be used to help qualitatively assess myocardial motion and pericardial tethering or to quantitatively measure myocardial strain. Strain encoding (SENC) utilizes myocardial tagging-by-tagging planes parallel to the image plane so that global longitudinal strain is assessed from short-axis views and global circumferential strain from long-axis views. This results in similar strain assessment to feature-tracking methods.
6. **Tissue/feature tracking.** Tissue/feature tracking is another method to assess myocardial strain imaging. Feature tracking is an analysis software that enables endocardial border tracking using routinely acquired, bright blood, SSFP long- and short-axis cine CMRI of the left ventricle (LV). This allows for pixels within the endocardium to be tracked across successive frames, and measures of deformation (strain) can be obtained. Global longitudinal strain measured by this methodology can identify subclinical myocardial

disease in patients with normal LV ejection fraction and has been a robust predictor of mortality in patients with dilated cardiomyopathy (DCM). It also can provide further differentiation between restrictive cardiomyopathy and constrictive pericarditis, as isolated constrictive physiology is associated with higher strain values. In addition, it has been studied to assess LV rotational indices of torsion, which is calculated as the difference between apical and basal rotation. Particular rotational patterns have been associated with cardiac amyloidosis and hypertrophic cardiomyopathy (HCM). The major advantage of tissue-/feature-tracking strain analysis is that postprocessing can be performed with routine cine CMR acquisition, thereby bypassing the need for dedicated pulse sequences. However, feature-tracking analysis requires additional postprocessing steps and has not yet been incorporated into routine clinical practice. However, automated postprocessing tools may enable feature-tracking strain assessment to be included into routine clinical assessment.

7. **Perfusion imaging.** In qualitative perfusion imaging, very fast gradient echo sequences are used for dynamic imaging of LV myocardial perfusion during the first pass of a gadolinium contrast agent during rest and stress states. Fast gradient echo techniques are commonly used, such as fast low-angle shot or B-SSFP with a prepulse to null or darken the myocardium. Normally perfused myocardium shows an increase in signal intensity because of gadolinium contrast, whereas abnormally perfused areas remain dark, reflecting hypoperfusion. There have been significant developments in quantitative perfusion, which can better characterize varying levels of coronary artery disease (CAD) severity more accurately, particularly in distinguishing between single-vessel and three-vessel disease and microcirculation. There are two approaches to aid in precise measurement of the arterial input function: dual bolus and single bolus. In dual-bolus technique, stress and rest perfusion are performed twice, first with a low dose of gadolinium for blood arterial input function and then repeated at a normal dose for the myocardium. In single-bolus

technique, a dual-sequence approach is utilized. There is full coverage with one slice that is then repeated and optimized for measuring the high gadolinium-concentrated blood. There are many models to solve the contrast exchange between the blood and the myocardium. Advances in the computational power of CMR have led to the development of full automation of quantitative perfusion by generating perfusion maps, with each pixel color coded in mL/g/min, which can make results available within a few minutes after acquisition. This automation has been validated against positron emission tomography (PET) with good agreement for rest/stress states, global/regional perfusion, and absolute/relative values and better reproducibility compared to PET.

8. **Delayed imaging.** Delayed hyperenhancement imaging for myocardial scar or fibrosis is performed 10 to 30 minutes after injection of gadolinium contrast using gradient echo sequences with an inversion recovery prepulse to null signal from the myocardium. Areas of myocardial scarring/fibrosis, protein infiltration, or significant edema have a larger extracellular space with a greater accumulation and slower washout of gadolinium and, therefore, appear bright compared with dark, normal myocardium on delayed imaging.
9. **T1 and extracellular volume (ECV) mapping.** In T1 mapping, T1 values are utilized to generate pixel maps to quantify the tissue T1 property. The sequences used for T1 mapping acquisition are based on inversion recovery, saturation recovery, or hybrid techniques, with the most common ones being the modified Look-Locker inversion recovery (MOLLI), shortened modified Look-Locker inversion recovery (shMOLLI), and saturation recovery single-shot acquisition (SASHA). The native T1 is the T1 relaxation time without the use of contrast agents, and it can be used to detect both focal and diffuse myocardial diseases in the interstitial and intracellular compartments. Native T1 values are elevated with myocardial water content, which is useful for assessing acute conditions such as myocardial edema and

inflammation in the setting of acute myocardial infarction (MI), myocarditis, and stress cardiomyopathy. It can also detect fibrosis and scar, as T1 values are higher compared to remote myocardium, as well as revealing infiltration by iron, fat, and amyloid. Postcontrast T1 values are used in association with native T1 values to determine the ECV, which is composed of the interstitial and intravascular spaces. ECV is used over postcontrast T1 values alone because it has much better correlation with histologic collagen volume fraction. ECV expansion occurs in multiple pathologic processes, including myocardial edema, rheumatic diseases, fibrosis, infiltrative disease, and HCM, and in vasodilator stress perfusion imaging secondary to intravascular expansion from coronary vasodilation. In addition, elevated ECV values are associated with ventricular remodeling, subsequent heart failure, and higher risk of mortality.

10. **T2 characterization.** T2 short-tau inversion recovery (T2-STIR) technique is a pulse sequence specifically developed for quantifying myocardial edema. Edema appears as a high-intensity signal, while the signal from fat and the blood pool is suppressed, which improves the contrast between normal myocardium, edema, and the LV chamber. T2 is limited by cardiac motion and elevated heart rates.

    Alternatively, T2 mapping techniques enhance SNR, decrease image artifact, and improve reproducibility while providing quantitative T2 measurements on a pixel-by-pixel basis. T2 values are also usually elevated in the setting of higher water content as it also represents intracellular and extracellular compartments. T2 mapping can help overcome incomplete blood suppression and the variation in myocardial signal from phased-array coils, which occurs in conventional T2-weighted sequences. Clinically, it is useful in detecting edema in acute MI, acute myocarditis, sarcoidosis, stress cardiomyopathy, acute cardiac allograft rejection, and drug-induced cardiotoxicity.

11. **Phase-contrast velocity mapping.** The phase difference in the spin of protons in moving blood compared with stationary protons

within a magnetic gradient is called the "spin phase shift" and is proportional to the velocity of the moving protons. A phase-encoded image is constructed, with the gray level of each pixel coded for velocity. Phase-contrast velocity mapping could be considered analogous to pulse wave Doppler echocardiography. It can be used to measure blood velocity and hence quantify cardiac output, shunts, and valve dysfunction. There are, however, limitations, given that the accuracy of this method is highly dependent on factors such as flow pattern, flow velocity, size, and tortuosity of the vessel. Flow-related signal loss can be a result of loss of phase coherence that can occur in cases of significant flow acceleration and even in higher orders of motion present in complex flow patterns.

12. **4D flow.** 4D flow provides time-resolved, 3D imaging. This allows for more accurate and precise assessment of valvular heart disease. Within one acquisition, all valves are visualized with direct quantification of flow and peak velocities without the limitations of geometric assumptions. It can also measure wall shear stress, viscous energy loss rate, and turbulent kinetic energy. Limitations include time-consuming image acquisition and postprocessing.
13. **MRA.** MRA of the great vessels typically involves a 3D fast gradient echo acquisition after injection of gadolinium contrast. The image resolution is typically $2 \times 2 \times 3$ mm^3, making MRA an excellent option for imaging of large- to intermediate-sized arteries, but less optimal for imaging of smaller vessels.

E. Contrast agents. A number of gadolinium chelates are used as contrast agents in clinical MRI. Gadolinium significantly shortens the relaxation time of nearby protons, thereby increasing their signal intensity. These contrast agents are safe, with a low side-effect profile. Prevalence of adverse reactions is approximately 2% and includes transient headache, nausea, vomiting, local burning or cool sensation, and hives. Anaphylactic reactions are extremely rare. Previously, gadolinium-based contrast agents (GBCAs) with linear structures were used more commonly but have been associated with

nephrogenic systemic fibrosis (NSF) in patients with chronic kidney disease (CKD). However, macrocyclic GBCAs have been relatively safe with respect to NSF, and class 2 agents have been shown to have very low to no risk for causing it. If macrocyclic GBCAs are being used, it is unnecessary to measure estimated glomerular filtration rate (eGFR) or avoid contrast in patients with advanced CKD not on dialysis. In patients who do undergo hemodialysis, the session should be scheduled as soon as possible and within 24 hours after the MRI. The risk of acute kidney injury is low as long as the recommended dose is used. Trace amounts of gadolinium deposition in the brain and other organs have been reported, including those with normal renal function. The significance of this is not yet known. Due to this, it is still advised that GBCAs only be used when medically necessary.

IV. PRACTICAL CONSIDERATIONS

A. Safety

1. **Magnetic force.** Cardiac MRI scanners typically utilize powerful magnets of 1.5 to 3.0 T, several tens of thousands of times stronger than the earth's magnetic field (0.00005 T). Large or small ferromagnetic objects in the vicinity of the MRI magnet bore can become fast-moving projectiles, which may cause severe injury to patients and/or damage the MRI scanner. Health care professionals working in the vicinity of an MRI scanner require MRI safety training and should be vigilant to the risk posed by patients and health care professionals not familiar with the danger.
2. **Magnetic field gradients.** Switching magnetic field gradients during a CMR study produces high acoustic noise levels (up to 115 dB) and can also lead to peripheral nerve stimulation. The Food and Drug Administration (FDA) has determined limits to the power of magnetic field gradients and noise exposure. Headphones and earplugs are recommended to prevent discomfort and hearing loss to patients and MRI staff in the vicinity of the scanner.
3. **Bioeffects of RF energy.** The majority of RF energy to the patient is dissipated as heat and is recorded as the specific absorption rate

(SAR). One SAR equals 1 J of RF energy per second per kilogram of body weight (ie, watts per kilogram). The recommended SAR limit for the whole body is 4 W/kg.

4. **Cardiovascular implantable electronic devices (CIEDs).** While cardiac pacemakers and defibrillators were previously considered to be absolute contraindications for cardiac MRI, numerous studies have demonstrated the minimal risk associated with performing MRI in patients with cardiac devices, regardless of MRI-conditional status. MRI-conditional CIEDs such as pacemakers and implantable cardioverter-defibrillators (ICDs) have been tested under modeling conditions to demonstrate MRI safety. Patients with abandoned leads/nonconditional cardiac devices may require additional consultation with electrophysiology to determine risk/benefits of proceeding with CMR. It is required that dedicated personnel who can program the CIED, perform advanced cardiac life support (ACLS), and monitor MR-conditional electrocardiogram (ECG) and MR-conditional pulse oximetry be present when scanning patients with cardiac devices. It is recommended that a defibrillator/monitor/external pacer and device programming system be immediately available. Device interrogation should occur beforehand to inhibit pacemakers or program them to asynchronous pacing in those who are dependent. ICD tachyarrhythmia detection should be disabled. After the CMR, device settings should then be restored. Some institutions recommend chest x-rays before and after to ensure the stability of the device and lead locations. Unless the benefits outweigh the risks, devices should not have been placed within 6 weeks due to incomplete endothelialization, possibly increasing the risk for device movement. In addition, patients should not undergo MRI if there are any fractured leads.

B. Patient preparation

1. **Screening.** All patients should be screened for contraindications to MRI before the procedure (see **Table 52.2**).

2. **Patient size.** Although the maximum table load weight limit is fairly generous (~250 kg or 550 lb), because of the fixed internal diameter of the magnet bore, very large patients may not fit within the MRI magnet. CMR scanners now have bore circumferences up to 70 cm. Discussion with the MRI technologist before scanning is recommended to determine the compatibility of onsite MRI scanners for patients with larger body sizes.
3. **Claustrophobia.** The enclosed space of the magnet may pose a problem for patients. The study can usually be successfully completed with the help of clear communication with the patient before and during the procedure and/or with light oral sedation (eg, lorazepam or alprazolam 0.25-0.5 mg) 30 to 60 minutes before the procedure.
4. **Attire.** Patients should wear a cotton hospital gown with no metal snaps. All metal items, jewelry, and nylon undergarments should be removed for reasons of safety and possible image degradation.
5. **Body coil.** Phased-array body coils are placed on the patient's torso over the imaging area of interest. These use several smaller coils to acquire RF signals simultaneously and to facilitate parallel imaging. Some of these coils, for example, enable the performance of 3D cardiac cine examinations with full ventricle coverage in a single breath-hold. The net result is not only better image quality but also reduced examination time for the patient.
6. **ECG monitoring.** A good electrocardiographic tracing is essential for CMR. Although three or four MRI-safe, nonmetallic electrodes are placed on the patient's chest and a single-lead signal is used to trigger or gate the MRI, the magnetic field affects the ECG tracing by inducing a voltage created by ions flowing within blood vessels (magnetohydrodynamic effect). This voltage artifact is commonly superimposed on the ST segment (during the ejection of blood in systole), increasing its amplitude and causing false QRS detection in certain algorithms. The use of vector cardiogram allows the R-R interval to be registered as a 3D spatial vector that varies in magnitude and direction throughout the cardiac cycle. Furthermore, the use of fiberoptic cables (instead of carbon leads)

has also decreased the potential ECG interference of RF pulses and/or gradient field switches.

7. **Emergencies.** CMR is not appropriate in patients who are clinically unstable because of difficulties monitoring and treating patients within the magnet bore. Although MRI-safe equipment is available, it is safer to prescreen the patient's clinical status and determine the need for CMR study before initiating the scanning.
8. **Pregnancy.** There is insufficient evidence regarding the safety of MRI in pregnant patients. Current guidelines state that MRI may be used in pregnant patients where other forms of nonionizing imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation. However, gadolinium administration in pregnant patients is contraindicated.
9. **Children.** CMRI may be necessary in pediatric patients with congenital and acquired cardiovascular disease. Typically, children younger than 8 years will require general anesthesia.

V. CLINICAL APPLICATIONS

A. Diseases of the aorta

1. **Aortic aneurysm.** MRI can clearly visualize both the aortic vessel wall and the lumen. It is a reliable method for the identification, characterization, and follow-up of thoracic and abdominal aortic aneurysms, with accuracy comparable to that of CT. A combination of spin-echo sequences for characterization of the vessel wall, gradient echo cine sequences for dynamic imaging of the aorta and aortic valve, and either 3D contrast-enhanced MRA (CE-MRA) for aortic and branch vessel luminography is typically used. Free-breathing whole-heart 3D MRA sequences (both with and without contrast) is also performed to acquire gated 3D imaging of the aortic root as well as the remainder of the thoracic aorta.
2. **Aortic dissection.** MRI is a highly sensitive and specific technique for the detection of aortic dissection (sensitivity 98%-100%, specificity 98%-100%). Spin echo, B-SSFP, and CE-

MRA are used to identify the intimal flap, true and false lumens, and involvement of aortic branch vessels, including the coronary arteries. Administration of contrast is not critical to the examination, making CMR particularly helpful in patients with significant renal impairment. In addition, potential complications of aortic dissection (eg, pleural effusion, pericardial tamponade, and aortic regurgitation) are easily evaluated. However, the longer study acquisition time with MRI compared with CT and its unsuitability for imaging of unstable patients limit its application in the acute setting. However, MRI is well suited for follow-up of both surgically and medically treated aortic dissections.

3. **Intramural hematoma and penetrating aortic ulcer.** Intramural hematoma can be considered as the forme fruste of aortic dissection because of the spontaneous rupture of vasa vasorum within the media of the aortic wall. It occurs in up to 30% of all acute aortic syndromes and appears as a smooth crescentic area of the thickened aortic wall without evidence of blood flow in the false channel on either B-SSFP or spin-echo sequences. Because of the short T1 relaxation time of fresh blood, differentiation from the adjacent mediastinal fat may be difficult. Intramural blood can be best detected on fat-saturated T1-weighted gradient echo or black-blood techniques. Furthermore, on spin-echo ("black-blood") imaging, the intramural hematoma may be isointense (acute) or hyperintense (subacute) relative to skeletal muscle. Penetrating aortic ulcers appear as deep ulcerations of an aortic atheroma that extend through the intima to disrupt the underlying media and cause bulging of the outer aortic contour. They commonly appear at the isthmus beyond the left subclavian artery and in the distal descending thoracic aorta near the diaphragm. If acute, there may be evidence of intramural bleeding in the rim adjacent to the ulcer.
4. **Atherosclerotic disease.** MRI can clearly show irregular thickening of the aorta in atherosclerotic disease. CE-MRA has good accuracy for detecting significant peripheral stenoses and occlusions.

5. **Aortic trauma.** MRI can detect chronic or missed aortic tears, usually related to a previous motor vehicle accident. Tears are usually found in the area of the ligamentum arteriosum and diaphragmatic hiatus and are characterized by a localized saccular aneurysm, with or without associated periaortic hematoma.
6. **Aortitis.** In patients with inflammatory disorders affecting the aorta such as Takayasu disease (which tends to also involve the arch branch vessels) or giant cell arteritis, MRI can accurately detect diffuse wall thickening of the thoracic and abdominal aorta (especially after gadolinium administration in T1-weighted images) as well as stenosis and occlusion of the aortic branch vessels (CE-MRA sequences). Special imaging sequences using T2 weighting and STIR for fat suppression allow assessment of wall edema and wall thickening/inflammation, respectively.
7. **Aortic stents and stent grafts.** Aortic stents and stent grafts can be safely imaged using MRI; however, both cine sequences (gradient echo and B-SSFP) are prone to ferromagnetic artifacts. Spin-echo imaging can be used to evaluate stent graft morphology. Artifacts may limit assessment for endoleak using CE-MRA. However, CT is ultimately the recommended imaging modality due to the significant artifact in MR. Invasive interventions under MRI guidance are becoming more possible as rapid imaging techniques and catheter technology continue to develop.

B. Assessment of ventricular function and CAD

1. **Assessment of global ventricular function.** CMR is the gold standard for the assessment of ventricular mass, volumes, and systolic function. A significant advantage of CMR is its reproducibility and accuracy compared with 2D planar or projection techniques that depend on geometric assumptions in order to define mass and volume determinations. As a result, small changes in myocardial mass and/or volume can be detected over time or because of therapy. A typical approach is to perform a short-axis stack of B-SSFP cine sequences through the LV and right ventricle (RV). Manual or semiautomated tracing of the endocardial borders at end diastole and end systole is later

performed off line, and ventricular volumes and ejection fraction are calculated.

2. **Assessment of regional ventricular function.** As mentioned before, development of multichannel phase-array coils has enabled parallel imaging and significant improvements in temporal resolution and scan times. This has led CMR to become superior to echocardiography for precise assessment of regional wall motion. B-SSFP cine sequences provide excellent blood-myocardial contrast that permits clear definition of the endocardial border. Furthermore, myocardial tagging methods have also improved the assessment of regional myocardial function.
3. **Myocardial ischemia and stress testing.** CMR stress testing can detect myocardial ischemia with either wall motion, qualitative perfusion analysis, or quantitative perfusion. Dobutamine stress CMRI can evaluate the presence of stress-induced wall motion abnormalities, while stress perfusion imaging with adenosine or dipyridamole can evaluate vasodilator-induced perfusion defects. Studies of stress CMR with dobutamine have revealed good sensitivity (83%-92%) and specificity (86%) for the detection of significant CAD on a per-patient level. Furthermore, CMR tagging may further improve the accuracy of dobutamine CMR for ischemia detection. Stress perfusion imaging by CMR has been shown to have slightly higher accuracy than that of thallium single-photon emission computed tomography (SPECT), with a sensitivity of 91% and specificity of 81% for the detection of significant CAD. Quantitative perfusion techniques at stress and rest have robust accuracy compared with PET and invasive measurements of coronary blood flow. Compared to qualitative perfusion, it is more accurate in identifying single-vessel versus three-vessel disease. In addition, stress CMR has the unique advantage of assessing involvement of the microvascular vessels and patients with myocardial infarction with nonobstructive coronary artery disease (MINOCA), including coronary plaque erosion or rupture, coronary vasospasm, distal coronary thrombosis/embolism, and spontaneous coronary artery dissection

(SCAD). Utilizing stress CMR has prognostic significance as well, as those with perfusion defects have worse clinical outcomes. The absence of ionizing radiation with MRI is an important consideration, particularly in younger patients. These advantages have led to stress CMR being included as a class I indication in the 2021 Chest Pain Guidelines for evaluating ischemia in cases of acute chest pain with intermediate risk.

4. **MI and viability.** T2-weighted spin-echo sequences with fat suppression may show areas of increased signal intensity consistent with tissue edema in the acute or subacute phase of an MI. This has been gaining interest as a target for clinical trials in acute coronary syndrome. The concept is that the myocardium at risk would correspond to the edematous minus the scarred area (seen on delayed enhancement). However, this technique has potential imaging artifacts (cardiac/respiratory motion, low SNR, slow flow, coil intensity profile, etc), which could hinder the reproducibility of results seen in single-center studies. The current state-of-the-art technique for myocardial scar detection remains delayed enhancement imaging with an inversion recovery gradient echo sequence 10 to 15 minutes after injection of a gadolinium contrast agent. This method shows areas of myocardial scarring as bright and normal myocardium as dark and has shown excellent correlation with the location and extent of scar on histopathologic analysis. The superior spatial resolution of CMR makes it more sensitive for the detection of myocardial scar, and in particular subendocardial scar, than SPECT or PET. In addition, detection of areas of microvascular obstruction, despite adequate epicardial vessel perfusion, can also be identified with CMR and appear to be associated with worse outcomes. The transmural extent of scar is associated with myocardial viability. Transmural or near-transmural scar (>50%) suggests nonviable myocardium, whereas the absence of myocardial scar suggests that functional recovery is likely post-revascularization.
5. **LV thrombus.** CMR is more sensitive than echocardiography for the detection of LV thrombus. Because of its high spatial

resolution and tissue characterization capabilities, CMR can be quite advantageous in establishing or ruling out the diagnosis of intracardiac thrombus. The typical signal characteristics would include lack of contrast perfusion on first pass of gadolinium and low-signal intensity on postcontrast delayed imaging with long inversion time (dark filling defect on the LV endocardial surface).

C. **Nonischemic cardiomyopathies.** There is increasing recognition of myocardial fibrosis occurring in a variety of conditions in the absence of ischemia, including hypertensive and diabetic heart disease, HCM, and idiopathic DCM. Several new CMR techniques have been developed for the quantification of nonischemic myocardial fibrosis, with contrast-enhanced T1 mapping using a MOLLI sequence being the most commonly used.

1. **DCM.** CMR is useful for precise assessment of cardiac morphology and function in patients with DCM. In addition, delayed enhancement imaging will typically show enhancement in a mid-myocardial distribution in case of idiopathic cardiomyopathy.
2. **HCM.** MRI is accurate for the evaluation of the pattern and extent of hypertrophy, systolic anterior motion of the mitral valve, resting left ventricular outflow tract (LVOT) obstruction, and secondary mitral valve pathology and regurgitation. Because of the precise anatomic definition provided by CMRI, it is particularly helpful in planning for surgical myectomy or alcohol septal ablation. CMR can also help identify abnormal chordal or papillary muscle attachments, which may contribute to LVOT obstruction and which have been reported in up to 20% of patients with HCM. Delayed enhancement is frequently seen in patients with HCM and corresponds to areas of interstitial fibrosis. It is typically seen in areas of increased wall thickness as well as RV insertion points in the interventricular septum. The extent of delayed enhancement in patients with HCM has been linked to sudden cardiac death and worse outcomes.
3. **Arrhythmogenic cardiomyopathies (ACMs).** CMR is frequently the imaging modality of choice in patients with suspected ACMs

to assess for the presence of ventricular dilation, dysfunction, regional hypokinesia, edema, and late gadolinium enhancement (LGE) for assessing fibrosis. In arrhythmogenic right ventricular cardiomyopathy (ARVC), the diagnostic criteria include regional RV dyskinesis/akinesis/dyssynchronous contraction in the setting of reduced RV ejection fraction (<40%) or increased indexed RV end-diastolic volume. Fibrofatty replacement of the RV myocardium on CMR is not a diagnostic criterion. CMR examination includes careful assessment of RV size and function and delayed enhancement imaging for identification of myocardial fibrosis.

4. **Myocarditis.** CMR has the unique ability to detect myocardial edema, increased blood flow and capillary leakage, necrosis, and fibrosis that can occur in myocarditis as well as regional and global contractile dysfunction. Together, these signs are able to help provide a more definitive, noninvasive, positive diagnosis of myocarditis. Increased T1 times with T1 mapping, increased ECV fraction, and increased T2 mapping times indicate myocardial edema, which is diffuse in myocarditis. LGE is typically not in a coronary artery distribution with mid- or epicardial involvement in chronic stages. In the post–COVID-19 era, CMR has become a valuable tool for assessing signs of myocardial injury and cardiac dysfunction. This noninvasive means of diagnosis can guide further patient management decisions.
5. **Genetic cardiomyopathies.** Multiple genetic cardiomyopathies can present as DCMs, ACMs, or HCMs. The phenotypes of these cardiomyopathies can be assessed with CMR, and patterns of enhancement can give suggestions as to the likely mutation. In addition, the presence and volume of LGE may have prognostic value in predicting hospitalization for heart failure, appropriate ICD discharge, and sudden cardiac death. Desmoplakin mutations clinically have episodic myocarditis and are more likely to show LGE, primarily in the inferior wall subepicardium but with occasional spread to the interventricular septum mid-myocardium. Filamin-C mutations are associated with an arrhythmogenic DCM

and have a similar LGE pattern in the subepicardium. Titin mutations can not only lead to DCM but also present with ventricular noncompaction or HCM, and its LGE pattern is typically mid-myocardial. Lamin A/C presents as ACM and/or DCM with mid-myocardial LGE pattern. Other genetic cardiomyopathy mutations that present as an ACM with mid-myocardial LGE patterns include bcl2, RNA-binding motif protein 20, and sodium voltage-gated channel alpha subunit 5.

6. **Infiltrative cardiomyopathy.** Infiltrative cardiomyopathy is typically characterized by normal ventricular size and systolic function, increased LV and/or RV wall thickness, severe diastolic dysfunction, and biatrial enlargement. CMR can clearly visualize the typical findings of infiltrative cardiomyopathy and help distinguish it from constrictive pericarditis, the main differential diagnosis. Also, specific CMR sequences can be used for the assessment of particular disease states and specific causes may be identified, particularly with the use of gadolinium enhancement. Cardiac amyloid CMR findings include diffuse subendocardial or transmural LGE with elevated T1 and ECV as well as increased wall thickness. It is not able to differentiate between light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) amyloid. In cardiac sarcoidosis, there is increased wall thickness with elevated T1 intensity and patchy LGE in noncoronary distribution. Fabry disease uniquely has reduced T1 intensity, elevated T2 in the basal inferolateral wall, and mid-myocardial LGE in the basal inferolateral wall. Hemochromatosis is characterized by extensive signal loss on T2-weighted images, because of iron deposition in the myocardium. Measurement of the T2 relaxation time of the myocardium (T2* technique) allows precise detection of the amount of iron overload. In addition, this T2* technique has been shown to be prognostically important, identifying patients with thalassemia at high risk for heart failure and arrhythmia.

D. **Diseases of the pericardium.** The normal pericardium appears on CMR as a thin (≤2 mm) curvilinear line between the epicardial and

pericardial fat. The normal pericardium is of low intensity on both T1- and T2-weighted imaging sequences.

1. **Pericardial effusions** are typically of low intensity on T1-weighted spin-echo images and of high intensity on gradient echo images. The exception is hemorrhagic effusion, which is of high intensity on T1-weighted spin-echo images and of low intensity on gradient echo images.
2. **Pericarditis and constriction.** Pericarditis is typically diagnosed when two of four criteria are met: typical chest pain, friction rub on examination, ECG findings, and new pericardial effusion. However, there can be diagnostic uncertainty in which CMR can provide additional clarity, particularly in chronic/recurrent pericarditis. MRI can readily define the presence and extent of parietal pericardial thickening, with ≥3 mm being considered pathologic, as well as the presence of pericardial effusion, which appears bright on SSFP sequences and dark on black-blood and late gadolinium phase-sensitive inversion recovery sequences. In acute inflammation, fast spin-echo/double-inversion recovery T1-weighted imaging nulls the blood and has high resolution, which helps enhance the tissue contrast between the myocardium, epicardial fat, pericardium, and mediastinal fat. T2-STIR is a particularly useful technique in active inflammation as it nulls the epicardial and mediastinal fat, making the signal-noise contrast of pericardial edema more apparent. In inflammatory pericarditis, the pericardium will typically have increased signal intensity on delayed enhancement imaging, reflecting neovascularization in the inflamed pericardium. LGE has a sensitivity of 94% to 100% for detecting pericardial inflammation. CMR has become the imaging technique of choice for the diagnosis and management of constrictive pericarditis. Typical features include pericardial thickening and tethering, associated with conical and tubular deformity of the RV and LV, respectively. Secondary changes include atrial enlargement, systemic and pulmonary vein dilation, hepatomegaly, ascites, and pleural effusions.

Phase velocity mapping can quantify blood flow and velocities across valves to evaluate caval and pulmonary vein flows, which can give indirect hemodynamic assessment of filling pressures. Cine sequences can demonstrate features of constrictive physiology, including diastolic septal bounce and abrupt cessation of diastolic filling. Furthermore, real-time cine sequences with free breathing can demonstrate the interventricular dependence with exaggerated septal shift toward the LV during inspiration. Tagged imaging and strain-encoded imaging can also provide additional characterization of constrictive physiology via quantifying regional tissue deformation. However, it is important to note that CMR is of limited value compared with CT in the evaluation of pericardial calcification because of its inability to visualize calcium (because of its lack of hydrogen ions).

MRI has been used to provide more personalized recommendations regarding the type and duration of treatment from both a pericarditis aspect and identifying concomitant myocarditis. As anti-inflammatory treatment decreases the sensitivity of inflammatory markers, it can be difficult to determine the length and intensity of anti-inflammatory treatments based on symptoms alone. Within a patient's clinical context, CMR can aid in staging inflammation and monitoring for progression or resolution. It can also guide therapy in those not responding adequately to current regimens and timing of anti-inflammatory treatment tapers in the settings of recurrent, chronic, and complicated pericarditis.

3. **Congenital absence of the pericardium.** This is often left-sided and can be complete or partial. It can be relatively easily demonstrated on CMR as it is typically associated with a leftward orientation and "teardrop" appearance of the heart. Insinuation of lung tissue between the aorta and the pulmonary artery and between the inferior surface of the heart and the left hemidiaphragm is also characteristically seen.
4. **Pericardial cysts.** These are benign developmental lesions formed when a portion of the pericardium is pinched off during

embryogenesis. Pericardial cysts are classically seen at the right cardiophrenic angle. They typically contain fluid and are well marginated. Spin-echo images demonstrate round or ovoid lesions that are often contiguous with the normal pericardium. Simple cysts demonstrate low-signal intensity on T1-weighted and high-signal intensity on T2-weighted images. Hemorrhagic or proteinaceous filled cysts show high-signal intensity on T1-weighted images.

E. Congenital heart disease. CMR has become a crucial tool in the management and follow-up of patients with congenital heart disease, particularly in cases with complex defects. Scans can be performed safely and reliably from infancy through adulthood. CMR provides excellent anatomic definition of simple and complex heart defects and precise, noninvasive quantification of valvular function, cardiac function (both LV and RV), and shunts. Common applications of CMR in adult congenital heart disease include noninvasive quantification of intracardiac shunts; assessment of scar in determining the risk of sudden cardiac death; evaluation of pulmonary regurgitation severity, ventricular volumes and function, and pulmonary artery branch vessel stenosis in patients post tetralogy of Fallot repair; identification of RV outflow tract or branch pulmonary artery obstruction in patients who are post arterial switch for dextro-transposition of the great arteries (D-TGA); evaluation of baffle stenosis or leak and RV dysfunction in patients post Mustard or Senning procedure for D-TGA; and assessment for dysfunction of the systemic ventricle in patients with congenitally corrected or levo-transposition of the great arteries (L-TGA). It can also be used to assess anomalous coronary artery anatomy and exclude ischemia.

F. Valvular heart disease. Although echocardiography remains the primary imaging modality for the diagnosis and management of valvular heart disease, CMR can provide additional important information in select cases. Particular strengths of CMR in the evaluation of valve dysfunction include an often clearer visualization of valve morphology, valve planimetry, precise quantification of regurgitant volumes, accurate and reproducible measurement of

ventricular volumes and function, and assessment of associated abnormalities (eg, mitral valve prolapse with associated myocardial fibrosis/mitral annular disjunction and bicuspid aortic valve with ascending aortic dilation). It can also provide further risk stratification. In aortic stenosis, accurate LV mass measurements are available via CMR to assess the effect of the stenosis on the LV. LGE identifying fibrosis can be seen in up to one-third of patients with severe stenosis, usually with concomitant significant LV hypertrophy, and is associated with a worse prognosis. This may be used to identify patients who may benefit from early surgery while still asymptomatic. In addition, in patients with CKD undergoing transcatheter aortic valve replacement (TAVR) evaluation, CMR is a safe alternative to CT for precise anatomical evaluation for procedural planning. In mitral regurgitation (MR), CMR is useful in also assessing mitral annular dysfunction and underlying myocardial disease in functional MR. CMR MR quantification is predictive of symptom development, LV dilation in initially asymptomatic patients, and regression of LV volumes postoperatively, which allows for the identification of asymptomatic patients appropriate for early surgery. In addition, diffuse myocardial fibrosis is predictive of requiring surgery over 3 years.

G. **Cardiac masses.** CMR plays a major role in the evaluation of cardiac masses, mainly because of its ability to provide, in addition to excellent anatomic detail, tissue characterization. Thrombus is the most common intracardiac mass. Fresh thrombus has higher signal intensity than myocardium on T1-weighted images. Older thrombi may have increased signal intensity on T1-weighted and decreased signal intensity on T2-weighted images. Thrombi usually have low-signal intensity on delayed enhancement imaging and do not demonstrate delayed enhancement, even with long inversion time. Myxomas are the most common intracardiac tumor and, in addition to having a heterogeneous and irregular appearance, typically have higher signal intensity than myocardium on T2-weighted spin-echo imaging. Lipomas have a distinctive short T1 and, therefore, high-signal intensity on T1-weighted images. Fat saturation sequences that

null lipomatous tissue help confirm the diagnosis. Fibromas are an uncommon cardiac tumor and are typically seen within the ventricular myocardium in pediatric or young adult patients. They have decreased signal intensity relative to myocardium on T2-weighted images and show rim enhancement on delayed imaging.

Primary malignant tumors of the heart are rare. Imaging findings suggestive of a malignant cardiac tumor include a right atrial location, invasiveness without regard to the anatomic borders (ie, involvement of >1 cardiac chamber, extension into the mediastinum or great vessels), associated hemorrhagic pericardial effusion, moderate or high contrast uptake on perfusion imaging (reflecting increased vascularity), and heterogeneous delayed enhancement. The most common is angiosarcoma followed by rhabdomyosarcoma. Angiosarcomas are most commonly seen in the right atrium and have a heterogeneous appearance with hyperintense areas on T1-weighted images. Delayed hyperenhancement shows heterogeneous enhancement, most marked in the periphery of the tumor. Metastatic heart disease is more common than primary cardiac tumors and typically involves the myocardium or pericardium. CMR is limited in its reduced sensitivity for the detection of calcification in cardiac masses.

H. Cardio-oncology. CMR has growing utility in the field of cardio-oncology beyond simple anatomic and physiologic assessment of cardiac masses. It can also assist with risk stratification prior to initiating chemotherapy and monitoring for subsequent toxicity. CMR enables sensitive evaluation of LV and RV function, strain assessments, noninvasive hemodynamic assessment of pulmonary hypertension, tissue characterization with T1/T2 mapping to assess for edema, stress-induced cardiomyopathy, pericardial disease, myocarditis, and underlying fibrosis with LGE. In addition, CAD, valvular heart disease, and infiltrative cardiomyopathies such as amyloid and iron overload can all be assessed and then monitored according to specific cancer therapy cardiotoxicity. This enables a more personalized delivery of cancer therapy and management of toxicity.

I. **Pulmonary veins.** Imaging of the pulmonary veins is being increasingly performed prior to and after pulmonary vein ablation, to assess pulmonary venous anatomy and patency and look for complications, particularly pulmonary vein stenosis.

VI. FUTURE APPLICATIONS

A. **Coronary artery assessment.** Coronary imaging with CMR is usually performed with gradient echo sequences, with either fat saturation or T2 prepulses to enhance the signal difference between the coronary lumen and the surrounding myocardium, as well as to decrease the venous signal. 3D acquisition with navigator-corrected (free-breathing) data set has higher SNR when compared with 2D sequences and has become the established approach to CE MR coronary angiography. Although CMR can be used reliably for the detection of coronary artery anomalies, it has not yet fulfilled its early promise for noninvasive imaging of coronary atherosclerotic disease. The coronary arteries provide significant challenges to imaging by MRI because of cardiac and respiratory motion, their small size and tortuosity, normal cyclic variations in coronary flow, and competing signal from neighboring blood pools.

B. **Advanced techniques**

1. **Molecular imaging.** MRI shows significant promise for the selective imaging of target cells using novel molecular contrast agents. Magnetically labeled mesenchymal stem cells have been successfully tracked by MRI in pig models used for stem cell therapy in myocardial injury. Supermagnetic nanoparticles have also been used to detect atherosclerotic plaque in both animal and human studies.
2. **Diffusion tensor imaging (DTI).** DTI applications to CMR are continuing to be developed for characterization of microstructural changes. DTI measures molecular water diffusion, which occurs preferentially along the long axis of cardiomyocytes. This can depict edema and scar along with changes to cardiac myofiber arrangements in MI, detect microstructural changes in HCM and

DCM, and microstructural abnormalities in congenital heart disease.

3. **Chemical exchange saturating transfer (CEST).** CEST is an emerging technique that focuses on myocardial metabolism by using the endogenous exchange of saturated protons with surrounding mobile water protons. Targets can be visualized by using the frequency-specific saturation of endogenous targets, such as fibrotic substrate, creatine, glucose, as well as exogenous targets such as paramagnetic CEST contrast agents. MRI reporter genes can also be targeted. This technique is not limited by light scattering or depth penetration, enables molecular image acquisition with anatomic detail, and could have future clinical use in chronic MI and amyloidosis.
4. **Cardiac magnetic resonance fingerprinting (cMRF).** CMRF is a developing approach to rapidly and simultaneously quantify multiple tissue properties, including T1, T2, and proton density. By directly incorporating RF pulse efficiency into the cMRF signal model, there are fewer assumptions in quantifying tissue characteristics, which improves scanner-to-scanner reproducibility. CMRF involves an accelerated acquisition of image frames with contrast weighting to induce sensitivity to properties of interest over time. A magnetic signal evolution model generates an individualized dictionary of "fingerprints" that is unique to each combination of tissue property values. An algorithm matches this dictionary with the image-derived signals. CMRF could better characterize multiple cardiomyopathies, including infiltrative, inflammatory, and ischemic.
5. **Elastography.** Cardiac MR elastography is a new noninvasive tool for evaluating myocardial biomechanical properties. Infiltrative cardiomyopathies and ischemic cardiomyopathies have been shown to have stiffer myocardium. Novel techniques are being assessed to optimize this tool as it could improve assessing LV wall stress, LV remodeling, diastolic function, and heart failure prognosis.

6. **Interventional CMR.** The use of CMR in interventional procedures is appealing because it may allow for radiation-free catheterization procedures. However, its main limitation is the availability of devices that are safe to use in an MR environment.

C. **Artificial intelligence.** Artificial intelligence and machine learning processes could help plan and optimize image acquisition, making it less time-intensive and more standardized across operators. Current applications are already implemented commercially to minimize motion artifacts and augment image reconstruction, segmentation, and quantitative analysis of images. CMR can also be utilized to enhance phenomapping analysis in various cardiomyopathies. Phenomapping is a type of unsupervised machine learning that is applied to data without a priori knowledge of the outcomes, thereby revealing mathematical relationships between data that can be used to cluster patients into different groups.

D. **Radiomics.** Radiomics is a novel analysis technique in which digital images are converted to data, which are subsequently analyzed to determine multiple numerical quantifiers of tissue character and shape. Disease conditions and outcomes could be identified with higher accuracy based on radiomic features, ultimately functioning as imaging-based biomarkers.

E. **Personalized medicine.** The sensitivity and specificity of CMR for a variety of cardiac conditions allow for more personalized risk stratification and tailored treatments. CMR can guide treatment length and medications in valvular disease, cancer, HCMs, and sudden cardiac death risk assessments.

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SUGGESTED READINGS

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SECTION X

Electrophysiologic Procedures

EDITOR: Thomas D. Callahan

CHAPTER 53

Electrophysiologic Studies

Balint Laczay and Shady Nakhla

I. INTRODUCTION. Electrophysiologic studies (EPS) are a specialized form of cardiac catheterization that help identify, characterize, and manage cardiac arrhythmias. Over the past 30 years, EPSs have advanced our knowledge of mechanisms of cardiac arrhythmias and revolutionized the way these arrhythmias are managed. The studies should be performed by trained clinicians with the help of skilled laboratory personnel in appropriately equipped laboratories. A joint task force of the American College of Cardiology and the American Heart Association, in collaboration with the Heart Rhythm Society, has published guidelines outlining the accepted indications and the training required for personnel performing EPS.

II. INDICATIONS. The indications for EPS can be divided into three broad categories: bradyarrhythmias, tachyarrhythmias, and syncope.

A. Bradyarrhythmias can be caused by sinus node dysfunction, atrioventricular (AV) nodal disease, or infranodal conduction system disease. EPSs for bradyarrhythmias are rarely necessary because the decision to implant a pacemaker depends primarily on the correlation between symptoms and documented bradycardia or demonstration of severe bradycardia or prolonged pauses. EPS should complement the clinical evaluation, conventional 12-lead electrocardiogram (ECG), and Holter or event monitor. EPS can be of value in identifying disorders associated with adverse outcomes, such as severe infranodal conduction system disease.

B. EPSs are of tremendous value in evaluating **tachyarrhythmias**. They are generally more successful in reproducing reentrant cardiac rhythms than those caused by triggered activity or enhanced

automaticity. Among patients with reentrant tachyarrhythmias, EPSs are useful in documenting the presence of the anatomic or physiologic substrate responsible for the arrhythmia, defining the electrical mechanism of the arrhythmia and its associated hemodynamic response, as well as guiding therapy. The response of the tachyarrhythmia during an EPS to various drugs or pacing maneuvers may also be helpful in further defining the underlying substrate and prognosis.

C. Patients with **syncope** of unknown etiology may benefit from EPS as it may reveal bradycardia or ventricular tachycardia (VT) to be the underlying disorder.

III. EQUIPMENT AND SETTING

A. The most important element in the performance of a safe and useful EPS is the presence of **well-trained personnel**. The presence of at least one trained physician and well-trained laboratory support personnel, including a nurse, as well as engineering assistance to maintain and repair the laboratory equipment is necessary. Personnel involved should be familiar with basic EP and electropharmacologic principles, the indications for EPS, and the various diagnostic and therapeutic modalities that can be used in the laboratory.

B. It is important that the laboratory be equipped with appropriate high-quality **radiographic equipment**.

C. Appropriate selection of **tools** is a very important aspect of the performance of a safe and cost-effective EPS. The minimum instrumentation required for a complete study is a stimulator, an amplifier, display monitors, reliable recording devices, and an external defibrillator.

1. The **stimulator** must be capable of burst pacing, delivery of at least three or four extra stimuli, synchronization to appropriate electric events during intrinsic or paced rhythms, and an adjustable current output. An appropriate unit should have a constant current source and minimal current leakage. It should also be relatively easy to manipulate.

2. The **junction box** connects the electrode catheters to the recording apparatus and the stimulator.
3. The presence of at least two functioning **external defibrillators** is extremely important, particularly during studies in which ventricular arrhythmias may be induced.
4. The presence of a cardiac surgical team in the same institution is not mandatory for routine EPS or simple radiofrequency (RF) ablation procedures. However, for more complex RF ablation procedures where full heparinization is used and where cardiac perforation is a potential complication, the presence of a cardiac surgical team allows for prompt, definitive therapy when surgical intervention is required.

D. Intracardiac signals are recorded using various electrode catheters.

1. The most common catheters used are **quadripolar woven Dacron polyester** or **polyurethane**. The electrodes of these catheters are capable of sensing electrical signals. The distal poles of these catheters can be used for pacing.
2. For general-purpose sensing and pacing in the atrium or ventricle, a **nondeflectable catheter** is usually sufficient. Deflectable catheters facilitate mapping and ablation by allowing more precise movement.
3. Interelectrode distance varies from 2 to 10 mm. Smaller interelectrode distance is useful for precise mapping and timing.
4. For most EPS, **bipolar recording** is used. However, in some situations, especially during mapping of tachyarrhythmias, **unipolar recordings** if interpreted correctly can be of value in localizing the earliest sites of activity.

IV. TECHNIQUES AND PROCEDURES

A. Preprocedural preparation

1. Before the patient is taken to the EP laboratory, a discussion of the indications and proposed procedure is conducted with the patient, and informed consent is obtained.

2. For most indications, EPS is an **elective** procedure. The patient's condition should be **clinically stable** at the time of the study. EPSs on patients who are unstable, including those with active, recent, or untreated coronary disease or those with clinical heart failure or clinical respiratory disease, carry much higher risk for complications.
3. **Electrolytes** and a **coagulation panel** are checked and verified as being within the acceptable range. **Serum creatinine** is noted should intravenous contrast be necessary during the procedure.
4. Conscious sedation is administered using a mild sedative (eg, a benzodiazepine) and analgesic (eg, fentanyl). **General anesthesia** can be used in certain anatomic ablations (eg, atrial fibrillation) or in circumstances where a patient cannot tolerate being awake during the procedure. Certain arrhythmias are less likely to be induced while under general anesthesia.
5. The patient is attached to continuous ECG and blood pressure monitoring devices.

B. Access and catheter placement

1. The usual approach to inserting electrode catheters is through the **femoral veins under local anesthesia** unless there is a clear contraindication to this approach, such as the presence of deep venous thrombosis, recent placement of an inferior vena cava filter, or other anatomic abnormalities (eg, interrupted inferior vena cava). In the latter situations or when a coronary sinus (CS) catheter is difficult to insert, a superior vein approach may be used. We routinely utilize vascular ultrasound to directly visualize the femoral venipuncture, particularly when patients are on anticoagulation. This real-time visualization clarifies anatomic variants and enables us to avoid inadvertent arterial needlesticks and multiple passes that can lead to bleeding complications. Sheaths are then introduced into the vein over guidewires via the modified Seldinger technique.
2. Up to three **introducers** are placed in each femoral vein depending on the planned procedure. For patients with **left-sided bypass tracts or left ventricular (LV) tachycardia**, access to the

left side of the heart is necessary. This can be achieved through the retrograde transaortic approach via femoral arterial access or by transseptal puncture via femoral vein access. Systemic heparin is used for all left-sided procedures, and the activated clotting time is monitored during the procedure to achieve adequate levels of anticoagulation.

3. For a complete EPS, three to four catheters are needed.
   a. One catheter is placed in the **CS** and/or **right atrium**, preferably in the appendage or against the septal or lateral walls. Another is placed in the **right ventricle (RV) (base, apex, or outflow region)**, and finally, another catheter is placed across the **tricuspid valve** to obtain a His electrogram.
   b. To obtain a **His electrogram**, the electrode catheter is advanced into the RV across the anterior septal portion of the tricuspid valve. Under gentle clockwise torque, the catheter is then slowly withdrawn to straddle the tricuspid valve. A high-frequency sharp deflection that precedes ventricular activation and follows septal atrial activation represents a **His** or **proximal right bundle potential**. If the catheter is withdrawn further, this sharp signal occurs slightly earlier. A satisfactory position of the His catheter is achieved when an atrial signal is recorded followed by the His potential and, finally, the ventricular potential is recorded via the same pair of electrodes.
4. In **supraventricular tachycardia (SVT)** studies, when a left-sided accessory pathway or left atrial origin is suspected, an octapolar or decapolar catheter may be placed in the CS rather than in the high right atrium. This more stable catheter position allows mapping of the left AV groove along the mitral annulus. Although the CS is easily entered from the superior venous approach, successful catheterization is expected in most attempts through the femoral approach as well. The use of a deflectable EP catheter increases the likelihood of successful CS cannulation. The catheter is placed in the CS with the proximal electrodes just inside the CS ostium (os).

C. Baseline assessment

1. When all the catheters are in place, a baseline ECG and intracardiac electrograms are obtained (**Figure 53.1**).

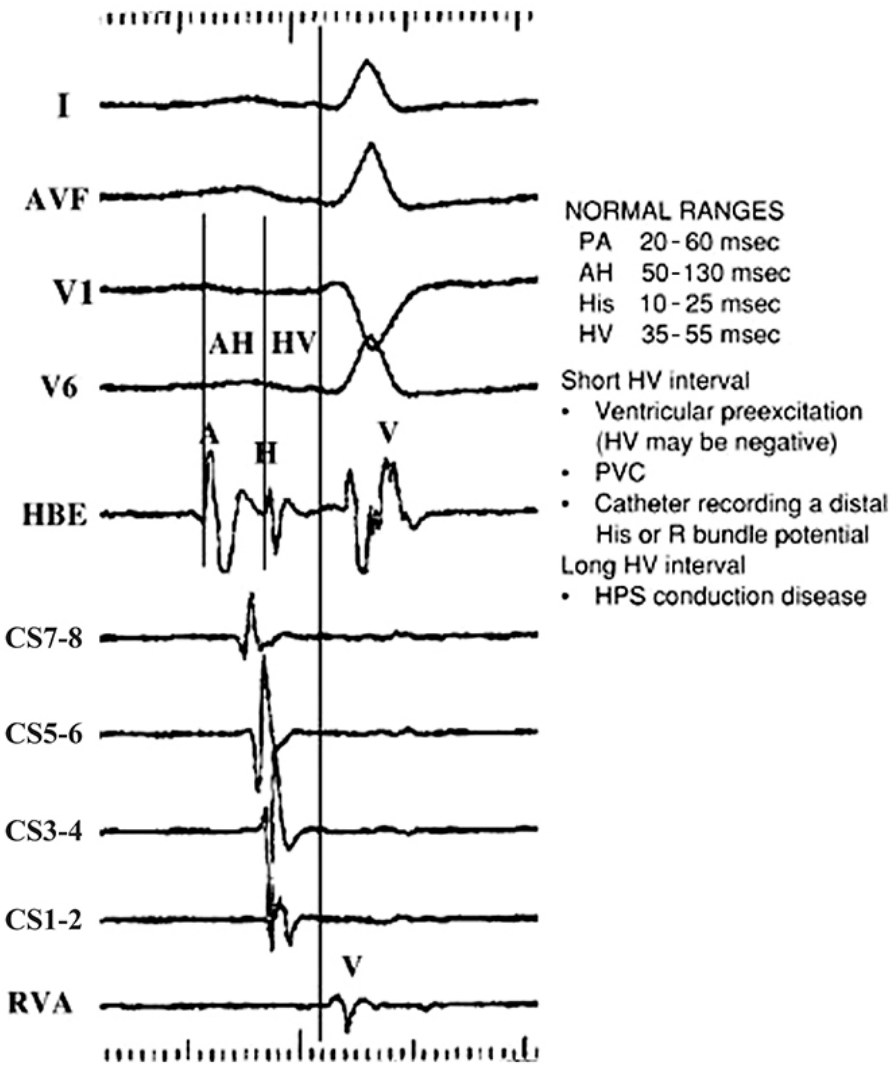
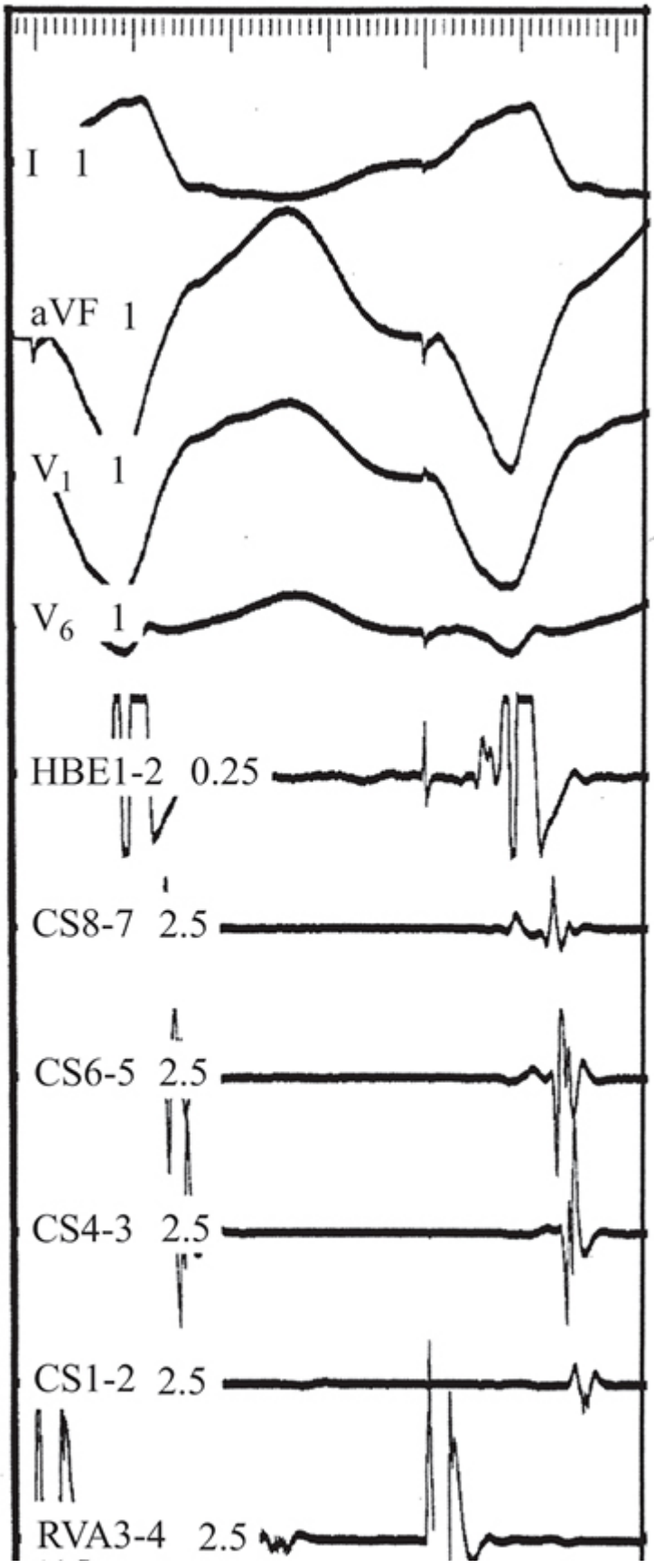


FIGURE 53.1 Normal baseline intervals. Typically, up to four surface ECGs (I, aVF, V_1, and V_6) are displayed along with atrial (CS), His (HBE), and ventricular (RVA) electrograms. CS7-8 refers to the proximal bipolar CS electrogram. Fast sweep speeds are used, ranging from 100 to 400 mm/s. On the time scale, each large division is 100 ms, and each minor division is 10 ms. In addition to intervals, patterns of atrial and ventricular activation should be evaluated. If the CS catheter is placed correctly (see text), the earliest A in sinus rhythm is seen on the HRA electrogram (not shown), then on the His electrogram, and progressively later along the CS electrograms. In the absence of bundle branch block or left-sided accessory pathway, the earliest ventricular activity is seen on

right-sided electrograms (His and RV electrograms). CS, coronary sinus; ECG, electrocardiogram; HBE, His bundle electrogram; HRA, high right atrium; RVA, right ventricular apex. (Reprinted with permission from Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. 2nd ed. Lippincott Williams & Wilkins; 2013.)

2. In general, **cycle lengths** rather than beats per minute are measured. The following measurements are made at baseline: sinus cycle length and PR, QRS, QT, AH, and HV intervals. To convert an arrhythmia's rate from cycle length to beats per minute, divide 60,000 by the cycle length to obtain the arrhythmia rate in beats per minute.
   a. The **AH interval** is measured from the onset of the local A deflection to the H deflection on the His electrogram.
   b. The **HV interval** is measured from the H deflection on the His electrogram to the earliest ventricular activity in any lead (surface or intracardiac).
3. When measurements are made during pacing, it is important to **measure from the resulting deflection** rather than from the pacing artifact to avoid errors caused by latency (delay between the pacing artifact and activation at the recording site).
4. All measurements are recorded in **milliseconds**. Interpretation of baseline intervals is shown in **Figure 53.2**.


I 1
aVF 1
V1 1
V6 1
HBE1-2 0.25
CS8-7 2.5
CS6-5 2.5
CS4-3 2.5
CS1-2 2.5
RVA3-4 2.5

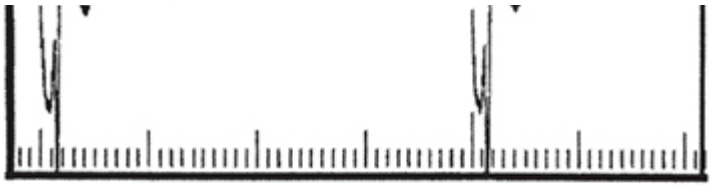


FIGURE 53.2 Programmed ventricular stimulation using double extra stimuli in a patient with atrioventricular (AV) node reentry tachycardia. Note that the earliest retrograde atrial activity is seen on the His electrogram. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

D. Programmed stimulation

1. After baseline measurements are made, programmed stimulation is performed. The protocol depends on the indication for the study and varies among institutions. During programmed stimulation, the **hemodynamic response** of the patient to pacing and induced tachycardia is closely monitored. For example, rapid ventricular pacing in patients with structural heart disease may result in transient hypotension. If this occurs, pacing should be limited in duration, and adequate time between pacing drive trains should be allowed for hemodynamic recovery.
2. **Pacing stimuli** are usually delivered with a 1- or 2-ms pulse width at twice diastolic pacing thresholds. This is important during ventricular stimulation because pacing at higher outputs increases the risk of inducing nonclinical rhythms. There are two main types of programmed stimulation: burst pacing and the extra stimulus technique.
   a. **Burst pacing** involves continuous pacing at rates faster than the patient's intrinsic rate.
   b. In the **extra stimulus technique**, premature beats are introduced either during intrinsic rhythm (sensed extra stimuli) or after a paced drive train (paced extra stimuli). Extra stimulus techniques are useful in evaluating refractory periods of the AV node, atrial tissue, ventricular tissue, and accessory pathways. It is possible to evaluate infranodal conduction system refractory periods with atrial or ventricular stimulation. Extra

stimulus techniques are also useful in inducing, terminating, and identifying reentrant arrhythmias.

(1) In the **sensed extra stimulus** technique, a single extra stimulus (S_2) is introduced initially with a coupling interval just below the intrinsic rate. The coupling interval is reduced progressively by 10 to 20 ms until the premature stimulus no longer captures. A pause of 2 to 5 seconds is allowed between stimulation sequences. Multiple extra stimuli (S_3, S_4) can be added if necessary, and the sequence can be repeated. This technique is useful in delineating the presence or participation of a suspected accessory pathway during tachycardia.

(2) In the **paced extra stimulus** technique, a drive train of 6 to 10 beats at a fixed cycle length is followed by a premature beat. The drive train cycle length (S_1S_1) usually ranges from 350 to 800 ms (most frequently, 400-600 ms) but depends on the resting heart rate. When this technique is used, testing at two drive train cycle lengths is recommended. The premature stimulus (S_2) is introduced with a coupling interval just below the S_1S_1. The coupling interval of the premature stimulus is decreased progressively by 10 to 20 ms until it no longer captures. The longest coupling interval (S_1S_2) that does not capture the myocardium is the absolute refractory period. S_3 and S_4 are added if necessary. This protocol can vary depending on the indication and operator preference.

E. Continuous monitoring and recording of external and intracardiac electrograms is maintained throughout programmed stimulation. When a particular event such as a tachycardia occurs, stimulation is stopped and the event evaluated. The operator should be ready to respond to the event appropriately, depending on the hemodynamic effect of the event. For example, induction of a sustained tachycardia may result in severe hypotension, angina, or loss of consciousness. In such circumstances, expeditious termination of the tachycardia is

indicated through overdrive pacing or cardioversion. The operator should also be ready to perform pacing or other maneuvers to further assess the mechanisms and reentrant circuit of the induced tachycardia.

V. ATRIAL STIMULATION

A. An atrial study is an integral part of an EPS. The only time an atrial study is not performed is in the presence of persistent atrial fibrillation.

1. **Burst atrial pacing** at incremental rates causes slowing of AV nodal conduction (a process known as decremental conduction) and eventually results in AV block. This can induce tachycardia, including AV nodal reentry tachycardia and AV reentrant tachycardia. Other forms of tachycardia unrelated to AV nodal conduction can also be induced, such as atrial flutter, atrial fibrillation, atrial tachycardia, and certain forms of idiopathic VT.
2. Burst pacing is performed by means of **continuous pacing** (eg, 10-20 stimuli) at a fixed cycle length starting at 100 ms below the baseline cycle length. Repeat burst pacing is performed at progressively shorter cycle lengths until 1:1 conduction through the AV node is no longer maintained. The shortest cycle length showing consistent 1:1 conduction through the AV node is recorded. This is called the 1:1 conduction limit of the AV node. Another interval that can be measured is the **functional refractory period** of the AV node, which is defined as the shortest output interval from the AV node to the His bundle given any input signal.
3. If a patient is believed to have **atrial flutter** or **atrial tachycardia**, repeat burst pacing at even shorter cycle lengths is performed until 1:1 atrial capture is no longer maintained.

B. Another form of atrial stimulation that is performed is paced extra stimulus.

1. The **effect of atrial premature beats** on the AH interval is assessed. The normal response of the AH interval is to progressively prolong with shorter A_1A_2 coupling. This is a direct

demonstration of the normal decremental conduction properties of the AV node.

2. At a critical A_1A_2, the AV node fails to conduct, and on the His electrogram, an atrial signal is seen without a His or ventricular deflection. This indicates that a **block has occurred in the AV node, which is called the AV node effective refractory period (ERP)**. It is important to continue stimulation until the atrial refractory period is reached because a gap phenomenon may occasionally exist.
3. In patients with **dual AV nodal physiology**, at a certain A_1A_2 interval, the AV nodal conduction time may abruptly increase (termed "jump"), which indicates the presence of more than one antegrade pathway through the AV node (fast and slow).
4. The **gap phenomenon** is demonstrated by apparent achievement of the AV nodal refractory period, followed by resumption of conduction at shorter A_1A_2 coupling intervals. The shorter A_1A_2 coupling interval causes a delay in conduction in the atrium itself termed "latency," which allows enough time to pass for the AV node to be able to conduct the impulse down to the ventricle.
5. If **narrow complex tachycardia** is induced, it is evaluated with regard to type, mechanism, response to maneuvers, and method of termination (see Section **IX.B.3**).

C. **Sinus node evaluation.** For patients who may have underlying sinus node dysfunction, sinus node tests are sometimes performed.

1. **Sinus node recovery time (SNRT)** is evaluated through burst pacing at various cycle lengths in the atrium for 30 to 60 seconds, followed by abrupt termination of pacing. This mechanism evaluates the automaticity mechanism of the sinus node. SNRT is the escape interval between the last paced atrial beat and the first atrial recovery beat. A **corrected sinus node recovery time (CSNRT)** is calculated by subtracting the baseline sinus cycle length from SNRT. A normal value for CSNRT is <550 ms.
2. **Sinoatrial conduction time (SACT)** is a combined measure of conduction in the atrial tissue that includes the area of the sinus

node and sinus node automaticity. The assumptions are, first, that the conduction times into and out of the sinus node are equal; second, that the pacing train does not alter the automaticity of the sinus node; and third, that the pacemaker site does not change after premature stimulation. The SACT is measured with one of two methods.

a. In the **Strauss method**, a premature atrial beat is used to reset the sinus node, and the return cycle length after the premature beat is measured. The basic cycle length is subtracted from the return cycle length. The remainder is the time necessary to penetrate and leave the sinus nodal tissue. The SACT is one-half this interval.

b. In the **method proposed by Narula**, the same measurements are obtained after pacing for eight beats at a rate slightly faster than the sinus rate. The upper range of the SACT is 100 to 120 ms.

3. The sensitivity of each individual (SACT and SNRT) test in diagnosing sinus node dysfunction is approximately 50% when used alone and 65% when combined. The specificity of the two combined tests is 88%, which gives the test a high positive predictive value. However, because of its low sensitivity, a normal test does not exclude sinus node disease. Practically, these tests are evaluated in conjunction with the patients' clinical symptoms to determine their need for pacemaker therapy.

VI. VENTRICULAR STIMULATION

A. Ventricular stimulation is performed in the evaluation of suspected SVTs or ventricular tachyarrhythmias. Some SVTs, such as unusual forms of AV nodal reentry or slow conduction retrograde accessory pathway, may be more easily induced with ventricular stimulation. To further characterize the tachycardia, the response of the tachycardia to premature ventricular beats can be assessed.

1. When ventricular stimulation is performed for the evaluation of ventricular or wide complex tachyarrhythmias, **pacing at two or**

more sites may be necessary. These sites are typically the RV apex and the RV outflow tract.

2. Before programmed stimulation is begun, pacing thresholds are determined, and the output of the pacing stimulus is set to twice the diastolic capture threshold. Higher outputs or coupling intervals shorter than 200 ms may cause induction of nonclinical arrhythmias, specifically ventricular fibrillation.

B. Burst pacing in the RV is one of two techniques used when assessing retrograde ventriculoatrial (VA) conduction in the evaluation of SVT.

1. The presence of retrograde atrial activation is documented, and the sequence or pattern of atrial activation is evaluated.
2. The **earliest atrial activity** during retrograde conduction via the AV node is typically recorded on the His electrogram (see **Figure 53.2**). This indicates that retrograde conduction has proceeded through the fast pathway of the AV node. Atrial activity is next seen in the CS electrodes, proceeding from the proximal electrodes near the CS os to the lateral electrodes posterior to the left atrium. If retrograde conduction proceeds via the slow pathway, the earliest atrial activity is seen on the electrodes near the CS os. **Absence of VA conduction**, with rare exceptions (eg, the Mahaim type of accessory pathway, which conducts only in the antegrade direction), excludes the presence of a bypass tract. The **presence of eccentric atrial activation** (late atrial activation on the His electrogram; **Figure 53.3**) suggests the presence of a retrograde conducting bypass tract.

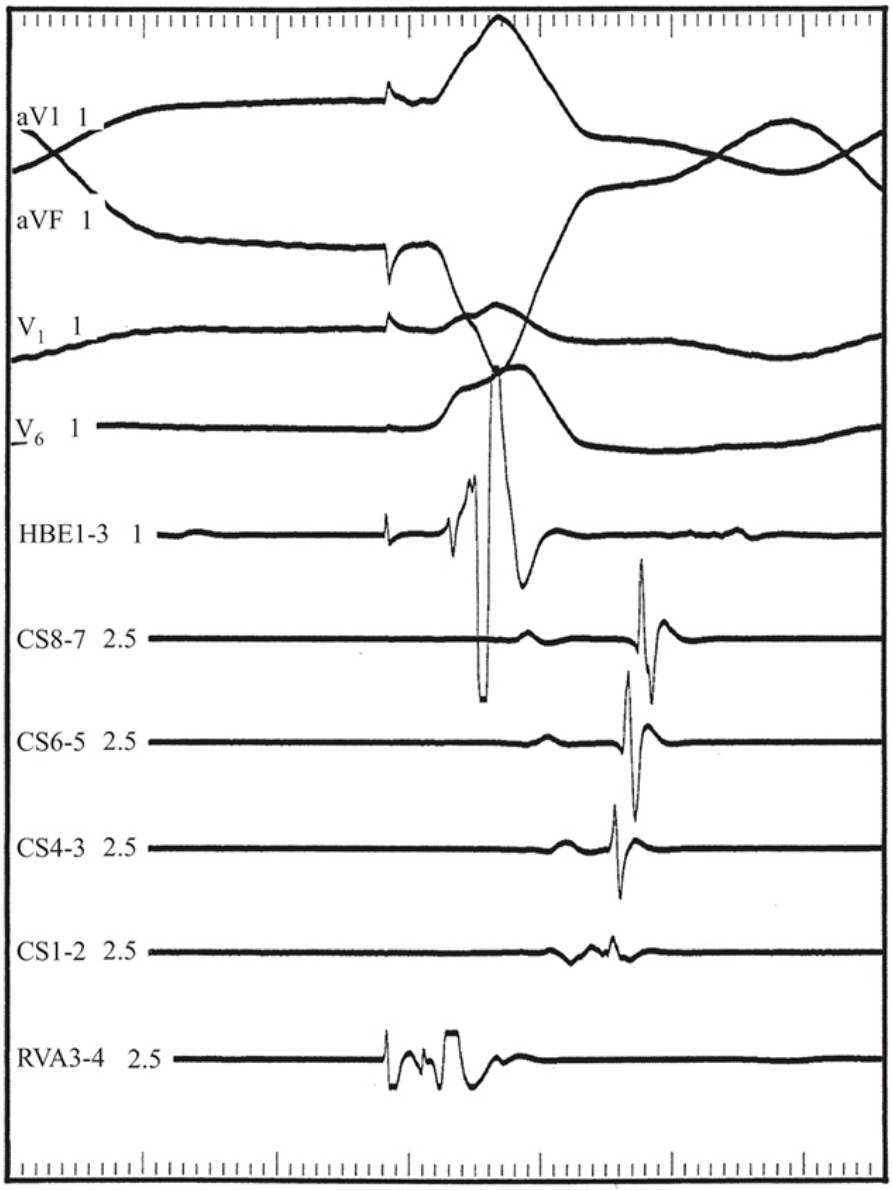


FIGURE 53.3 This is an example of a 17-year-old patient with left lateral manifest pathway. Ventricular stimulation results in retrograde atrial activation, with the earliest atrial signal seen in CS1-2 (eccentric atrial activation). CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

3. For some patients with no evidence of retrograde VA conduction, infusion of low doses of **isoproterenol** or a small dose of atropine (0.5 mg) restores this property to the AV node.
4. The shortest paced cycle length capable of 1:1 conduction to the atrium is documented.

C. Premature ventricular stimulation is another technique used to evaluate retrograde conduction properties of the heart.

1. If retrograde conduction is present, the refractory periods of the conducting pathways are determined with the extra stimulus technique.
2. In patients with **retrograde VA conduction through the AV node**, conduction block of a ventricular premature beat frequently occurs in the His-Purkinje system rather than in the AV node. His-Purkinje conduction block is more likely to occur at long drive trains (ie, long S_1-S_1 coupling intervals). Such drive trains are, therefore, more likely to induce AV reentry tachycardia (using a bypass tract) by facilitating retrograde His-Purkinje block and allowing a retrograde-conducted beat through the pathway to propagate antegrade down the AV node.

D. In patients being evaluated for **ventricular arrhythmias**, programmed stimulation with extra stimuli is the initial technique used. Pacing at two drive train cycle lengths (eg, 600 and 400 ms) is performed with single, double, and triple extra stimuli. These drive trains are often repeated from two different locations in the RV. Simultaneous atrial pacing at the same drive train cycle length is sometimes necessary to avoid competition from the intrinsic atrial pacemaker.

E. Like the A_1A_2 technique described earlier, **V_2 is introduced at progressively shorter coupling intervals** (V_1V_2) until V_2 no longer captures (ventricular refractory period). Then V_2 is set at a coupling interval longer than the refractory period, and **V_3 is introduced** at progressively shorter coupling intervals until it no longer captures. The use of **triple extra stimuli** (V_3V_4) is usually reserved for patients being evaluated for ventricular arrhythmias. A pause of 3 to 5 seconds is allowed after each cycle to assess response and for the patient to recover after ventricular pacing. An increase in the number of extra stimuli increases the sensitivity of the study in reproducing clinical arrhythmias but at the cost of a lower specificity due to initiation of polymorphic VT or ventricular fibrillation. If programmed

stimulation with ventricular extra stimuli does not induce VT in a patient at very high risk, other techniques may be used. One is **burst pacing in the ventricle**. A series of about 10 paced ventricular beats is introduced at a constant cycle length. The paced cycle length is then decreased by 50 to 100 ms in successive bursts until reaching within 50 ms of the predicted refractory period of the RV, when the decrements proceed at 10-ms intervals until 1:1 capture is no longer maintained or 200 ms is reached. Burst pacing in the atrium can sometimes induce idiopathic LV tachycardia or VT involving the conduction system in susceptible patients.

F. In some patients, particularly those with underlying dilated cardiomyopathy, **bundle branch reentry (BBR) tachycardia** (**Figure 53.4**) may be induced.

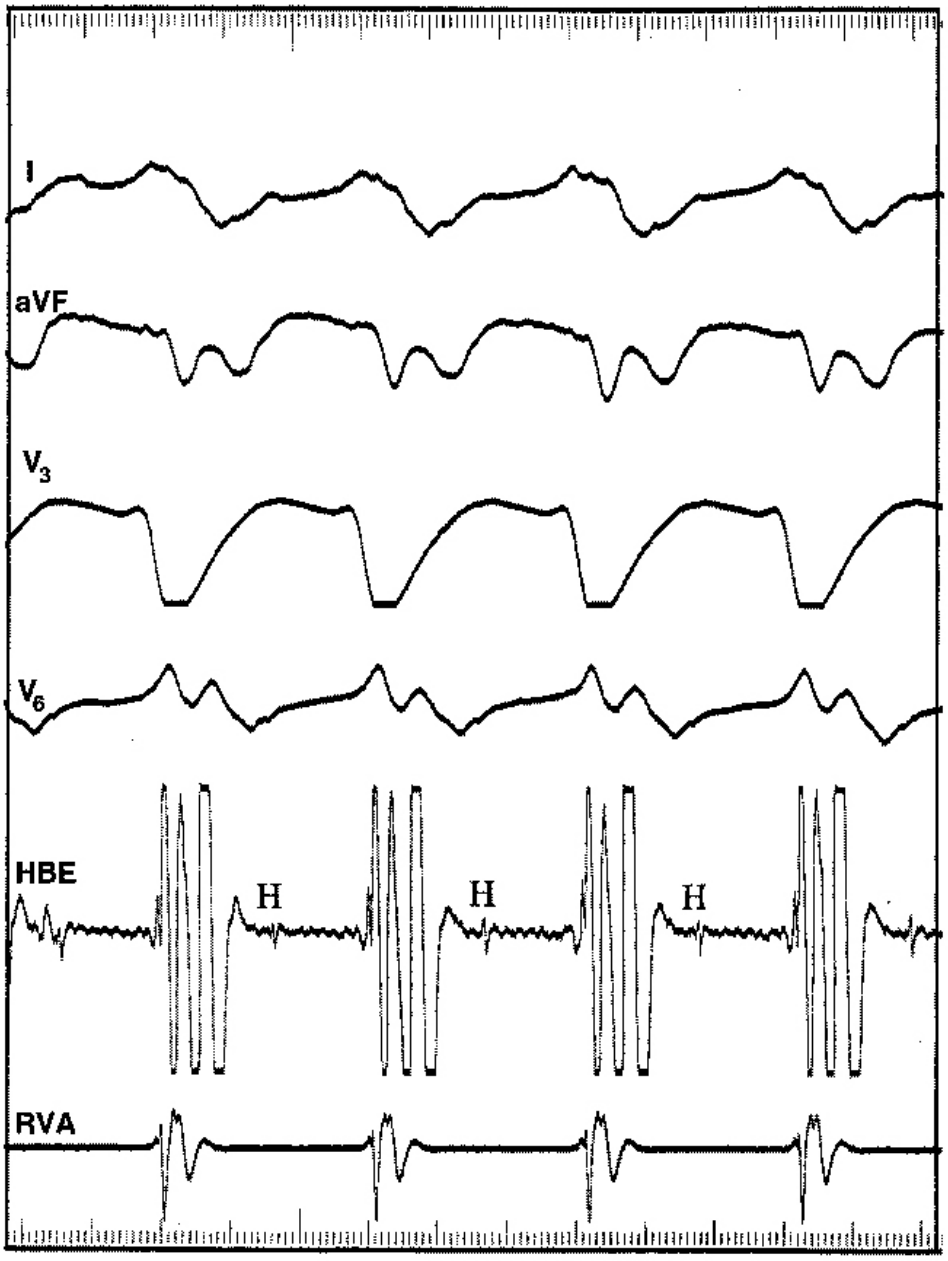


FIGURE 53.4 Bundle branch reentry tachycardia. This example is from a 52-year-old man with dilated cardiomyopathy who presented with syncope. This ventricular tachycardia exhibits left bundle branch block morphology, and there is an H deflection preceding every V on the His electrogram. To be absolutely certain of this diagnosis (as opposed to myocardial ventricular tachycardia with retrograde His), one has to look for cycle length variation and document that changes in the H-H interval precede changes in the V-V interval. HBE, His bundle electrogram; RVA, right ventricular apex.

1. This type of tachycardia usually involves the right bundle branch as the antegrade limb and the left bundle branch as the retrograde limb of the reentrant circuit. It is usually a rapid and hemodynamically unstable tachycardia.
2. Because His bundle refractoriness increases after a pause, a short-long-short stimulation sequence from the ventricle can be used to cause retrograde block in the right bundle so that the paced stimulus can conduct retrograde up the left bundle branch and possibly initiate tachycardia if the right bundle branch is no longer refractory for antegrade conduction.
3. The sequence most commonly used consists of a 6-beat drive train at 400 ms, followed by V_2 coupled at 600 to 700 ms. V_3 is then introduced at a coupling interval of 100 ms longer than the refractory period of the ventricle. V_2V_3 is progressively decreased until V_3 no longer captures. The goal is to cause block in the right bundle, allowing retrograde conduction to proceed up the left bundle and find the right bundle to have recovered and capable of conducting antegrade, thus establishing a reentrant circuit. V_4 can be introduced if necessary.

II. INDUCTION OF VENTRICULAR FIBRILLATION

Under certain circumstances, the operator may decide that induction of ventricular fibrillation is necessary. This is valuable when testing implantable defibrillators for detection of arrhythmias and during assessment of defibrillation thresholds. Ventricular fibrillation can be induced by means of direct application of alternating current or rapid ventricular pacing at high output. The current can be delivered through a catheter electrode or through the **implantable cardioverter–defibrillator (ICD)** lead. Another means of inducing ventricular fibrillation is to deliver a low energy shock (around 1 J) via the intracardiac leads at the peak of the T wave.

III. USE OF CARDIOACTIVE DRUGS DURING ELECTROPHYSIOLOGIC STUDIES.

Cardioactive drugs can be used during EPS as diagnostic or therapeutic

agents. The drugs most commonly used are isoproterenol, procainamide, atropine, and adenosine.

A. Isoproterenol in doses ranging from 0.5 to 5 mcg/kg/min is used during EPS to facilitate induction of SVTs and ventricular tachyarrhythmias.

1. For patients with SVTs that are AV node dependent, isoproterenol facilitates conduction through the AV node by means of shortening its refractoriness.
2. For patients with SVTs that are driven by automaticity such as certain atrial tachycardias, isoproterenol can enhance automaticity and promote induction of these arrhythmias.
3. It is not absolutely certain how isoproterenol facilitates induction of VT, but possible mechanisms include enhanced conduction, altered refractoriness, and enhanced automaticity related to delayed afterdepolarization.
4. Isoproterenol is particularly useful in evaluating patients with exercise-induced VT and special types of RV outflow tract tachycardia. Isoproterenol is contraindicated in the presence of critical coronary artery disease.
5. Adrenergic stimulation with high doses of isoproterenol (up to 20 mcg/min) also effectively induces repetitive rapid discharges from the pulmonary veins that frequently trigger initiation of atrial fibrillation (see Section **IX.B.3**).

B. Procainamide is used less frequently during EPS. Among patients believed to have advanced underlying conduction disease, the response of the infranodal conduction system to procainamide infusion (10-15 mg/kg) is assessed during sinus rhythm and with atrial pacing.

1. Considerable prolongation of the HV interval or induction of infranodal block with atrial pacing at cycle lengths longer than 400 ms is considered by many experts to be evidence of His-Purkinje disease. Procainamide can facilitate the induction of atrial and ventricular arrhythmias by means of slowing conduction.

2. Procainamide is often used to prevent recurrent atrial fibrillation when programmed atrial stimulation is necessary. An example would be a patient with atrial flutter who is being evaluated for ablation and is easily induced into atrial fibrillation during programmed stimulation.
3. Procainamide was widely used in the past for risk assessment among patients with inducible VT. Studies have shown that patients with suppressible VT have better long-term prognosis (lower rate of clinical recurrence and lower mortality) than those with nonsuppressible VT. However, with the wider use of ICDs and evidence of their superiority even among persons with suppressible VT, this application of procainamide may be of historical interest only.
4. In the correct clinical context, procainamide may be used to unmask a Brugada pattern on surface ECG when the diagnosis is uncertain.

C. **Adenosine,** in doses that produce transient AV block (6-18 mg), is used frequently in EPS of patients with SVT to define the mechanism of the tachycardia, establish AV node dependence, or document the presence or absence of accessory pathway conduction before and after RF ablation. It may also be used after atrial fibrillation ablation to hyperpolarize atrial tissue and unmask dormant conduction due to tissue injury postablation.

IX. INTERPRETATION OF FINDINGS IN ELECTROPHYSIOLOGIC STUDIES

A. **Bradyarrhythmia evaluation.** EPSs are *not* indicated when symptomatic bradycardia is documented. Among patients who have a clear indication for implantation of a permanent pacemaker, findings of EPS are unlikely to alter clinical decision-making. However, EPSs are more helpful in patients believed to have symptoms related to underlying **sinus node dysfunction or conduction system disease** when noninvasive monitoring has failed to document a correlation between bradycardia and symptoms. EPSs are also helpful in assessing patients who continue to have symptoms after permanent pacemaker implantation.

1. **Baseline evaluation.** Sinus bradycardia, sinus arrest with junctional or ventricular escape, various degrees of heart block, and intraventricular conduction delay, either isolated or in various combinations, may occur among patients with bradycardia and can be further evaluated by examining intracardiac recordings.
    a. **Conduction intervals** are measured and evaluated. Disease in the AV node often produces prolongation in the AH interval, whereas disease in the infranodal conduction system produces prolongation in the HV interval.
    b. A long HV interval is suggestive but not diagnostic of an underlying bradyarrhythmia. It is commonly associated with wide QRS on surface ECG. A long HV interval at rest can be considered an indication for prophylactic pacemaker implantation (class IIa) if it exceeds 100 ms.
    c. A **split His** signal can be seen if the location of infranodal block is within the His bundle itself. This can be a cause of high-grade block despite a normal QRS on surface ECG.
    d. Documentation of intermittent spontaneous infranodal block or infranodal block in response to atrial pacing (**Figure 53.5**) or upon administration of procainamide is an indication for implanting a permanent pacemaker.

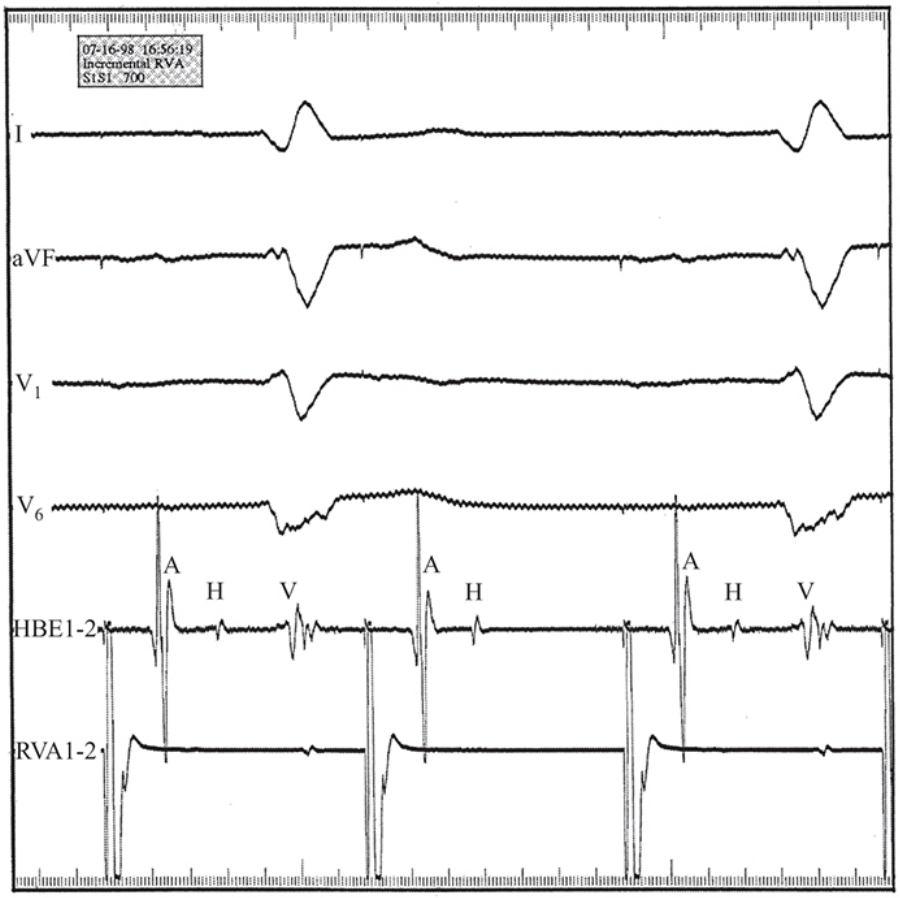


FIGURE 53.5 Infrahisian block in response to slow atrial pacing. This tracing is from a 70-year-old man who presented with syncope. Baseline H-V was 110 ms. As shown in this tracing, burst pacing in the right atrium at a cycle length of 700 ms resulted in intermittent infrahisian block (H deflections not followed by V). This patient had a dual-chamber pacemaker implanted. HBE, His bundle electrogram; RVA, right ventricular apex.

2. Programmed stimulation

a. After baseline intervals are measured, **SNRT and SACT** are determined. SNRT is used to evaluate automaticity of the sinoatrial node.

b. Rapid pacing causes overdrive suppression of the sinus node. Among patients with sinus node dysfunction, recovery time after cessation of pacing is prolonged. The situation is similar to sudden termination of atrial fibrillation, which can be followed by a prolonged postconversion pause.

c. After cessation of pacing, the longest SNRT following pacing at varying cycle lengths and secondary pauses is documented. Secondary pauses are those intervals related to the sinus beats that occur after the first escape beat. CSNRT, which is calculated by subtracting baseline cycle length from SNRT, is considered abnormal if it exceeds 550 ms.

d. SACT is used to evaluate conduction velocities in the atrium and in tissues surrounding the sinoatrial node. SACT is performed with the methods described earlier. A normal SACT is between 50 and 125 ms. When both CSNRT and SACT are normal, symptoms are uncommon. The sensitivities of CSNRT (54%) and SACT (51%) combined are higher (64%), and the specificity is approximately 88%. The low sensitivity of these tests limits their value in predicting the development of symptoms in asymptomatic patients.

e. AV nodal and infranodal conduction system integrity are tested with atrial stimulation techniques. Attention is paid to the AH and HV intervals during atrial pacing.

(1) The refractory period of the AV node is determined at two cycle lengths. The shortest cycle length with 1:1 AV conduction is also determined.

(2) The normal AV nodal response to burst pacing at short cycle lengths is second-degree Mobitz I AV block. HV interval prolongation or infrahisian block is not typically observed. If it occurs at cycle lengths longer than 400 ms, HV interval prolongation suggests significant underlying His-Purkinje disease.

(3) Prolongation of the AV nodal refractory period is most frequently caused by high vagal tone or concomitant use of medications. It has no predictive or diagnostic value in evaluating patients believed to have bradycardia. However, a long AV nodal refractory period may mask underlying abnormal His-Purkinje refractoriness, and enhancement of AV nodal conduction with atropine or isoproterenol may be necessary during EPS.

3. **Carotid sinus massage** is performed in all patients undergoing evaluation of bradycardia or syncope.
    a. Firm pressure is applied over the carotid artery pulsation behind the angle of the mandible.
    b. A **positive cardioinhibitory response** is present if pauses of 3 seconds or more occur. A **vasodepressor response** is present if blood pressure decreases by >50 mm Hg in the absence of marked bradycardia. Mixed responses are common.

B. SVT evaluation. One of the most important elements in the evaluation of tachyarrhythmias is careful analysis of the surface ECG during clinical tachycardia. This can give several clues to the underlying diagnosis and make the EPS more focused. Most SVTs that are induced in the EPS laboratory are reentrant. They include AV nodal reentry tachycardia, orthodromic AV reentry tachycardia, atrial flutter, and reentrant atrial tachycardia. Automatic tachyarrhythmias are relatively uncommon, except in acutely ill patients. They characteristically exhibit a warm-up phenomenon and are difficult to induce with extra stimulus techniques but may be induced with drugs such as isoproterenol.

1. **Baseline evaluation**
    a. Resting ECG and intracardiac recordings can provide important information about a possible cause even before any tachycardia is induced. The presence of a short PR interval on the ECG and wide QRS complex with a slurred initial deflection suggests preexcitation.
    b. Absence of preexcitation at rest does not rule out the presence of an accessory pathway. A **concealed pathway**, which conducts retrograde but not antegrade, can still be present even if the QRS and PR interval are normal. For the diagnosis of SVT, an atrial and a ventricular study have to be performed.
    c. If tachycardia is not induced with the baseline study, programmed stimulation in the atrium and ventricle is repeated with isoproterenol.

d. Some SVTs, particularly those involving AV reentry using a bypass tract, can be induced with ventricular stimulation, whereas atrial flutter and atrial tachycardia are rarely induced by means of ventricular stimulation.

2. Programmed stimulation begins with burst pacing in the ventricle to document and characterize VA conduction. The absence of VA conduction practically excludes a concealed bypass tract, and ventricular extra stimulus technique may not need to be performed unless VT is suspected.

a. Earliest retrograde atrial activity is usually seen on the His electrogram during normal retrograde atrial activation through the AV node. Earliest retrograde atrial activity on the distal CS electrogram, if the position of the CS catheter is correct, suggests the presence of a left-sided accessory pathway (see **Figure 53.4**). Earliest atrial activity in the proximal CS electrodes suggests a posteroseptal pathway or AV node slow pathway conduction.

(1) Eccentric atrial activation is any atrial activation that does not activate the AV node and the area around the AV node first. This is frequently seen with retrograde ventricular stimulation when the retrograde impulse finds the AV node refractory and another pathway for conduction is present. The site of earliest atrial activation is then in the distal CS catheter and not in the proximal area closest to the AV node/His bundle. Evidence of eccentric atrial activation may not be clear during burst pacing when there is fusion of retrograde impulses arriving through both the AV node and the accessory pathway.

(2) The retrograde 1:1 cycle length should be documented.

(3) Programmed ventricular stimulation is performed with single premature beats at two drive train cycle lengths (eg, 600 and 400 ms). During programmed stimulation, the following are recorded:

(a) Retrograde refractory periods

(b) The pattern and any changes in retrograde atrial activation

(c) The site of retrograde VA block

(d) The presence of dual-retrograde AV node function

(4) If an accessory pathway is found, its retrograde 1:1 conduction cycle length and refractory period are documented.

b. During atrial stimulation, particular attention is paid to the **AH and HV intervals**.

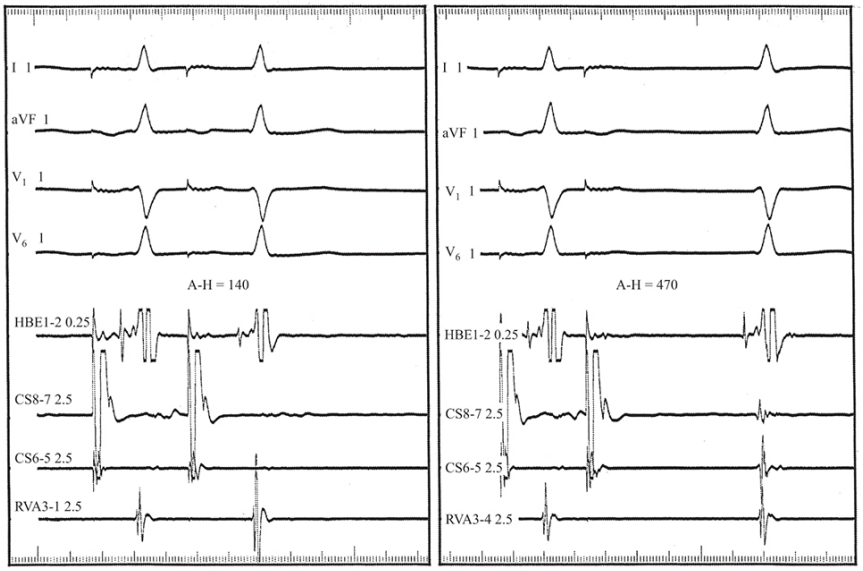


FIGURE 53.6 Atrioventricular (AV) nodal jump and echo. A 10-ms decrement in S_1S_2 resulted in marked prolongation of A_2H_2 by >300 ms. In addition, an echo beat with a short H-A is seen on the coronary sinus (CS) electrogram, a definite evidence of dual AV node physiology. The atrial premature beat, blocked antegrade in the fast pathway, was conducted with sufficient delay in the slow pathway to encounter a nonrefractory retrograde fast pathway. HBE, His bundle electrogram; RVA, right ventricular apex.

(1) Sudden prolongation of A_2H_2 of >50 ms in response to a decrement of 10 ms in A_1A_2 is called a **jump** (**Figure 53.6**) and has been classically described as a sign of dual AV

nodal physiology. However, more recent reports have demonstrated that the normal AV node can have dual pathways even if this "jump" is not demonstrated. Furthermore, initiation of AV nodal reentrant tachycardia does not require the presence of such a jump in the AV nodal conduction curve.

(2) Induction of reentrant tachycardias generally requires three factors. There must be **unidirectional block** in one pathway. Second, there must be **conduction delay** down the second pathway. This delay gives time for **recovery of retrograde conduction**. In the case of AV nodal reentry, antegrade block in the fast pathway combined with critical delay in the slow pathway allows the impulse to conduct retrograde up the fast pathway and excite the atrium. This first retrograde-conducted atrial depolarization is called an **echo beat** (see **Figure 53.6**). If this echo beat succeeds in conducting antegrade down the slow pathway again and retrograde up the fast pathway, sustained AV nodal reentry occurs.

(3) **Induction of AV nodal reentry** is facilitated by the use of shorter drive train cycle lengths and, if necessary, the use of more than one extra stimulus or rapid burst atrial pacing. Occasionally, initiation of AV nodal reentry requires ventricular pacing or premature beats. Isoproterenol or atropine is given if pacing maneuvers alone cannot induce tachycardia.

(4) In the presence of an accessory pathway, the site of critical delay is also in the AV node. However, to induce orthodromic AV reentry tachycardia, antegrade block of an atrial impulse has to occur in the accessory pathway so that it is excitable by the time the same impulse propagates through the AV node and ventricle and arrives to conduct retrogradely through the accessory pathway to the atrium (**Figure 53.7**).

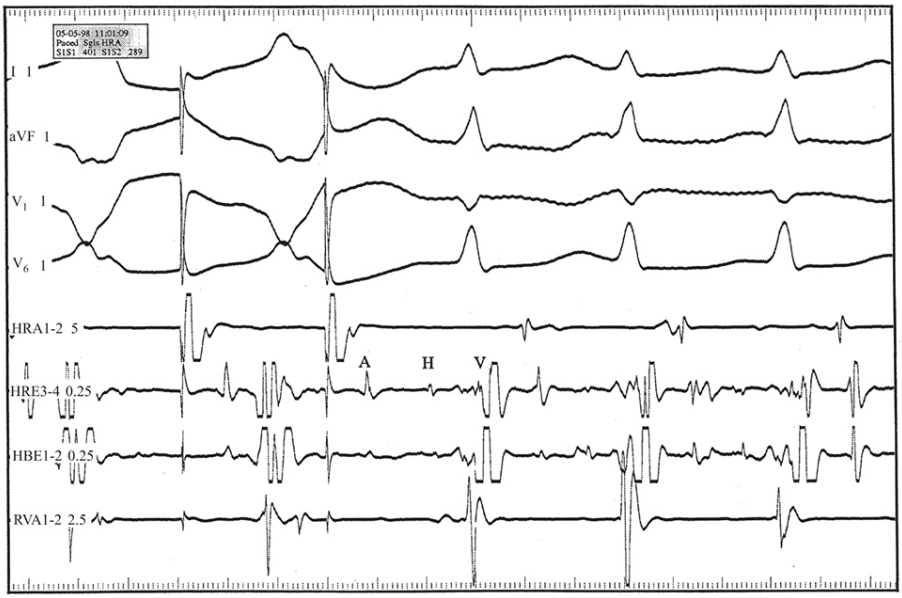


FIGURE 53.7 Orthodromic atrioventricular (AV) reentry tachycardia. In this example from a patient with a manifest right-sided accessory pathway, premature atrial stimulation (S) blocks in the accessory pathway (resulting in a narrow QRS complex), conducts with a longer A-V, and reexcites the atrium. The tachycardia is narrow complex, with an H-A interval of 180 ms. The earliest A is seen on the high right atrial catheter. AV, atrioventricular; HBE, His bundle electrogram; HR, high right atrium; RVA, right ventricular apex.

3. Evaluation of induced tachycardia

a. If a tachycardia is induced, the first assessment is its **hemodynamic effect**. Hemodynamically unstable tachycardia should be immediately terminated. Only if the tachycardia is hemodynamically stable can further evaluations during tachycardia be conducted.

(1) Whether the QRS is narrow or wide, the relationship between the atrial rate and the ventricular rate is noted (AV association or dissociation).

(2) Lack of a 1:1 AV relation excludes AV reentry tachycardia. AV nodal reentry tachycardia usually exhibits a 1:1 relationship; however, in rare instances, AV node reentry tachycardia can exhibit 2:1 AV conduction.

(3) If the atrial rate is faster than the ventricular rate, the diagnosis is **atrial tachycardia or atrial flutter**,

depending on the rate and pattern of atrial activation.

(4) If the ventricular rate is faster than the atrial rate, the diagnosis is VT. Alternative causes for AV dissociation include AV nodal reentry tachycardia with block in the upper common pathway, reentry tachycardia with a nodofascicular pathway, or a junctional tachycardia with retrograde block.

b. When a **1:1 AV relationship** exists, **further evaluation** is needed. The following observations and techniques are helpful in arriving at the most likely mechanism:

(1) **Atrial activation.** The sequence of atrial activation during tachycardia is important in the differential diagnosis of SVT. Accurate placement of catheters is extremely important; catheter misplacement can lead to inappropriate conclusions or interventions. The **earliest site of atrial activation** is noted. As previously mentioned, if the earliest atrial activation is in the distal CS, a left atrial tachycardia or AV reentry using a left-sided accessory pathway is most likely. If an accessory pathway is located in the posterior septum, the earliest A is seen in the proximal CS electrogram. This is also true if the atria are being activated through the slow pathway of the AV node, as in atypical AV nodal reentry tachycardia.

(2) The presence of **cycle length variation** during tachycardia helps predict the activation sequence. For example, a change in AA coupling interval before an equal change in HH or VV interval (with changing VA) suggests that the atrial activity leads the ventricular activity, leading to a diagnosis of atrial tachycardia.

(a) In cases of wide complex tachycardia in which there appears to be a 1:1 relation between H and V, HH interval change preceding VV interval change suggests SVT with aberrancy or BBR tachycardia.

(b) Cycle length variation may also be helpful when there is **slowing of tachycardia with the development of**

bundle branch block and acceleration with resolution of the block. This finding, referred to as **Coumel law**, is suggestive of AV reentry using an accessory pathway ipsilateral to the bundle branch block as the retrograde limb. This can be appreciated on the surface ECG. In fact, prolongation in tachycardia cycle length in association with a bundle branch block is caused by prolongation of the VA interval. The activation wavefront must travel down the contralateral bundle and across the intraventricular septum before it reaches the pathway. The change in cycle length is more pronounced with lateral pathways than with septal pathways.

(3) **HA and VA intervals.** A constant HA or VA relation despite cycle length variation (even in the absence of bundle branch block) is highly suggestive of **AV nodal reentry or accessory pathway–mediated tachycardia**. The change in tachycardia cycle length is caused by varying antegrade conduction time through the AV node. The VA time can also be used to differentiate AV nodal reentry from AV reentry. A VA interval <70 ms is rarely seen with AV reentry and strongly suggests the diagnosis of AV nodal reentry (**Figure 53.8**). VA times in excess of 70 ms are seen with AV reentry and atypical AV nodal reentry (the so-called fast-slow or slow-slow AV nodal reentry).

(4) **Introduction of premature beats during tachycardia.** Premature ventricular beats are typically introduced during tachycardia at intervals when the His bundle is refractory. Because the normal retrograde path (His-AV node) is refractory, preexciting the atrium with a premature ventricular beat at those intervals is diagnostic of the presence of an accessory pathway capable of retrograde conduction. Consistent termination of tachycardia with such premature beats without retrograde conduction to the

atrium is also diagnostic of AV reentry and excludes atrial tachycardia.

(5) **Pacing maneuvers during SVT.** During SVT, ventricular pacing maneuvers can be a useful first step in diagnosing the mechanism of tachycardia. Ventricular pacing at a cycle length slightly faster than the tachycardia cycle length is referred to as ventricular overdrive (VOD) pacing. Successful entrainment occurs when VOD resets the tachycardia such that the atrial rate is accelerated to the paced ventricular cycle length and returns to the tachycardia cycle length when ventricular pacing stops and the tachycardia continues. An atrial-atrial-ventricular response upon cessation of VOD, or V-A-A-V response, is diagnostic of atrial tachycardia. A V-A-V response is most consistent with a reentry tachycardia. The relationship of the postpacing interval to the tachycardia cycle length can then be helpful in differentiating the type of reentry tachycardia.

(6) **Initiation and termination of tachycardia.** To understand the mechanism of tachycardia, it is important to know the mechanism of initiation. For reentry to occur, block in one limb of the reentrant circuit and slow conduction in the other limb must take place. It is important to review the stimulation sequences that did not induce tachycardia and compare them with those that did. A sudden jump in the AH interval suggests, but is not diagnostic of, AV nodal reentry. Orthodromic AV reentry tachycardia develops during atrial stimulation after antegrade block in the accessory pathway takes place in combination with a critical delay in the AV node. With ventricular stimulation, AV reentry tachycardia develops after block occurs in the AV node or His-Purkinje system. Termination of the tachycardia simultaneous with AV node block (A with no H) suggests AV node dependence and is helpful in

excluding AV node–independent tachycardias (atrial tachycardia and flutter).

4. **Significance of induced tachycardia.** With the exception of atrial fibrillation, induced reentrant SVTs signify the presence of an established anatomic circuit. After comparison with the clinical arrhythmia, the induced tachycardia can be considered clinically significant unless clear differences exist. If a wide complex tachycardia with a supraventricular mechanism is induced, the recording is compared with a clinical recording. If the QRS morphology is different from the clinical arrhythmia, a search for a ventricular arrhythmia may be warranted.
5. **Atrial flutter,** a special type of atrial tachycardia that involves a well-defined anatomic circuit, is amenable to curative catheter ablation techniques.

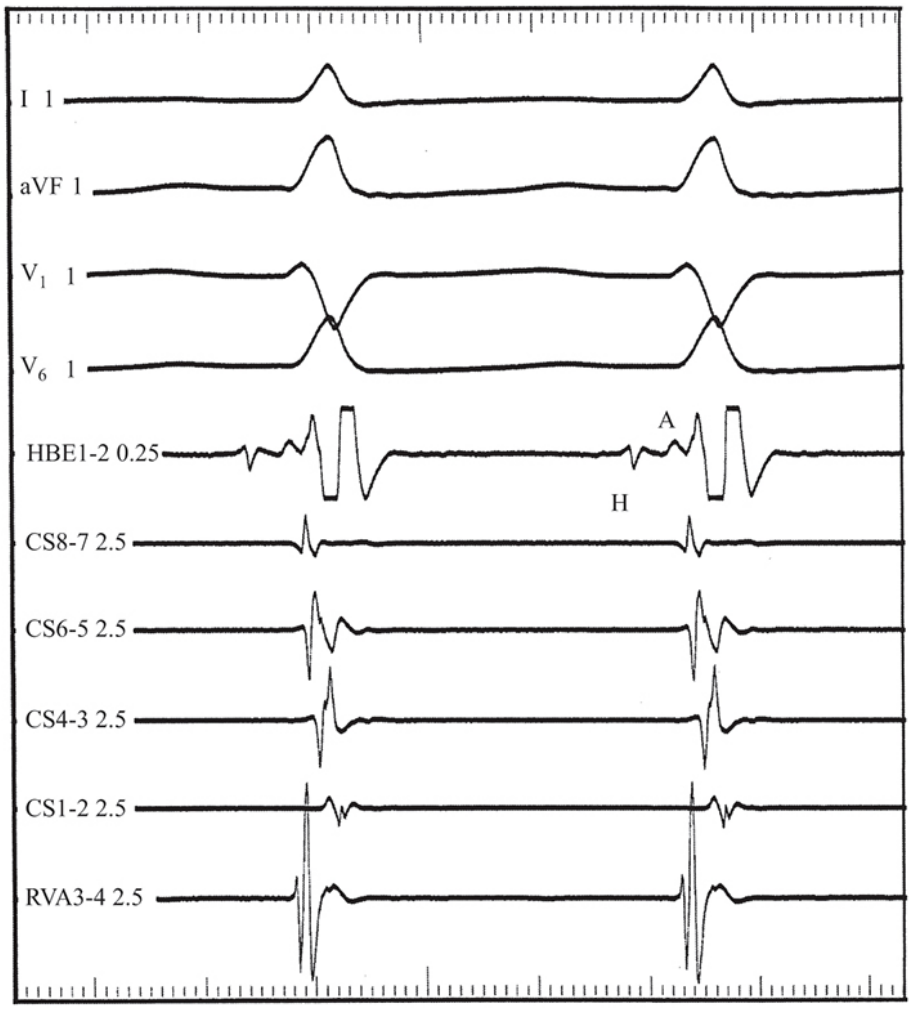


FIGURE 53.8 Atrioventricular (AV) node reentry tachycardia. Tachycardia is narrow complex and characterized by very short V-A interval and an H-A interval of <70 ms. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

a. In the typical form of atrial flutter, the waveform travels counterclockwise around the tricuspid annulus. The circuit is bounded anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and its inferior medial continuation as the eustachian ridge. The site of functional block appears to be in the isthmus region, which is the narrow corridor between the inferior tricuspid annulus and the inferior vena cava. The site of conduction delay or slowing appears to be caused by transverse conduction block into the crista, forcing the wavefront to enter

the crista at its superior end before propagating down the crista into the isthmus region.

b. To induce counterclockwise atrial flutter, progressively more rapid (approximately 250-200 ms) burst pacing appears to be most successful and is performed anywhere medial to the isthmus. The impulses block in the isthmus and conduct counterclockwise around the tricuspid ring with sufficient delay to sustain atrial flutter. If burst pacing is used lateral to the isthmus, clockwise atrial flutter may be induced. Successful ablation of typical atrial flutter necessitates generation of bidirectional isthmus block by applying a line of RF lesions that spans the posterior isthmus from the tricuspid valve to the inferior vena cava (the cavotricuspid isthmus).

c. Less commonly, different types of atrial flutter in which the cavotricuspid isthmus is not part of the circuit are induced. These atypical flutters have many varieties and locations but share a common reentrant circuit that revolves around an area of conduction block or delay, usually scar tissue. They are more often seen in patients who have undergone prior cardiac surgery or catheter-based procedures. Treatment involves creating an ablation line from the area of scar to an anatomic barrier or ablating critically narrowed reentrant paths within a scarred region. The success rates in ablating these atypical forms of atrial flutter are not as high as isthmus-dependent flutters.

6. Atrial fibrillation. Although atrial fibrillation is commonly induced during an EPS, routine EPS in patients with atrial fibrillation does not provide much clinical value, except in patients with an accessory pathway. EPS in patients with an accessory pathway assists in risk stratification for sudden cardiac death if atrial fibrillation were to occur in the future. Refer to the chapter entitled “Catheter Ablation” for more details about RF ablation therapies for atrial fibrillation.

C. Evaluation of accessory pathways

1. The **most common locations** for accessory pathways in decreasing order of frequency are left free wall, posterior region, posteroseptal region, right free wall, and the anteroseptal region. Concealed accessory pathways (no evidence of antegrade conduction) with only retrograde conduction are more common than manifest pathways, which have antegrade conduction manifested by delta waves on the surface ECG, the slurred initial deflection of the QRS that suggests preexcitation.
    a. **Right-sided accessory pathways** are more likely than left-sided accessory pathways to be associated with **congenital heart disease**. An unusual type of right-sided accessory pathway is the atriofascicular accessory pathway, which originates in the right atrium, transverse the right anterior region of the tricuspid valve annulus, and insert in the region of the right bundle or the right-sided Purkinje network. These accessory pathways have unidirectional antegrade conduction with decremental conduction properties similar to an AV node. These pathways are frequently referred to as Mahaim pathways and typically do not conduct retrogradely.
    b. **Multiple accessory pathways** are more frequently encountered on the right side and in survivors of sudden death. In these patients, the most common combination is posteroseptal and right free wall pathways.
    c. Both antidromic and orthodromic AV reentrant tachycardias require participation of the accessory pathway. In rare instances, antidromic tachycardia can involve one accessory pathway in the antegrade direction and a second pathway in the retrograde direction.
2. Evidence of preexcitation is supported by the presence of a **short HV interval** (<35 ms) **at rest** or with atrial pacing and the appearance of increasing preexcitation either with atrial pacing or with administration of drugs that cause AV nodal conduction slowing, or with autonomic maneuvers. The EP properties of the accessory pathway are examined, including its antegrade and retrograde conduction and refractory periods. If tachycardia is

induced during atrial or ventricular stimulation, its mechanism is defined according to the techniques discussed earlier. This depends on whether the tachycardia is narrow or wide complex.

3. **Orthodromic AV reentry tachycardia** is commonly initiated by a ventricular premature stimulus that blocks in the His-Purkinje system or, rarely, in the AV node, but conducts in a retrograde direction over the accessory pathway. It can also be induced by an atrial premature stimulus (echo beat) that blocks the accessory pathway and conducts slowly over the AV conducting system. Induction is facilitated by the presence of a relatively **long antegrade refractory period of the accessory pathway** or a **long retrograde refractory period of the His-Purkinje system**.
4. **Antidromic AV reentry tachycardia** (**Figure 53.9**) can be initiated with burst pacing in the atrium or with a premature atrial stimulus that **blocks in the AV node** and **conducts over the accessory pathway**. Less often, it can be induced with a premature ventricular stimulus that blocks the accessory pathway in a retrograde manner and conducts over the AV node. Induction of antidromic tachycardia necessitates excellent retrograde conduction over the His-Purkinje system and AV node. It almost always involves a free wall accessory pathway as the antegrade limb and is frequently associated with the presence of multiple accessory pathways.

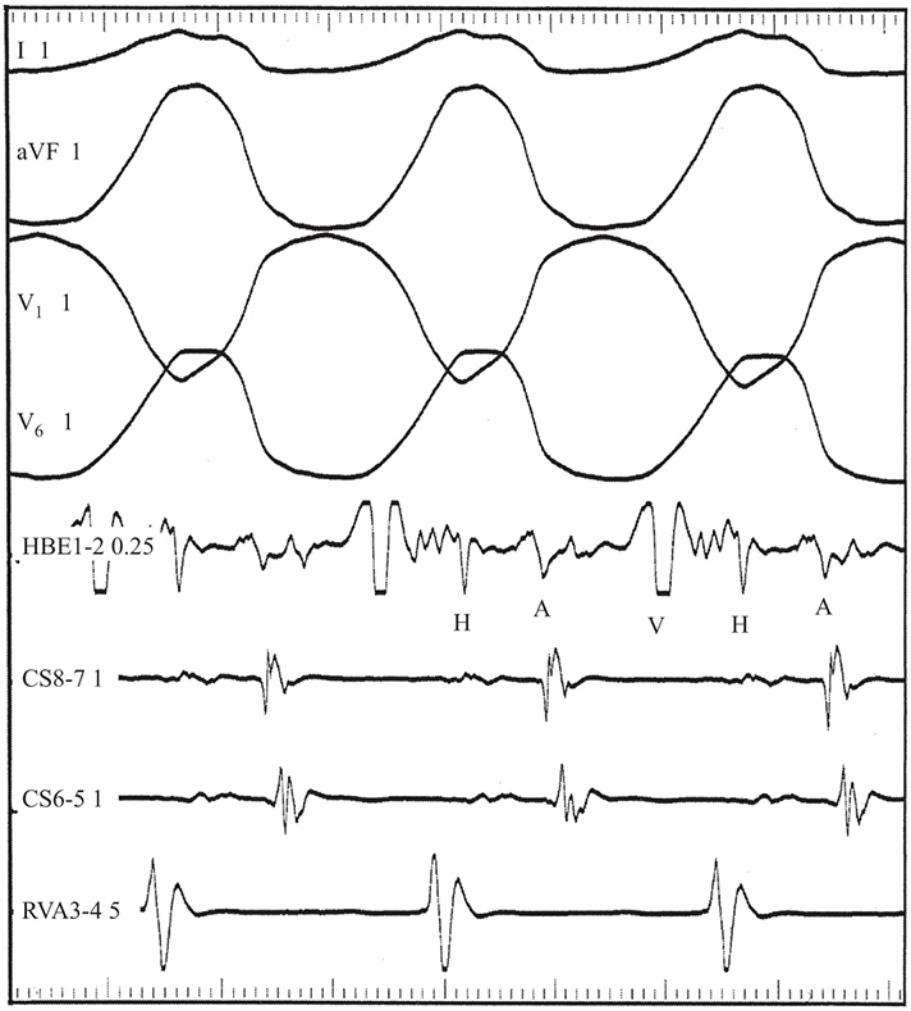


FIGURE 53.9 Antidromic atrioventricular (AV) reentry tachycardia. This tachycardia was induced with atrial burst pacing in a young patient with two right-sided manifest accessory pathways. The tachycardia is rapid and wide complex, with the earliest retrograde A seen in HBE1-2, consistent with retrograde activation through the AV node. AV node reentry with antegrade activation using the accessory pathway (bystander accessory pathway) was excluded by the lack of evidence of dual AV node physiology. CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

5. **Localizing accessory pathways.** Several criteria exist for localizing the ventricular and atrial attachments of accessory pathways. These criteria rely on using the high lateral leads I and aVL to determine the location of the pathways in the left/right axis, using the inferior leads II, III, and aVF to determine the

location in the superior/inferior axis and using the precordial leads to identify the relationship to the interventricular septum.

a. Surface electrocardiographic localization

(1) Delta wave vectors

(a) Left lateral: negative I, aVL; positive II, III, aVF, V_1-V_6

(b) Left posterior wall: positive I, aVL; negative II, III, aVF; positive V_1-V_3/V_4

(c) Posteroseptal: positive I, aVL; negative II, III, aVF; R/S <1 in V_1

(d) Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2

(e) Anteroseptal: positive I, aVL; positive II >III; negative V_1-V_6

(2) P-wave morphology during orthodromic tachycardia

(a) Left lateral: negative I, aVL; positive III >aVF >II; negative V_5 and V_6

(b) Posteroseptal: positive aVR, >aVL; negative II, III, aVF

(c) Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2

b. Localization during EPS

(1) Pacing from multiple atrial sites: Shortest A-delta occurs with pacing close to the atrial insertion site of the accessory pathway and results in maximal preexcitation.

(2) Retrograde atrial activation during orthodromic tachycardia and V pacing

(a) Atrial activation sequence

i. Left and right free wall: eccentric

ii. Posteroseptal: A_{CSos} earlier than A_{His}

iii. Anteroseptal: A_{CSos} later than A_{His}

(b) Atrial activation sequence when a ventricular premature stimulus is delivered during tachycardia at the time when His is refractory

(c) The earliest site of atrial activation identifies the site of atrial insertion of an accessory pathway.

(3) Relationship of local ventricular electrogram to delta: Earliest V correlates with ventricular insertion site. This may be slightly offset or oblique compared with the atrial insertion site.

(4) Effects of bundle branch block

(a) Bundle branch block increasing the VA interval by >35 ms; ipsilateral free wall accessory pathway

(b) With bundle branch block ipsilateral to septal accessory pathways, the increase in VA times is <25 ms.

(c) Left anterior fascicular block can increase VA times 15 to 35 ms with left free wall accessory pathway, particularly with an anterolateral left-sided accessory pathway.

(5) Recording of accessory pathway potential: sharp spike 10 to 30 ms before the onset of the delta wave

6. Identifying the presence of multiple accessory pathways

a. Changing antegrade delta waves during sinus rhythm, atrial pacing, atrial fibrillation, and with antiarrhythmic drugs

b. Evidence of multiple routes of retrograde atrial activation

(1) Changing VA time or activation sequence

(2) Failure to prolong VA time with ipsilateral bundle branch block

c. Orthodromic tachycardia with antegrade fusion

d. Preexcited tachycardia

(1) Antegrade conduction over septal accessory pathway

(2) Antidromic tachycardia faster than orthodromic tachycardia

e. Atypical patterns of preexcitation

f. Mismatch of site of antegrade preexcitation and retrograde atrial activation during AV reentry tachycardia

D. VT evaluation

1. The most common reason for performing EPS on patients with suspected ventricular arrhythmias is documentation of inducible tachycardia, testing the effect and response to antitachycardia pacing and defibrillation, and endocardial mapping to direct attempts at ablation. Recent trials have stratified patients with ischemic or nonischemic cardiomyopathy, congestive heart failure, and reduced LV ejection fraction at higher risk for sudden cardiac death and thus reduced the usefulness of EPS in determining the need for ICD implantation.
2. An **atrial study** is considered for all patients undergoing evaluation of VT. This serves three main purposes: diagnosis of the underlying advanced conduction system disease, documentation of coexisting SVT, and induction of rare forms of VT that may be inducible only with atrial pacing.
3. **Programmed ventricular stimulation** is performed as described earlier. If VT is not induced despite programmed stimulation from two RV sites (RV apex and RV outflow tract), repeat stimulation can be performed after isoproterenol infusion. However, isoproterenol should not be given to patients with active ischemic heart disease. It is primarily of value to those with exercise-induced or catecholamine-dependent VT. LV stimulation is not necessary because RV stimulation techniques have adequate sensitivity and specificity, and the risk of left heart catheterization is avoided. If no VT is induced with any of these techniques, the arrhythmia is deemed noninducible.
4. **Techniques for terminating induced VT.** Pacing terminates as many as 85% of induced VTs in the laboratory. Success is more likely to be achieved with slower tachycardia rates (<200 beats/min) and in hemodynamically tolerated tachycardias. Other factors predictive of successful pacing include the site of stimulation in relation to the tachycardia zone, ventricular

conduction properties, and refractoriness. Pacing can also accelerate tachycardia, an important consideration when antitachycardia pacing is being considered.

5. **Techniques for terminating tachycardia with pacing.** One technique entails the use of one or more **progressively earlier premature ventricular stimuli**. The other technique uses **burst pacing** to overdrive the tachycardia, but there is a greater risk of accelerating the tachycardia into a hemodynamically unstable arrhythmia. Techniques that can be used if pacing fails include delivery of ultrarapid train stimulation and synchronized direct current cardioversion.
6. There are a variety of **responses to programmed stimulation**. What is important is the correlation between these responses in different populations of patients and future risk of adverse outcome. For example, induction of single or double BBR beats has no bearing on long-term outcome among persons with normal LV function and is not considered an abnormal finding. Induction of sustained monomorphic VT, particularly among persons with reduced LV ejection fraction, identifies a subset of patients at high risk for sudden death.

   a. Sustained monomorphic VT

   (1) Induction of sustained monomorphic VT is the **most important response** and has the highest predictive value. This is particularly true if the induced tachycardia is similar to the clinical arrhythmia in both rate and structure. Patients with easily induced VT (eg, with single premature beats) have worse outcomes than those in whom tachycardia is more difficult to induce. It is important to document reproducibility of VT during programmed stimulation. Slow, sustained tachycardia, particularly in patients with ischemic substrate, is typically more reproducible than more rapid tachycardias and tachycardias in those with nonischemic cardiomyopathies. Sustained tachycardia has clearly worse prognostic implications than nonsustained tachycardia. There is no

agreement on what constitutes an abnormal response among patients with nonsustained tachycardia or whether any therapeutic intervention should be pursued for these patients.

(2) Among patients with ischemic substrate, programmed stimulation induces sustained monomorphic VT in as many as 95% of patients with a history of clinical sustained VT, approximately 60% of those with nonsustained VT, and approximately 50% of patients experiencing sudden cardiac death. Induction of sustained monomorphic VT in any of the above subsets has very high specificity (>90%) for spontaneous clinical VT and sudden death. Testing at two RV sites increases sensitivity without sacrificing specificity.

(3) Patients with **nonischemic substrate** are more challenging to evaluate because EPSs are less sensitive and specific. Although inducible sustained monomorphic VT has a worse prognosis than the noninducible type, the positive predictive value of abnormal results of EPS is at best 70%. Patients with negative results of EPS are still at high risk for sudden death, even if they have no prior clinical events. The prognosis may be more favorable if inducible tachycardia is suppressed by drugs, but the risk of future events continues to be high. One can never be reassured about the outcome among patients with nonischemic cardiomyopathy using results of EPS.

(4) **BBR tachycardia** is a type of VT with a well-defined macro reentrant circuit. It occurs most often among patients with dilated cardiomyopathy and is frequently symptomatic.

(a) In the **typical pattern**, the impulse travels antegrade down the right bundle branch, across the interventricular septum, and retrograde up the left bundle branch. The tachycardia exhibits a left bundle branch block pattern, with a **His deflection preceding**

every QRS complex. In sinus rhythm, the **HV interval is abnormally long**, and during tachycardia, it is at least equal and frequently longer than the baseline HV.

(b) In rare instances, it is difficult to differentiate BBR tachycardia from an SVT with aberration or from a myocardial VT with retrograde His deflections.

(c) BBR tachycardia is frequently rapid and exhibits AV dissociation. If cycle length variation takes place, it is important to assess the order of changes in the HH and VV intervals. If HH changes take place before VV changes, BBR is likely. A VV change that occurs before HH change and is also associated with a variation in the HV interval suggests myocardial VT.

(d) Treatment with **antiarrhythmic agents**, including amiodarone, is not helpful and may lead to stabilization of the reentrant circuit. BBR tachycardia is curable with RF ablation of the right bundle.

b. Polymorphic VT frequently occurs with high-output stimulation. It is also more likely to occur with increasing numbers of extra stimuli.

(1) Interpretation of the induction of polymorphic VT depends on the clinical situation. For example, inducible polymorphic VT in a survivor of sudden cardiac death is considered significant. In a patient with ventricular ectopy and normal ventricular function, inducible polymorphic VT is a nonspecific response.

(2) Similar interpretation applies to **induced ventricular fibrillation**. If the patient has never had clinical VT or ventricular fibrillation and has no underlying heart disease, the induced ventricular fibrillation is considered a nonspecific finding that does not warrant therapy.

c. Patients with **hypertrophic cardiomyopathy** represent another subset for whom the predictive value of EPS is problematic.

Induction of sustained monomorphic VT, induction of ventricular fibrillation without aggressive stimulation protocols, and induction of ventricular arrhythmias with atrial pacing or as a result of atrial fibrillation are generally considered to be **poor prognostic signs**.

d. Summary. It is important to have a thorough understanding of the underlying clinical problem and anatomic substrate to assess the appropriateness of any EPS finding for an individual patient.

(1) Repetitive responses caused by BBR are usually physiologic, whereas intramyocardial repetitive ventricular responses are abnormal. However, neither of these responses should be used to guide therapy.

(2) Induced polymorphic VT and ventricular fibrillation can be considered nonspecific findings or clinically significant depending on the clinical circumstances. However, they should not be used to guide drug therapy in any situation.

(3) Induced sustained monomorphic VT identical to the clinical arrhythmia has the highest sensitivity and specificity and has greater importance in predicting outcome.

(4) The importance of nonsustained VT remains controversial. Noninducibility in patients with nonischemic cardiomyopathy or survivors of sudden cardiac death may not provide prediction as accurate as that for patients with underlying ischemic substrate and documented nonsustained VT. Therapeutic decisions have, therefore, been individualized.

(5) Guidelines derived from studies, including the Multicenter Automatic Defibrillator Implantation Trials (MADIT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have obviated the need for performing EPS before deciding to implant ICDs in particular patient populations.

7. **Mapping of VT.** Mapping of VT involves identification of the **electroanatomic substrate** in question **(areas of scar, delayed activity, low voltage signal)**. This can be achieved by mapping the chamber in question, usually with a multielectrode catheter.
   a. Mapping can be performed with steerable electrode catheters during EPS or can involve introduction of specialized multielectrode catheters.
   b. Mapping should be performed in the suspected chamber of origin. The surface ECG and clinical features guide in this determination. Multiple mapping schema can be used to identify the location of tachycardia, with the most appropriate one chosen depending on the clinical circumstances.
   c. Activation mapping takes place during the tachycardia. In an ideal scenario, the whole cycle length of the clinical tachycardia is encompassed in the chamber of interest, identifying a tachycardia circuit and isthmus with regions corresponding to diastolic corridors and exit sites. Because this lengthy process has to take place during tachycardia, it must be hemodynamically tolerable. If the mapped chamber is clear of signals critical to the VT circuit, one should consider whether the substrate involves another chamber or is mid/epicardial in origin.
   d. Sites of origin of tachycardia in patients with ischemic heart disease are usually found in the peri-infarction zone or in the border of an LV aneurysm. To confirm the site, entrainment from that site is performed. Entrainment involves transient overdrive pacing and resetting of the tachycardia without terminating the tachycardia. When entrainment is achieved within the reentrant circuit inside the slowly conducting scarred regions of the heart, or isthmus, pacing produces QRS morphologic match on all 12 surface ECG leads, which is referred to as **concealed fusion**. The return cycle length of activation at the site of pacing after cessation of pacing equals the tachycardia cycle length (**Figure 53.10**). These observations imply that the pacing site is within the region of

scar critical for VT propagation. Further measurements are completed to ascertain the exact location of pacing relative to the VT isthmus (exit site vs diastolic).

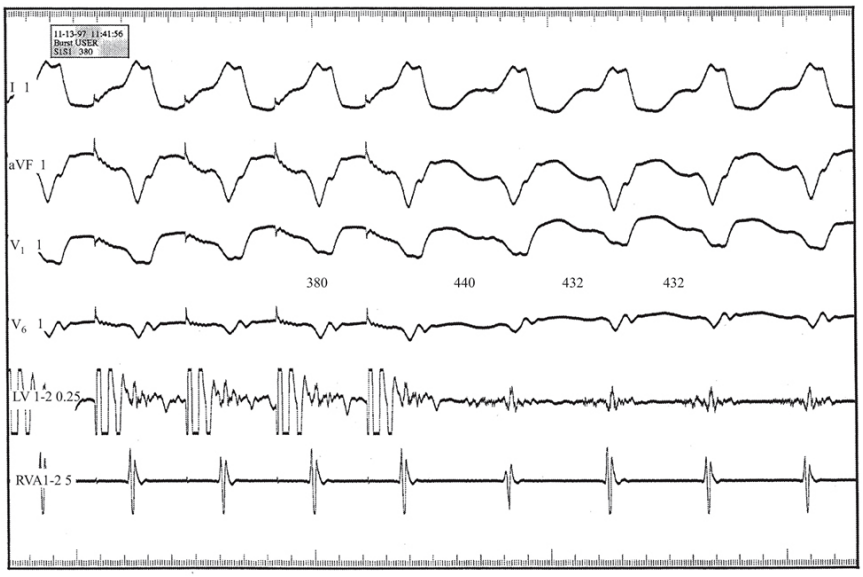


FIGURE 53.10 Entrainment of ventricular tachycardia. Pacing at a rate slightly faster (380 ms) than tachycardia cycle length at a site believed to be the isthmus of the tachycardia resulted in QRS morphology very similar to the native ventricular tachycardia (concealed entrainment) in all 12 leads (only four leads shown). In addition, the postpacing interval is very close to the tachycardia cycle length, suggesting that the pacing site is within the tachycardia circuit. Application of radiofrequency energy at this site resulted in successful ablation of this tachycardia. LV, left ventricular; RVA, right ventricular apex.

e. Pace mapping can be used in the evaluation of patients with hemodynamically unstable tachycardia. Ventricular pacing is performed at various sites at rates that do not cause hemodynamic instability. The site where pacing results in QRS match with clinical tachycardia usually corresponds to the exit sites of the tachycardia circuit. This technique typically requires induction and rapid termination of VT in the EP lab, with either pace termination or DC cardioversion in order to obtain a 12 lead of the VT because subtle differences in ECG

lead placement between outpatient ambulatory ECG's and the EP lab can alter the surface morphology.

f. **Electroanatomic mapping systems** allow the measurement of tissue voltage and activation, timing providing accurate delineation of scar tissue and its boundaries. Thus, mapping in sinus rhythm allows for delimitation of the scar and areas of the scar border that are likely sites of tachycardia exit. This allows for the operator to understand the patient's substrate without having to induce tachycardia and put the patient at risk of hemodynamic instability. Pace mapping can be used to identify those sites around the scar that correspond to tachycardia exits. Linear lesions, performed to interrupt these exit sites responsible for reentrant circuits, can be undertaken, allowing successful ablation of tachycardias that would not be otherwise mapped because of patient intolerance of any sustained tachycardia. Alternatively, an intra-aortic balloon pump or percutaneous LV assist device may be considered to assist with mapping and ablation during prolonged or hemodynamically unstable VT.

g. Mapping can also be performed intraoperatively when endocardial resection is considered. Although this approach can still be used, it is infrequently recommended, because other approaches described earlier in combination with implantable defibrillators have yielded good patient survival and excellent success in eliminating problematic VTs.

h. Some patients, including many with nonischemic cardiomyopathy or certain variants such as Chagas disease and hypertrophic cardiomyopathy, may require both endocardial and epicardial approaches to VT mapping and ablation. Percutaneous access into the epicardial space is obtained with a subxiphoid approach under fluoroscopic guidance and small injections of contrast until the parietal pericardium is penetrated. In patients with dense pericardial adhesions that may limit catheter movement, an intraoperative subxiphoid

incision or open sternotomy may be considered to allow for greater exposure and access.

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CHAPTER 54

Fundamentals of Cardiac Pacing

Alan Kiang and Bruce L. Wilkoff

I. INTRODUCTION. An estimated 1% to 1.5% of the general population lives with a permanent pacemaker (PPM) or implantable cardioverter-defibrillator (ICD), otherwise known as cardiac implantable electronic devices (CIEDs). A basic understanding of the pacing functions of CIEDs is essential to the practice of general cardiology.

II. BASIC COMPONENTS OF CARDIAC PACEMAKERS

A. Pulse generator. The pulse generator, often referred to as the "can," is the small titanium housing containing the battery as well as all the circuitry and components needed to process incoming cardiac signals and deliver appropriate pacing stimuli.

B. Lead system

1. **Terminal pin.** The male portion of the proximal segment of the lead that connects to the pulse generator
2. **Lead body.** Consists of conductors and insulation. The conductors are the "wires" that connect the electrodes to the terminal pin. The insulation, usually a polymer composed of silicone rubber, polyurethane, or a copolymer, surrounds the conductors and insulates them from each other as well as the surrounding environment.
3. **Electrodes.** These are the uninsulated segments of the lead that interface directly with myocardium to allow for transmission of electrical current. Older pacing leads were unipolar, meaning they had only one electrode. Today, pacing leads are either bipolar (two electrodes) or quadripolar (four electrodes). In a bipolar lead, the

"tip" electrode functions as the stimulating electrode or cathode, while the "ring" electrode, located ~1 cm proximal to the tip, functions as the anode. Unipolar leads have only the tip-cathodal electrode, while some other electrode within the pacing circuit, such as the CIED can or defibrillation coil, functions as the anode. In quadripolar leads, which are typically used for coronary sinus pacing in cardiac resynchronization therapy (CRT), any electrode can be used as the cathode or anode.

4. **Fixation device.** Passive fixation leads have small projections of the insulating polymer near the distal electrode, which anchor the leads to the endocardial trabeculae. Most active fixation leads have a helical corkscrew, sometimes retractable, which is screwed into the myocardium. Implantations done today are predominantly with active fixation leads.

C. **Magnetic switch.** All CIEDs (except certain leadless pacemaker [LPM] models) have a magnetic switch, which can be activated by placing a magnet of sufficient strength directly on the patient's chest where the device is located. In older generation CIEDs, a **reed switch** was used as the magnetic switch. Most devices today use a **Hall-effect sensor**, which is more reliable than a reed switch and is less likely to be inadvertently activated by ambient magnetic fields in the environment.

1. **Magnet response in pacemakers (PMs).** When the magnetic switch is activated in a PM, the device will pace asynchronously (DOO, VOO, or AOO) at a factory preset rate. The rate varies with the device manufacturer and may also change once the device battery status has reached the elective replacement interval (ERI). Some manufacturers allow the magnet response in their PMs to be programmed.
2. **Magnet response in ICDs.** When the magnetic switch is activated in an ICD, the device will no longer detect or treat ventricular tachyarrhythmias. The pacing function of the ICD is unaffected. Tachycardia detection and therapies are restored upon removal of the magnet. As with PMs, some manufacturers allow the magnet response in their ICDs to be programmed.

III. BASIC PACING-RELATED DEFINITIONS

A. Capture threshold. This is the lowest energy output from the device that can consistently result in myocardial capture/depolarization. In practice, it is defined as a voltage at a given pulse width and can be measured by holding the pulse width constant while decreasing the output voltage until myocardial capture is intermittent or no longer seen. It can also be defined as a pulse width at a given voltage, which can be measured by holding the voltage constant while decreasing the pulse duration until myocardial capture is intermittent or no longer seen, although this definition is rarely used in practice. For both atrial and ventricular leads, ideal capture thresholds are <1.0 V at a pulse width of 0.5 ms, though values up to 2.5 V at 0.5 ms are considered acceptable at the time of implant if multiple lead repositioning attempts have not achieved a lower threshold. Of note, it is not possible to assess atrial capture thresholds if a patient is in atrial fibrillation (AF) or atrial flutter.

B. Pulse amplitude. This refers to the voltage of the pacing stimulus. It is programmable and defined in units of volts. As a rule of thumb, it should be programmed to 1.7 times (often rounded to 2 times) the capture threshold in order to provide an adequate safety margin.

C. Pulse width. This refers to the duration of the pacing stimulus. It is programmable and defined in milliseconds. It is typically set to 0.4 to 0.5 ms but, in some cases, can be set to as short as 0.2 ms or as long as 1.5 ms.

D. Sensing. This is the amplitude, in millivolts, of the patient's native P or R waves (electrograms) that can be "seen" by the atrial or ventricular leads, respectively. It can be measured by direct measurement of the amplitude of the atrial and ventricular electrograms. It can also be indirectly measured by programming the device to pace at a lower rate than the intrinsic rhythm within the chamber of interest, then gradually raising the **sensitivity** until the device begins to pace. Ideally, P waves should be >1.2 mV and R waves should be >5.0 mV. Of note, if a patient has no underlying rhythm in the chamber of interest, it will not be possible to assess sensing in that lead/chamber.

E. Sensitivity. Not to be confused with sensing, sensitivity is defined as the minimum amplitude of signal that will be counted by the device as an intrinsic atrial or ventricular beat. It is a programmable threshold and is defined in millivolts. Lowering the sensitivity (ie, approaching 0 mV) will lead to better sensing of intrinsic rhythms at the expense of a higher risk of mischaracterizing unwanted signals (eg, T waves, lead noise, myopotentials) as true activity in the chamber of interest, a phenomenon known as oversensing. Conversely, raising the sensitivity (ie, moving away from 0 mV) will mitigate the risk of oversensing but may increase the risk of undersensing, which is the failure to detect true activity in the chamber of interest, especially for lower amplitude rhythms (ventricular fibrillation [VF], AF, premature ventricular contractions [PVCs], premature atrial contractions [PACs]). Therefore, programming the sensitivity is a balancing act between the competing risks of oversensing and undersensing. The historical rule of thumb has been to program the sensitivity to one-third to one-half of the measured sensing amplitude. That being said, now that bipolar leads are standard and T-wave discrimination algorithms are quite robust, oversensing has become less of an issue, and it is now common to see sensitivity programmed at lower ratios, that is, one-fifth to one-fourth the sensing, in order to minimize undersensing. Certain clinical scenarios may influence the decision to program sensitivity lower or higher. For example, if there is concern that AF episodes are not being detected due to the lower amplitude of the AF waveform, then it might be better to program the atrial lead sensitivity on the lower end of the spectrum. As another example, oversensing could be deadly for a patient who is completely PM dependent with no underlying escape rhythm, and in this case, one might err on programming the ventricular lead sensitivity on the higher end of the spectrum. Or, if a patient is having frequent PVCs, then one might program the ventricular lead sensitivity on the lower end of the spectrum, in order to avoid undersensing of the PVCs that can lead to R-on-T phenomenon.

F. Impedance. Measured in units of ohms, impedance is defined as the opposition to electrical current between any two electrodes in a PM system. Normal impedance between the tip-to-ring electrodes in a bipolar lead should be between 300 and 1,500 ohms. Impedance in a unipolar configuration (eg, lead tip to can) is usually 10% to 20% lower than the bipolar configuration due to the larger surface area of the can compared to the ring electrode. Of note, impedance and resistance are related but distinct concepts. Resistance is a measurement of a circuit's opposition to steady-state direct current, whereas impedance, which reflects the combined effects of resistance, capacitance, and inductance, is a more generalized measurement of circuit's opposition to any current, whether it is direct current, alternating current, or a changing current. Because a PM circuit comprises not only resistive elements but also capacitive elements (eg, the electrode-tissue interface) and inductive elements (eg, the conductor coils), the term and concept of impedance are more accurate to use than resistance.

G. Polarity. Polarity refers to the sensing or stimulation vector, usually programmable to unipolar or bipolar for pacing leads and true bipolar or integrated bipolar for ICD leads. Devices with unipolar leads can only be programmed unipolar. Almost all PM leads now are currently either bipolar or quadripolar and can be programmed to the available electrodes to provide independently programmable sensing and pacing in unipolar or bipolar vectors. That is, it is possible to program a lead to sense bipolar but pace unipolar, and vice versa.

1. **Unipolar.** In this configuration, the cathode is the lead tip, and the anode is the CIED can. This results in a large sensing and stimulation "antenna" and produces large PM artifact (spikes) on the electrocardiogram (ECG). Advantages of the unipolar configuration include better sensing of PVCs and low-amplitude signals. Disadvantages include oversensing of extraneous signals, especially pectoralis or diaphragmatic muscle activity (myopotentials). In terms of pacing, inadvertent skeletal muscle stimulation may occur, and large PM artifacts on the ECG may obscure native electrical activity.

2. **Bipolar.** In modern practice, this is the default configuration for most PM leads. In this configuration, both electrodes are at the end of the lead—the cathode at the distal tip and the anode at the proximal ring. This results in a smaller sensing "antenna" with smaller PM artifact (spikes) on the ECG. Myocardial stimulation occurs as a negative charge from the cathode travels through the myocardium and back to the anode. Advantages of the bipolar configuration include less myopotential oversensing and skeletal muscle stimulation, and the smaller PM artifact on the ECG does not obscure native wave morphology. Disadvantages include worse sensing of PVCs and low-amplitude signals.

H. PM dependence. A patient is considered PM dependent if their underlying rhythm in the absence of pacing results in hemodynamic instability, systemic hypoperfusion, or significant symptoms at rest. There is no absolute cutoff in heart rate that defines PM dependence, though practically speaking, most clinicians would consider an underlying rhythm slower than 30 to 40 beats/min as indicative of PM dependence. Of note, a high percentage of pacing reported on device interrogation does not necessarily indicate PM dependence, as percentage of pacing is highly influenced by device programming. For example, if a patient's underlying rhythm is a hemodynamically stable rhythm at 50 beats/min but their device is programmed to a base rate of 70 beats/min, then their interrogation will show near 100% pacing.

I. ERI, also known as elective replacement time (ERT) or recommended replacement time (RRT). These are terms signifying that a device has reached 3 to 6 months of battery life remaining and should be scheduled for generator change within this timeframe.

J. End of life (EOL). This term indicates that complete battery depletion is imminent and generator change should be performed urgently. In order to preserve remaining battery life, devices at EOL may revert to VVI pacing and may lose the ability to be interrogated.

IV. PACEMAKER MODE NOMENCLATURE.

The North American Society of Pacing and Electrophysiology and the British Pacing and

Electrophysiology Group initially published a "pacemaker code" in 1983. Guidelines were later revised in 2002, and the five-position code remains the accepted nomenclature for PM therapy (**Table 54.1**). A description for each position is as follows:

TABLE 54.1 Revised NASPE/BPEG Generic (NBG) Code for Antibradycardia, Adaptive Rate, and Multisite Pacing

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programmability, rate response	Multisite pacing
Letters	O = none	O = none	O = none	O = none	O = none
	A = atrium	A = atrium	T = triggered	R = rate response	A= atrium
	V = ventricle	V = ventricle	I = inhibited		V = ventricle
	D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)

BPEG, British Pacing and Electrophysiology Group; NASPE, North American Society of Pacing and Electrophysiology.

A. The first position refers to which chambers can be paced. "A" indicates only the atrium can be paced, "V" indicates only the ventricle can be paced, "D" stands for dual and indicates both the atrium and the ventricle can be paced, and "O" indicates no chamber can be paced.

B. The second position refers to which chambers can be sensed and, like the first position, can be "A," "V," "D," or "O."

C. The third position refers to what the response of the PM will be to any sensed event. "I" stands for inhibit, which means the device can only withhold pacing in response to sensing; "T" stands for trigger, which means the device can only pace in response to sensing; "D" stands for dual, which means the device can either withhold or give pacing in response to sensing; and lastly, "O" means the device can neither inhibit nor trigger.

D. The fourth position refers to a rate response. "R" means the rate response is on, and the device can adjust the pacing rate in response to physical activity sensed by an activity sensor. "O" means the rate response is off. In practice, the fourth position is typically only mentioned if the rate response is on, that is, "AAIR, VVIR, or DDDR." If the rate response is off, it is simply omitted, that is, "AAI, VVI, or DDD" instead of "AAIO, VVIO, or DDDO."

E. The fifth position refers to multisite pacing. "A" means the device paces in more than one location in the atria, "V" means the device paces in more than one location in the ventricles, "D" means the device paces in more than one location in both the atria and the ventricles, and "O" means there is no multisite pacing. The fifth position is rarely used in clinical practice. As an example, the full nomenclature for a biventricular (ie, CRT) pacemaker (BiVP) or defibrillator programmed to pace and sense in both the ventricles with rate response on would be "DDDRV," but in usual practice, such a device would simply be labeled as "DDDR."

V. BASIC PACING MODES

A. VVI (ventricular demand pacing). In this mode, the device senses and paces in the ventricle only and completely ignores the atrium. Although VVI pacing protects the patient from lethal bradycardias, atrioventricular (AV) synchrony is not restored or maintained. VVI pacing is usually used in temporary pacing. In permanent devices, VVI mode is only appropriate for patients who are permanently in AF or atrial flutter.

B. AAI (atrial demand pacing). In this mode, the device senses and paces in the atrium only and completely ignores the ventricle. This mode is appropriate for patients with sinus node dysfunction who have intact AV conduction. Because there will be no ventricular support if AV block should occur, careful testing of AV conduction is necessary before enabling this mode. This mode is infrequently used in the United States, except as part of automatic mode switch (AMS) algorithms designed to minimize ventricular pacing.

C. AV sequential pacing

1. **DDI.** There is both atrial and ventricular sensing and pacing, but no atrial tracking can occur. **Tracking** refers to pacing of the ventricle in response to activity sensed in the atrium. The ventricular rate is, therefore, dissociated from the atrial rate when intrinsic AV conduction is absent. This mode is rarely used, except during AMS, which is discussed later.
2. **VDD.** In this mode, atrial tracking and sensing can occur, but not atrial pacing. It is, therefore, appropriate for patients with intact sinus node function but impaired AV conduction. It is rarely used.
3. **DDD.** This mode provides the most physiologic pacing and is the most commonly used mode. The pacer can be totally inhibited with normal sinus rhythm, can pace the atrium with spontaneous ventricular depolarization, can pace the ventricle in response to a spontaneous P wave, and can sequentially pace both the atrium and the ventricle. This mode is most appropriate in patients who have impaired AV conduction with either an intact or dysfunctional sinus node.

D. Asynchronous pacing

1. **VOO.** In this mode, sensing is off and pacing in the ventricle occurs at the programmed rate, regardless of intrinsic ventricular activity. There is a risk of R-on-T phenomenon with this mode; therefore, it is only appropriate for use in emergency situations or in closely monitored conditions such as in the operating room (OR).
2. **AOO.** In this mode, sensing is off and pacing in the atrium occurs at the programmed rate, regardless of intrinsic atrial activity. There is a risk of inducing AF with this mode. Outside device testing, it is virtually never used.
3. **DOO.** In this mode, sensing is off and sequential pacing in the atrium followed by the ventricle at a programmed AV delay occurs, regardless of intrinsic atrial or ventricular activity. There is a risk of inducing both AF and VF with this mode; therefore, it is only appropriate to use in emergency situations or in closely monitored conditions such as in the OR.

E. Modes versus hardware. Although modes technically refer to the way a device is programmed, they are also commonly used in shorthand to imply the number or types of leads that a device has. For example, "VVI-PPM" or "VVI-ICD" implies that a device is a single-chamber device with only one lead in the right ventricle (RV). "VDD-PPM" or "VDD-ICD" usually implies a device with a special RV lead that has an extra proximal electrode that can sense, but not pace in the atrium. "DDD-PPM" or "DDD-ICD" implies a dual-chamber device with a right atrial (RA) and an RV lead. Of note, **dual chamber** is a term that implies leads in the RA and RV and should not be confused with the term **biventricular**, which implies a CRT device that has leads in the RV and left ventricle (LV), regardless of the presence of an atrial lead.

VI. PACEMAKER TIMING CYCLES AND INTERVALS.

A PM can be thought of as a series of timing cycles. An understanding of how these timing cycles interact can facilitate the analysis of PM rhythms. A timing cycle runs until the cycle is completed or until it is reset. Completion of a timing cycle results in the release of a pacing output or the initiation of another timing cycle. **Figure 54.1** illustrates the basic timing cycles and intervals for a dual-chamber PM in DDD mode. The terms that appear in this figure are defined as follows:

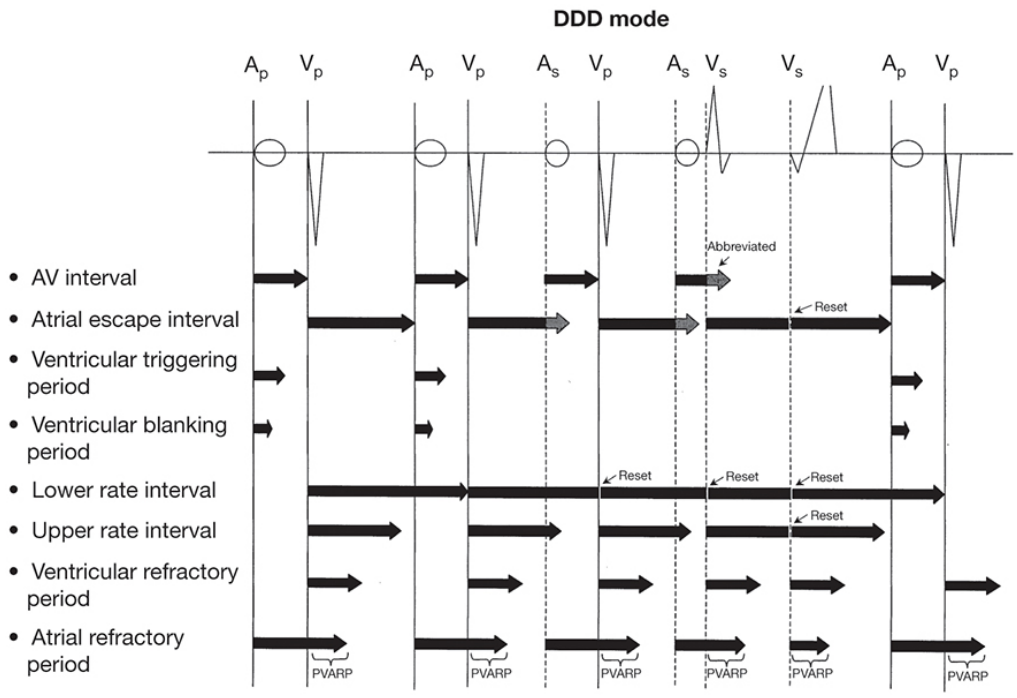

FIGURE 54.1 Timing cycles and intervals for a dual-chamber pacemaker DDD.

- A_p = atrial-paced event. Signifies that the device delivered an atrial-pacing stimulus
- A_s = atrial-sensed event. Signifies that the device sensed a signal in the atrial channel above the programmed atrial sensitivity threshold
- V_p = ventricular-paced event. Signifies that the device delivered a ventricular-pacing stimulus
- V_s = ventricular-sensed event. Signifies that the device sensed a signal in the ventricular channel above the programmed ventricular sensitivity threshold
- **AV interval** = AV pacing interval (also known as AV delay). This is the programmable period between an atrial-sensed or atrial-paced event and a ventricular-paced event. The AV interval following an A-sensed event is typically programmed 30 to 70 ms shorter than that following an A-paced event in order to maintain mechanical AV synchrony. This is because the atrial lead is usually located some distance away from the intrinsic source of atrial depolarization (ie,

the sinus node), such that atrial contraction is already in progress by the time an atrial-sensed event is registered.

- **Atrial escape interval:** This is the period initiated by a ventricular-sensed or ventricular-paced event and ending with the next atrial-paced event.
- **Ventricular blanking period:** This is a ~25- to 50-ms interval after an atrial-paced event where signals on the ventricular lead are assumed to be far-field oversensing of the atrial-pacing artifact (called **cross talk**) and are, therefore, ignored.
- **Ventricular triggering period:** Also called the **cross-talk detection window** or **safety-pacing window**. This is a ~50 to 100 ms interval immediately following the ventricular blanking period. If a ventricular-sensed event occurs during this interval, it triggers a "safety-pacing" stimulus in the ventricle to be delivered within 100 to 120 ms of the atrial-paced event, shorter than the usual AV interval. The rationale is that a ventricular-sensed event in the ventricular triggering period could be either cross talk from the trailing edge of the atrial-pacing artifact or a PVC, with no way to distinguish between the two. If it is the former, then the safety-pacing stimulus will prevent ventricular asystole. If it is the latter, then the safety-pacing stimulus will be delivered early enough to occur before the T wave of the PVC, thereby avoiding R-on-T phenomenon. If the safety-pacing stimulus were to be delivered at the usual AV interval, then there would be a higher risk of pacing on the T wave of the PVC, leading to ventricular tachycardia (VT)/VF. Not all device manufacturers feature safety pacing.
- **Lower rate interval (LRI):** This is the programmable interval at which the PM paces in the absence of sensed intrinsic events. When converted to a rate (beats per minute), this is also known as the **lower rate limit (LRL)** or **base rate**: In atrial-based timing, the device will tolerate fluctuations in the ventricular rate to ensure the atrial rate does not fall below the LRL. In ventricular-based timing, the device will tolerate fluctuations in the atrial rate to ensure that the ventricular rate does not fall below the LRL. Most current devices use a hybrid of both atrial- and ventricular-based timing. Relevant to the LRI is

hysteresis, which is a pacing feature that can be programmed on or off. Hysteresis attempts to allow the heart's native conduction system to predominate and, therefore, modifies base rate behavior. This feature works by using a longer escape interval after a sensed beat than after a paced beat. For example, the device sets the hysteresis rate at 50 beats/min, whereas the basal rate is 60 beats/min. Therefore, if the patient's intrinsic rate is >50 beats/min, the device will not pace. However, if the patient's rate falls below 50 beats/min, the pacer will pace at 60 beats/min. As hysteresis can appear as an unusually long delay on the ECG strip, it can be misinterpreted as failure to pace or as inappropriate sensing.

- **Upper rate interval (URI):** This is the programmable interval that begins with every V-sensed or V-paced event and must elapse before another V-paced event is permitted to occur in response to an A-sensed event. When converted to a rate (beats per minute), it is also known as the upper rate limit (URL) or maximal tracking rate (MTR). If an A-sensed event falls within the URI, then the device will wait until the URI is over to deliver the V pace. If an A-sensed event falls outside the URI, then the device will deliver the V pace at the usual programmed AV delay. The resulting effect is that the PM will never pace the ventricle at a rate faster than the URL, regardless of the intrinsic atrial rate. If the intrinsic atrial rate is at or below the URL, then the device will pace in the ventricle in a 1:1 manner. As the intrinsic atrial rhythm rises above the URL, then the device will begin to "drop" P waves in a pattern that emulates AV nodal Wenckebach.
- **Ventricular refractory period (VRP):** This is the interval initiated by a ventricular-sensed or ventricular-paced event, during which signals in the ventricular channel will be ignored. The purpose is to ensure that any given ventricular depolarization is only counted once and to avoid counting the repolarization waveform (ie, the T wave).
- **Atrial refractory period (ARP):** Also called total atrial refractory period (TARP). This is the interval initiated by an A-sensed or A-paced event, during which signals in the atrial channel are ignored. It is the sum of the AV interval and the **postventricular atrial**

refractory period (PVARP). Like the VRP, the ARP ensures that any given atrial depolarization is only counted once and that cross talk from a ventricular-pacing stimulus is ignored. Furthermore, the programmable PVARP ensures that any retrograde P waves are ignored, a function that is crucial in preventing pacemaker-mediated tachycardia (PMT).

II. RATE-ADAPTIVE PACING. The purpose of rate-adaptive or rate-responsive pacing is to increase the pacing rate in response to physical exertion as measured by an activity sensor. This allows the PM to emulate the function of the sinus node for patients with chronotropic incompetence or atrial arrhythmias that preclude reliable sensing of native sinoatrial rhythm. This function is expressed with the letter "R" in the fourth position (AAIR, VVIR, DDDR, and so on). Most devices today measure physical exertion either by detecting body movement with an accelerometer or by estimating respiratory rate from fluctuations in chest wall impedance. The maximum heart rate at which a device is permitted to pace in response to the activity sensor is programmable and is called the **maximal sensor rate (MSR)**.

III. AUTOMATIC MODE SWITCHING. AMS is a feature that allows a PM to switch pacing modes depending on what is most appropriate for the patient's underlying rhythm at any given time. AMS algorithms fulfill two main purposes, as discussed below.

A. Preventing tracking of atrial tachyarrhythmias. In this type of AMS, if a device detects that a patient has gone into AF, atrial flutter, or atrial tachycardia, it will switch from DDD to a nontracking mode, such as VVI or DDI. This will prevent fast and irregular ventricular pacing due to atrial tracking of the arrhythmia. Once the atrial tachyarrhythmia resolves, the device switches back to DDD. Of note, some devices allow the base rate during mode switch to be set at a different value from the normal base rate in DDD mode. This is sometimes referred to as the **"fallback rate."**

B. Reducing ventricular pacing. In many patients, prolonged high burden of RV pacing can lead to or worsen ventricular dysfunction. Therefore, it is desirable to utilize intrinsic AV conduction whenever

possible and to RV pace only when necessary. Some manufacturers have, therefore, developed AMS algorithms to accomplish this goal. When this type of AMS is programmed on, a device will operate in AAI mode primarily but will switch to DDD mode if it senses that intrinsic AV conduction is lost—during this transition period, the heart rate may drop below the programmed LRL. It will then periodically monitor for recovery of AV conduction and switch back to AAI mode if this is the case.

IX. INDICATIONS FOR PACEMAKER IMPLANTATION.

The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) published updated guidelines for indications for PM implantation in 2018, which are summarized in **Table 54.2**.

TABLE 54.2 Indications for Permanent Pacing (Per 2018 ACC/AHA/HRS Guidelines)

	Class I	Class II	Class III
Sinus node dysfunction (SND)	**1.** Symptomatic sinus bradycardia or sinus pauses **2.** Symptomatic sinus bradycardia or sinus pauses resulting from required drug therapy for which there are no alternative therapies	IIa: **1.** Symptoms attributable to sinus bradycardia or sinus pauses in the setting of tachy-brady syndrome **2.** Symptomatic chronotropic incompetence	**1.** Sinus bradycardia or sinus pauses in asymptomatic patients (regardless of heart rate or pause duration) **2.** Sinus bradycardia or sinus pauses occurring during sleep (regardless of heart rate or pause duration) **3.** Sinus bradycardia or sinus pauses in patients whose symptoms are clearly

	Class I	Class II	Class III
			documented to occur in the absence of bradycardia

	Class I	Class II	Class III
Atrioventricular block (AVB)	**1.** Second-degree Mobitz type II AVB, high-grade AVB, or third-degree AVB not attributable to a reversible or physiologic cause, regardless of symptoms **2.** Second-degree AVB, third-degree AVB, or HV interval of 70 ms or greater in the setting of neuromuscular diseases associated with conduction disorders including muscular dystrophy (such as myotonic dystrophy type 1) or Kearns-Sayre syndrome (with additional defibrillator capability as needed if expected survival >1 y) **3.** Symptomatic bradycardia in the setting of permanent AF **4.** Symptomatic AVB as a consequence of medically	IIa: **1.** Symptomatic second- or third-degree AVB in the setting of chronic stable doses of medically necessary drug therapy (reasonable to proceed with permanent pacing without further observation for drug washout or reversibility) **2.** Second-degree Mobitz type II or third-degree AVB in the setting of an infiltrative cardiomyopathy, for example, sarcoidosis or amyloidosis (reasonable to proceed with permanent pacing without further observation for reversibility, with defibrillation capability as needed if expected survival >1 y) **3.** PR interval >240 ms and LBBB in the setting of Lamin A/C mutations, including limb-girdle and Emery-Dreifuss muscular	**1.** First-degree AVB, second-degree Mobitz type I AVB (Wenckebach), or 2:1 AVB believed to be at the level of the AV node, with symptoms not temporally correlated with the AVB **2.** Asymptomatic first-degree AVB, second-degree Mobitz type I AVB (Wenckebach), or 2:1 AVB believed to be at the level of the AV node **3.** AVB attributable to a known reversible and nonrecurrent cause, which has fully resolved with treatment of the underlying cause (eg, drug toxicity, Lyme disease) **4.** Asymptomatic vagally mediated AVB

	Class I	Class II	Class III
	necessary drug therapy	dystrophies (with defibrillator capability as needed if >1 y expected survival) **4.** Marked first- or second-degree Mobitz type I AVB with symptoms clearly attributable to the AVB IIb: **1.** Symptomatic second- or third-degree AVB associated with thyroid function abnormalities but without clinical myxedema (reasonable to consider permanent pacing without further observation for reversibility) **2.** PR >240 ms, QRS >120 ms, or fascicular block in the setting of neuromuscular diseases such as myotonic dystrophy type 1 and expected survival >1 y (with defibrillator capability as needed)	
After the acute phase of MI	**1.** Second-degree Mobitz type II		**1.** SND or AVB that resolves after a

	Class I	Class II	Class III
	AVB, high-grade AVB, alternating BBB, or third-degree AVB that persists after a waiting period 2. Symptomatic SND that persists after a waiting period		waiting period 2. New BBB or fascicular block in the absence of AVB
Chronic conduction system disease (BBB or fascicular block with 1:1 AV conduction)	1. Syncope with BBB and HV interval 70 ms or greater, or evidence of infranodal block during EP study 2. Alternating left/right BBB	IIa: 1. Conduction disease in the setting of Kearns-Sayre syndrome and expected survival >1 y (with defibrillator capability as needed) IIb: 1. QRS >110 ms in the setting of Anderson-Fabry disease and expected survival >1 y (with defibrillation capability as needed)	1. Asymptomatic patients with isolated conduction disease and 1:1 AV conduction
After cardiac transplantation	Same as general guidelines for SND and AVB		
Post–cardiac surgery (includes CABG, MAZE, AVR, MVR, TVR)	1. New postoperative SND or AVB associated with persistent symptoms or hemodynamic		

	Class I	Class II	Class III
	instability and does not resolve		
Post-TAVR	1. New AVB associated with persistent symptoms or hemodynamic instability and does not resolve	IIb 1. New persistent LBBB after TAVR (as opposed to close surveillance, which is IIa indication)	
Postsurgical myectomy or alcohol septal ablation	1. Persistent second-degree Mobitz type II AVB, high-grade AVB, or third-degree AVB (adding on defibrillator capability if high risk for SCD and survival >1 y is IIa indication)		
Adult congenital heart disease	1. Same as above guidelines for SND and AVB		1. In selected adults with ACHD and venous to systemic intracardiac shunts, placement of endocardial pacing leads is potentially harmful.
Epilepsy		1. IIaIn severe symptomatic bradycardia (ictal bradycardia) in the setting of medically refractory epilepsy,	

Class I	Class II	Class III
	permanent pacing is reasonable to reduce the severity of symptoms.	

Class I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.

Class IIa: Conditions for which there is evidence and/or general agreement that pacing can be beneficial, useful, and effective.

Class IIb: Conditions for which the usefulness/efficacy of pacing is uncertain or not well established.

Class III: Conditions for which there is evidence and/or general agreement that pacing is not beneficial and in some cases may be harmful.

ACHD, adult congenital heart disease; AF, atrial fibrillation; AVR, aortic valve replacement; BBB, bundle branch block; CABG, coronary artery bypass grafting; EP, electrophysiologic; LBBB, left bundle branch block; MI, myocardial infarction; MVR, mitral valve replacement; SCD, sudden cardiac death; TAVR, transcatheter aortic valve replacement; TVR, tricuspid valve repair.

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X. TRANSVENOUS PACEMAKER IMPLANTATION: PERTINENT ISSUES FOR NONIMPLANTING CLINICIANS

A. Preoperative assessment. Several issues must be addressed for the patient scheduled for PM implantation.

1. History and physical examination. An ongoing indication for pacing should be confirmed, especially if the presenting bradyarrhythmia has resolved (eg, due to a reversible etiology, or recovery of conduction after heart surgery). Informed consent should be documented. Attention should be given to any findings that may affect the site and approach for PM implantation, such as patient handedness (PMs are generally implanted on the contralateral side) and presence of infection or other skin abnormalities over the implant site. If possible, all nontunneled central venous catheters and chest tubes should be removed to

minimize risk of CIED infection at the time of implant. For dialysis patients, a device should not be implanted on the same side as an existing or planned AV fistula or tunneled dialysis catheter. As PM implantation is typically performed under conscious sedation, patients should be stable from a hemodynamic and respiratory status and should be able to tolerate laying flat.

2. **Testing**
   - **a.** Posteroanterior and lateral chest radiograph
   - **b.** 12-Lead ECG
   - **c.** Basic metabolic panel, complete blood count, prothrombin time/international normalized ratio (PT/INR), partial thromboplastin time (PTT), type, and screen
   - **d.** If there is any reason to suspect subclavian vein stenosis or occlusion on the side of planned device implantation (eg, history of radiation, mastectomy, deep venous thrombosis [DVT], long-term indwelling lines, prior CIED on that side), it is helpful to have imaging of the venous system prior to device implantation. This can be in the form of a computed tomography (CT) scan with contrast or a venogram done under fluoroscopy. For patients with renal dysfunction or iodinated contrast allergy, a venogram with CO_2 as the contrast agent can be used as an alternative. If the subclavian vein is occluded, then the options are to implant on the contralateral side or to perform venoplasty on the ipsilateral side.

B. Anticoagulant management. Anticoagulation management surrounding the time of CIED surgery is ultimately at the discretion of the individual implanter. However, the below reflects the usual institutional practice at Cleveland Clinic:

1. **Unfractionated heparin.** Heparin is discouraged in patients having CIED procedures. Heparin infusions are typically discontinued 4 to 6 hours before CIED implantation and are only resumed if absolutely necessary 72 hours following implantation. Early resumption of therapeutic heparin carries a significant risk of pocket hematoma.

2. **Enoxaparin.** Enoxaparin is discouraged in patients having CIED procedures. For twice-daily therapeutic enoxaparin, the evening dose on the day prior to CIED implantation is typically held and is, like heparin, resumed only if absolutely necessary 72 hours following implantation. As with unfractionated heparin, early resumption of therapeutic enoxaparin is associated with a significant risk of pocket hematoma.
3. **Prophylactic subcutaneous heparin or enoxaparin.** Prophylactic dose of heparin or enoxaparin is typically okay to give the evening before implantation and is held on the morning of implantation. They can be resumed the morning after implantation, provided there is adequate hemostasis.
4. **Warfarin.** Warfarin is preferable compared to heparin products and can be continued through CIED surgery as long as the INR is in the lower end of the therapeutic range, that is, between 2.0 and 3.0. Accordingly, warfarin is the preferred agent for patients who cannot tolerate any interruption in anticoagulation (mechanical valve, high-risk DVT/pulmonary embolism [PE]). Such patients should have finished bridging and already be therapeutic on warfarin before undergoing CIED implantation, since heparin/enoxaparin must be held for at least 72 hours following implant. Lead extraction cases are an exception due to the higher risk of bleeding/cardiac perforation, which may necessitate surgical rescue; in such cases, INR should be normal or near-normal going into the case. For extractions in the setting of mechanical valves, typically, the patient is brought to the OR with a normal INR and a heparin infusion that is stopped on the morning of the procedure; warfarin is then restarted the same evening of the procedure without heparin/enoxaparin bridging. Vitamin K should be avoided as this will significantly prolong the time to reach therapeutic INR afterward.
5. **Direct oral anticoagulants (DOACs).** DOACs are also preferred to heparin products with regard to periprocedural anticoagulation. Apixaban and rivaroxaban should be held 24 hours before PM implantation. Dabigatran should be held 24 hours before PM

implantation in patients with a creatinine clearance (CrCl) >80 mL/min, 36 hours for CrCl 50 to 80, and 48 hours for CrCl <50. DOACs are typically resumed 48 to 72 hours after implantation, provided there is ongoing hemostasis of the pocket. In situations where the risk/benefit profile favors minimal interruption in anticoagulation, such as an active DVT or AF with high stroke risk, implanters may elect to hold a DOAC for only 12 hours and resume in as little as 12 to 24 hours following implantation. For lead extraction cases, DOACs should be held twice as long preoperatively compared to a standard CIED implant or generator change (eg, holding apixaban/rivaroxaban for 48 hours instead of 24 hours).

6. **Antiplatelet agents.** Both aspirin and P2Y12 inhibitors should be withheld, if possible, for 5 days prior to CIED surgery. They can be restarted the day after surgery if there is adequate hemostasis. In situations where withholding antiplatelet agents is risky, such as in the setting of a recently placed coronary stent or in extensive coronary or peripheral arterial disease, it would be reasonable to accept a higher risk of device hematoma and to continue these agents through CIED surgery.

C. Postoperative workflow

1. **General precautions.** Patients are usually placed on bedrest for 4 hours and admitted for overnight observation on telemetry after PM implantation. For generator changes, patients are placed on 2 hours of bedrest to allow for sedation to wear off and are typically discharged home the same day. Acetaminophen is adequate for pain control in most cases, though narcotics may occasionally be needed.
2. **Imaging.** Posteroanterior and lateral chest radiograph should be obtained to document the proper position of the PM leads and connection of the terminal pins to the pulse generator. The radiograph should also be examined for evidence of pneumothorax, pericardial effusion, or pleural effusion.
3. **Resuming anticoagulation.** As discussed above, with the exception of warfarin, anticoagulation should not be aggressive in

the early postimplantation period because of the risk of PM pocket hematoma, which has been associated with an increased risk of complications such as reoperation and infection. Administration of therapeutic doses of unfractionated or low-molecular-weight heparin in the week following device implantation will increase the risk of hematoma and should almost never be done. Depending on operator preferences, DOACs can usually be restarted 1 to 3 days after the procedure. Warfarin typically does not need to be held going into the procedure, but if it was held, it can usually be restarted on the same day.

4. **PM interrogation.** Prior to discharge, device interrogation should be performed by the device clinic or the on-call clinician to ensure that the device is functioning appropriately. This includes confirmation of appropriate pacing and sensing thresholds as well as lead impedances. Capture thresholds are expected to rise over the first 2 to 6 weeks after implantation; therefore, the device output should be programmed with an adequate safety margin to account for these changes.
5. **Discharge planning.** Once the chest radiograph and device interrogation have been completed, and after ensuring the incision site is free of bleeding or hematoma, the patient is ready for discharge. Discharge instructions should include patient education regarding the recognition of PM pocket complications, such as signs of infections, bleeding, or hematoma. Patients should avoid showering or getting the implant site wet for the first week and avoid submerging the incision underwater for 6 weeks. They should also avoid heavy lifting or vigorous activity (especially forceful abduction) with the arm ipsilateral to the implant site for 6 weeks. However, they should be encouraged to use the ipsilateral arm in light activities, including combing hair and raising the arm over the head to prevent the development of a frozen shoulder. For this reason, the use of slings after CIED surgery is no longer routinely recommended.

D. Acute complications of PM implantation

1. **Pneumothorax/hemothorax.** The risk of pneumothorax/hemothorax from PM implantation ranges between 1% and 2%. Usually, this is asymptomatic and detected only by chest radiograph. A large, symptomatic, expanding, or persistent pneumothorax/hemothorax often necessitates placement of a chest tube.
2. **Pocket hematoma.** This is one of the most common complications of PM implantation and is often due to small-vessel venous bleeding inside the PM pocket or retrograde flow of venous blood along the PM leads into the pocket. The incidence ranges between 5% and 10%. Signs and symptoms may include pain, swelling, and, sometimes, bleeding at the pocket site. Most hematomas are small enough to be managed conservatively with pressure dressings, elevation (head of bed at least 45°), and analgesics. The patient should be positioned on their side contralateral to the PM site. Large hematomas may compromise the integrity of the incision site and may require evacuation in the electrophysiology laboratory or OR. Percutaneous insertion of a needle to drain a hematoma increases the risk of infection and should be avoided.
3. **Cardiac perforation and tamponade.** Perforation may lead to pericardial effusion and cardiac tamponade and should be suspected in the patient with chest pain, pericardial friction rub, or hypotension after PM implantation. Incidence is <1%. Urgent echocardiography should be performed to rule in or rule out the diagnosis. The hemodynamically unstable patient with tamponade will require urgent pericardiocentesis and drainage of the effusion.
4. **Diaphragmatic stimulation.** Stimulation of the left diaphragm may occur with a pacing lead at the RV apex, particularly at high pacing outputs. The possibility of cardiac perforation should be considered. Stimulation of the right diaphragm may occur due to stimulation of the right phrenic nerve by a displaced atrial lead. Reduction in the PM output voltage or lead repositioning may be necessary. With coronary sinus leads, stimulation of the left

diaphragm is commonly encountered and may be mitigated by adjustment of the output voltage or the pacing vector.

5. **Lead dislodgement.** Pacing leads may become dislodged soon after implantation before the lead has become more fixed in place through clotting and fibrosis. Lead dislodgement may be suspected by noncapture, high lead impedance, undersensing, or oversensing on telemetry or ECG and may be confirmed by chest radiography or formal PM testing. Atrial lead dislodgements account for most lead dislodgements.
6. **Venous thrombosis.** Thrombosis of the subclavian vein on the side of device implantation is usually a chronic complication but may present acutely with symptomatic swelling of the neck or arm, necessitating treatment with systemic anticoagulation.

E. Chronic complications of PM implantation

1. **Infection.** The reported incidence of PM infection is 1.9 per 1,000 device-years based on a large cohort study spanning 30 years. The number of PMs implanted annually continues to increase, and yet, the rate of device-related infections is increasing at a disproportionately higher rate. Recognition of these infections and appropriate treatment is critical for health care providers managing patients with cardiac implantable devices. The infection may involve only the PM pocket or the entire system, with subsequent life-threatening sepsis. There is a higher incidence with repeat operations (eg, pulse generator replacement). Causative organisms tend to be skin flora, such as *Staphylococcus* species. Treatment should include intravenous (IV) antibiotics; however, antibiotic therapy rarely eradicates the infection unless the entire PM system (generator and leads) is removed. Mortality rates for device-related endocarditis range from 31% to 66% without device removal. Mortality improves to 18% or less with a combined approach of medical therapy and complete device removal. The timing of system removal depends on the clinical status of the patient; however, prolonged delays should be avoided.
2. **Intravascular thrombosis or obstruction.** Vascular complications are common with device therapy. They range from

asymptomatic venous occlusion to extremity edema. Mortality from vascular complications is rare. Initial treatments may include heat and upper extremity elevation. Symptomatic thrombosis of the subclavian or axillary veins may require anticoagulation or systemic thrombolytic therapy. Superior vena cava (SVC) stenosis or occlusion may require percutaneous balloon dilatation or surgical consultation for consideration of repair.

3. **Lead malfunction.** Over time, leads may develop fractures in the conductor coils or breaks in insulation. Either of these can lead to issues with sensing and capture. An insulation breach may result in low impedance, whereas a fracture usually results in high impedance.
4. **Twiddler syndrome.** This is a condition in which the PM is twisted or turned upside down in the pocket due to manipulation by the patient (either intentionally or unintentionally). The leads may become twisted, resulting in excessive traction on the leads and dislodgement.

XI. PERIOPERATIVE MANAGEMENT OF CARDIAC IMPLANTABLE ELECTRONIC DEVICES.

Perioperative CIED management is a common reason for cardiology consultation. The main concern is the risk of **electromagnetic interference (EMI)** during surgery, which can cause noise that is then oversensed by the device as native cardiac rhythm, potentially leading to deleterious device behavior. For PMs, EMI can have three main effects: (1) oversensing EMI noise in the ventricular channel causes pacing inhibition, which may then result in unstable bradycardia or asystole if a patient is PM dependent; (2) oversensing EMI noise in the atrial channel may lead to tracking of noise and rapid ventricular pacing if the PM is set to DDD or VDD mode; and (3) prolonged or repetitive EMI noise may trigger a device's noise reversion algorithm, which then initiates asynchronous pacing as a protective measure. For ICDs, EMI can be oversensed as VT/VF and result in inappropriate antitachycardia pacing (ATP) or shocks. Appropriate reprogramming of a CIED in the perioperative period can prevent the above issues. A general guideline for perioperative device management

and programming is discussed below, though clinicians should ultimately review and defer to institution-specific protocols.

A. Preoperative assessment

1. A recent device interrogation within 1 to 2 weeks of surgery should have been done to determine whether the device is a PM or ICD, to assess the baseline function of the device and leads, and to assess the underlying rhythm (which, in turn, determines the patient's degree of PM dependence).
2. It should be determined whether the risk of clinically significant EMI during the surgery/procedure is high enough to warrant preemptive reprogramming of the device. **In usual clinical practice, the only EMI sources that fulfill the criterion of high EMI risk are the use of monopolar electrocautery above the umbilicus and the use of radiofrequency (RF) ablation above the umbilicus**, assuming standard left or right infraclavicular CIED position. Monopolar electrocautery below the umbilicus, RF ablation below the umbilicus, bipolar electrocautery, and other sources like shockwave lithotripsy and peripheral nerve stimulators all carry a negligible risk of EMI such that routine preoperative device reprogramming is not recommended. Most electrocautery is monopolar, from the tip of the cautery tool to a grounding patch, usually on the thigh.

B. Perioperative programming. The decision to reprogram a device prior to surgery depends on the risk of EMI, the degree of PM dependence, and whether the device is an ICD.

1. **For surgery where the EMI risk is low,** no reprogramming of pacing function needs to occur as the device should continue to function normally throughout the procedure. If the device is an ICD, tachytherapies (ATP and shocks) do not need to be disabled.
2. **For surgery where the EMI risk is high and the patient is not PM dependent**, rate response and noise reversion should be disabled, and the device should be set to an inhibited nontracking mode (DDI or VVI). If the device is an ICD, tachytherapies should be disabled.

3. **For surgery where the EMI risk is high and the patient is PM dependent**, rate response and noise reversion should be disabled, and the decision to program the device to either a nontracking mode (DDI or VVI) or asynchronous pacing (DOO or VOO) mode should be individualized, taking into account surgeon/anesthesiologist preference. If the device is an ICD, tachytherapies should be disabled.
    a. **Deciding on asynchronous pacing.** In most cases, asynchronous pacing is unnecessary as even in the presence of "high EMI risk," it is uncommon for EMI-induced inhibition of pacing to result in clinically significant bradycardia. Moreover, asynchronous pacing carries the risk of inducing VT/VF due to R-on-T phenomenon, which may then require external defibrillation. If the surgical/anesthesia team has no strong preference, then a reasonable approach would be to start the case with a nontracking mode only while monitoring for bradycardia/asystole during surgery; if significant pacing inhibition is observed during the case, then one could always revert to asynchronous pacing at that time. If at any point a decision is made to proceed with asynchronous pacing, the risk of R-on-T should be mitigated by setting the asynchronous pacing to a rate that is well above the rate of the underlying escape rhythm; however, even after doing this, it is still possible to have R-on-T due to PVCs, and the surgical/anesthesia team must be aware of this risk. Of note, the threshold to program an ICD to pace asynchronously should be even higher than for a PM and should generally be avoided. This is because the ICD patient population has a high prevalence of structural heart disease, which significantly increases the risk of inducing VT/VF.

C. **Intraoperative management.** In all cases, continuous telemetry should be used to monitor for bradyarrhythmias or tachyarrhythmias. Equipment for transcutaneous pacing and external defibrillation should be immediately available.

D. Postoperative assessment. Following surgery, the CIED should be reprogrammed to baseline settings. A repeat device interrogation should be performed to confirm stable lead function. In the case of cardiac surgery, a chest x-ray should be done to evaluate for lead damage or dislodgement.

XII. MAGNETIC RESONANCE IMAGING COMPATIBILITY IN CIEDS

A. Effects of magnetic resonance imaging (MRI) scans on CIEDs. During an MRI scan, a patient is exposed to (1) a static magnetic field that remains on for the entire scan, (2) a gradient magnetic field that cycles on and off rapidly throughout the scan, and (3) pulses of RF radiation that also cycle on and off rapidly throughout the scan. These electromagnetic perturbances have several effects on CIEDs, which are detailed below.

1. **Activation of the magnetic sensor (Reed switch/Hall-effect sensor).** The static and gradient magnetic fields have the potential to activate the Reed switch on older CIEDs, thereby enabling magnet mode. This is less of a concern with newer CIEDs, in which the Reed switch has been replaced by Hall-effect sensors that are less likely to be inadvertently activated. Moreover, most manufacturers now enable their devices to be programmed in a temporary "MRI mode," during which the device simply ignores input from the magnetic sensor.
2. **Mechanical forces exerted upon the leads or pulse generator.** The static and gradient magnetic fields have the potential to exert mechanical forces upon the pulse generator and leads themselves, potentially causing patient discomfort or even lead dislodgement/perforation. Newer CIEDs now contain much lower amounts of ferromagnetic material compared to older devices and so the risk of device movement is much lower, but not completely zero.
3. **Induction of currents within the leads.** The gradient magnetic fields and RF pulses can induce current within the device leads. These currents will manifest as noise on the leads, which can result in inappropriate inhibition of pacing, inappropriate tracking

of atrial noise, and, in the case of ICDs, inappropriate VT/VF detections and shocks. These issues are largely circumvented by programming the CIED to a mode where the noise is simply ignored (eg, asynchronous pacing for PM-dependent patients, pacing or tracking off for non–pacer-dependent patients, and tachytherapies off for ICDs). Rarely, the induced currents are strong enough to cause pacing of the heart that is completely independent of the pulse generator, a phenomenon that cannot be prevented through device reprogramming. Fortunately, advancements in lead design have made newer leads much less susceptible to RF interference and current induction by time-varying magnetic fields.

4. **Tissue heating.** In addition to causing noise, the currents induced in the leads by emitted RF energy may cause heating and scarring of the myocardium at the lead tip, similar to what occurs at the tip of an RF ablation catheter. The resulting myocardial scar at the lead tip location can lead to decreased sensing and increased capture thresholds. Again, advancements in lead design have fortunately made newer leads less susceptible to RF interference and associated tissue heating. Of note, fractured leads, epicardial leads, or capped/abandoned leads are at especially high risk for RF-induced tissue heating.

B. **MR-conditional versus non–MR-conditional devices.** The first "MR-conditional" devices were Food and Drug Administration (FDA) approved in 2011, and today, most if not all new devices from major CIED manufacturers are classified as such. In these devices, the leads and generator have been engineered to minimize the effects of MR interference as much as possible. While MR-conditional devices are not completely immune to MR interference, they are considered practically safe in the MRI environment, assuming that they are programmed appropriately at the time of the scan and are only used in conditions where key parameters such as magnetic field strength and RF power are kept within the limits set by the CIED manufacturer. Determining whether a CIED is MR conditional can be done by looking up the device model number on the manufacturer's

website, or by contacting a device representative. It is important to recognize that a CIED system is only MR conditional if all components (generator and leads) are MR conditional and at least 6 weeks have elapsed since device implantation. CIED systems that mix/match MR-conditional and non–MR-conditional components are overall considered non–MR conditional. Mixing/matching of components from different manufacturers also renders the device non–MR conditional, even if all the individual components are MR conditional. Lastly, the presence of any abandoned leads, lead fragments, fractured leads, epicardial leads, or generators implanted in a location other than the left/right prepectoral space (eg, the abdomen) also renders the system non–MR conditional.

C. Obtaining an MRI in a patient with an MR-conditional CIED.

The process for performing an MRI in patients with CIEDs is typically protocolized through a collaboration between radiology and electrophysiology departments and may vary among institutions. Generally speaking, the process involves/requires the following:

1. **Review of a recent chest x-ray** to assess for the presence of fractured leads, abandoned leads, epicardial leads, or a nonstandard generator location, which may affect MR conditionality.
2. **Review of a recent device interrogation** to assess the patient's underlying rhythm and to ensure that the device has adequate battery life and that the leads are functioning well.
3. **Immediately prior to the MRI, the device is reprogrammed.** For patients with an unstable underlying rhythm and are dependent on pacing, the device is set to asynchronously pace (eg, DOO, VOO). For patients with a stable underlying rhythm and are not dependent on pacing, the device is set to a nontracking inhibited mode (eg, AAI, VVI, DDI), or is simply set to not pace at all (eg, ODO, OVO). If the device is an ICD, tachytherapies are programmed off. If possible, rate response, magnet mode, and noise reversion algorithms should be disabled on all devices.
4. **During the MRI**, the patient should be kept on continuous pulse oximetry and telemetry and must be monitored for hemodynamic

stability throughout the study. An external defibrillator must be immediately available. Even with the appropriate programming changes, arrhythmic events due to the following mechanisms are still possible: (1) R-on-T phenomenon due to asynchronous pacing, (2) atrial or ventricular stimulation caused by current induction in the leads, (3) loss of capture due to tissue heating or lead dislodgement, and (4) coincidental occurrence of VT/VF, which will no longer be aborted by the device since tachytherapies are disabled.

5. **Immediately after the MRI, the device is reprogrammed** to the baseline settings and reinterrogated to ensure that generator and lead function have remained stable.

D. Obtaining an MRI in a patient with a non–MR-conditional CIED. The protocol for these patients is institution specific, and this should be reviewed. Typically, the preferred solution is always to determine if an alternative imaging modality can be used to answer the clinical question. If there is no alternative, it is still possible to proceed with an MRI in most cases, as long as the increased risk of MR interference/complications is acknowledged and discussed with the patient beforehand. Despite the theoretical risks, studies looking at MRIs done on patients with non–MR-conditional devices have demonstrated a low incidence of clinically significant complications, even in the presence of epicardial, fractured, or abandoned leads. In addition to all the same steps described above for MR-conditional systems, the process for obtaining an MRI in patients with non–MR-conditional CIEDs typically involves consultation with the electrophysiology service and documentation of a risk/benefit discussion with the patient before proceeding with the scan.

III. COMMON CONCERNS RELATED TO PACEMAKERS

A. Concern for PM malfunction. Occasionally, cardiology will be consulted for concern for PM malfunction. Typically, this concern arises when a device is pacing less than expected, or more than expected. Sometimes, what appears to be malfunction is actually **pseudomalfunction,** which is when the device is functioning as

intended/programmed with no deleterious effects but produces unexpected ECG findings, often because of specialized algorithms. In other cases, there is true device malfunction that has deleterious consequences, and this can be either due to suboptimal programming or due to a structural problem with the device or leads. A combination of surface ECG interpretation, device interrogation, and an understanding of PM function and timing cycles is often needed to distinguish among these possibilities and to make an accurate diagnosis. An introductory framework for approaching such situations is discussed below.

1. **Less or slower pacing than expected**
    a. **Oversensing.** "Oversensing results in underpacing." If a device misinterprets nonphysiologic signals as intrinsic cardiac activity, then pacing will be inappropriately inhibited. On surface ECG, there will be a lack of pacing stimuli where one would otherwise expect them. EMI noise, noise due to lead malfunction or dislodgement, cross talk, myopotentials, or T waves are all possible sources of oversensing. In terms of lead malfunction, both **insulation breaches (suggested by low impedance)** and **conductor fractures (suggested by high impedance)** can result in noise. Evaluation with a chest radiograph can sometimes reveal a visible fracture in the lead or gross dislodgement.
    b. **Loss of capture.** Here the device attempts to pace but is unable to capture the myocardium. This usually manifests on the ECG as pacing spikes without a corresponding atrial or ventricular complex. Most commonly, loss of capture is due to a lead issue. Lead conductor fracture, insulation breaks, and dislodgments can all raise the capture threshold. Hyperkalemia, acidemia, class IC antiarrhythmics, and myocardial scarring due to cardiomyopathy or infarction can also raise the capture threshold. Sometimes, a pacing stimulus that falls during the refractory period after a coincidentally timed intrinsic beat (such as on a PVC during safety pacing) will resemble

noncapture—this is normal device behavior and is a type of pseudomalfunction.

c. **Specialized algorithms** such as **hysteresis** and **AMSs**, discussed previously, can both result in a device pacing at a lower rate than the programmed base rate. In addition, some devices have **sleep rates** where the base rate is lowered at night. Lastly, some devices have a feature called **noncompetitive atrial pacing (NCAP)** that is intended to prevent pacing within the vulnerable period of the atrium, which can induce AF. When NCAP is enabled, a PAC that falls within the PVARP forces the device to wait an interval of ~300 ms before it is allowed to A pace again, even if this means exceeding the programmed LRI. As a result, the pacing rate may at times fall below the base rate when NCAP is enabled. Review of a recent interrogation report to see if such features are enabled can help determine if these algorithms are responsible for the observed ECG findings.

2. **More or faster pacing than expected**

a. **Undersensing.** "Undersensing results in overpacing." A device failing to detect intrinsic activity within a chamber will pace inappropriately in that chamber. The surface ECG will show pacing spikes that are earlier than expected relative to the last intrinsic beat. Undersensing may arise from a lead issue (dislodgment, conductor fracture, insulation breach) or may be due to a low endocardial signal (scarring, ectopic beats). In some cases, undersensing can be **functional undersensing**, which is when an intrinsic beat falls coincidentally within a refractory period and is ignored as part of normal device function—if this happens repeatedly, it may require adjustment of the device settings, but usually, it is an example of pseudomalfunction.

b. **PMT.** PMT is defined as a tachycardia that can only be sustained by the continued active participation of the PM. The various mechanisms of PMT are described below.

(1) **Endless-loop tachycardia (ELT).** This is the classic form of PMT. In ELT, ventricular-pacing results in retrograde conduction up the AV node, producing a retrograde P wave that is then sensed by the atrial lead, triggering another ventricular-pacing event, which then perpetuates the cycle. ELT is typically initiated when a PVC occurs prior to the next P wave, which is when the AV node is available for retrograde conduction. ELT can also be initiated by atrial undersensing, atrial oversensing, or loss of atrial capture. Usually, ELT occurs at a rate that matches the programmed URL. This is because the retrograde P wave will usually fall within the URI—which must then elapse before the device delivers the corresponding V pace. This results in the V-V interval equaling the URI, which means the ventricular rate equals the URL. Therefore, one should suspect ELT if the surface ECG shows a regular ventricular-paced rhythm with a rate that is "stuck" at the URL. Occasionally, retrograde conduction can be slow enough such that the retrograde P wave falls outside the URI, and in this case, the ELT rate will be slower than the URL. The diagnosis of ELT can be confirmed by interrogating the PM, which should show an A_s-V_p rhythm with a 1:1 VA relationship—switching the device temporarily to a nontracking mode such as DDI should then terminate the tachycardia in both the atrium and the ventricle. ELT can be prevented by programming the PVARP long enough to cover the retrograde VA conduction time. However, if the retrograde VA time is long, then this will significantly limit the URL of the device. As an alternative, one can rely on device-based algorithms that automatically extend the PVARP for one beat following a PVC, or algorithms that detect and terminate ELT as it arises.

(2) **Tracking of atrial tachyarrhythmia.** In this type of PMT, rapid ventricular pacing occurs as a dual-chamber PM

attempts to track the rapid atrial rate during atrial tachycardia, AF, or atrial flutter. Management involves switching the device to a nontracking mode such as DDI or VVI until the atrial arrhythmia has resolved. As discussed earlier, many devices do this automatically.

(3) **Tracking of atrial noise.** Here, noise on the atrial channel is misinterpreted as a true signal and triggers ventricular pacing. Management involves switching the device to a nontracking mode such as DDI or VVI until the source of atrial noise has been diagnosed and eliminated.

(4) **Overly sensitive or inappropriate rate response pacing.** Here, the device is rapidly pacing either the atrium or the ventricle in response to the rate-response activity sensor being inappropriately activated. This may be due to a rate-response setting that is too sensitive, or because the activity sensor is picking up nonphysiologic activity (unusual arm movements, physical manipulation of the device site, hyperventilation, mechanical ventilation, etc.). Management involves disabling rate-response until the rate-response sensitivity can be corrected, or until the source of nonphysiologic activity resolves.

B. Audible or vibratory alerts. Most CIEDs are programmed to beep or vibrate if certain alert conditions are met. The underlying trigger for the alert can range from nonurgent (eg, battery life at ERI, volume status alerts) to urgent issues (eg, lead integrity, frequent VT detections). If beeping/vibration is noted, device interrogation should be performed to diagnose the underlying alert. If a patient is at home, they can be instructed to send in a remote transmission using their home monitoring system—if this occurs during afterhours, all device manufacturers should have local representatives on call who can assist with this. If a patient has no means to make a remote transmission, the device representative may be able to decipher the meaning of the alert based on its pattern/duration; however, if this is inconclusive then the patient should be instructed to go the nearest facility that can perform on-site device interrogation.

C. **Withdrawal of care.** If a patient is transitioning to hospice/comfort care due to a terminal illness and no longer wishes to receive shocks from their ICD, this discussion with the patient and family and their decision should be clearly documented and cardiology or electrophysiology should be consulted to disable the device if time permits. In a time-sensitive scenario where death is imminent or undesired shocks are already occurring, a magnet can be used to disable tachytherapies while awaiting device reprogramming. If a patient has already expired, tachytherapies should be disabled prior to an autopsy or device explantation in order to avoid injury to the person performing the explantation. Unlike ICDs, PMs do not need to be reprogrammed or turned off when a patient is being transitioned to hospice/comfort care or has expired.

D. **Environmental sources of EMI**

1. **Cell phones**

a. **RF interference.** Historically, cell phone EMI was caused by RF interference by the cellular signal itself. A large study from the 1990s showed that when cell phones were held directly over the device pocket, clinically significant RF interference (leading to noise oversensing) occurred 7% of time. No clinically significant interference was observed when the cell phone was held next to the ipsilateral ear. This led to the FDA recommendation that cell phones should be kept at least 6 inches away from a CIED. Since then, technological advances that have enabled cell phones to transmit signal with less power, as well as improvements in signal filtering and noise reduction algorithms in CIEDs, have greatly reduced the incidence of RF interference between cell phones and CIEDs, now estimated to be less than 1% according to more recent studies.

b. **Magnetic interference.** More recent Apple iPhone models, starting with the iPhone 12, contain a relatively strong magnet (marketed as “MagSafe”) used for wireless charging and attachment of accessories. After the release of the iPhone 12 in 2020, in vivo studies were published showing that placing the

phone over the device pocket did frequently trigger magnet mode in CIEDs from all major manufacturers. This was publicized in the media and led to a response from Apple to release a list of all Apple products that have the potential to interfere with CIEDs. In addition, it led to the FDA to reiterate their original recommendation to keep phones at least 6 inches away from CIEDs. So far, there have been no reports published of phones from any other manufacturers with the ability to trigger magnet mode, though in theory any phone or device with a magnet strong enough carries this risk.

2. **Smartwatches** have become popular accessories especially among cardiac patients for their arrhythmia monitoring capabilities. Like smartphones, they also contain magnets for accessories and wireless charging. So far, there have been reports of certain magnetic wristbands associated with the watches that are able to trigger magnet mode in CIEDs, though no reports of the watches themselves triggering magnet mode.
3. **Metal detectors/airport security.** Although the metal detectors in public places such as airports may raise an alarm because of detection of a PM, there is generally no significant interference with PM function. Patients should avoid lingering around these devices and pass through them at a normal speed. However, the handheld metal detectors do have the ability to be sensed by the PM or ICD and should be avoided. Encourage patients to use the backscatter scanners often employed at airport security and remind patients to carry their CIED manufacturer card to facilitate these situations.
4. **Electronic article surveillance (EAS)** is a type of antitheft system consisting of a gate that produces an electromagnetic field through which individuals must walk. The field may result in PM interference, primarily inhibition of PM output. Patients with unipolar dual-chamber PMs are particularly susceptible to interference from EAS systems. Patients should be instructed to walk through EAS systems at a normal pace and not to linger around them.

5. **Industrial electrical equipment.** This includes devices, such as arc welders, that may generate strong electrical fields. The strength of the electrical field varies among various types of equipment and, if sufficiently strong, may interfere with unipolar PMs. Patients may require individual environmental testing to ensure safety.
6. **Microwave ovens.** Because of better sealing of microwave ovens and improved shielding of pulse generators, interference with PMs by microwave ovens is no longer considered a significant problem.
7. **High-voltage power lines and electrical substations.** These areas may cause inhibition or asynchronous pacing in unipolar PMs if the patient is quite close to the electrical field. At usual public distances from such areas, there should be no PM interference.

IV. LEADLESS PACEMAKERS.

Despite great advances in the design and implantation of PMs, patients who receive a transvenous PM remain at significant risk for long-term complications, such as lead infection, lead malfunction, and pocket infection. These complications are essentially not an issue for LPMs, where the battery, pulse generator, and electrodes are fully contained inside a small cylindrical housing, which is then implanted within the heart itself.

A. Advantages compared to traditional transvenous pacing

1. **Very low risk of infection.** Because LPMs do not involve hardware in the venous system or subcutaneous tissue, infection of an LPM is extremely rare. Since LPMs entered mainstream practice circa 2016, over 200,000 devices have been implanted and only four cases of infection have been published.
2. **No risk of lead malfunction.** In transvenous systems, long-term wear and tear of the leads can result in conductor fracture or insulation breaches, which can then lead to over-/undersensing or loss of capture. Since LPMs do not have leads, this is not an issue.
3. **No risk of venous occlusion.** Since LPMs do not involve transvenous leads, there is no concern for causing venous

occlusion or stenosis over time.

4. **Lack of a device pocket.** Since LPMs reside entirely inside the heart, the surgical creation of a subcutaneous pocket is not needed. Once the initial groin access site has healed, patients with LPMs live with no outwardly visible signs of having a PM. This spares the patient from pocket-related issues such as infection or hematoma, as well as any cosmetic concerns related to having a surgical incision and device pocket.

B. Disadvantages compared to transvenous devices

1. **Acute procedural risks.** LPM implantation involves maneuvering a large-bore sheath within the RA and RV. Since the delivery sheath is much larger and stiffer than a typical PM lead, there is a higher risk of hemodynamically significant cardiac perforation and tamponade compared to transvenous PM implantation. In addition, large-bore access of the femoral vein also confers the risk of access site complications, such as groin hematoma, retroperitoneal bleeding, and AV fistula.
2. **Lack of defibrillation capability.** Since LPMs have pacing capability only, they are unable to provide shocks for ventricular tachyarrhythmias. They are also, at the time of this writing, unable to provide ATP since it is unsafe to administer ATP without also having the ability to defibrillate.
3. **Inability to provide BiVP or conduction system pacing (CSP).** At the time of this writing, LPMs are limited to implantation in the RV and are unable to provide BiVP or CSP. Therefore, they are ill suited for patients who have an indication for CRT or patients with systolic dysfunction and anticipated high pacing burden.
4. **Limited retrievability in the long term.** While transvenous lead extraction has become an established procedure with relatively high success rates, the retrieval of LPMs beyond the short-term period is still largely uncharted territory. All LPM models are designed to be retrievable with a snare in the short term, in the event of any acute issues following implantation (eg, dislodgement, elevated capture thresholds). Retrieval in the long term is more difficult due to the device endothelialization that

occurs over time. For this reason, once an LPM has run out of battery life, the manufacturer-recommended practice is to program it off and leave it in the patient permanently. If pacing is still needed, then another LPM can be implanted at a different site within the RV, or a transvenous system can be implanted instead. That being said, there have been case reports of successful retrieval of LPMs as far out as 6 years postimplant.

5. **Suboptimal atrial sensing and lack of atrial pacing.** The Micra VR and Aveir VR LPMs have no atrial sensing or pacing. The Micra AV has atrial sensing that suffers from poor reliability. The recently approved Aveir DR can provide true atrial sensing and pacing but may not be widely available for some time.

C. **Patient selection.** When determining whether leadless pacing is an appropriate option for a given patient, it is important to assess the degree to which each of the following applies:

1. **The need to avoid indwelling transvenous leads and subcutaneous device pocket.** LPMs are most appropriate in situations where there is a compelling reason to avoid transvenous hardware. Most commonly, this is due to an anticipated high risk of device infection (eg, prior device infection, endocarditis, end-stage renal disease [ESRD], IV drug use, recurrent skin/soft tissue infections). However, it can also be due to issues with venous access, such as in patients with preexisting venous stenosis/occlusion, lymphedema, or SVC syndrome. Occasionally, it may simply be a matter of strong patient preference to avoid a transvenous system.
2. **The need to maintain consistent AV synchrony.** As discussed above, AV synchrony is nonexistent in the Micra VR and Aveir VR and is not totally reliable in the Micra AV. Until true dual-chamber LPMs such as the Aveir DR become more mainstream, LPMs are most appropriate in situations where AV synchrony does not matter (ie, permanent AF/atrial flutter), or in situations where imperfect AV synchrony during pacing is not expected to significantly impact the quality of life (eg, a sedentary patient or a patient needing infrequent pacing).

3. **The need for BiVP or CSP.** Patients who require pacing but have preexisting systolic dysfunction may not do as well with RV-only pacing as they would with BiVP or CSP.
4. **The need for a bridge to transvenous device implantation.** At some centers, leadless pacing is used in certain situations as a bridge to transvenous pacing. For example, if a PM-dependent patient with a transvenous PM develops a device infection and undergoes extraction, they will have an LPM implanted and be discharged from the hospital. Once they complete their antibiotic course, they will then return for LPM retrieval and transvenous system reimplantation.

D. Contraindications. As discussed above, there are several situations where an LPM would be disadvantageous compared to conventional transvenous pacing and would, therefore, be relatively contraindicated. In terms of absolute contraindications for LPM implantation, they include (a) the presence of an inferior vena cava (IVC) filter, (b) the presence of a mechanical tricuspid valve, and (c) femoral venous anatomy unable to accommodate large-bore access.

E. MRI compatibility. All LPMs currently on the market are MR conditional, meaning that they are safe to be used in an MRI scanner provided certain manufacturer-specified conditions/precautions are met.

F. Current models

1. **Medtronic Micra VR.** This was the first FDA-approved LPM, entering the market in 2016. It has ventricular sensing and pacing only. It is delivered to the heart via a 27-French femoral venous sheath and utilizes a tines-based fixation mechanism. Battery life lasts up to 13 years. It possesses an internal accelerometer, which allows for rate-responsive pacing in response to the patient's physical activity.
2. **Medtronic Micra AV.** This is the second FDA-approved LPM, entering the market in 2020. It is distinguished from the Micra VR by its ability to sense in the atrium as well as the ventricle, which theoretically allows for tracking of atrial activity and, therefore, AV synchrony. Notably, the hardware of the Micra AV and Micra

VR are virtually identical, and what allows for atrial sensing in the Micra AV is a programming upgrade that uses the existing accelerometer to detect device movement resulting from atrial contraction. However, this method of atrial sensing suffers from poor reliability; therefore, the Micra AV remains a suboptimal long-term solution for patients who need consistent AV synchrony. Battery life of the Micra AV ranges between 8 and 13 years.

3. **Abbott St. Jude Aveir VR.** This is the third FDA-approved LPM, entering the market in 2022. It has ventricular sensing and pacing only. It is also delivered to the heart via a 27-French femoral venous sheath but utilizes a helix-based fixation mechanism. It has an accelerometer to allow for rate-responsive pacing. Battery life is up to 10 years. Of note, the Aveir is a revised and rebranded version of the St. Jude Nanostim, which, due to battery problems, had previously been discontinued in 2016 prior to achieving FDA approval.
4. **Abbott St. Jude Aveir DR.** This is a dual-chamber LPM system, which just very recently received FDA approval in July 2023. It involves implantation of two separate LPMs, one in the RV and one in the RA. These two devices can then communicate with each other and facilitate true dual-chamber sensing/pacing and, therefore, AV synchrony.

G. Future models in development

1. **Boston Scientific EMPOWER.** This is a single-chamber LPM that is currently being tested in the "MODULAR ATP" clinical trial (NCT04798768). Its distinguishing feature is its ability to communicate with a Boston Scientific EMBLEM Subcutaneous ICD (S-ICD) implanted in the same patient. Together, the LPM and S-ICD can provide single-chamber pacing, ATP, as well as defibrillation without the implantation of any transvenous leads.

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CHAPTER 55

Cardiac Resynchronization Therapy

Mohammad H. Abbasi and John Rickard

I. INTRODUCTION. The prevalence of heart failure (HF) in the United States has increased considerably in the past two decades as a result of the aging population and better medical management of left ventricular systolic dysfunction (LVSD). Despite rapid advances in medical therapy, many patients with advanced HF continue to have limited options. A subset of patients with LVSD and ventricular conduction delay are at high risk for HF progression and a poor outcome. Since the late 1970s, various investigators have shown that left bundle branch block (LBBB), right ventricular (RV) pacing, or intraventricular conduction delay (IVCD) is associated with a less favorable hemodynamic profile in both patients with LVSD and normal controls. **The mechanism for this phenomenon is believed to stem from asynchronous and inefficient contraction of opposing areas of the ventricular myocardium. More importantly, restoring synchronization, either via simultaneous pacing of the RV apex and the left ventricular (LV) free wall or with timed LV free wall activation, can lead to significant hemodynamic improvement**> Starting in the 1990s, small observational studies suggested benefit from synchronous pacing. Larger randomized clinical trials confirmed these findings. Cardiac resynchronization therapy (CRT) was first approved for maximally medically managed patients with persistent New York Heart Association (NYHA) class III or IV HF symptoms with LVSD and a prolonged QRS duration. Further randomized studies, powered for mortality, showed a significant survival benefit with CRT or the combination of CRT with a defibrillator (CRT-D). More recently, CRT has been shown to be beneficial in less symptomatic patients. Unfortunately, not all patients who are selected

for CRT based on current guidelines appear to respond. The terms "responder" and "nonresponder" to CRT have been criticized by many who argue that the natural history of disease progression in any individual patient is not known; hence, some patients who appear to be "nonresponders" may have done even worse if CRT were not employed. Such patients have been referred to as "nonprogressors." Complicating matters further is that there is no uniform definition of response. In order to address these issues, novel conduction system pacing (CSP) strategies, including His-Bundle pacing and left bundle branch area pacing (LBBAP), are currently under investigation as adjuncts or alternatives to traditional CRT to promote ventricular synchrony.

II. MECHANISM OF LEFT VENTRICULAR DYSSYNCHRONY. The normal pattern of electrical activation of the ventricular myocardium, once the impulse passes through the atrioventricular (AV) node, starts in the His bundle, followed by simultaneous activation of the right and left bundles of the Purkinje system and then by myocardial depolarization. The Purkinje system is electrically isolated from the rest of the myocardium until it reaches its exit points at the Purkinje-myocardial junctions. As a result, typical LV myocardial activation occurs from the apex to base and simultaneously in the septum and in the LV free wall and is described as synchronous. Because of tight electromechanical coupling of the myocardium, synchronous ventricular activation is followed by synchronous ventricular contraction.

In the setting of conduction delay, the electromechanical coupling of the heart is disrupted, leading to dyssynchrony. Over time, electromechanical uncoupling leads to impaired stroke volume, worsened mitral regurgitation (MR), prolonged LV isovolumetric events, and impaired diastolic filling. These effects contribute to adverse remodeling in the already impaired heart, creating a vicious cycle that perpetuates this process into worsening LVSD and clinically more advanced HF. As a result, when comparing patients with similar degrees of LVSD, **those with conduction delay have a worse overall prognosis**. CRT has been shown to reverse this deleterious process. Synchronized pacing has been shown to improve LV function without

increasing oxygen demand, suggesting that the improvement is related to better efficiency of the LV chamber.

Interestingly, dyssynchronous activation and contraction also have an undesirable effect in patients **without** LVSD. When compared with normal controls, patients with LBBB have a lower LV ejection fraction (LVEF), are more likely to develop HF, and have a 10-fold greater risk of cardiovascular morbidity and mortality. In some patients (patients with chronic LBBB, frequent premature ventricular contractions, or chronic RV pacing), the conduction delay itself may cause deterioration in the LVEF. In this population, treatment with CRT can have profound effects, potentially even normalizing LV function.

III. TYPES OF DYSSYNCHRONY

A. AV dyssynchrony. In the setting of PR prolongation or QRS widening, the atrial contribution to LV filling is abnormal. Atrial systole can occur too early with respect to ventricular diastole, leading to early truncation of passive LV filling. Compromised LV filling leads to lower cardiac output via the Frank-Starling mechanism.

B. Interventricular dyssynchrony. Early RV activation present during LBBB, IVCD, or RV pacing leads to early RV contraction, creating a pressure gradient between the RV and the LV with septal bowing that negatively affects LV filling, diminishing LV preload and cardiac output. Previously, interventricular dyssynchrony was thought to be the major contributor to adverse events in patients with HF and conduction disease and hence the primary target for CRT. Whereas correction of interventricular dyssynchrony with CRT may diminish septal bowing, this is no longer believed to be the primary driver of improved outcomes with CRT.

C. Intraventricular dyssynchrony. In the presence of conduction delay, there is a substantial delay in the activation of certain LV segments compared with others, leading to an inefficient back-and-forth mechanical interaction, leading to inefficient myocardial contraction. In the case of a native LBBB, for example, there is a significant delay in activation between the early activated septum and the late activated

posterolateral wall, often resulting in profound delays between segments and worsening of MR. **Mitigation of intraventricular dyssynchrony** is the primary cause of improved myocardial performance with CRT.

IV. ASSESSMENT OF DYSSYNCHRONY. In addition to the three varieties of dyssynchrony already discussed, dyssynchrony can also be categorized as mechanical versus electrical. Electrical dyssynchrony refers to delays in depolarization, whereas mechanical dyssynchrony refers to delays in contraction, among LV segments. **Importantly, current measures of electrical and mechanical dyssynchrony sometimes show poor agreement**. For example, almost all clinical trials use prolonged QRS duration—a crude marker of electrical dyssynchrony—as a requisite for inclusion. The relationship, however, between QRS duration and mechanical dyssynchrony has been poor. Studies have revealed that up to 30% of patients with a prolonged QRS duration do not have mechanical dyssynchrony as assessed by magnetic resonance imaging (MRI) or echocardiography, whereas up to 30% of patients with a normal QRS duration and symptomatic HF have evidence of mechanical dyssynchrony on MRI or echocardiography. Although measures of both electrical and mechanical dyssynchrony remain an area of active research, there are no widely accepted, standardized measures of either at this time. Currently, the bulk of research on dyssynchrony has been dominated by the various metrics of mechanical dyssynchrony, mostly using echocardiographic techniques. Unfortunately, indices of mechanical dyssynchrony have been disappointing in predicting outcomes of CRT. The main difficulty with all measures of mechanical dyssynchrony has been reproducibility across centers. In the large, multicenter PROSPECT trial, multiple echocardiographic measures of mechanical dyssynchrony were tested. **None, however, were found to be sensitive and specific predictors of subsequent response to CRT**.

V. ROLE OF CARDIAC RESYNCHRONIZATION THERAPY. The primary aim of CRT is **to improve systolic LV performance via an improvement in chamber efficiency**, thereby leading to symptomatic improvement in patients with HF and LVSD. In clinical trials, the **LVEF improved by**

an average of 5% with significant improvement in MR and was accompanied by symptomatic improvement, as evidenced by increased 6-minute walk time and quality of life index score (QOLS). **The remodeling of the LV takes at least 3 months**. On average, the LV systolic and diastolic dimensions decrease significantly following prolonged CRT. In studies in which biventricular (BiV) pacing was switched off after prolonged synchronized pacing, the systolic benefits disappeared rapidly; however, the LV dimensions were maintained for a longer period of time, suggesting that actual LV remodeling took place during CRT. There is also evidence that CRT may lead to electrical remodeling of the heart, although this effect is less well understood. Evidence from randomized clinical trials powered for mortality, in addition to symptomatic improvement, supports the use of CRT either alone or in combination with an implantable cardioverter-defibrillator (ICD) in patients with ischemic and nonischemic etiologies of severe LVSD.

VI. SUMMARY OF MAJOR CLINICAL TRIALS OF CARDIAC RESYNCHRONIZATION THERAPY.

Most clinical trials evaluating CRT have addressed its role in patients in normal sinus rhythm (NSR) with severe LVSD and evidence of dyssynchrony as suggested by prolonged QRS duration. Early studies of CRT compared patients with CRT pacemaker (CRT-P) devices with optimal medical therapy alone and enrolled patients with NYHA class III to IV HF. Over the years, trials progressed to enrolling patients with minimally symptomatic HF and compared patients with CRT-D devices to those with an ICD alone.

A. MUSTIC (2001). This was a single-blind, randomized, controlled crossover study that enrolled 67 patients with HF with LVSD, NYHA class III symptoms, QRS duration 150 ms or longer, and in NSR. Each patient underwent implantation of CRT-P and two phases of device programming: 3 months of backup-only pacing (VVI 40 beats/min) and 3 months of BiV pacing. A total of 48 patients completed both phases of the study (9 withdrew prior to randomization, 10 only completed a single phase). The primary outcome—6-minute walk distance (399 ± 101 vs 326 ± 134 m, 23% improvement, $P < .001$)—as well as the secondary outcomes—

quality of life score (29.6 ± 21.3 vs 43.2 ± 22.8, 23% improvement, $P < .001$) and peak oxygen uptake (16.2 ± 4.7 vs 15 ± 4.9 mL kg^{-1} min^{-1}, 8% improvement, $P = .029$)—favored the active pacing phase. Although absolute numbers were small, there were fewer HF hospitalizations (3 vs 9, $P < .05$) during the active pacing phase, and 85% preferred the active pacing phase.

B. MIRACLE (2002). This was a double-blind, randomized controlled trial that enrolled 453 patients with HF with LVEF ≤35%, moderate-severe HF symptoms, and QRS duration 130 ms or longer. Patients were randomized to CRT-P plus conventional medical therapy versus conventional medical therapy alone. At 6 months, 6-minute walk distance (39 vs 10 m improvement, $P = .005$), quality of life improvement (−18.0 vs −9.0, $P = .001$), time on a treadmill during exercise testing (81 vs 19 s improvement, $P = .001$), and change in LVEF (+4.6% vs −0.2%, $P < .001$) all favored the CRT group. In addition, there were fewer hospital admissions in the CRT group (8% vs 15%, $P < .05$). This trial led to the approval of CRT devices by the Food and Drug Administration.

C. MIRACLE-ICD (2003). This was a double-blind, parallel-controlled trial that enrolled 369 patients with LVEF ≤35%, NYHA class III to IV symptoms, QRS duration 130 ms or longer, and at high risk of ventricular arrhythmia on optimized medical therapy. Patients were randomized to CRT-D implantation with a BiV pacing strategy (CRT on, ICD on) or no pacing (CRT off, ICD on). At 6 months, patients who received BiV pacing had improvements in quality of life score (−17.5 vs −14, $P = .02$), NYHA functional class (−1 vs 0, $P = .007$), peak oxygen consumption (1.1 vs 0.1 mL kg^{-1} min^{-1}, $P = .04$), and treadmill exercise duration (+56 vs −11 s, $P < .001$). In this way, MIRACLE-ICD established that combining CRT with ICD is safe.

D. COMPANION (2004). This was an unblinded randomized trial that enrolled 1,520 patients with HF, NYHA class III to IV symptoms, and QRS duration 120 ms or longer. Patients were randomized 1:2:2 to medical therapy alone versus medical therapy plus CRT-P versus medical therapy plus CRT-D. The primary composite end point of death from any cause or hospitalization for any cause at 12 months

occurred in 68% of patients in the medical therapy group, 56% in the CRT-P group (hazard ratio [HR] 0.81, 95% confidence interval [CI] 0.69-0.96, $P = .014$) and in 56% in the CRT-D group (HR 0.80, 95% CI 0.68-0.95, $P = .010$). Of note, 18 hospitalizations in the medical therapy group and 1 hospitalization in the device group were considered elective and were excluded from the primary end point. The relative risk of all-cause death at 12 months was nominally lower by 24% in the CRT-P group ($P = .059$) and significantly lower by 36% in the CRT-D group ($P = .003$).

E. **CARE-HF (2005).** This was an unblinded randomized trial which enrolled 813 patients with LVEF ≤35%, NYHA class III to IV, HF for at least 6 weeks, QRS duration 120 ms or longer, and LV end-diastolic dimension of 30 mm or greater on optimal medical therapy. Patients were randomized to either medical therapy alone or medical therapy plus CRT. After a mean follow-up of 29.4 months, patients randomized to CRT had a lower incidence of the primary composite end point of death from any cause or unplanned cardiovascular hospitalization (39% vs 55%, HR = 0.63, $P < .01$). All-cause mortality (20% vs 30%, HR = 0.64, $P < .002$) was lower in the CRT group.

F. **MADIT-CRT (2009).** A randomized, double-blinded, clinical trial that enrolled 1,820 patients with minimally symptomatic HF, NYHA class I to II symptoms, LVEF ≤30%, and QRS duration of 130 ms or longer. Patients were randomized in a 3:2 ratio to CRT-D versus ICD alone. After a mean follow-up of 2.4 years, the primary composite end point of death or nonfatal HF event occurred in 17.2% of the CRT-D group and in 25.3% of the ICD group (HR in the CRT-D group 0.66, 95% CI 0.52-0.84, $P = .001$). This benefit was driven primarily by a reduction in nonfatal HF events, with similar rates of all-cause death in both groups.

G. **ECHO-CRT (2013).** A large clinical multicenter trial examining the role of CRT pacing in patients with EF <35%, narrow QRS (<130 ms), and echocardiographic evidence of LV dyssynchrony. Dyssynchrony was defined by means of color-coded tissue Doppler imaging as an opposing wall delay in the peak systolic velocity of 80

ms or more in apical four-chamber or apical long-axis views or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of 130 ms or more in the mid-LV short-axis view. All patients underwent device implantation but were randomized to have CRT pacing on (404 patients) or off (405 patients in which device settings were set to minimize RV pacing). Mean QRS duration was 105 ms. The study was terminated because of futility where the CRT group had increased mortality (11.1% vs 6.4%; HR 1.81; *P* = .02). This study suggested that implanting CRT in patients with a narrow QRS may be harmful.

H. BLOCK-HF (2013). This randomized, double-blinded, clinical trial enrolled 918 patients with an indication for pacing for AV block and expected need for frequent pacing (>40%), HF with NYHA class I to III symptoms, and LVEF >50%. Of note, of the 918 patients enrolled, only 691 underwent randomization. All patients received either a CRT-P or CRT-D device and were randomly assigned to standard RV pacing (342 patients) or BiV pacing (349 patients). The primary composite outcome consisted of all-cause death, urgent care visit for HF requiring intravenous therapy, and a 15% or greater increase in LV end-systolic volume (ESV) index. After a mean follow-up of 37 months, the primary outcome occurred in 55.6% of patients in the RV pacing group and in 45.8% of patients in the BiV pacing group (HR 0.74, 95% CI 0.60-0.90). The secondary outcome of death or HF hospitalization was less common in the BiV pacing group (HR 0.78, 95% CI 0.61-0.99). Overall, this trial established CRT as the preferred modality of pacing in patients with preserved LVEF with AV nodal disease requiring a pacemaker with expected frequent ventricular pacing.

VII. FACTORS ASSOCIATED WITH IMPROVED OUTCOMES IN CARDIAC RESYNCHRONIZATION THERAPY

A. Women have continually derived improved outcomes in multiple studies compared with men. Although the reason for this has been debated, it is likely due to a lower LV mass at the same QRS duration (more relative dyssynchrony) compared to men.

B. Patients with **nonischemic cardiomyopathy** appear to be more likely to derive benefit via reverse ventricular remodeling than patients with ischemic cardiomyopathy.

C. Patients with **LBBB**, either native or paced, are more likely to experience improved LV function with CRT than are patients with a wide QRS without an LBBB.

D. Patients with a very **wide QRS duration (>150 ms)** appear to have improved outcomes compared with patients with a modestly wide QRS duration (120-149 ms).

E. Lead position is an important determinant of response. **Apical lead positions are inferior** to mid and basal positions. Septal locations such as pure anterior or posterior locations (in the great cardiac vein that parallels the left anterior descending artery [LAD] or the middle cardiac vein that parallels the posterior descending artery) are inferior to lateral locations.

F. QLV and RV-LV timing. Electrical delay or electrical dyssynchrony is a key factor when predicting response to CRT. Electrical delay can be easily measured in the electrophysiology lab at the time of CRT implant. The SMART-AV QLV substudy looked at the relationship between the intrinsic electrical delay of the LV and clinical end points. LV electrical delay was defined by the time interval from the first QRS deflection on surface electrocardiogram (ECG) to the local intrinsic activation at the LV stimulation site (QLV) as measured in the electrophysiology lab. The goal of optimizing CRT is to deliver electrical stimuli in an area that has the latest activation within the LV. The study found that when the observed QLV was >95 ms, patients with HF had the best improvements in EF, ESV, end-diastolic volume (EDV), and quality of life measurements at 6 months follow-up. Measuring the time between the RV and LV electrograms is a similar measure to QLV, with the advantage that this time is easily measurable through CRT devices. Whereas the utility of QLV and RV-LV timing in terms of selecting lead location and choosing pacing vectors has been encouraging, neither as of yet have been shown to be sensitive nor specific for predicting long-term outcomes.

III. CURRENT GUIDELINES AND RECOMMENDATIONS. Based on the inclusion criteria from the available large randomized trials at that time, the 2021 American Heart Association/American College of Cardiology Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult gives CRT the following indications (**Table 55.1**):

TABLE 55.1 Current Recommendations for the Use of CRT in Patients With HF

Recommendation	Class	Level of Evidence
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on GDMT, in sinus rhythm with an LBBB with a QRS complex ≥150 ms	I	A
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on GDMT who are in sinus rhythm with an LBBB QRS 120-149 ms	IIa	B
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on GDMT who are in sinus rhythm with a non-LBBB QRS ≥150 ms	IIa	A
Patients with depressed LV function, EF ≤35%, and anticipated to require frequent ventricular pacing (>40%)	IIa	C
Patients with atrial fibrillation if ventricular pacing is required or QRS criteria above are met and rate control (including AV node ablation) will result in nearly 100% ventricular pacing	IIa	B
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, on GDMT, and NYHA III or ambulatory class IV, with non-LBBB with QRS 120-149 ms	IIa	B
Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, on GDMT, and NYHA II with non-LBBB with QRS >150 ms	IIa	B
Patients with ischemic etiology of depressed LV function, EF ≤30%, sinus rhythm, NYHA class I on GDMT, and LBBB QRS ≥150 ms	IIa	C
CRT is not recommended in patients on inotropic support, except in special cases when patients are listed for transplant	III	C

Recommendation	Class	Level of Evidence
or have LV assist device or in patients with less than 1 y survival.		
CRT is not recommended in patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration <150 ms.	III	B

CRT, cardiac resynchronization therapy; EF, ejection fraction; GDMT, guideline-directed medical therapy; HF, heart failure; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association.
Adapted from Epstein AE, DiMarco JP, Ellenbogen KA, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;51(21):e1-e62.

A. Class Ia (level of evidence A): In patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on guideline-directed medical therapy (GDMT) for ≥3 months or ≥40 days after myocardial infarction (MI), in sinus rhythm with an LBBB with a QRS complex ≥150 ms

B. Class IIa: In patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on GDMT for ≥3 months or ≥40 days after MI who are in sinus rhythm with an LBBB QRS 120 to 149 ms (level of evidence B); sinus rhythm with non-LBBB QRS ≥150 ms (level of evidence A); patients anticipated to require frequent ventricular pacing (>40%) (level of evidence C); or atrial fibrillation if ventricular pacing is required or QRS criteria above are met and rate control (including AV node ablation) result in nearly 100% ventricular pacing (level of evidence B)

C. Class IIb: Patients with ischemic or nonischemic etiology of depressed LV function, EF ≤35%, and NYHA class II, III, or ambulatory class IV, on GDMT for ≥3 months or ≥40 days after MI with non-LBBB QRS 120 to 149 ms and NYHA III/ambulatory IV on GDMT (level of evidence B); in patients with non-LBBB with QRS >150 ms and NYHA II on GDMT (level of evidence B); in patients with ischemic cardiomyopathy who have an EF <30%, LBBB QRS ≥150 ms (level of evidence C)

D. CRT is not recommended in patients on inotropic support, except in special cases when patients are listed for transplant or have LV assist device or in patients with less than 1 year survival (level of evidence C); patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration <150 ms (level of evidence B)

IX. IMPLANTATION PROCEDURE. Unlike conventional transvenous pacemaker or ICD implantation that requires lead placement in the right atrium and/or the RV only, BiV pacing requires LV lead implantation. Initially, this was achieved via a thoracotomy; however, currently, up to 98% of BiV devices are placed via a transvenous approach. Although now used infrequently, some patients are still referred for a thoracotomy after a failed transvenous approach.

The procedure is performed in an electrophysiology laboratory under sterile conditions. All patients receive preprocedural antibiotics at least 30 minutes before the procedure. A subcutaneous pocket is first prepared, making sure that appropriate hemostasis is achieved. Typically, a cephalic or axillary vein is used for access. The right atrial and RV leads are implanted in a manner similar to a pacemaker or ICD implantation. The LV lead is placed through the coronary sinus (CS) into a branch on the lateral free wall of the LV. Modern CRT systems use quadripolar LV pacing leads, which allows flexibility in pacing vectors. Performing an occlusive CS venogram may help identify the appropriate vein. Various sheaths, catheters, and guidewires are available to cannulate the CS and advance the pacing lead into the appropriate vein. Although the optimal site for LV lead placement is controversial, many experts agree that septal positions (straight anterior or posterior) and apical positions are suboptimal. Once the lead is advanced, its location

should be confirmed by fluoroscopy, typically in the left anterior oblique (LAO) view. The goal is to document base to mid-posterolateral LV lead placement and maximal LV-RV lead separation in the LAO view. A steep angulation in the LAO view tends to be the most accurate. Pacing thresholds are acceptable if <3 V at 0.5 ms. Diaphragmatic capture is excluded by high-voltage pacing. If high pacing threshold or diaphragmatic stimulation occurs, the lead should be repositioned. CS trauma is occasionally noted during lead placement, and it may range from dissection to frank perforation. Because the pressure in the venous system is low, serious sequelae are unusual, and cardiac tamponade is rare. After adequate LV lead placement and confirmed appropriate LV lead function, care must be taken during guidewire, CS platform, and stylet removal, to prevent disruption of lead position. The majority of lead dislodgements tend to occur within the first 24 to 48 hours as patients resume activity. For this reason, patients are encouraged to ambulate prior to discharge to ensure a stable lead position.

X. PROGRAMMING AND FOLLOW-UP. Currently, multiple configurations for BiV pacing exist. The available pacing configurations vary by the device manufacturer. Changing configurations for pacing can be very useful in cases of poor thresholds or diaphragmatic stimulation.

Ventricular pacing must be **continuous** during CRT in order to obtain maximal benefit. Most often, DDD mode with a short AV delay (80-110 ms) to suppress native AV conduction is employed. Alternatively, fusion pacing algorithms have been developed in which RV pacing is limited or completely omitted and the LV-paced wavefront fuses with intrinsic conduction. Such algorithms have been found to be noninferior, but not superior, to traditional CRT.

Follow-up of CRT devices includes a 12-lead ECG to assess for BiV capture and device interrogation to assess pacing thresholds. Patents should have a posteroanterior and lateral chest ray to confirm the lead position and to rule out pneumothorax. In those patients who are deemed nonresponders, echocardiography may be used to optimize the AV delay based on Doppler mitral valve inflow patterns or Doppler aortic valve velocity time integral. Limited studies suggest that AV programming may lead to a better acute hemodynamic response to CRT in certain

patients. The value of VV optimization is of considerable debate. In addition, specialized CRT clinics may help troubleshoot device issues, treat arrhythmias, maximize congestive heart failure (CHF) medications, and optimize the AV interval. Although such clinics are limited mostly to specialized centers, such clinics have shown improved outcomes in patients receiving CRT.

XI. SUMMARY. CRT has emerged as an effective therapy in patients with LVSD refractory to CHF medications and a wide QRS duration. Major clinical trials have proven significant morbidity and mortality benefits from CRT first in patients with advanced heart and more recently in those with minimal symptoms. The issue of nonresponse to CRT continues to be a major problem, and much ongoing research continues to be dedicated to predicting which patients will respond to this therapy. Adding complexity to the matter is a new designation known as nonprogressor who previously would have been deemed a nonresponder when in actuality has derived benefit from CRT. Although many studies have shown some predictive ability of various imaging modalities, none to date has been shown to be a reliable predictor of response that could be utilized across multiple centers. Although the response to CRT in patients with a native LBBB or RV-paced rhythm is well documented, the response in patients with right bundle branch block (RBBB) or a nonspecific IVCD continues to be debated.

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SUGGESTED READINGS

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RELEVANT BOOK CHAPTER

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CHAPTER 56

Antitachycardia Devices

Andrew D. LaCombe and Ayman A. Hussein

I. INTRODUCTION

A. The modern implantable cardioverter-defibrillator (ICD) is a multifunctional, multiprogrammable electronic device designed to abort life-threatening arrhythmias. It is programmed to automatically detect and manage episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), or bradycardia. Current ICDs are able to deliver multitiered therapies, which may include a combination of antitachycardia pacing (ATP), cardioversion, and defibrillation. The devices also offer bradycardic support, which may include rate-responsive single- or dual-chamber pacing and automatic mode switch function. Modern ICDs are able to deliver resynchronization therapy, a significant advancement in the management of heart failure. The devices are also able to store electrograms (EGMs), which can be easily retrieved. This function can be of immense use for follow-up management of the patient and programming of the device.

Multiple clinical trials have demonstrated the efficacy of ICDs to accurately detect and manage sudden cardiac death (SCD). ICDs are superior to conventional medical therapy in both primary and secondary prophylaxis of SCD. The majority of patients who have indications for an ICD implant are those with left ventricular (LV) dysfunction, both ischemic and nonischemic.

B. Mirowski first introduced the concept of an ICD in the 1960s, with the first human implant reported in 1980. Early ICD implantations required a thoracotomy for placement of an epicardial lead system. Subsequent advancements in device and lead technology over the past 35 years have significantly reduced the size of the pulse

generator, while improving programmability and diagnostic data stored within the device. An improved understanding of VF, defibrillation, and cardiac pacing has resulted in the development of biphasic shock waveforms and transvenous pace/defibrillation lead systems that preclude the need for epicardial patches. As a result, modern ICDs are increasingly more compact, provide expansive programming capability, and offer convenience with added features, such as remote interrogation.

C. To avoid complications associated with vascular access in patients who have an indication for ICD therapy but who do not require pacing, a new generation of ICD systems can be implanted without transvenous access. The **subcutaneous ICD** (S-ICD) was developed over the past couple of decades and allows for defibrillation therapy without venous access. The pulse generator is implanted under the skin on the lateral chest wall and connected to a defibrillation lead that is tunneled along the left lateral margin of the sternum. In 2012, the U.S. Food and Drug Administration (FDA) approved the use of S-ICDs after several initial studies demonstrated comparable efficacy in cardioversion of induced and spontaneous VT and VF when compared to conventional transvenous systems. These initial studies also showed that inappropriate shocks occurred at similar rates compared to conventional transvenous ICDs.

D. Inappropriate shocks with S-ICDs have been found to occur with issues in rhythm discrimination and device oversensing. However, technological advances in device algorithms and programming over the years have reduced the rate of inappropriate shocks with S-ICDs. Additional studies have been added to the literature, including the randomized prospective PRAETORIAN trial, which compared S-ICDs to transvenous ICDs and found S-ICDs to be noninferior in regard to device complications and inappropriate shocks. Given concerns that prior studies were not representative of patient populations with more comorbidities, the prospective UNTOUCHED trial was performed and demonstrated the lowest inappropriate shock rate in S-ICD trials and one of the lowest inappropriate shock rates in all ICD studies.

E. Contemporary S-ICDs are limited in regard to pacing therapies, but there are ongoing trials involving novel coordinated therapy with leadless pacemakers to provide pacing and defibrillation benefits without the complications involved with transvenous systems.

II. IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR COMPONENTS

A. The current-day ICD is a sophisticated and intelligent computer. It consists of a generator and leads. The ICD generator consists of a battery, capacitors, DC-DC converter using an oscillator rectifier mechanism, a microprocessor, and telemetry communication coils and their connections. The generator serves as an active electrode within the shocking configuration in most of the modern ICDs and is thus called the "hot can." The newest generation of ICDs utilizes a lithium manganese dioxide battery. These can generate approximately 3.2 V at full charge. Because most ICDs use two batteries connected in series, the full initial voltage is approximately 6.4 V. The generator has capacitors that can charge within 7 to 30 seconds to store up to 30 to 40 J of energy. This can be delivered to the heart within a 10- to 20-ms interval when therapy is required.

B. The three essential functions of the ICD—**tachycardia detection, tachycardia therapy, and bradycardia pacing**—are delivered through the active electrodes, which are the noninsulated segments of the leads. Most of the current-day leads have sensing and pacing electrodes at the tip and distal (right ventricle [RV]) and proximal (superior vena cava [SVC]) shocking coils. The function of ventricular sensing and pacing is achieved by a technology similar to that in pacemakers. This is done through two "dedicated bipolar" electrodes at the distal end of the RV lead (tip/ring). Sometimes, it may be achieved by "integrated bipolar" electrodes, wherein the bipole is formed by the tip of the ventricular lead and the distal shocking coil (tip/coil). Ventricular pacing in biventricular ICDs is from the tip of the RV and LV leads, respectively, to either the ring (true bipolar) or the distal shocking coil (integrated bipolar). To avoid the problem of "double counting," most newer devices restrict the ventricular sensing function to the RV lead alone.

C. For the delivery of shock therapy, most systems now incorporate either the RV coil, SVC coil, and pulse generator can or the RV coil and can without an SVC coil.

III. INDICATIONS AND CONTRAINDICATIONS. The 2017 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death are the most current guidelines detailing ICD indications, with other sections added to the **2008 ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities**. The guidelines stratify the various indications as class I, class II (a and b), and class III (no benefit and harm) on the basis of the data from clinical trials and opinion of a panel of experts. **Class I indications** are conditions for which there is evidence and/or general agreement that ICD therapy is beneficial, useful, and effective. **Class IIa indications** are conditions for which there is evidence and/or general agreement that ICD therapy can be beneficial, useful, and effective. **Class IIb indications** are conditions for which the usefulness/efficacy of ICD therapy is uncertain or not well established. **Class III indications/contraindications** are conditions for which there is general agreement that ICDs are not useful and possibly harmful. In regard to the ICD indications listed in **Table 56.1**, it is important to avoid using ICDs in patients with terminal illnesses for whom expected meaningful survival is less than 12 months.

TABLE 56.1 Indications and Contraindications for ICD Implantation

Class I

- ICM with LVEF ≤30%, NYHA class I, ≥40 d post-MI, and ≥90 d after revascularization
- ICM with LVEF ≤35%, NYHA class II or III, ≥40 d post-MI, and ≥90 d after revascularization
- ICM with LVEF ≤40% and NSVT, with inducible VF or sustained VT on EPS
- NICM with LVEF ≤35%, NYHA class II or III, ≥3 mo heart failure GDMT

- ICM or NICM with SCD from VT/VF, or evidence of unstable VT or stable sustained VT after evaluation to define the cause of the arrhythmia and exclude completely reversible causes
- ICM with LVEF ≤35% and likely arrhythmogenic syncope
- IHD with unexplained syncope and EPS with sustained monomorphic VT
- Survival of SCD from either VF or idiopathic polymorphic VT
- HCM with SCD from VT/VF or experience hemodynamically unstable VT
- Cardiac channelopathies with survival of SCD
- Symptomatic catecholaminergic polymorphic VT with syncope or sustained VT on beta-blockers
- Short QT syndrome with either sustained VT/VF or SCD
- Brugada syndrome and type 1 ECG pattern, with either unexplained syncope, sustained VT/VF, or SCD
- Symptomatic, high-risk LQTS and ineffective or intolerance to beta-blockers
- Early repolarization ECG pattern with either sustained VT/VF or SCD
- Neuromuscular disorders (similar indications as NICM)
- Arrhythmogenic RV dysplasia with ≥1 risk factor for SCD
- Cardiac sarcoidosis with either LVEF ≤35%, sustained VT or SCD survival
- ACHD with SCD from VT/VF after exclusion of reversible causes
- ACHD with unstable VT after evaluation for reversible or treatable conditions
- Subcutaneous ICD for patients who meet indication without a need for pacing therapies and have either high infectious risk or poor vascular access

Class IIa

- NICM with likely arrhythmogenic syncope or positive EPS
- HCM with ≥1 risk factor for SCD
- HCM with either NSVT or abnormal blood pressure with exertion, and additional SCD risk modifiers
- Survivors of SCD from coronary spasm, without benefits from medical therapies

- Nonhospitalized advanced therapy candidates, ICM, NYHA class IV
- Nonhospitalized with LVEF ≤40%, awaiting OHT without other ICD indication
- LVAD and sustained VT or VF
- Cardiac involvement from Emery-Dreifuss or limb-girdle type IB dystrophy
- Cardiac sarcoidosis and LVEF >35%, with either syncope, myocardial scar, indication for pacing, or sustained ventricular arrhythmias on EPS
- Lamin A/C mutation cardiomyopathy and ≥2 risk factors for SCD
- Arrhythmogenic RV dysplasia, syncope due to likely VT/VF
- ACHD and syncope with either significant hypertrophy or moderate ventricular dysfunction
- Tetralogy of Fallot with spontaneous sustained VT or inducible VT/VF
- Subcutaneous ICD for patients who meet indication without a need for pacing

Class IIb

- NICM with LVEF ≤35%, NYHA class I, ≥3 mo heart failure GDMT
- HCM with either NSVT or abnormal blood pressure with exertion
- Survivors of SCD from coronary spasm, in addition to medical therapies
- Heart transplant patients with LV dysfunction and severe allograft vasculopathy
- Asymptomatic LQTS and resting QTc >500 ms on beta-blockers
- ACHD, LVEF <35% with additional risk factors or symptoms despite GDMT
- Giant cell myocarditis with either VF or unstable VT
- Myotonic dystrophy type 1 with pacemaker indication

Class III: No Benefit

- HCM genotype without SCD risk factors
- Medical refractory heart failure, NYHA class IV, and not candidates for advanced therapies or CRT with pacing and defibrillator therapies

Class III: Harm

- Incessant VT or VF that is not sufficiently controlled
- Patients with indications for an ICD and pacing therapies should not undergo subcutaneous ICD implantation.

ACHD, adult congenital heart disease; ATP, antitachycardia pacing; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; EPS, electrophysiology study; GDMT, guideline-directed medical therapy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; ICM, ischemic cardiomyopathy; IHD, ischemic heart disease; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LQTS, long QT syndrome; MI, myocardial infarction; NICM, nonischemic cardiomyopathy; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; OHT, orthotopic heart transplantation, SCD, sudden cardiac death; RV, right ventricular; VF, ventricular fibrillation; VT, ventricular tachycardia.
Adapted from Al-Khatib S, Stevenson W, Ackerman M, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *J Am Coll Cardiol*. 2018;72:14:e91-e220.

IV. IMPLANTATION

A. Device implantation. Currently, available devices are small enough to allow implantation in the left pectoral region. Animal studies have shown that the defibrillation efficacy of the hot-can ICDs is superior in the left pectoral or axillary regions, followed by the right pectoral and then the abdominal sites. A right pectoral system may be necessary in patients who have vascular access problems on the left side or who have undergone pectoral surgery (eg, mastectomy). For patients with high defibrillation thresholds (DFTs), additional lead placement, such as a subcutaneous array or coil, an azygous coil, a coronary sinus coil, or an epicardial patch, may be necessary. Epicardial patch placement is usually reserved for patients who have failed to meet implantation criteria with a transvenous lead system or if there has been previous bilateral pectoral or tricuspid valve replacement surgery.

For pectoral implants, a single 5- to 8-cm incision is made transversely below the clavicle, about 1 cm below and parallel to the deltopectoral groove. Transvenous lead placement is achieved through a subclavian vein puncture or by cephalic vein cutdown. An “extrathoracic” subclavian vein puncture or cephalic vein cutdown

for access minimizes the risk of pneumothorax and also the risk of lead failure caused by subclavian crush injury.

B. Lead placement. The lead is advanced to the RV apex under fluoroscopic guidance, where the tip is secured via an active fixation screw or embedded in the trabeculae with passive fixation tines. It is important to assess the quality of signals at the time of implant because it is the best guide to the adequacy of long-term sensing of the lead. The DFT is optimized with the lead placed at the RV apex; therefore, this position is often preferred, even if there is a compromise of the sensing thresholds. If there is already a pacemaker lead in the RV apex, then septal placement of the lead tip is chosen so that the lead tips are at maximal distance from each other to avoid device-device interactions. On occasion, placing an additional pacing-sensing lead in the RV may be necessary when the defibrillation efficacy and pace-sense function of the leads are optimized at different locations.

C. Threshold studies. The lead is tested for pace-sense thresholds using an external high-voltage system analyzer or pacing system analyzer. In general, an acute pacing threshold of 2 V or less, R-wave amplitude of 5 mV or more, and lead impedance within the accepted range of the manufacturer (typically 300-1,200 Ω) are necessary to meet the implant criteria. The lead is secured within the pocket with a suture sleeve tie-down. If the device uses an atrial and/or an LV lead, then these are implanted at this time. The leads are attached to the pulse generator, and the system is placed in either a submuscular or a subcutaneous pocket. The pulse generator should be placed with excess lead coiled posteriorly to reduce the risk of damaging the leads at the time of generator change and to maximize the ability to communicate with an external programming wand. The device is then interrogated to ensure appropriate communication. Pace-sense thresholds are again tested by telemetry to demonstrate consistency.

D. Defibrillation testing is best assessed by **evaluating the DFT**, which is defined as the lowest delivered shock strength required for successful defibrillation. A synchronized sinus test shock may be performed by delivery of a low-energy (<2 J) synchronized shock on

the QRS complex. This low-energy test allows the assessment of sensing as well as shock impedance (typically 35-90 Ω). For the purpose of defibrillation testing, VF is typically induced with a shock on T wave. Alternatively, or if shock on the T wave is unsuccessful, ultrafast burst pacing (30-ms intervals) or application of an alternating current may be used. Appropriate ICD detection and effective therapy are verified. In our lab, we do not perform routine DFT testing; however, when performed, we will start with 25 to 30 J to decide if system reconfiguration is needed. Usually, a maximum of three device-based therapies are attempted before rescue with external defibrillation at maximum energy. Two successful therapies that are at least 10 J less than the maximal output of the device are generally required. In general, this approach identifies the level of energy required to achieve a 50% to 75% success rate of defibrillation. Defibrillation therapy is then programmed at a level of at least 10 J over the DFT. Rarely, a patient may require the addition of a shocking coil in the SVC, azygous vein, or subcutaneous coil to achieve an adequate safety margin.

Complications involving DFT testing are infrequent but can include hypotension, transient worsening of heart failure, thromboembolic events, respiratory complications, and death. Prior prospective randomized studies have compared transvenous ICD implantation with and without DFT testing and found the defibrillation efficacy of ICD implantation without DFT testing noninferior. Over time, there has been a trend toward ICD implantation without DFT testing for most patients. Although the risk of failing defibrillation is low, guidelines recommend DFT testing in patients receiving S-ICDs. It is also reasonable to consider DFT testing in patients undergoing right-sided ICDs or ICD generator replacement in addition to patient-specific comorbidities that could increase the risk of failed shock therapies. ***Reasons to avoid DFT testing*** include left atrial or LV thrombus, atrial fibrillation without therapeutic anticoagulation, hemodynamic instability, severe aortic stenosis, severe unrevascularized multivessel or left main coronary artery disease, active ischemia, recent stroke, or significant

respiratory comorbidity that would inhibit the use of adequate sedation.

E. Risks and complications. The risks involved with implantation are similar to those of pacemaker insertion. Operative risks include bleeding, pneumothorax, hemothorax, infection, myocardial damage, vascular/cardiac perforation, tamponade, thromboemboli, deep venous thrombosis, acceleration of arrhythmias, air embolism, and death. A rare but dangerous complication is the occurrence of electromechanical dissociation or refractory VF during DFT testing. Because of the nature of the procedure, a separate standby external pacemaker-defibrillator should be immediately available for rescue therapy should the implanted device fail to appropriately treat an arrhythmia. The overall mortality rate is much less than 1%. Late complications include chronic nerve damage, erosion, extrusion, fluid accumulation, infection, formation of hematomas/cysts, keloids, lead migration, lead dislodgment, and venous occlusion.

V. DEVICE REPLACEMENT

A. Battery status is determined by the measured voltage, and this is retrieved with device interrogation. Generator replacement is generally recommended when the device reaches a battery voltage of around 2.6 V, termed *elective replacement indicator*. In such situations, the generator should be replaced within a few months. With continued depletion of the battery voltage, the generator reaches end of life, a situation that indicates a more urgent need for generator replacement as the battery voltage drops below 2.2 V. This may lead to longer charge times and incomplete or inappropriate function of the device.

B. Pulse generator replacement represents a vulnerable period for the ICD/lead system. A 4-fold increased risk of infection has been reported with ICD pulse generator replacement. Pocket reintervention for any indication involves increased infectious risk with cardiovascular implantable electronic devices (CIEDs). CIED infection is associated with significant patient morbidity and mortality in addition to increased financial costs. Strategies to reduce

CIED infection include antibiotic prophylaxis, good surgical technique, and an antibiotic device envelope in selected patients. In the prospective randomized WRAP-IT trial, patients undergoing generator replacement, device system upgrade, initial cardiac resynchronization therapy-defibrillator (CRT-D), or other device pocket revision with an adjunctive antibiotic envelope demonstrated a significant reduction in CIED infections compared to standard of care. In the past, manufacturers have had multiple-lead models of variable pin lengths and diameters. Beginning in 1991, they adopted the 3.2-mm international pace-sense standard (IS-1) and the 3.2-mm defibrillation standard (DF-1). Prior to an attempted device replacement, assessment of the lead model should be done to verify that the appropriate replacement header or adapters are available at the time of surgery.

C. Leads may be inadvertently damaged during the exploration of the pocket or during the exchange of pulse generators. Intraoperative assessment of lead function is imperative prior to introducing the replacement generator to the operative field. Replacement of a pace-sense or defibrillation lead may be necessary and requires the use of a different device header.

VI. TACHYCARDIA DETECTION AND THERAPY

A. EGM and tachycardia sensing. The ICD senses the intracardiac EGM signal via the implanted ventricular sensing electrodes. Recognition of a ventricular arrhythmia depends mainly on the analysis of the R-R intervals (heart rate is determined similarly). The accuracy of the EGM depends on the health of the adjacent myocardium and appropriate contact. The accuracy also depends on far-field signals from the muscles, atrium, or other sources of electromagnetic interference. The sensed signals are passed through a band-pass filter that consists of high- and low-frequency cutoffs to represent true signal events. The accuracy of signals in newer devices has been further improved by analysis of the signal frequency, slew rate, amplitude, EGM width, autogain, and autothreshold. These variables are important in helping the device differentiate VT and VF

from other events like atrial fibrillation, sinus tachycardia, and other supraventricular tachycardias (SVTs), thus reducing the incidence of spurious shocks.

Each EGM event and R-R interval is marked and detected, and there are various algorithms that attempt to identify events as either normal or abnormal. "Abnormal" events include bradycardia that requires pacing, VT requiring ATP or low-energy synchronized shocks, or VF requiring defibrillation. Most algorithms depend on the ventricular rate criterion. Other variables, such as the suddenness of onset, variation in cycle length, and change in EGM morphology, help to increase the specificity for diagnosis but at a cost of reduced sensitivity. These should be adjusted and programmed on the basis of individual requirement and clinical scenario of each patient.

B. Event detection occurs if the device reaches a specified number of intervals programmed by the physician to detect VT or VF, at which point the ICD delivers the prescribed therapy. Most devices reconfirm the ongoing episode to avoid therapy for nonsustained events. After delivery of therapy, the device either confirms termination of the episode or meets the criteria for redetection, and the next programmed therapy is delivered. The ICD automatically adjusts its sensitivity thresholds following sensed and paced events through an autogain mechanism. This allows the device to automatically adjust its sensitivity during a tachycardia episode in response to the changing amplitude of the ventricular signal.

C. Atrioventricular (AV) sequential devices incorporate programmable dual-chamber supraventricular criteria that may help to exclude inappropriate management of supraventricular tachyarrhythmias.

D. Tachycardia therapy. Most devices allow for programming of several tachycardia zones. The VT zone is programmed with a lower detection cutoff that would include any clinical VT events. Ideally, the cutoff rate for the detection of tachycardia should be above the patient's maximal heart rate to avoid therapy for sinus tachycardia. ATP is a programmed set of pulses delivered by the device in order to infiltrate reentry VT circuits and terminate the VT. ATP schemes

include burst pacing and ramp pacing. Burst pacing sequences deliver a set of ventricular pulses at a fixed cycle length, shorter than that of the VT. Ramp pacing consists of a set of ventricular pulses in which each subsequent cycle length is incrementally shorter than the preceding one. This is a more aggressive ATP scheme as there is a higher risk of VT acceleration or degeneration into VF with this therapy. Overall, some studies have shown about 90% success in termination of VT with ATP.

Following a failed ATP attempt, interburst decrement allows a more aggressive shortening of the intervals during either a burst or a ramp attempt. The first pulse of a burst or ramp sequence (S_1) is delivered at a calculated percentage of the tachycardia cycle length. The S_1 percentage cycle lengths, number of pulses, interburst decrement, and number of ATP attempts are all programmable features. In addition, cardioversion therapy (1-36 J) can be programmed in a VT zone. All VT zones have a programmable time limit on episode duration, at which point the device defaults to the next zone. Also, if a tachycardia is accelerated to a faster arrhythmia, then the ICD will deliver the therapy appropriate for the rate of the accelerated tachycardia.

E. Defibrillation therapy. Successful ICD management of VF can occur only with rapid defibrillation therapy. To avoid any delay to defibrillation, ICDs can now deliver ATP during the time needed for capacitor charging before shock delivery. When this ATP therapy is successful, the device will abort charging prior to shock delivery. All devices are programmed with a VF zone because of the risk of acceleration with ATP or cardioversion. Because of the hemodynamic instability seen with fast VT or VF, most devices are typically programmed to manage any sustained episode with rates higher than 180 to 200 beats/min with defibrillation therapy. The device should be programmed with at least a 10-J safety margin over the DFT observed either at implant or during follow-up testing. If DFTs are not performed, the first shock and subsequent shocks are typically programmed for the maximum available energy. Up to six additional shocks may be programmed, with maximal outputs programmed at

the second or third shock and onward. Several ICD programming trials have demonstrated that a longer detection delay before ICD shock delivery reduces inappropriate shocks. The Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) trial was a large, randomized study that demonstrated using a rate cutoff of 200 beats/min with a 2.5-second delay before device therapy initiation is associated with a significant reduction in unnecessary ICD therapy and all-cause mortality in patients with primary prevention ICDs.

VII. BRADYCARDIA DETECTION AND THERAPY

A. With the exception of S-ICDs, currently available ICDs provide basic VVI pacing with separate programmable postshock lower rate limit and output. Dual-chamber devices have an atrial lead for diagnostics and AV-synchronized pacing. These devices allow multiple programmable pacing modes, including single- and dual-chamber, fixed rate, or rate-responsive pacing with automatic mode switch. This obviates the need for a separate dual-chamber pacemaker. In addition, they may reduce the inappropriate shocks attributed to SVT. Dual-chamber devices may also have capabilities to detect and treat atrial arrhythmias in a manner similar to that for the ventricular arrhythmias. In patients without any pacing indications, it may actually be detrimental to pace the RV, especially in patients with preexisting LV dysfunction. This has been well demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. Such patients should be programmed for either backup pacing in the VVI mode or programming algorithms that minimize ventricular pacing should be used. Conversely, biventricular ICDs should be programmed to maximize ventricular pacing.

B. In AV-synchronized devices, the ICD can continue to sense tachyarrhythmias in both chambers, regardless of the programmed bradycardic pacing mode. To maintain proper sensing, both atrial and ventricular sensing thresholds are adjusted with autogain. The ICD has multiple blanking periods to avoid postpacing polarization, T-wave oversensing, and cross talk between chambers. To avoid

undersensing of tachyarrhythmias, short cross-chamber blanking periods after paced events and no cross-chamber blanking after sensed events are necessary. The AV synchronous devices have programmable refractory periods available for bradycardia functions, but these refractory periods do not affect tachyarrhythmia detection.

III. MAGNET FUNCTION

A. Confusion abounds concerning the function of a magnet with ICDs. The pulse generator contains a reed switch that is closed when a magnet is placed over the device. Closure of the reed switch prevents delivery of tachyarrhythmia therapy. Unlike pacemakers, bradycardia pacing is not affected by the use of a magnet in ICDs. Normal device therapy resumes when the magnet is removed and the reed switch opens.

IX. MANAGING AND FOLLOWING PATIENTS

A. In the United States, the government mandates patient registration and tracking. Once registered, a patient receives a permanent identification card to carry at all times. A MedicAlert is strongly encouraged. Manufacturer guidelines suggest that patients should follow up every 3 to 6 months depending on clinical status. Even if remote follow-up is available, it should be supplemented by annual clinic visits. Patients should be informed that they are likely to receive therapies. At the follow-up visit, a history of symptoms that might suggest tachyarrhythmias should be obtained. The diagnostic and episode data should be reviewed. Current devices also include stored episode EGMs to allow review of aborted shocks as well as delivered therapies. Device pacing and sensing thresholds should be obtained. There are no specific guidelines for follow-up testing of ICD defibrillation function. In general, patients experiencing device activation should be evaluated shortly after an event to assess for safe and appropriate device function. When device function or concomitant antiarrhythmic therapy is modified, an evaluation of the sensing, pacing, and DFTs is often necessary. Practice patterns vary widely regarding empirical device programming and electrophysiologic testing of modified ICD programming. Some

sources recommend that operating a motor vehicle should be avoided for 6 months following a symptomatic arrhythmic event.

B. In general, ICD pulse generators have a 5- to 10-year longevity depending on the usage and number of active leads. The programmer allows evaluation of battery status. As the device approaches the elective replacement interval, follow-up visits should be intensified. In general, once the device reaches the elective replacement interval, it operates normally for at least 3 months, depending on the frequency of therapy. Capacitor deformation occurs during periods when no shocks are delivered and results in longer charge times as well as decreased battery longevity. Current ICDs perform an automatic capacitor reformation that charges the capacitors and delivers the energy to an internal test load. This function improves subsequent charge times and battery longevity.

C. Typically, 40% of patients receive a therapy within the first year after implantation and 10% per year thereafter. If multiple ICD discharges are experienced, medical attention should be sought emergently.

D. Inappropriate shocks have been estimated to occur in 10% to 15% of patients with ICDs. These inappropriate therapies contribute to significant morbidity and distress for the patient. Early studies including MADIT II and SCD HeFT demonstrated an association between inappropriate shocks and greater all-cause mortality. Importantly, these studies did not use SVT-VT discrimination algorithms. The MADIT-RIT study found that reprogramming ICD therapy to reduce inappropriate shocks brought about a reduction in all-cause mortality during an average follow-up of 1.4 years. Recently, a single-center cohort study, involving nearly 1,700 patients, investigated the association between inappropriate ICD shocks and adverse outcomes. Over a 10-year period, this study found no association between inappropriate ICD therapy and increased mortality. **Failure to discriminate between ventricular and supraventricular rhythms is the most common reason for inappropriate shocks**. It is important to evaluate the patients for appropriateness of therapy. The most common cause of inappropriate shocks is atrial fibrillation with a fast ventricular rate. Shocks

delivered during physical exertion noted to have gradually increasing heart rates and gradually decreasing V-V intervals suggest sinus tachycardia. Therapy is likely to be inappropriate in this setting also. Ideally, the cutoff rate for the detection of tachyarrhythmias should be greater than the patient's maximal heart rate. In many cases, the VT rate falls within the patient's achievable sinus rate. Programmable enhancements, such as sudden onset and sustained high rate, can allow sinus tachycardia overlap into the VT zone without delivery of an inappropriate shock. Additional enhancements such as morphology discrimination of the ventricular EGM as well as the introduction of dual-chamber devices with timing intervals, marker channels, and mode-switching capabilities have improved the specificity of device therapy. The annual rate of inappropriate shocks has fallen from as high as 50% for SVT alone in early studies to as low as 1% in modern clinical trials with optimal device programming involving higher VT and VF rate detection thresholds and longer detection intervals in addition to sophisticated SVT-VT discrimination algorithms. Patients who are likely to benefit most from these algorithms are those with slower monomorphic VT, those at risk for atrial fibrillation with rapid ventricular rates, or those capable of exercising to sinus rates in the VT zone.

E. In the event of multiple ICD discharges, a magnet can be used to inhibit ICD therapy so that the underlying rhythm can be appropriately assessed and managed. The device should be interrogated as soon as possible to assess ICD function and facilitate diagnosis. If an SVT is present, then it should be managed as medically appropriate. For patient comfort, the magnet should be left in place to inhibit ICD therapy until the device can be reprogrammed or the SVT is terminated. If VF is present, the device is assumed inoperable and cardiopulmonary resuscitation with external defibrillation should be applied.

F. Patients receiving ICDs may suffer from significant psychological and emotional disturbances. Education and psychological support are beneficial in improving these patients' quality of life.

X. ELECTROMAGNETIC INTERFERENCE. Patients should be counseled to avoid sources of electromagnetic interference because such interference may cause the pulse generator to become inhibited and either fail to deliver appropriate therapy or deliver inappropriate therapy. Potential sources of electromagnetic interference include industrial transformers, radiofrequency transmitters such as radar, therapeutic diathermy equipment, arc welding equipment, toy radio transmitters, antitheft devices, and magnetic security wands. The safe use of medical technologies such as electrosurgery, lithotripsy, external defibrillation, and ionizing irradiation can be accomplished by deactivating tachytherapies before the event. Shielding of the device is also appropriate when possible. The device should be evaluated for appropriate operation following exposure. Magnetic resonance imaging (MRI) is contraindicated for some devices; however, most newer generation ICDs have been deemed MRI compatible by the FDA. Reports of interference created by cellular phones may be related to either a magnetic field from within the phone or the radiofrequency signal generated by the phone. It is suggested that if a patient with ICD wishes to use a cellular phone, it should be held to the ear opposite the device and should not be carried in a pocket close to the device.

XI. FUTURE. ICD implantation rates have risen tremendously over the past two decades. Multiple clinical studies have demonstrated the role of ICDs in the primary and secondary prevention of SCD. Multiple trials have also demonstrated the role of an ICD in combination with cardiac resynchronization therapy (CRT) in reducing mortality and hospital admissions in patients with heart failure. Improvements in electronic technology will continue to expand the programming capabilities of these devices while reducing their size. S-ICDs are available and provide a less invasive approach for patients who have an indication for ICD therapy but do not require pacing. ICD lead technology is also expected to improve, thereby decreasing the number of lead-related complications. Leadless device systems are in clinical trials and may be an option for select patients in the future.

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CHAPTER 57

Catheter Ablation

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I. INTRODUCTION AND HISTORICAL BACKGROUND.

Ablation of cardiac arrhythmias forms the cornerstone of the modern practice of cardiac electrophysiology. Cardiac surgeons and cardiac electrophysiologists worked together to develop surgical management of refractory arrhythmias in the 1960s and 1970s. In the 1980s, the serendipitous discovery that direct current could be applied to intracardiac structures through percutaneously placed intracardiac electrode catheters to achieve focused ablation moved the nonpharmacologic management of cardiac arrhythmias out of the operating room and into the electrophysiology laboratory. The advent of catheters that could channel alternating current at radiofrequency (RF) levels in the 1990s to safely and strategically target arrhythmogenic myocardial tissue led to the exponential growth of the practice of catheter ablation.

II. GENERAL OVERVIEW

A. Patient selection/indications

1. Catheter ablation of cardiac arrhythmias is a very effective tool for properly selected patients. Both efficacy and safety weigh heavily in the risk/benefit profile of the procedure.
2. Ablation can be considered a primary therapy in arrhythmias where success rates are typically high. Examples include typical right atrial (RA) flutter, atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), atrial tachycardia (AT), paroxysmal atrial fibrillation (AF) with a structurally normal heart, and ventricular tachycardia (VT) in structurally normal hearts. Ablation for arrhythmias such

as persistent AF, atypical atrial flutter, and scar-related VT tends to have a lower success rate, and its benefit (relative to standard medical therapy) depends on individual patient circumstances.

B. Contraindications

1. Patients should be hemodynamically stable, and any heart failure (HF) should be well compensated prior to beginning a catheter ablation procedure.
2. Active infections should be appropriately managed.
3. Ongoing bleeding issues should be addressed as well.
4. Patients with breathing difficulty, airway problems, or difficulty lying flat must have these problems addressed because some procedures can be lengthy and several hours of bedrest is required after any catheter ablation procedure.
5. Often consultation and assistance from an anesthesiologist is required to safely conduct the procedure—many ablations are performed under general anesthesia because it improves patient comfort and catheter stability in arrhythmias, such as AF.

C. Vascular access

1. Catheter ablation builds on the concepts of cardiac catheterization as well as catheter-based electrophysiology studies. As such, percutaneous vascular access is critical for a successful procedure. Femoral venous and arterial access are the primary sites utilized for catheter ablation. Ablation in the RA and right ventricle (RV) are almost always performed via the femoral venous access site, although internal jugular or subclavian access may be used in rare circumstances. Left atrial (LA) ablation is typically performed via the femoral venous site using a transseptal puncture to cross from the RA to the LA. Left ventricular (LV) ablation can be performed via venous access and transseptal puncture or a femoral arterial access site then crossing retrograde across the aortic valve.
2. Ultrasound-guided percutaneous access has proven effective for reducing vascular access complication rates and should be considered standard of care to maintain appropriate patient safety,

especially when procedures are performed with minimal interruption of chronic oral anticoagulation.

3. For certain arrhythmias, epicardial ablation is required. Percutaneous access to the pericardial space can be accomplished using fluoroscopic guidance with subxiphoid approach and a standard Tuohy needle. A wire is then introduced into the pericardial space, and a sheath is placed over the wire. Ablation catheters can then be placed into the pericardial space through the sheath and carefully manipulated to the appropriate ablation targets. When performed by operators with appropriate experience and skill level with this approach, the overall rate of complications is reasonably low. This approach is sometimes not feasible in patients with prior open-heart surgery secondary to the presence of adhesions. Furthermore, the risk of complications may be prohibitively high in patients with moderate-to-high pulmonary arterial systolic hypertension. Alternative epicardial access methods (eg, the use of pericardial CO_2 insufflation to improve access safety) are currently in development.

D. Anticoagulation

1. In patients with arrhythmias that require chronic oral anticoagulation, multiple studies have demonstrated the safety of minimal or no interruption of anticoagulation.
2. Any ablation requiring the presence of catheters in the LV or LA should be performed with heparin infusion initiated after vascular access is established and with a goal activated clotting time (ACT) in the range of 300 to 450 seconds depending on the type and length of the procedure. In some circumstances, heparin infusion may be required even for RA and RV interventions (eg, when using catheters with higher thrombogenic potential).
3. For patients taking a direct oral anticoagulant (DOAC; ie, oral factor Xa inhibitor or oral thrombin inhibitor) undergoing arterial access, the agent should be held 24 to 48 hours prior to the procedure. For patients on warfarin, the international normalized ratio (INR) level should be considered for the safety of arterial access. Decisions regarding a specific INR target or timing for

holding a DOAC should be based on an individual patient's risk/benefit ratio with regard to bleeding and risk for thromboembolic complications The risk of epicardial access complications is particularly high in anticoagulated patients; for this reason, anticoagulation is almost always held/reversed immediately prior to epicardial access.

E. Equipment

1. Catheter ablation requires all the standard equipment typically found in any electrophysiology laboratory, including cinefluoroscopy, hemodynamic monitoring, high-fidelity recording systems, electrical stimulator for pacing, cardioverter/defibrillator, an RF generator, and electroanatomic mapping (EAM) equipment. If specialized ablation techniques are employed (ie, cryoablation, electroporation, laser, high-intensity–focused ultrasound, microwave, robot-assisted procedures), then the appropriate equipment for these techniques would also be needed, but these are not considered standard to every interventional electrophysiology laboratory.
2. Three-dimensional (3D) EAM systems. The development of these systems has enabled a significant increase in the efficacy of catheter ablation. The basic principle of EAM is to identify the location of one or more catheters with high spatial resolution. A 3D anatomic model of the chamber or chambers of interest can be created using a roving catheter to define the borders of the chamber. In addition, electrical information such as voltage and activation timing can be visually superimposed upon the 3D anatomic map. These systems also catalog locations paired with electrograms as well as locations of ablation lesions. Two primary modalities currently exist in clinical practice. The systems have very similar output but significantly different mechanisms to identify and track catheter location.

a. Magnetic-based mapping

(1) This system utilizes low-intensity magnetic fields to triangulate the position of catheter tips within the body. An electromagnetic location pad is attached to the fluoroscopy

table beneath the patient, and sensors within the catheters detect the low-intensity magnetic fields generated by the location pad. The system is able to detect both the real-time position and orientation of the catheter.

(2) **Pitfalls.** The map is created in reference to a fixed magnetic array. Movement of the patient can shift the cardiac structures relative to the map and can necessitate remapping.

b. Impedance-based mapping

(1) Impedance-based mapping systems rely on locator patches applied to the patient's skin. An electrical signal is emitted from the patches, creating a voltage gradient along three different axes. The degree of voltage detected by the catheter electrodes determines their 3D position. This reliance primarily on electrical impedance leads to more versatile catheter compatibility, because of the nonrequirement of a special sensor in the catheter, as well as slightly faster signal acquisition. Impedance-based systems can also give an estimate of a catheter's proximity to the endocardium.

(2) **Pitfalls.** Impedance-based systems may be slightly less accurate compared to magnetic systems because stable and consistent measurements rely on a stable volume status. Using an irrigated tip ablation catheter can lead to significant changes in volume status throughout the course of a procedure, thereby hindering the reliability of stable and consistent electrical impedance measurements throughout the course of a procedure.

c. The newest generations of EAM systems combine magnetic and impedance-based data with the goal of providing the best of both technologies.

3. Ablation energy/catheters

a. Radiofrequency ablation (RFA). The passage of alternating RF current across the catheter-tissue interface causes local

heating (resistive heating) that then dissipates further into the tissue (conductive hearing). Once the tissue is heated to a temperature over 50 °C, irreversible tissue injury occurs. Heating occurs in proportion to the amount of power delivered and the degree of tissue resistance to energy conduction (relative to the resistance of the blood pool). Blood passing over the surface of the catheter-tissue interface serves to cool the area by means of convection. This balance of conductive heating and convective cooling helps maintain a balance in the temperature generation. This balance is critical for safe and effective lesion formation. As the temperature reaches and exceeds 100 °C, blood boils and extensive char and coagulum forms on the catheter tip. This can lead to excessive tissue destruction (the so-called “steam pops”) and increased risk of embolism of char and coagulum.

b. Irrigated tip catheters

(1) Ablation of arrhythmias such as AF and scar-mediated VT requires a significantly larger area of ablation, and thus longer time of active ablation, than ablation for arrhythmias with a more focal mechanism (ie, AT, AVNRT, or AVRT). Using standard RFA catheters requires a delicate titration of power to avoid excessive tissue heating, steam pops, and embolism of char and coagulum, which could lead to an excessive risk of stroke.

(2) To address this problem, catheters with irrigated tips were developed to augment convective cooling of the catheter-blood pool interface. Irrigated tip catheters are now considered standard of care for AF ablation as well as any other ablation procedures that require more extensive ablation, such as ischemic scar–related VT ablation. Using an irrigated tip catheter can improve lesion size.

c. Contact force catheters

(1) Force-sensing catheters incorporate specially designed sensors into the tip of an irrigated RFA catheter to provide

the operator with feedback regarding the amount and direction of force at the catheter tip.

(2) There are two primary designs for contact force-sensing catheters. One uses feedback from the mechanical deformation of springs, and the other takes advantage of the physical properties of light waves reflected in a small chamber that can change in size based on the degree of force applied (based on the Fabry-Perot interferometer).

(3) Both catheters work in conjunction with 3D EAM systems to relay the information back to the operator. Specific force and force-over-time criteria can be defined to give the operator credit for a "good" ablation lesion. Studies have shown that utilizing this approach for AF catheter ablation has led to more effective ablation procedures.

d. Phased-array catheters. Multielectrode phased-array RFA catheters have been developed with the goal of delivering a pattern of ablation lesions (both circular and linear) in a more efficient and timely manner. These catheters are not irrigated. In theory, these catheters should lead to more efficient and shorter ablation; however, in practice, they have shown a higher rate of embolic phenomena than the rate seen with irrigated tip RFA catheters.

e. Cryoablation

(1) Cryoablation accomplishes tissue destruction by cooling tissues to very low temperatures. Cryoablation catheters deliver cryorefrigerant to the targeted tissue to rapidly lower the tissue temperature. As temperatures within the tissue fall below −40 °C, ice crystals form in both the extracellular and intracellular compartments, leading to mechanical destruction. In addition, ice crystals form first in the extracellular compartment causing an acute change in the osmotic gradient, leading to the movement of water out of cells and subsequently leading to their desiccation. After the cryorefrigerant is stopped, the tissue is passively rewarmed by the surrounding blood. This process leads to

additional cellular damage and death because circulatory function is restored and a hyperemic process causes hemorrhage and coagulation necrosis. Further ischemia occurs as the tissue becomes edematous because of the malfunctioning and porous microcirculation. With time, inflammation leads to fibrosis and scar tissue formation within the damaged area.

(2) ***Cryoballoon catheters***

(a) Special cryoablation catheters are available to accomplish pulmonary vein isolation (PVI). An expandable balloon is mounted on the tip of the catheter, and this balloon is expanded by filling it with cryorefrigerant. The catheter is positioned within the os of each pulmonary vein (PV), and the balloon delivers the hypothermic injury to a circumscribed area within the PV antrum. A central lumen within the catheter allows for a circular mapping catheter to be placed in the PV distal to the balloon to monitor for electrical isolation.

(b) Randomized trials examining RF versus cryoablation to achieve PVI have shown equal efficacy and equal overall safety. There is a significantly higher rate of phrenic nerve injury with cryoballoon ablation, but the large majority of these injuries lead to only temporary diaphragmatic paralysis. This is counterbalanced by a lower rate of cardiac perforation/tamponade. Procedural time with cryoballoon PVI is also slightly shorter on average than procedural time for RF PVI.

f. Pulsed field ablation (PFA). Pulsed electrical field energy is a nonthermal source in which cell death is mediated by a series of ultra-short high-voltage punctuated electrical energy applications that alter the permeability of the cell membrane and form irreversible pores. The effect on different tissues depends on the dosage and formula delivered with several factors at play, including voltage, waveform, frequency,

duration, and rate of delivery, among others. In animal models, PFA in atrial myocardial tissue resulted in transmural irreversible electroporation without histologic evidence of extracellular matrix damage, smooth muscle injury, or neuronal injury. As a result, PFA has emerged as a potentially safer alternative to conventional RFA or cryoablation with a lower likelihood of phrenic nerve injury or atrioesophageal fistula at the studied doses of energy delivery. Whether this is due to tissue specificity or regeneration from an intact extracellular matrix remains an area of further investigation. Clinical studies for PFA have been performed predominantly in patients with paroxysmal and persistent AF, with results demonstrating shorter procedure times and a favorable safety profile. Though acute success is promising, long-term efficacy compared to conventional techniques remains similar to date. PFA in ventricular tissue is currently being investigated in animal studies.

g. Alternative strategies

(1) Chemical ablation. In drug-refractory ventricular arrhythmias and/or AF/perimitral atrial flutter that has failed conventional ablation techniques, ethanol ablation can be considered. Ethanol is a water-soluble compound that rapidly crosses the cell membrane. In high concentration, it alters the protein structure of the phospholipid bilayer, resulting in cell death. Intravascular infusion of ethanol can additionally cause sclerosis of the injected vessel. Historically, transcoronary ethanol ablation has been performed in patients with drug-refractory ventricular arrhythmias that have failed conventional RFA catheter. Coronary ethanol ablation is limited by the risk of complications, including coronary arterial dissection, thrombosis, and large infarction territory. If the anatomy is suitable, retrograde coronary venous ethanol ablation is a safer alternative to reaching deeper substrate in refractory arrhythmias. For persistent perimitral atrial flutter/AF, the

vein of Marshall (VOM) is targeted. The VENUS trial demonstrated greater freedom from AF and AT at 90 days in patients with persistent AF who underwent VOM ablation plus PVI compared to PVI alone. Though randomized, this was a single-center study and needs further validation. In ventricular arrhythmias, meticulous venous mapping based on the earliest activity is required to select the appropriate venous branch for ethanol infusion.

(2) **Radiation therapy.** In high-risk patients with refractory ventricular arrhythmias that have failed conventional ablation, stereotactic body radiotherapy (SBRT) is an alternative. Borrowing from oncology, SBRT allows for targeted high-dose treatment, resulting in cell death. Preclinical findings suggest the ability to cause fibrosis and electrical isolation with single-dose SBRT. There is a small but growing body of clinical evidence suggesting a significant reduction in VT burden and implantable cardioverter-defibrillator (ICD) therapies with SBRT. Current data are limited by variations in treatment protocols, and long-term myocardial side effects of radiation therapy are not well elucidated. While future studies will help to answer these questions and standardize treatment regimen, SBRT is an option for reducing VT burden in patients with refractory ventricular arrhythmias.

F. Mapping. Successful ablation relies heavily on careful mapping of the targeted arrhythmia. Various mapping techniques exist to help localize arrhythmias and determine the best ablation sites.

1. Activation mapping (**Figure 57.1**)

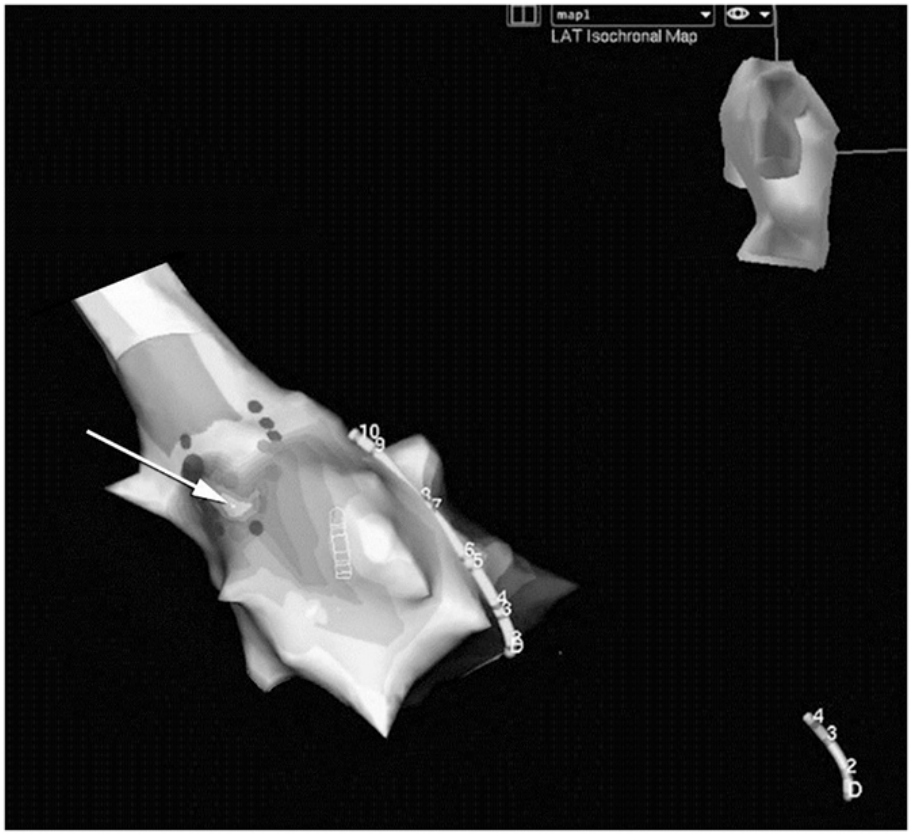

FIGURE 57.1 Activation mapping of focal arrhythmia. Activation mapping of the right atrium displayed in right lateral projection. The earliest activation is displayed in white in this image (arrow) and is located at the high crista terminalis.

a. This technique is commonly used in mapping focal and reentrant arrhythmias. Multiple electrodes placed in various anatomic locations can help elucidate the timing and path of activation of an arrhythmia. To perform activation mapping, the arrhythmia of interest must be sustained and hemodynamically tolerated by the patient. A stable reference electrogram is also needed—for ventricular arrhythmias, this can be a surface QRS complex, but p waves can often be difficult to discern in atrial arrhythmias, necessitating an intracardiac electrogram for reference purposes. Once electrodes are placed and a stable reference is determined, then a roving mapping catheter records local activation from various positions in relationship to the

reference. For focal arrhythmias, the earliest site of activation in relationship to the reference is typically the target for ablation. For reentrant arrhythmias, the operator seeks to define the circuit. An area of slowed or constrained conduction that is critical to the arrhythmia circuit is the target for ablation.

b. Pitfalls

(1) This technique only provides the earliest site in the chamber being mapped (when mapping focal arrhythmias).

(2) Reentrant circuits in complex/abnormal substrate may contain multiple areas of slow conduction that make identification of the critical circuit difficult.

(3) Generally, it is only possible to gather reliable activation information from the surface of the structure of interest (ie, endocardium and/or epicardium). If the origin of the arrhythmia is mid-myocardial, endocardial/epicardial maps may be difficult to interpret.

(4) Creating a high-density map becomes quite difficult if the arrhythmia of interest is not frequent and/or sustained.

(5) Ectopic beats, whether spontaneous or catheter induced, can distort the map if these beats are included in the map.

2. Entrainment mapping (**Figures 57.2 and 57.3**)

FIGURE 57.2 Entrainment mapping within the circuit of an atrial flutter. The return cycle length after the last paced beat is measured and, in this case, is almost identical to the tachycardia cycle length, suggesting the site being paced is within the critical circuit.

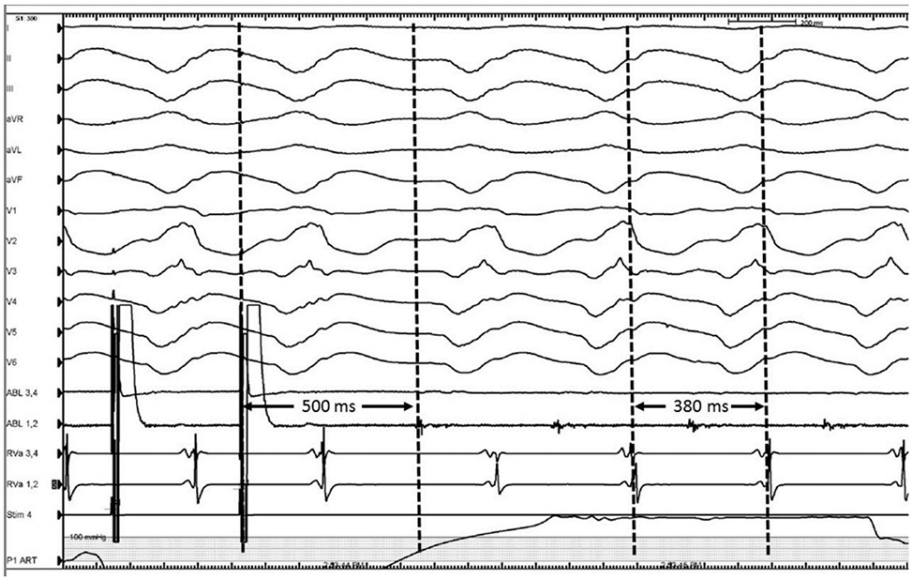

FIGURE 57.3 Entrainment mapping outside the circuit of ventricular tachycardia. The return cycle length after the last paced beat is measured and, in this case, is more than 100 ms longer than the tachycardia cycle length, suggesting the site being paced is outside the critical circuit.

a. Entrainment is typically used for reentrant arrhythmias to define the arrhythmia circuit. Overdrive pacing is performed from various locations at a slightly faster cycle length than the arrhythmia. When performed at a location within the arrhythmia circuit, the return cycle length after cessation of pacing should be equivalent to the arrhythmia cycle length. Conversely, when pacing outside the circuit, the return cycle length will be significantly longer than the arrhythmia cycle length.

b. Pitfalls

(1) Overdrive pacing may break or accelerate the arrhythmia.

(2) Local capture may not be possible in areas of diseased/scarred myocardium.

3. Pace mapping

a. Pace mapping is typically used to confirm or localize focal arrhythmias or the exit site from the zone of slow conduction in reentrant arrhythmias. When pacing from the site of origin of arrhythmias with a focal mechanism, the paced morphology of the surface electrograms should exactly match that of the arrhythmia—this is most useful for ventricular arrhythmias because subtle morphology changes are difficult to discern in surface p waves. For scar-related reentrant ventricular arrhythmia, pacing at the location where the arrhythmia circuit exits the scar should produce a QRS morphology identical to the clinical arrhythmia.

b. Pitfalls

(1) Local capture may not be possible in areas of diseased/scarred myocardium.

(2) Pacing from a blind loop connected to the critical circuit may yield a perfect pace match for a site that is not truly part of a reentrant circuit.

G. Ablation targets

1. Anatomic targets

a. Atrial fibrillation

(1) Most AF triggers arise in the area where the PVs connect to the LA. Approximately 15% to 30% of patients undergoing AF ablation will have non-PV triggers. In addition, even in patients with non-PV triggers, the PV sleeves are also thought to play an important role in sustaining AF ("AF substrate").

(a) **Pulmonary vein isolation**

i. Given that most triggers arise in the area where the PVs join the LA, most patients respond well to PVI alone.

ii. The most efficacious and safest method for achieving PVI is antral ablation. Posterior LA wall ablation is a topic of debate but should be considered in re-do cases and persistent AF.

(b) **Ablation of non-PV triggers and non-PV substrates.** Non-PV triggers and/or substrates of AF typically include specific anatomic areas, such as the superior vena cava (SVC)-RA junction, LA posterior wall, crista terminalis, coronary sinus ostium, ligament of Marshall area, and the interatrial septum. Several stepwise mapping and ablation techniques exist to address these targets, although there is currently no gold standard approach. This is an active area of research that may be especially beneficial for patients with nonparoxysmal AF (especially those who failed prior PVI).

b. Atrioventricular nodal reentrant tachycardia

(1) Rapidly conducting and more slowly conducting (fast and slow pathways) inputs into the compact AV node (AVN) are key components of the circuit that supports AVNRT. The fast and slow pathway inputs have typical anatomic locations lending themselves to therapy with ablation using an anatomic approach.

(2) The anatomic triangle of Koch outlines the components of the AVN. The triangle's borders are the septal aspect of the tricuspid annulus anteriorly, the tendon of Todaro (septal continuation of the eustachian ridge) posteriorly, and the anterior aspect of the coronary sinus ostium inferiorly. The compact AVN lies at the apex of this triangle. Just superior and anterior to the apex of the triangle is the bundle of His. Fast pathway inputs to the compact AVN lie posterior and superior to the tendon of Todaro. Slow pathway inputs lie anterior to the coronary sinus and inferior to the location of the compact AVN. In some individuals, slow pathway

fibers also lie in the proximal coronary sinus and/or on the LA side of the septum at the level of the mitral annulus.

(3) Consistent with their respective names, fast pathway fibers demonstrate more rapid conduction velocity and slow pathway fibers demonstrate slower conduction velocity. During normal rhythm, impulses travel down both AVN pathways simultaneously, although only the fast pathway wavefront activates the His bundle; the slow pathway wavefront is usually of no consequence because it encounters refractory fast pathway and His tissue. That is why dual AVN physiology is a very common finding that usually does not result in any arrhythmias. However, in certain situations, there can be a critical prolongation of the conduction time through the slow pathway such that when the impulse reaches the fast pathway region, it finds the area repolarized. This tissue now acts as an excitable gap and sets up a reentrant circuit involving the AVN and its inputs. Typical AVNRT conducts antegrade along the slow pathway and retrograde along the fast pathway, whereas atypical AVNRT conducts in opposite directions. Rare atypical variants can be isolated to slow pathway fibers with slightly different conduction properties—the so-called "slow-slow" or "intermediate-slow" variants.

(4) During ablation of AVNRT, the catheter is positioned at the tricuspid annulus anterior to the coronary sinus ostium. Ablation of the tissue between the tricuspid annulus and the coronary sinus ostium eliminates AVNRT in approximately 95% of cases by abolishing the ability of the slow pathway to conduct in a 1:1 ratio. A long sheath with a slight septal curve is helpful to reach the target area. Electrograms at the tip of the ablation catheter should show a small atrial signal with a larger ventricular signal in a ratio of 1:10 to 1:3. The use of smaller and nonirrigated RF catheters and starting with a low level of energy all lead to the lowest risk possible of damaging the compact

AVN. A stable catheter position within the more inferior region of the triangle of Koch is essential for a safe ablation because the more superior the catheter moves, the risk of damage to the compact AVN increases.

(5) Ablation with RF energy should elicit a junctional rhythm when the catheter is positioned at an effective location. These junctional beats may subside as ablation continues, but the presence of junctional beats during application of RF energy is strongly associated with a successful ablation. During junctional rhythm, retrograde conduction to the atrium over the fast pathway can be observed and RF energy is stopped immediately if this retrograde conduction is interrupted because it is an early warning sign of impending damage to the compact AVN.

(6) A 6-mm tip cryoablation catheter can also be used to ablate AVNRT. Ablation is carried out in a similar location. Compared to RFA, cryoablation of AVNRT has a lower rate of damage to the AVN; however, this comes at the cost of a higher rate of arrhythmia recurrence.

(7) Variant forms of AVNRT are also typically treated by ablation along the anatomic slow pathway to eliminate 1:1 conduction over the slow pathway. The most efficacious strategy maps the earliest retrograde atrial activity either during tachycardia or during ventricular pacing. This area of early retrograde atrial activation is targeted for ablation. In "slow-slow" variants, this often corresponds to the anterior aspect of the proximal coronary sinus, and in "fast-slow" variants, this often corresponds to a location between the tricuspid annulus and the coronary sinus ostium.

c. AV junction ablation

(1) Ablation of the AV junction in combination with a pacemaker is an extremely effective method for controlling symptomatic AF. This management approach is typically reserved for patients who continue to have symptomatic

AF despite aggressive medical management and/or ablation of AF. The primary drawback of this management approach is that the patient becomes pacemaker dependent.

(2) Ablation targets the compact AVN region with the goal of leaving the patient with a junctional escape rhythm. To accomplish this, an ablation catheter locates the His position, usually located at about 1 o'clock on the tricuspid valve (TV) annulus in the left anterior oblique (LAO) fluoroscopic view. The catheter is then moved inferiorly and toward the atrium around the atrial mid-septal region. An ideal electrogram shows a 1:1 to 1:2 atrial to ventricular ratio with a very small His. Alternatively, a unipolar electrogram should show a completely negative His electrogram when the catheter is in the ideal position.

(3) When the catheter is in the correct position, application of RF energy should result in an accelerated junctional rhythm within a few seconds followed by complete AVN block within 30 seconds. If AVN block does not occur, then a new position should be sought as further ablation at a nonoptimal site will result in edema and significantly decrease the likelihood of success. A left-sided approach targeting left-sided His electrograms can be utilized in the small minority of cases in which a right-sided approach fails.

(4) Through an unclear mechanism, patients are more susceptible to torsades de pointes immediately after AV junction ablation. For that reason, it is common practice to program the base rate of their pacemakers to 70 or 80 bpm after the procedure. The base rate is then gradually lowered over the subsequent 1 to 3 months.

d. Sinus node (SN) modification

(1) When the SN develops an inappropriately elevated baseline rate that leads to symptoms, medications typically serve as first-line therapy to bring the sinus rate back into the normal range and relieve symptoms. However, many

patients do not respond to medical management, and an ablation approach can be utilized to manage these patients.

(2) The anatomic location of the SN is targeted for modification with the aim of slowing the sinus rate. The SN typically underlies the crista terminalis in the area of the lateral RA wall. The more cranial portions near the SVC-RA junction typically demonstrate faster rates, and the more caudal portions demonstrate slower rates. Ablation targeting the cranial portion of the SN can help control the rapid rates found in patients with inappropriate sinus tachycardia. Activation mapping during tachycardia can help confirm that this anatomic location is indeed the location of the earliest atrial activation during tachycardia. Careful attention is needed to identify the course of the phrenic nerve. High-output pacing is performed during ablation to capture the phrenic nerve, and ablation is stopped immediately if there is any decrease in diaphragmatic capture. Compound motor action potential (CMAP) monitoring can also be used to monitor the strength of diaphragmatic contraction during ablation. An epicardial balloon is a useful tool that physically separates the phrenic nerve from the SN tissue, allowing for safer RF delivery through the endocardial and/or epicardial surface.

2. Focal targets

a. Atrial tachycardia

(1) AT arises from a small focus that activates independently of other atrial tissues and does not depend upon macro-reentry to sustain the arrhythmia.

(2) Activation mapping is critical to identify the site of origin for AT. A stable reference is chosen, and with guidance from a 3D EAM system, local activation timing during the tachycardia compared with the reference is plotted onto a 3D anatomic model of the chamber(s) of interest. Once the site of earliest activation is identified, ablation is carried out in this region.

(3) Noninducibility of the arrhythmia after ablation using programmed atrial stimulation and isoproterenol infusion is an acceptable end point for ablation.

b. Premature depolarizations

(1) Premature atrial depolarizations (PADs) or premature ventricular depolarizations (PVDs) can lead to significant symptom burden for some patients. PADs can trigger AF. In addition, a high burden of PVDs can lead to a nonischemic cardiomyopathy and HF. Although these can be managed with medications, catheter ablation can be quite effective, especially in patients who failed or wish to avoid medical therapy.

(2) Surface electrocardiogram (ECG) morphology can be used to estimate the location of premature depolarizations, but the most efficacious and precise approach involves activation mapping to locate the earliest focal site of activation. A 3D EAM system provides an excellent display of the activation map to assist with localization of the site of the earliest activation. Intracardiac electrograms at this site typically precede the onset of the surface P wave (in PADs) or QRS (in PVDs) by 20 to 40 ms, and unipolar recordings demonstrate a QS pattern. Pace mapping at this site should match the clinical PVD morphology.

(3) A stable and readily identifiable reference from the chamber of interest (atrial for PADs, ventricle for PVDs—can be surface QRS) is required in order to have an accurate activation map. Ablation targeting the earliest activation site should eliminate the premature beats.

c. Outflow tract VT

(1) VT arising from the RV or LV outflow tract areas typically occurs in patients without underlying structural heart disease. The mechanism is usually triggered activity, leading to a focal site of origin. These arrhythmias will often terminate with verapamil or adenosine.

(2) Ablation is often the first-line management for these types of ventricular arrhythmias because it confers a high rate of success.

(3) Surface ECG morphology can provide a very close estimate of the site of origin. Activation mapping is critical to identifying the appropriate ablation target. Ablation with an irrigated catheter at the site of earliest activation leads to a high rate of success.

(4) The actual focus causing the arrhythmia may be endocardial, mid-myocardial, or epicardial. In most cases, an endocardial approach is effective because the distance between the two surfaces is relatively small in many of the outflow tract areas. However, in a small subset of patients, the arrhythmia may arise from an area known as the LV summit—this is an epicardial site bounded by the proximal left anterior descending and proximal left circumflex arteries and the great cardiac vein as it branches into the anterior interventricular vein. An endocardial approach is often attempted, but the success rate is lower, given the distance that the ablation energy must travel to the epicardial site in this area. A catheter-based epicardial approach is often problematic and ineffective, given the amount of epicardial fat in this area and the proximity to the major coronary arterial branches. If an endocardial approach at the LV summit area fails, the next alternative is to place the ablation catheter through the coronary sinus and out to the greater cardiac vein targeting the earliest area of activation in this region. If both approaches fail and ablation remains strongly indicated, then the only alternative may be an open surgical approach.

3. Reentrant targets

a. Atrial flutter

(1) **Typical atrial flutter** is dependent upon a macro-reentrant circuit involving the cavotricuspid isthmus (CTI) within the RA. This form of atrial flutter typically presents a

much more straightforward and uncomplicated ablation; therefore, the threshold for ablation of this type of atrial flutter is lower than for atypical atrial flutter. Typical atrial flutter has a characteristic appearance on surface ECG. The flutter waves in leads II, III, and aVF deflect in the same direction as each other but opposite the direction of the flutter wave in lead V_1. If the flutter waves in II, III, and aVF are negative and in V_1 are positive, this is termed **counterclockwise typical atrial flutter**. On the other hand, positive flutter waves in the inferior leads with negative flutter waves in V_1 signify **clockwise typical atrial flutter**. Clockwise and counterclockwise refer to the expected direction of propagation through the RA with respect to the tricuspid annulus when viewed from the RV apex.

(2) Atrial flutter demonstrating flutter waves with any other pattern that does not fit with that defined for typical atrial flutter is termed **atypical atrial flutter**. Atypical atrial flutter also has a reentrant mechanism, but the location and size of the circuit can vary widely. These arrhythmias often occur in patients with prior open-heart surgery or ablation of atrial arrhythmias. Any process leading to focal scarring within atrial tissue can predispose a patient to these arrhythmias. The ablation of atypical atrial flutter can present a greater challenge. However, with careful mapping techniques, the critical circuit for maintenance of the arrhythmia can often be successfully delineated and targeted for ablation. Therefore, patients with atrial flutter refractory to medical therapy should be offered therapy with catheter ablation.

(3) Typical CTI-dependent flutter

(a) The CTI is an anatomically constrained area that is critical to the maintenance of typical RA flutter. An effective line of ablation that transects this structure will terminate the arrhythmia. The line of ablation

stretches from the TV annulus back to the inferior vena cava-RA junction. Lesions should be delivered to the central portion of the CTI (6 o'clock position on the tricuspid annulus in the LAO radiographic view) because more septal positions can potentially affect inputs to the AVN and the more lateral region is thicker and can be trabeculated, making ablation significantly more difficult and less effective.

(b) After completion of ablation, block is confirmed with differential pacing. The mapping/ablation catheter is positioned lateral to the ablation line and pacing is performed from the mapping catheter, and the conduction time from the pacing stimulus to local activation in the coronary sinus is recorded. Pacing is then performed from the coronary sinus, and time to local activation at the mapping catheter is measured. These 2 times should be similar and typically 150 ms or greater if bidirectional block across the line has been achieved. Similar maneuvers can be carried out with the mapping catheter just medial to the ablation line, and conduction times should be very short at that location. Measuring conduction times prior to ablation can be helpful to use as a comparison, especially in patients with delayed interatrial conduction at baseline.

(c) Additional ablation end points also include noninducibility and a change in the RA activation sequence. When the atrial flutter does not recur during programmed stimulation with rapid atrial pacing and extra-stimulus pacing with the patient at rest and on isoproterenol infusion, the end point of noninducibility is said to have been reached. If a multielectrode catheter is properly positioned within the RA, then the RA activation sequence can be visualized with RA pacing from sites lateral and medial to the ablation

line. If a bidirectional block is present, the wavefront should move sequentially across the catheter electrodes rather than spreading out in both directions from the pacing impulse and colliding somewhere within the RA, creating a chevron pattern of activation rather than a sequential pattern.

(4) Atypical flutter

(a) Atypical atrial flutter usually arises in patients who have **areas of scar tissue within one or both atria**. Often, these patients have had prior ablation or open-heart surgery. Pathologic processes that produce atrial scar formation—such as long-standing AF, cardiac amyloidosis, congenital heart disease, or other structural heart disease—can also lead to atrial scar formation. The atypical atrial flutter reentrant circuit depends upon these areas of scar to create conduction block and slowed conduction so that reentry can occur. Often, patients do not have one area of scar, and once one circuit that can support atrial flutter is ablated, then others are identified either during the procedure or, at some time, after the procedure, making ablation of these arrhythmias more difficult and leading to a higher recurrence rate than that of typical atrial flutter.

(b) Careful mapping is critical to successful ablation of atypical atrial flutter. The techniques of activation mapping and entrainment previously described in combination with visualization by 3D EAM are essential. Once a circuit is identified, ablation is carried out to eliminate areas of slowed conduction, identified by fractionated electrograms, and to connect to areas of nonconduction.

(c) For example, **patients with prior PVI** can present with an atypical atrial flutter that conducts along a circuit around the mitral valve annulus—the so-called perimitral flutter. Perimitral flutter is typically treated

by ablating from the mitral annulus to another LA structure that shows no conduction; often one of the electrically isolated PV.

b. Scar-related VT

(1) Scar-related VT is a reentrant tachyarrhythmia; therefore, the critical circuit can be identified using the principles of entrainment. The circuit relies on a narrow isthmus of myocardium capable of conduction through the scar. The conduction through this circuit is typically slow and delayed and is represented by local mid-diastolic potentials.

(2) To perform entrainment of VT, the arrhythmia must be sustained, monomorphic with a stable cycle length, and hemodynamically tolerated by the patient long enough for entrainment pacing to be performed. The goal is to locate a site within the VT circuit that is located within the narrow, constrained diastolic isthmus that can be targeted with ablation. The mapping catheter is used to search for areas within the scar demonstrating mid-diastolic potentials starting at the edges and working deeper into the scar. Once mid-diastolic potentials are located, entrainment pacing is performed at a cycle length slightly faster than the tachycardia cycle length (TCL)—entrainment is confirmed by acceleration to the paced cycle length with constant fusion. Once entrainment is confirmed, then pacing is terminated.

(a) **Manifest fusion** suggests that the pacing site is outside of a protected isthmus, whereas **concealed fusion** suggests that the pacing is within a protected isthmus.

(b) The postpacing interval (PPI) is examined on the mapping catheter—measured from the final pacing stimulus to the return of the local electrogram. If pacing from a site within the protected isthmus, then the PPI will be the same as the TCL (PPI − TCL = 0).

(c) When the above findings confirm that the mapping catheter is located within the protected isthmus, the timing from the pacing stimulus to the surface QRS reveals whether the location is near the entrance to the isthmus, somewhere in the middle, or near the exit. **The exit site and the mid-isthmus are the ideal sites for ablation**. A stimulus to QRS time that is very near the TCL (generally less than 30%) is consistent with a location near the exit. As the stimulation to QRS time increases to a duration nearer the TCL, the location of the catheter becomes closer to the entrance site.

(3) Using all of these criteria for VT entrainment mapping in scar-related VT avoids ineffective ablation within bystander sites and blind loops/cul-de-sacs.

c. Atrioventricular reentrant tachycardia

(1) AVRT is a **reentrant arrhythmia dependent on an abnormal connection between the atrium and the ventricle termed a bypass tract**. The tachyarrhythmia travels along a circuit involving the atrium, the AVN, the ventricle, and the accessory pathway. The accessory pathway is targeted for ablation to treat these arrhythmias, given that it is typically a small, focal connection between the atrium and the ventricle that is not an essential part of the normal conduction system.

(2) AVRT can be antidromic (traveling retrograde across the AVN and atrial tissue and antegrade through the bypass tract manifesting as a wide QRS) or orthodromic (traveling antegrade across the AVN and retrograde across the accessory pathway). Activation mapping during antidromic AVRT will show the earliest ventricular activation at the site of the accessory pathway. Conversely, activation mapping during orthodromic AVRT will show the earliest atrial activation at the site of the accessory pathway.

(3) Ideal ablation targets should show a fused A and V electrogram and can sometimes show a small, high-

frequency signal known as a pathway potential.

4. Substrate targets

a. Atrial fibrillation

(1) Atrial tissue that exhibits complex fractionated atrial electrograms (CFAEs) possibly represents substrate that sustains AF because it represents tissue with slowed conduction, thereby slowing and/or disrupting the propagation of atrial depolarization wavefronts.

(2) Utilizing 3D EAM systems, CFAEs can be mapped, marked, and then targeted for ablation. Multiple CFAE definitions and mapping algorithms exist, and an optimal strategy is yet to be defined.

b. Scar-related VT. Not all patients requiring catheter ablation for control of ventricular arrhythmias will be ideal candidates for entrainment mapping. In circumstances where VT is difficult to induce or hemodynamically intolerated, a substrate modification approach can be useful to decrease the burden of ventricular arrhythmias.

(1) Substrate modification combines pace mapping with voltage mapping of the ventricular endocardium. Using a 3D EAM system, the endocardial voltage within the chamber of interest is displayed along with an anatomic shell of the ventricular endocardium. Voltage data are projected onto the anatomic shell in color-coded manner so that scarred myocardium can be visualized.

(2) Detailed mapping is performed in the area of scar suspected to be involved in the VT circuit. Locations with low-voltage, conduction slowing, late potentials, and/or local abnormal ventricular activity (LAVA) are noted and targeted for ablation. In addition, pacing is performed at various sites within the scar and compared to the clinical arrhythmia. Areas within the scar that demonstrate an excellent pace map match are also targeted for ablation.

H. Postprocedural management

1. **Major complications.** The overall rate of major **complications is on the order of 3% to 6%**, depending on the procedure type and patient comorbidities.
    a. **Vascular access**
        (1) Major vascular access complication rates are on the order of 1% to 2%.
        (2) As stated previously, when ultrasound-guided access is performed, these rates have been shown to be as low as 1% or less.
        (3) Possible complications include hematoma, retroperitoneal bleeding, pseudoaneurysm, and AV fistula.
    b. **Cardiac perforation and tamponade.** The rate of this complication is also 1% to 2%, with lower rates for supraventricular tachycardia ablations.
    c. **Thromboembolism.** With appropriate anticoagulation for procedures involving instrumentation in the LA and/or LV, the overall rate of stroke, transient ischemic attack, or systemic embolization is 1% or less.
    d. **Death.** The estimated rate of death as a complication is exceedingly low at about 0.1%. However, the mortality rate is much higher in nonelective cases (eg, ablation of patients, who presented in VT storm).
    e. **Other.** The rate of other major complications is overall about 0.5% to 1.0% or less.
        (1) **Atrial esophageal fistula**
            (a) This is a potentially devastating but avoidable complication of ablation along the posterior wall of the LA where it overlies the esophagus. Utilizing an esophageal temperature probe to monitor esophageal temperatures within the esophagus during ablation, ablation energy is titrated to maintain temperatures below 38 °C. With this technique, the rate of atrial esophageal fistula is approximately 0.1%. Importantly, this complication typically materializes **several weeks**

after the ablation (presentation with fever, chest pain, confusion, and focal neurologic deficits 1-4 weeks after PVI). Patients with suspected atrial esophageal fistula **should NOT undergo endoscopy**; instead, this diagnosis needs to be verified with urgent computed tomography (CT) scan followed by urgent surgical repair.

(b) PV stenosis is a known possible complication of PVI that may develop several months after the procedure. However, it is now seen only infrequently owing to procedural modifications (current practice is to deliver PVI lesions far out of the PV ostium) and the fact that most PV stenosis cases may be asymptomatic. Rare cases require percutaneous PV stenting.

(2) Injury to conduction system. The overall rate of injury to the conduction system is approximately 0.5%. However, when the target for ablation lies in close proximity to the AVN or His Purkinje system, the risk of this complication increases (eg, AVNRT ablations).

(3) Genitourinary trauma. For procedures requiring placement of an indwelling bladder catheter because of either use of general anesthesia or length of the procedure, the risk of damage to the genitourinary system is approximately 0.5%.

(4) Pulmonary edema. The use of irrigated tip RFA catheters can lead to a significant amount of intravascular fluids over the course of an ablation procedure. Careful attention should be paid to the balance of fluid input and output throughout the procedure and diuretics utilized as needed. Pulmonary edema still occurs in approximately 0.5% of cases.

f. Complications unique to VT ablation

(1) Catheter ablation of VT carries all the typical risks noted above. However, there are unique complications specific to VT ablation that should be kept in mind.

(2) **Hemodynamic instability.** Induction of VT can lead to hemodynamic instability from the tachyarrhythmia and/or because many patients with medically refractory VT have significant structural heart disease with reduced ventricular systolic function. Hence, it is vital to ensure that a patient's HF is well treated and well compensated prior to proceeding with VT ablation. In order to ablate hemodynamically unstable ventricular arrhythmias, hemodynamic support in the form of inotropes, LV assist device, extracorporeal membrane oxygenation, or an Impella device may be considered (notably, the use of intra-aortic balloon pumps in this regard has been shown to be ineffective). The PAINESD score that assigns 5 points for chronic obstructive pulmonary disease (COPD), 3 points for age >60, 6 points for ischemic cardiomyopathy, 6 points for New York Heart Association (NYHA) class III or IV HF, 3 points for LV ejection fraction (LVEF) <35%, 5 points for VT storm, and 3 points for diabetes can be calculated to assess the risk of hemodynamic instability. Scores ≤8 are low risk and ≥15 are high risk. While the PAINESD score is a well-established and validated risk stratification algorithm, it remains unknown whether the use of mechanical circulatory support affects procedural outcomes in high-risk individuals.

(3) **Coronary artery injury**

(a) Injury to coronary arteries can occur with either endocardial or epicardial approaches, but it is more common with epicardial approach. A coronary angiogram prior to mapping and ablation can help identify coronary artery locations and courses, thereby lowering the risk of coronary artery injury. The ostium of each coronary artery may be injured during ablation of outflow tract VT arising from either the right or left coronary cusp. An angiogram can be performed to mark the ostia, or intracardiac echocardiography can

visualize the level of the coronary artery and ensure that the ablation catheter remains well below that level.

(b) **Epicardial ablation of VT raises the overall risk of the procedure to a rate as high as 14%.** The higher risk is due in large part to higher incidence of pericardial bleeding complications, coronary artery injury, and phrenic nerve injury.

2. Management of anticoagulation

a. Appropriate management of anticoagulation before, during, and after AF or atrial flutter ablation leads to very low rates of thromboembolic events.

b. An oral anticoagulant must be started prior to the AF/atrial flutter ablation procedure. Ideally, the patient should be anticoagulated for a period of 3 to 4 weeks prior to the procedure. If this is not possible, a transesophageal echography (TEE) can be performed prior to starting the procedure, and if no intracardiac thrombus is detected, the procedure can be performed with initiation of therapeutic anticoagulation immediately following the procedure. Using anticoagulation in the weeks preceding the procedure allows a clinician to be sure that the patient will tolerate anticoagulation well and eliminates the need for bridging anticoagulation if warfarin is utilized.

c. The AF/atrial flutter ablation procedure can be safely performed **with limited interruption of therapeutic oral anticoagulation**. Warfarin can be continued without interruption if the INR remains within the typical therapeutic window in the periprocedural period. DOACs taken twice daily (dabigatran and apixaban) should be held on the morning of the procedure and restarted immediately following the procedure. The last dose of rivaroxaban prior to the procedure should be taken about 18 hours before the estimated start time of the procedure, and it should also be resumed immediately following the procedure.

d. During procedures involving **instrumentation in the LA or LV (ie, including, but not limited to, AF/atrial flutter ablation), intravenous heparin bolus and infusion should be initiated after vascular access is achieved**. The infusion should be adjusted, and additional boluses given to maintain a target ACT of approximately 350 to 400 seconds. After completion of the procedure, heparin should be partially reversed with protamine prior to removal of vascular sheaths (target ACT less than 200-250 seconds for venous sheaths). Once the patient is tolerating oral intake, they should be given a dose of their oral anticoagulant, which will subsequently be resumed on its routine schedule.

e. Pericardial access should not be performed in anticoagulated patients. If an anticoagulant is already present, it should be transiently reversed (eg, using protamine, fresh frozen plasma [FFP]). Once pericardial access is established and deemed safe (eg, observing no significant accumulation of blood in the pericardium), systemic anticoagulation can resume, if appropriate.

3. Other postprocedural considerations

a. Patients are typically monitored overnight after the procedure to ensure that there are no obvious early complications. The use of vascular closure devices and collagen plugs has helped facilitate the same-day discharge, particularly in AF ablation. Telemetry monitoring of the cardiac rhythm should be performed. If a patient has a permanent pacemaker or defibrillator in place, it should be interrogated to ensure that there have been no changes with regard to the pacing and sensing parameters of the individual leads.

b. After AF ablation, monitoring for recurrences varies widely between providers and institutions. At our institution, careful monitoring is implemented to accurately determine success rates and to help guide postprocedural management. The patient is supplied with a two week cardiac monitor (Zio; iRhythm technologies) post ablation and at 3, 6, and 12 month

intervals. This allows the provider to have a reasonable idea of the patients' response to the procedure at the time they return for a 3-month follow-up visit. The monitoring period can be extended on a case-by-case basis. This also allows the provider to make plans with the patient regarding the management of antiarrhythmic medications and the need for repeat ablation procedures.

c. Therapeutic anticoagulation should be continued for at least 4 to 6 weeks following ablation of AF or atrial flutter, similar to patients undergoing cardioversion. Guidance for anticoagulation beyond this time should be based on individual patient risk for thromboembolic complications related to AF. At our institution, anticoagulation is typically continued until the 3-month follow-up when a cardiac CT is performed to rule out PV stenosis. Ablation procedures for AF should never be performed with the sole goal of obviating a patient's need for anticoagulation as there is no evidence to suggest that AF ablation reduces a patient's long-term risk for thromboembolic complications.

III. SUMMARY. Catheter ablation has grown to become the standard of care for definitive management of tachyarrhythmias both as first-line therapy for certain arrhythmias and when medical management fails for other types. Catheter ablation is minimally invasive and often quite effective. As with any procedure, the risks and benefits for an individual patient must always be weighed to determine if a catheter ablation procedure is the appropriate management strategy.

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SECTION XI

Common Cardiology Procedures

EDITOR: **Brian P. Griffin**

CHAPTER 58

Temporary Cardiac Pacing

Christopher S. Massad and Bryan J. Baranowski

I. INDICATIONS

A. Acute hemodynamically significant bradycardia or asystole. Temporary pacing is indicated in patients with acute hemodynamically significant bradycardias, including sinus arrest, advanced atrioventricular (AV) blocks, and asystole. Reversible causes such as AV nodal blocker or digoxin toxicity and electrolyte disturbances such as hyperkalemia should be identified and reversed prior to implantation of a permanent pacemaker.

B. Termination of tachycardias. Overdrive pacing can be used to terminate tachyarrhythmias in both the atria and the ventricles. When a reentrant circuit is present (atrial flutter, supraventricular tachycardia, monomorphic ventricular tachycardia), the affected cardiac chamber can be paced starting at a rate of 10 to 15 beats/min faster than the tachycardia. This **burst pacing** technique (akin to the antitachycardia pacing feature on implantable defibrillators) is typically initiated for 8 to 12 beats and then abruptly stopped. If the tachycardia persists, the pacing rate is increased by 10 beats/min incrementally. An alternative pacing maneuver, **ramp pacing**, involves decreasing the interval between successive pacing impulses but is technically challenging to perform using temporary cardiac pacing equipment and has been shown to be less efficacious in terminating tachycardias compared with burst pacing. **The advantage of overdrive pacing is avoidance of direct current cardioversion**, but the **major complication is potential conversion to a faster, more unstable rhythm** (atrial or ventricular fibrillation), particularly with faster and longer pacing sequences. Temporary pacing is also indicated in patients with bradycardia-dependent or

long-QT–triggered ventricular tachycardias (torsade de pointes) to suppress further arrhythmia occurrences.

C. **Condition where there is a chance of recovery.** In certain conditions where there is a reasonable chance of conduction recovery (eg, Lyme disease, myocarditis, postcardiac surgery, or inferoposterior myocardial infarction), temporary pacing may be utilized while performing regular surveillance (pacing turndown) of the underlying rhythm to determine if permanent pacing will be needed.

D. **Bridge to permanent pacing.** Temporary pacing may be used as a bridge to permanent pacing in patients with complete heart block, high-grade second-degree block (Mobitz II), severe sinus node dysfunction, and asystole where **conduction recovery is not expected**. Generally, temporary pacing in this setting is for patients with an acute illness (endocarditis or systemic infection elsewhere) that delays permanent pacemaker placement.

E. **Acute myocardial infarction.** Indications for temporary pacing in this setting include the development of a new bifascicular block (right bundle branch block [RBBB] with either left-axis [left anterior hemiblock] or right-axis deviation [left posterior hemiblock]), new left bundle branch block (LBBB) with first-degree AV block, alternating LBBB and RBBB, Mobitz type II block, and complete heart block. Patients with right ventricular infarction and loss of AV synchrony may benefit from AV sequential pacing.

F. **Acute aortic regurgitation.** Pacing to increase heart rate in patients with acute severe aortic regurgitation can reduce diastolic filling time and improve hemodynamics by increasing cardiac output and decreasing left ventricular end-diastolic pressure.

G. **Prophylactic.** Prophylactic temporary pacing *may be* considered in the following settings: (1) in patients undergoing right heart catheterization and/or myocardial biopsy with a preexisting LBBB; (2) in patients with complex intervention to the right coronary artery because this supplies the AV nodal artery in 90% of individuals; (3) cardioversion in patients with sick sinus syndrome, although generally the use of transcutaneous pacing backup is preferred; (4) or

in patients with new first-degree AV block with acute endocarditis (especially of the aortic valve). Patients who are undergoing alcohol septal ablation for hypertrophic cardiomyopathy typically receive prophylactic transvenous pacers, given the significant risk of complete heart block during the procedure. Patients who are undergoing balloon aortic valvuloplasty and percutaneous aortic valve replacement have a temporary pacemaker placed for overdrive pacing, which transiently reduces cardiac output and minimizes the risk of displacement of the valvuloplasty balloon during inflation.

H. Electrophysiologic studies. Temporary atrial, ventricular, His, and coronary sinus pacemakers are frequently used in electrophysiologic studies.

I. Ischemic evaluation. Ischemic evaluation may be rarely performed via rapid atrial pacing.

II. PACING MODES

A. Transcutaneous pacing. Transcutaneous ventricular pacing involves placement of large surface area, high-impedance electrodes on the anterior (over lead V_3 or the palpable cardiac apex) and posterior chest walls (inferior aspect of the scapula, to the left or right of the spine). It usually requires long pulse widths (20-40 ms) and high outputs of up to 100 to 200 mA. Transcutaneous pacing is most useful in code situations and may also be useful when transvenous pacing is contraindicated. It avoids the complications associated with transvenous pacing, such as pneumothorax, right ventricular perforation, infection, bleeding, and venous thrombosis. Failure to capture and severe patient discomfort necessitating sedation are common.

B. Transesophageal or transgastric pacing. This technique uses a flexible electrode on the tip of a catheter that is advanced down the esophagus to a position just behind the left atrium and is usually successful in achieving atrial pacing. The electrode can also be advanced to the fundus of the stomach to pace the ventricle through the diaphragm. However, ventricular pacing is difficult to achieve

consistently and without intolerable pain to the patient, and for this reason, it is rarely used.

C. Epicardial pacing. Temporary epicardial pacing wires are typically placed at the time of open-heart valve surgery, given there is a 6% rate of permanent pacemaker implantation prior to discharge in this population, as compared with 0.8% after coronary artery bypass grafting. Longer cross-clamp times, multiple valve surgical procedures, absence of preoperative sinus rhythm, and reoperation are all predictors of the need for pacemaker implantation in the valvular surgery population. The electrodes are typically removed with gentle traction when they are no longer needed or no longer functional.

D. Transvenous pacing

1. Relative contraindications

a. Poor vascular access

b. Bleeding disorders or anticoagulant therapy. If the international normalized ratio is >1.8 and platelets are <50,000, then these conditions should be corrected prior to placement of a transvenous pacer if possible.

2. Patient preparation

a. Informed consent should be obtained for the procedure. However, if the patient is hemodynamically unstable because of a cardiac arrhythmia that could be improved with a pacemaker, this procedure is indicated emergently without the need for consent.

b. If the procedure is elective, peripheral intravenous access should be obtained before the start of the procedure.

c. The procedure should be performed in a monitored setting that is equipped for cardiopulmonary resuscitation and has fluoroscopy available.

3. Technique

a. Lead choice. Multiple varieties of active and passive fixation leads exist. There is evidence that active fixation leads allow for greater pacemaker stability and fewer complications than

passive fixation leads. However, active fixation leads can be technically more challenging to place.

b. Sites. The preferred site for pacemaker insertion is the right internal jugular vein. The femoral, subclavian, and external jugular veins can also be used. However, if a permanent pacemaker will eventually be inserted, the subclavian vein site ipsilateral to the planned permanent pacemaker site should be avoided, if possible.

c. Position. The patient should be placed supine in bed but may be moved to the Trendelenburg position for internal jugular and subclavian vein cannulation.

d. Placement

(1) Ventricular pacing. A venous sheath is inserted into one of the central veins, through which pacing leads are passed. For certain active fixation leads, the lead is loaded first with an inner curved stylet. The pacing lead is advanced through the venous sheath under fluoroscopic guidance (usually 20°-30° left anterior oblique projection). The lead is advanced to the tricuspid valve and turned clockwise or counterclockwise to direct the tip anteriorly. An attempt is made to cross the valve directly. If unsuccessful, gentle pressure is applied and the lead is torqued, allowing the middle portion to prolapse across the valve into the right ventricle. If the tricuspid valve is difficult to traverse, it may be possible to enter the right ventricle by looping the tip of the lead against the lateral atrial wall and then rotating the loop medially (counterclockwise) toward the septum. Another option is to reshape the lead manually (stylet if using certain active fixation leads), increasing the tip bend before attempting to traverse the tricuspid valve. Once the lead has entered the right ventricle, the lead can be advanced into the right ventricular outflow tract (RVOT), then slowly pulled back until it drops, and then subsequently advanced into the apex as it drops. When placing certain active fixation

leads, after advancing the lead to the RVOT, the inner curved stylet should be removed and replaced with a straight stylet prior to pulling the lead back to the apex. Some degree of buckling is acceptable; however, excessive buckling increases the risk of perforation. Ideally, the pacemaker tip should be near the apex of the right ventricle. **The ideal placement site is on the diaphragmatic surface or "floor" of the right ventricle anywhere between its midpoint and its apex**. The floor of the more proximal ventricle is a second choice; the true apex is not a good choice for placement of the catheter tip. The paced electrocardiogram from this location usually shows an LBBB pattern with left-axis deviation. Ventricular pacing can also be done with the tip in the RVOT if the catheter cannot be placed on the floor of the right ventricle in a stable position. The pacer tip is considerably less stable at this site compared with the right ventricle floor and is more likely to be displaced; however, this is an acceptable position for a screw-in temporary pacing wire. Pacing from this location will show an LBBB pattern with an inferior axis. The use of a balloon-tipped temporary pacing electrode can aid in the advancement of the electrode into the proper position. To ensure maximum lead stability with certain active fixation leads, it is imperative that adequate slack be seen following stylet removal (a heel should be seen fluoroscopically in the inferior right atrium) *and* that suture sleeves are tied down tightly to the skin.

(2) **Atrial pacing.** The right atrium is the easiest chamber to reach, but locating a stable position can prove difficult (the right atrial appendage is preferred). For passive atrial pacing, a J-tipped atrial pacing catheter is used. Alternatively, an active fixation lead can be screwed in. The atrial appendage is directed anteriorly above the tricuspid annulus, and multiple planes are frequently

helpful in verifying the location. (The catheter appears as a "J" in the left anterior oblique projection or as an "L" in the right anterior oblique projection.)

(3) Both atrial and ventricular pacing may be performed by placing the catheter in the coronary sinus. The coronary sinus in its proximal portion courses along the left atrium. Ventricular pacing may be achieved by positioning the catheter in a cardiac vein off the coronary sinus. The threshold in the coronary sinus is frequently high, but sometimes, it may be a more stable location for atrial pacing than the atrial appendage. Steerable electrophysiologic pacing catheters may be useful in such patients.

e. Testing. Once a pacing lead is in a stable position, threshold testing should be performed. The distal electrode of the pacing lead is used as the cathode and connects with the negative terminal of the generator, whereas the ring is used as the anode and connects with the positive terminal. The pacing lead is attached via cable to the pacemaker generator.

(1) Pacing capture threshold. Pacing should be started at a rate of 10 to 20 beats/min faster than the intrinsic rate with 5 mA output. If capture is not seen at this point, the catheter needs to be repositioned. Once capture is seen, the output is slowly decreased until loss of capture is seen. The **lowest capturing current is the pacing stimulation threshold**. If the catheter is in good position, the threshold typically should be <1 mA. Pacing output should be programmed three times the threshold, but pacing is usually performed at a minimum of 5 mA (even if 3 times the threshold is <5 mA). This is because minor dislodgment can cause major changes in the threshold and add a safety margin.

(2) Sensing threshold. This is the degree to which the pacemaker sees native cardiac signals (in millivolts). The sensing threshold should only be tested if the patient has an

intrinsic rhythm. Set the pacing rate to 10 beats/min below the patient's intrinsic rate. Lower the sensitivity so that the pacemaker is sensing intrinsic rhythm. You should see the sensing indicator light on the generator flash with each intrinsic beat. Increase the sensitivity until the sensing indicator light is no longer flashing and the pacing indicator light begins to flash. This is the sensitivity threshold. To avoid competitive pacing and the possibility of an "R-on-T" phenomenon, lower the capture output to 0.1 mA before testing. The pacer should be set at one-half the sensing threshold.

(3) **AV interval.** For dual-chamber pacing, the AV interval will need to be programmed. A default of 150 ms is frequently used, but the optimal AV delay may be different in individual patients. Patients with diastolic ventricular dysfunction may need longer AV delay for ventricular filling. In patients with marginal cardiac reserve, obtaining cardiac output measurements at various AV intervals and heart rates may help determine the optimal AV interval and heart rate.

f. Postplacement chest radiography. A postprocedural chest radiograph should be obtained to look for pneumothorax. For right ventricular apical pacing, in the posteroanterior view, the electrode tip should be located to the left of the spine. In the lateral view, the electrode tip should be directed inferiorly and anteriorly. For pacing through the coronary sinus, the tip should be to the left of the spine, directed posteriorly and superiorly.

g. Pacer care

(1) Check the catheter insertion site daily for signs of infection and apply a new sterile dressing at regular intervals.

(2) Obtain a daily 12-lead surface electrocardiogram, ideally with and without pacing, to assess changes in native conduction.

(3) Check pacemaker function daily by determining the sensing and pacing threshold, and check the underlying

rhythm daily by decreasing the pacing rate gradually to "off." Abrupt termination in pacing may increase the risk of long pauses.

h. Complications

(1) Related to central venous access, including hematoma at the puncture site, inadvertent arterial puncture, arteriovenous fistula, subcutaneous emphysema, brachial plexus injury, pneumothorax, hemothorax, thoracic duct injury, air embolism, venous thrombosis, and infection

(2) Cardiac arrhythmias such as premature atrial or ventricular contractions, nonsustained ventricular tachycardia, and new RBBB. These are usually of no consequence (although the latter can result in complete heart block in the setting of a preexisting LBBB).

(3) Myocardial perforation with cardiac tamponade. Normally, the unipolar recording from the tip shows pronounced ST elevation in comparison with the proximal electrode. ST depression from the tip is associated with perforation. If perforation is suspected, an echocardiogram should be obtained immediately to assess for pericardial effusion. Even a very small pericardial effusion can cause hemodynamic collapse. If tamponade is suspected, emergency pericardiocentesis should be performed. If perforation is suspected and the patient is hemodynamically stable, the temporary pacemaker should be withdrawn only when the physician has all equipment available and is prepared to perform an elective pericardiocentesis.

(4) Lead dislodgment, particularly with passive fixation leads, leading to failure of capture

(5) Pacemaker dysfunction, including generator failure and lead oversensing or undersensing

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CHAPTER 59

Electrical Cardioversion

Joshua Parker and Jeffery Courson

I. INTRODUCTION. Delivery of electrical countershock to terminate cardiac arrhythmias is a safe and effective technique that is routinely performed in most hospitals. *Cardioversion* is defined as the delivery of energy synchronized to the QRS complex, whereas random delivery of shock during the cardiac cycle (usually done for terminating ventricular fibrillation) is termed *defibrillation*.

II. MECHANISM. Although it has long been recognized that the application of an electrical shock to the myocardium can restore a normal rhythm, knowledge of the fundamental mechanism underlying defibrillation remains incomplete. A rapidly delivered electric shock depolarizes the myocardial cells and creates a zone of myocardium with an extended refractory period. Activation fronts encountering tissue with a prolonged refractory period will not be able to propagate, thus terminating both macro- and micro-reentrant circuits. **Atrial fibrillation and ventricular fibrillation are generally agreed to be more electrically stable rhythms and thus require higher current delivery** for termination, whereas in less stable arrhythmias, only regional depolarization in the path of an advancing wavefront is required. The most common waveform shapes used in external defibrillation are the **monophasic** and **biphasic** waveforms. In biphasic waveforms, the polarity at each electrode reverses partway through the defibrillation waveform. The use of a biphasic waveform in cardioversion and defibrillation has been shown to be associated with increased efficacy and may reduce the development of postshock arrhythmias.

III. INDICATIONS AND CONTRAINDICATIONS. The indications and contraindications of cardioversion are listed in **Tables 59.1** and **59.2**,

respectively. **Cardioversion should not be performed in patients with sinus rhythm or when the abnormal rhythm is secondary to increased automaticity (eg, multifocal atrial tachycardia and junctional tachycardia). If the presenting rhythm is ventricular fibrillation or ventricular tachycardia with hemodynamic compromise, the only clear contraindication to defibrillation is a clear expression of the patient's (or patient's surrogate's) informed wish not to be resuscitated**.

TABLE 59.1 Indications and Contraindications for Cardioversion and Defibrillation

INDICATIONS

Cardioversion

1. Atrial fibrillation/atrial flutter

- **A.** Patient with atrial fibrillation/atrial flutter >48 h (or unknown) duration and anticoagulation for >3-4 wk (INR 2-3)
- **B.** Acute-onset atrial fibrillation/flutter with associated hemodynamic compromise
  - **1.** Angina pectoris
  - **2.** Myocardial infarction
  - **3.** Pulmonary edema
  - **4.** Hypotension
  - **5.** Heart failure
- **C.** Atrial fibrillation/flutter of unknown duration and absence of thrombus in the left atrium or left atrial appendage on biplane transesophageal echocardiogram
- **D.** Atrial fibrillation/flutter <48 h duration → precardioversion anticoagulation is optional depending on thromboembolic risk

2. Atrial tachycardia

3. Atrioventricular nodal reentrant tachycardia

4. Reentry tachycardias associated with Wolf-Parkinson-White syndrome

5. Ventricular tachycardia

Defibrillation

1. Ventricular fibrillation

2. Ventricular tachycardia with hemodynamic instability

CONTRAINDICATIONS
Cardioversion

1. Known atrial thrombus and no emergent indication

2. Sinus rhythm/tachycardia

3. Tachycardias associated with increased automaticity

   A. Multifocal atrial tachycardia

   B. Junctional tachycardia

   C. Accelerated idioventricular rhythm

4. Digitalis toxicity

5. Severe electrolyte imbalance and nonemergent indication

6. Unknown duration of atrial fibrillation or atrial flutter in a nonanticoagulated patient in the absence of transesophageal echocardiogram

7. Patient who cannot be safely sedated

Defibrillation
Prior expression of patients who wish not to be resuscitated

INR, international normalized ratio.

TABLE 59.2 Indications for Electrical Cardioversion in Patients With Atrial Fibrillation

Class I

- In pursuing a rhythm-control strategy, cardioversion is recommended for patients with AF or atrial flutter as a method to restore sinus rhythm.
- AF with a rapid ventricular response or atrial flutter that does not respond promptly to pharmacologic therapies and contributes to myocardial ischemia, heart failure, or hemodynamic instability
- Patient with tachycardia with AF or atrial flutter and preexcitation that is associated with hemodynamic instability

Class IIa

- Repeated cardioversions are reasonable in patients with persistent AF, provided that sinus rhythm can be maintained for a clinically meaningful period between cardioversion procedures.

AF, atrial fibrillation.
Adapted from January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64(21):e1-76.

IV. PROCEDURE

A. Patient preparation

1. **Informed consent** should be obtained from the patient or surrogate (if the patient is unable to comprehend and give meaningful informed consent).
2. In elective cases, the patient should **fast for a minimum of 6 to 8 hours**.
3. A review of the patient's medical **history and a focused physical examination** should be performed. **Special attention should be paid to the airway**. The inability to visualize the uvula, inability to open the mouth with at least 2 cm between the teeth, and difficulty in extending the neck are factors that may make potential intubation difficult and may suggest the need for the presence of an anesthesiologist during the procedure.
4. The patient's **medication and anticoagulation status** (for patients with atrial fibrillation or flutter) should be confirmed and incorporated into a careful evaluation of the patient's thromboembolic risk. Because patients may not always have symptoms with arrhythmias such as atrial fibrillation and atrial flutter, convincing historical or electrocardiographic evidence of the tachycardia initiating within 48 hours should be documented prior to cardioverting a patient with atrial fibrillation or atrial flutter in the absence of adequate anticoagulation.
5. **Anticoagulation** is a key factor for patients with atrial fibrillation or flutter (**Table 59.3**) to prevent thromboembolism. Three classes of oral anticoagulants are now available for thromboembolic

prophylaxis. Direct oral anticoagulants (DOACs)—dabigatran (direct thrombin inhibitor), rivaroxaban (factor Xa inhibitor), apixaban (factor Xa inhibitor), and edoxaban (factor Xa inhibitor)—are now recommended over warfarin in DOAC-eligible patients. All four of these DOACs have been compared to the oral vitamin K antagonist, warfarin, in large randomized clinical trials of long-term management of atrial fibrillation and were shown to be at least noninferior in efficacy with lower rates of bleeding. For DOAC-ineligible patients, warfarin remains an excellent option for protection against thromboembolic events with a good safety profile as long as the international normalized ratio (INR) is closely monitored and the dose adjusted to keep the INR between 2 and 3.

TABLE 59.3 Anticoagulation Status and Cardioversion for Atrial Fibrillation/Flutter

Anticoagulation Before Cardioversion

1. Administer oral anticoagulation with DOAC[a] (no need for laboratory monitoring) or warfarin and ensure therapeutic INR (>2) for nonvalvular atrial fibrillation/flutter for a minimum of 3 wk prior to cardioversion (target INR 2-3).**or**

2. Anticoagulate with heparin[b] to achieve a PTT 1.5-2 times control OR start DOAC. Screen for thrombus in the left atrium or left atrial appendage by transesophageal echocardiography.

- **A.** If no thrombus, cardiovert and continue heparin while loading warfarin or continue DOAC. With regard to warfarin, continue heparin until INR is therapeutic (≥2). If DOAC is used, it would be reasonable to continue heparin until anticoagulation status is therapeutic, which is about 8-12 h.**or**
- **B.** If thrombus is visualized, anticoagulate for 3-4 wk with either warfarin (target INR 2-3) or DOAC and recheck transesophageal echocardiogram to confirm thrombus is resolved prior to cardioversion.

3. If emergent indication

Administer heparin (unless contraindicated) to achieve PTT 1.5-2 times control OR, if tolerating oral intake, start DOAC prior to or immediately after cardioversion.

Anticoagulation After Cardioversion

Oral anticoagulation for at least 4 wk with DOAC or warfarin for a target INR 2-3 if no contraindications

DOAC, direct oral anticoagulant; INR, international normalized ratio; LMWH, low-molecular-weight heparin, PTT, partial thromboplastin time.

[a]Includes dabigatran, rivaroxaban, apixaban, and edoxaban.

[b]Limited data support the use of LMWH before or after cardioversion (level of evidence C). The use of LMWH in such clinical situations must be individualized after careful determination of the risks and benefits involved.

6. A 12-lead electrocardiogram (ECG) should be obtained to **confirm the presenting rhythm**, as well as to discern any suggestion of electrolyte abnormality (hypokalemia or hyperkalemia) or drug toxicity (digitalis). If any of these is suspected, appropriate blood levels should be checked. Routine measurement of digoxin levels is not recommended.
7. **Peripheral venous access** should be obtained for elective cases.
8. A good-quality **continuous ECG** should be obtained. Good contact of the electrodes is essential; thus, proper skin preparation, including shaving of the chest hair (if present), is recommended.
9. **Oxygen and airway management** equipment (including suction with suction catheters, bag valve mask, laryngoscope, endotracheal tubes, and pulse oximeter) is required and should be checked prior to the procedure.

B. Technique

1. Once the patient is adequately prepared and an appropriately trained physician is present, **cardioversion patches are placed and the patient is sedated**.
2. **Electrode placement.** Electrode placement on the chest is important to maximize current flow through the heart, which is required to terminate the arrhythmia.
   a. Patches or paddles may be placed in the anteroapical, left anteroposterior, and right parasternal-left paravertebral positions.
   b. Although there is insufficient evidence to recommend a single position for all cardioversion attempts, the right parasternal-left

paravertebral electrode patch position has been associated with better current delivery to both atria and is particularly useful in patients with atrial abnormalities (eg, atrial septal defect and rheumatic valve disease). Therefore, this electrode position is favored in our laboratory for cardioversion of atrial fibrillation (**Figure 59.1**).

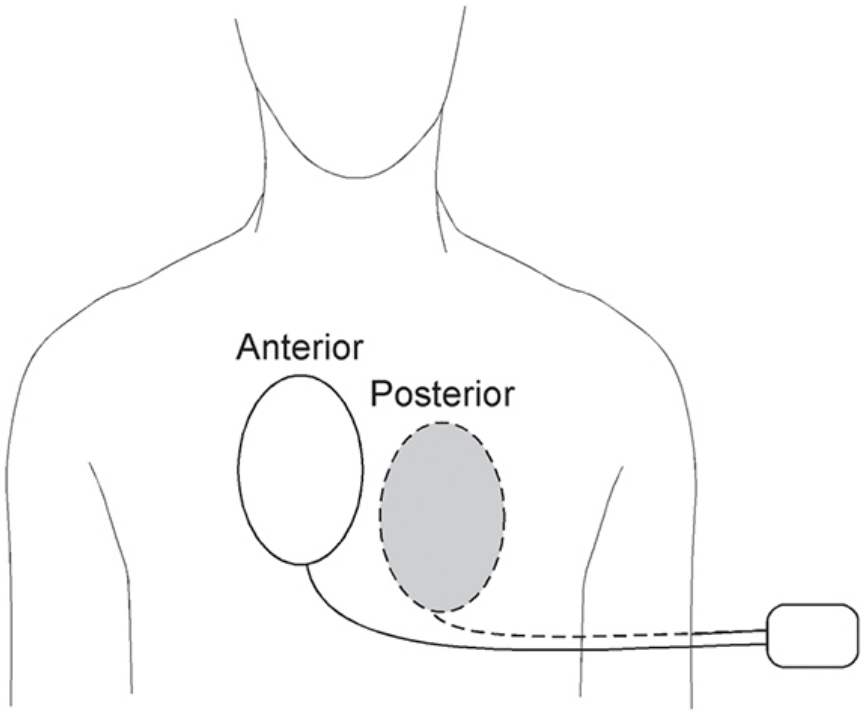

FIGURE 59.1 Right parasternal-left paravertebral electrode patch position.

c. Internal cardioversion (using a right atrial catheter and a coronary sinus catheter as electrodes or using a right atrial and a posteriorly placed external electrode) for cardioverting patients who are morbidly obese or patients who are resistant to external cardioversion is now rarely necessary, given the widespread availability of biphasic cardioversion.

3. Sedation. Short-acting sedatives should be administered before all elective cardioversions in an effort to minimize or even eliminate discomfort. Commonly used agents include methohexital (0.5-0.6 mg/kg body weight), etomidate (0.2-0.6 mg/kg body weight over

30-60 seconds), propofol (0.7-1.2 mg/kg, followed by 0.5 mg/kg every 3-5 minutes as needed), and midazolam (0.5-2 mg over 2 minutes, repeated every 2-3 minutes if necessary). Adequate sedation is confirmed by a lack of response to verbal and pressure stimuli and loss of eyelash reflex. Airway, breathing, and oxygenation should be monitored until the patient makes a complete recovery, and appropriate support is provided as needed.

4. **Energy selection.** The success of cardioversion is dependent on adequate energy delivery to the heart. This, in turn, is dependent on the energy output, current vector, and the transthoracic impedance.

   a. The commonly used energy selection for various arrhythmias is outlined in **Table 59.4**. The energy selected differs between monophasic and biphasic devices.

TABLE 59.4 Initial Energy Selection for Commonly Encountered Arrhythmias

	Energy Output (J)	
Arrhythmia	**Monophasic**	**Biphasic**
Ventricular fibrillation (or unstable ventricular tachycardia)	200	120
Atrial fibrillation	200	100
Atrial flutter	50	50
Supraventricular tachycardia	150	100
Ventricular tachycardia (stable)	100	50-100

   b. Impedance is defined as opposition to electrical flow or current. Higher impedance results in a reduction in current delivery to the myocardium. Therefore, initial energy selection should be individually tailored after consideration of important patient factors such as body habitus and the presence of lung disease, which may affect impedance. All efforts should be made to reduce impedance. A key factor that modulates impedance is electrode size, with optimal size approximating

the size of the heart. Although smaller electrodes increase impedance, larger ones are associated with current wastage. The optimal diameter of an electrode for an adult patient is approximately 8 to 12 cm. Other measures to reduce impedance include application of pressure on the electrodes (approximately 12 kg) during shock delivery, shock during end expiration, better skin-electrode interface and use of conducting gels, and repeat administration of shocks. Conversely, increasing interelectrode distance and interposition of soft tissue or pulmonary parenchyma increases impedance.

5. **Synchronization.** Once the underlying rhythm is confirmed and a good-quality ECG is obtained, the synchronized mode is switched on (except for defibrillation, where the mode must be asynchronous). **Synchronization is essential to prevent delivery of shock during the vulnerable period** (from 80 ms before to 30 ms after the apex of T wave) and prevent resultant ventricular fibrillation. Defibrillators are designed to time the shock to the R wave during synchronization mode. The position of the timing artifact on the R wave is confirmed on the monitor and a printout, because the defibrillator may rarely synchronize with the T wave. Conversely, when defibrillating, the mode must be asynchronous because a lack of identifiable QRS complex prevents a defibrillator in the synchronous mode from discharging.
6. **Delivery of shock.** Once the patient is adequately prepared, the electrodes are adequately positioned, and the appropriate output and mode are selected, the adequacy of sedation should be reconfirmed. The defibrillator capacitors are charged, the ancillary staff are warned to stay clear of the patient, proper synchronization is reconfirmed, and the appropriate shock is delivered. The patient is immediately assessed for adequacy of airway, breathing, and circulation. The ECG is inspected to confirm rhythm, and if sedation is still adequate, the procedure is repeated if necessary. The patient is monitored until complete recovery (generally 1 hour). Anticoagulation and antiarrhythmic medications (if any) must be addressed before discharge. All patients cardioverted for

atrial fibrillation or atrial flutter should be therapeutically anticoagulated for at least the subsequent 4 weeks, regardless of thromboembolic risk due to changes in cardiac conduction and myocardial stunning that occur postcardioversion.

V. COMPLICATIONS OF CARDIOVERSION. Complications after cardioversion are uncommon but include the following.

A. Thromboembolism. About 1% to 2% of patients with atrial fibrillation not anticoagulated before cardioversion develop arterial embolization after the procedure. In appropriately anticoagulated patients, the incidence of embolism is extremely low. In the Assessment of Cardioversion Using Transesophageal Echocardiography trial, comparing anticoagulation for 3 weeks before cardioversion with transesophageal echocardiography (TEE)-guided therapy, the incidence of embolism was 0.5% in the conventional arm and 0.8% in the TEE-guided arm. TEE-guided cardioversion is now widely used in patients who require cardioversion urgently but have not been adequately anticoagulated for 3 weeks.

B. Arrhythmias. It is common for patients to have premature atrial contractions or premature ventricular contractions following cardioversion. Although some patients exhibit transient sinus arrest or atrioventricular block, this is usually self-limited. However, the ability to provide emergent temporary transthoracic pacing should be available for the rare patient who needs it. Malignant ventricular tachyarrhythmias are rare but may occur if the shock is delivered during the vulnerable period due to inappropriate shock synchronization. The risk of malignant tachyarrhythmias is increased in the setting of hypokalemia or digoxin toxicity.

C. Injuries. The incidence and severity of chest wall burns can be reduced by the use of conductive gel, good skin and electrode contact, and the lowest effective energy output.

D. Airway compromise. Excessive sedation may be associated with respiratory depression. This is more likely in the older patients or those with hepatic or renal dysfunction. Appropriate adjustment of

medications and monitoring of airway and oxygenation until complete recovery will minimize any undue effects of excessive sedation.

E. Myocardial depression. Cardioversion is a safe procedure with a wide margin of safety. Transient ST-segment elevation without apparent myocardial damage and minor elevations in creatine kinase myocardial band isoenzyme or troponin I have been reported in rare instances. Rarely, patients have developed pulmonary edema after direct current cardioversion.

F. Injuries to the operator. Injuries to the operator are rare, with an incidence <1 in 1,700 in one series. Most are minor electrical injuries and manifest as extremity paresthesias. Major electrocution is extremely rare, and the reported cases have all been associated with equipment malfunction. Cardioversion in the presence of wet skin or nitroglycerin ointment can lead to arcing and may present a fire hazard.

VI. TROUBLESHOOTING

A. Monitor does not work. This is usually related to a mechanical problem. The power source, lead connections, and monitor lead electrode patches should be checked.

B. Timing artifact falls on T wave. The monitoring lead should be changed, and the correct position of the timing artifact confirmed prior to cardioversion.

C. Capacitor does not discharge. When operating in the synchronized mode, the capacitor will not discharge until it recognizes a synchronized QRS. The switch should be pressed until the capacitor discharges. If this method fails, the monitoring lead should be changed and cardioversion attempted again.

D. Unsuccessful cardioversion.

1. The first step should be to repeat the ECG to check the underlying rhythm and confirm the diagnosis in order to differentiate between failure to cardiovert and successful cardioversion followed by recurrence of the presenting arrhythmia.

2. For patients who truly fail to cardiovert, a repeat attempt using a higher energy level may be considered. A biphasic device should be used, if available, and all possible measures to reduce impedance applied.
3. Another option for patients who truly fail to cardiovert is to reposition the patches for improved myocardial capture. If not done initially, application of pressure on the electrodes (approximately 12 kg) during shock delivery can improve contact and decrease impedance.
4. Unsuccessful cardioversion may be secondary to a deranged metabolic milieu, and reversible causes (such as electrolyte imbalance or thyrotoxicosis) should be corrected.
5. Patients who are on long-term amiodarone therapy may present with atrial fibrillation as the first manifestation of amiodarone-induced hyperthyroidism, which may, in turn, make cardioversion more difficult.
6. In resistant cases where a biphasic device is unavailable, reversing the polarity of the electrodes with cardioversion at maximal energy, using two defibrillators to increase current, or using internal cardioversion may be an option.
7. The use of appropriate antiarrhythmic drugs may facilitate cardioversion and maintenance of sinus rhythm, and the procedure may be repeated after loading with appropriate drugs. Pretreatment with 1 mg ibutilide has been shown to increase the likelihood of successful cardioversion. Ibutilide administration has been associated with the development of torsade de pointes. At our institution, patients pretreated with ibutilide are also given 1 g of intravenous magnesium sulfate in order to minimize this risk.
8. Predictors of unsuccessful cardioversion in persistent atrial fibrillation include longer atrial fibrillation duration, underlying structural heart disease, left atrial enlargement, and cardiomegaly.

III. SPECIAL SITUATIONS

A. Left atrial appendage occlusion (LAAO). LAAO is a mechanical alternative to anticoagulation in patients with atrial fibrillation/flutter

with elevated thromboembolic risk and elevated bleeding risk or contraindications to anticoagulation. Catheter-based techniques have led to an increasing number of patients with LAAO devices, and cardioversion in these patients is increasingly common. **There is limited evidence to guide management of cardioversion in patients who have undergone LAAO, surgical or percutaneous**. The safety of stopping anticoagulation after LAAO is determined on a case-by-case basis, often with careful analysis of competing thromboembolic and bleeding risks. When anticoagulation can be safely restarted, a standard approach with ≥3 weeks of therapy prior to and 4 weeks of therapy after cardioversion is preferred. Performing at least one TEE in patients not receiving anticoagulation is recommended to assess for device position, absence of device-related thrombus, and peridevice leak prior to performing any cardioversion. If a thrombus is identified, either within the appendage remnant (usually postsurgical closure) or device related, then anticoagulation with resolution of thrombus is advised prior to pursuing cardioversion. Although both device embolization and device rotation after cardioversion have been reported, the overall frequency and risk of these complications appear to be extremely low; however, observational studies are underpowered to adequately demonstrate safety. Larger, randomized controlled trials are necessary to validate the safety of cardioversion after LAAO, especially in the absence of anticoagulation.

B. **Preexisting permanent pacemaker or implantable cardioverter-defibrillator.** Electric current can conduct along the implanted electrode lead and cause myocardial injury. This may manifest as a temporary or permanent increase in stimulation threshold, and, when pronounced, this may manifest as the failure of capture-exit block. This can be avoided by **positioning electrodes away from the device**; therefore, the anteroposterior position is preferred. The device should be interrogated before and after cardioversion.

C. **Pregnancy.** Successful cardioversion has been carried out in all trimesters of pregnancy without ill effects on the mother or the fetus. Fetal heart rate monitoring is recommended during the procedure.

III. SUMMARY. Electrical cardioversion remains a safe, effective, and readily available procedure for terminating tachyarrhythmias. Therapeutic anticoagulation, when necessary, is paramount to maintaining the safety profile of cardioversion. Additional studies investigating the role of anticoagulation and the need for preprocedural and postprocedural imaging when cardioverting patients with a history of LAAO are warranted.

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CHAPTER 60

Right Heart Catheterization

Parth Parikh and Pavan Bhat

I. INTRODUCTION. In 1947, Dexter et al observed that the pressure recorded by a catheter wedged in the pulmonary artery (PA) was similar to the filling pressure in the left ventricle (LV). In 1970, Swan and colleagues reported that PA catheterization could be performed by using a specially designed balloon-tipped catheter. Refinements in catheter technology have allowed right heart catheterization (RHC; also known as PA catheterization, or Swan-Ganz catheterization) to assume its role as an integral diagnostic tool for cardiologists and intensivists. RHC remains the gold standard for hemodynamic monitoring and assessment of cardiac output (CO), and it can be helpful in diagnosing and treating critically ill patients with cardiovascular disease.

Although hemodynamic data obtained from RHC are useful in select patients (see Section II), the routine use of RHC in the broader medical or surgical intensive care unit (ICU) populations has not been shown to be helpful. Large observational studies, small randomized studies, and meta-analyses have demonstrated no benefit in length of hospital stay or survival when RHC is used routinely in any clinical circumstance, including severe heart failure (HF). Illustrating this, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial randomized 433 patients with New York Heart Association (NYHA) class IV HF to therapy guided by either clinical assessment or clinical assessment plus PA catheterization and found there was no difference in the primary end point of survival during the first 6 months after hospitalization.

There was a slight increase in in-hospital adverse events in the PA catheter (PAC) group; however, there were no deaths related to PAC use

and no difference in in-hospital or 30-day mortality. Thus, while most studies of RHC have been limited by selection bias and confounding, the routine use of RHC is discouraged. However, there is consensus that utilization in carefully selected patients may be an essential component of patient care.

II. INDICATIONS AND COMMON USES. See **Table 60.1** for American College of Cardiology (ACC) indications for using PA catheterization.

TABLE 60.1 Common Indications for the Use of Right Heart Catheterization

Heart Failure (HF)
• To differentiate between cardiogenic and noncardiogenic pulmonary edema
• To differentiate between cardiogenic and noncardiogenic shock and to guide its pharmacologic or mechanical support
• To guide therapy in patients with biventricular HF
• To diagnose pericardial tamponade when echocardiography is unavailable or nondiagnostic
• Perioperative management of patients with decompensated HF undergoing high-risk surgery
• To identify reversible PH in patients undergoing heart transplant evaluation
• To identify symptomatic patients who may have elevated filling pressures on exertion with an exercise right heart catheterization
Acute Myocardial Infarction
• To differentiate between cardiogenic and hypovolemic shock
• To guide pharmacologic and/or mechanical support of cardiogenic shock in patients with or without coronary reperfusion therapy
• Short-term guidance of pharmacologic and/or mechanical support in acute mitral regurgitation (MR) before surgery
• To establish severity and for short-term guidance of pharmacologic and/or mechanical support of ventricular septal rupture before surgery

- To guide management of right ventricular infarction that does not respond to intravascular volume expansion, low doses of inotropic drugs, and/or restoration of heart rate and atrioventricular synchrony
- To manage acute pulmonary edema that does not respond to treatment with diuretics, nitroglycerin, other vasodilators, and/or low doses of inotropic drugs

Perioperative Use in Cardiac Surgery

- To determine the etiology of low cardiac output (hypovolemia vs ventricular dysfunction) when examination and echocardiography are inconclusive
- To differentiate between right and left ventricular dysfunction and pericardial tamponade when examination and echocardiography are inconclusive
- To guide management of severe low cardiac output syndrome
- To diagnose and guide management of PH in patients with systemic hypotension and evidence of inadequate organ perfusion

Pulmonary Arterial Hypertension

- To exclude postcapillary (elevated pulmonary capillary wedge pressure) causes of PH
- To diagnose and establish the severity of precapillary (normal pulmonary capillary wedge pressure) PH
- To select and establish the safety and efficacy of long-term vasodilator therapy based on acute hemodynamic response to vasodilator therapy during the procedure
- For hemodynamic assessment before lung transplantation

Advanced HF Therapies

- To evaluate whether the patient would benefit from additional short- or long-term durable mechanical support
- To evaluate candidacy for listing for heart transplant

HF, heart failure; PH, pulmonary hypertension.
Adapted from Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document. Present use of bedside right heart catheterization in patients with cardiac disease. *J Am Coll Cardiol*. 1998;32(3):840-864. Copyright © 1998 American College of Cardiology. With permission.

A. **Acute myocardial infarction (MI)** complicated by hypotension, congestive HF, sinus tachycardia, right ventricular (RV) infarction, or mechanical complications (such as ventricular septal defect [VSD], pericardial tamponade, or acute mitral regurgitation [MR])

B. **Assessment of volume status** in patients in whom physical signs may be unreliable (eg, patients who are morbidly obese or ventilated patients)

C. **Severe LV failure** to guide inotropic, diuretic, and afterload reduction management

D. **Differentiation between various shock states** (eg, cardiogenic, distributive, or hypovolemic) and guidance of therapies

E. **Risk stratification for patients during heart transplant evaluation**

F. **Cardiac tamponade.** Although echocardiography is the diagnostic test of choice, PA catheterization may be used when echocardiography is not readily available or nondiagnostic and the risk or difficulty of pericardiocentesis is high.

G. **Assessment of the level and magnitude of an intracardiac shunt**, especially if echocardiography is nondiagnostic

H. **Differentiation between constrictive and restrictive cardiac physiology**

I. **Severe pulmonary hypertension (PH)** and assessment of pulmonary vasculature response to vasodilatory agents

J. **High-risk cardiac patients during preoperative, intraoperative, and postoperative periods** to monitor volume status and CO

K. **Severe acute respiratory distress syndrome (noncardiogenic pulmonary edema)** during positive end-expiratory pressure trials to assess CO

III. **CONTRAINDICATIONS.** The absolute contraindications to PAC placement are right-sided endocarditis, a mechanical tricuspid or pulmonic valve prosthesis, thrombus or tumor in a right heart chamber, uncooperative patient, and terminal illness for which invasive management is considered futile. Relative contraindications are profound coagulopathy (international normalized ratio >2 or platelet count <20,000-50,000),

bioprosthetic tricuspid or pulmonic valve prosthesis, newly implanted pacemaker or defibrillator (unless fluoroscopic guidance is used), and left bundle branch block (LBBB). The latter is a relative contraindication because local trauma to the functioning right bundle while introducing the PAC may result in complete heart block and hemodynamic instability. **Consequently, temporary pacing should be immediately available when inserting a PAC in patients with preexisting LBBB**. If RHC is essential in patients with thrombocytopenia, coagulopathy, or active anticoagulation, then the use of a micropuncture needle should be considered. Finally, it is advisable to treat pneumothorax/hemothorax of the contralateral lung before proceeding, in the event of an ipsilateral pulmonary injury.

IV. TECHNIQUE

A. Venous introducer/sheath insertion. It is important to obtain informed consent in plain language from the patient before the procedure, addressing the utility and major complications of PA catheterization (**Table 60.2**). Once the procedure is ready to commence, a checklist system should be utilized to ensure safety and success, including a time-out process that confirms "right patient, right procedure, and right site of access." The use of a central line kit is a convenient way to streamline the procedure. The patient should be prepped and draped in a sterile manner from head to toe during the catheter insertion, regardless of the insertion site chosen. Multiple sites can be used for introducer placement; however, **a site that can be readily compressed, such as the internal jugular (IJ) vein, is preferred. Localization and entry into the vein are best performed under ultrasound guidance because an imaging-guided approach decreases procedural complications**. Cannulation of the vein utilizing anatomic landmarks should be considered only when ultrasound guidance is unavailable.

TABLE 60.2 Complications of Right Heart Catheterization

Related to the Introducer
Arterial puncture

Bleeding from insertion site
Pneumothorax
Nerve injury/Horner syndrome
Air embolism
Related to the Catheter Passage
Arrhythmia (PVC, NSVT, VF)
Complete heart block or RBBB
Coiling
Valve trauma PA/RV perforation
Related to the Catheter
Thrombosis
Thrombophlebitis
PA infection bacteremia ± endocarditis
Balloon rupture ± embolization

NSVT, nonsustained ventricular tachycardia; PA, pulmonary artery; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricular; VF, ventricular fibrillation.

1. The **IJ vein** (**Figure 60.1**) has multiple advantages, including easy compressibility and reduced risk of pneumothorax compared to the subclavian site. The right side is preferred because the venous course from the right IJ, brachiocephalic, and superior vena cava is a direct path to the right atrium (RA). The disadvantages of the IJ vein are the potential for accidental carotid artery puncture and limited neck mobility for patients.

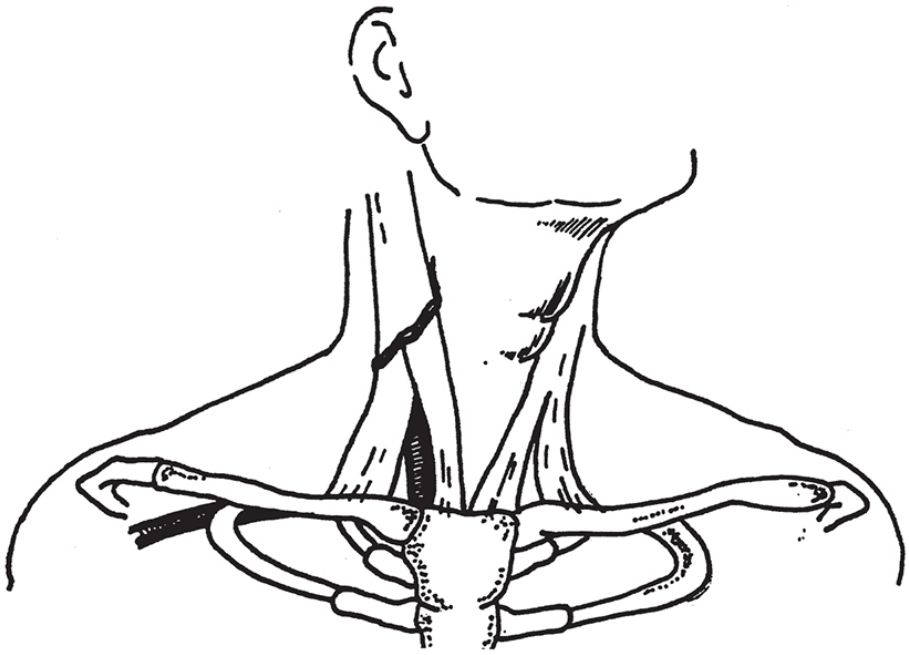


FIGURE 60.1 Neck anatomy.

a. The patient should be placed in Trendelenburg (or flat if unable to recline), as the IJ will enlarge from venous pooling, and access is often easier in this position.

b. The IJ vein can be entered via an anterior or posterior approach. The anterior approach uses the triangle created by the two heads of the sternocleidomastoid muscle and the clavicle.

(1) A finger should be placed on the carotid artery to identify its position and to retract it medially. Approximately 3 to 5 mL of local anesthetic (ie, 1% lidocaine) should be given in the tissue overlying the vein.

(2) The needle should be inserted at the apex of the triangle and advanced in the direction of the ipsilateral nipple at a 45° angle. The vein will usually be entered 3 to 5 cm from the skin surface (this may vary, and ultrasound should be used to guide access).

(3) In cases of difficult access, predisposition to bleeding, or proximity to the carotid artery, a micropuncture needle

should be considered. Conversely, the vein may be located with a finder needle (20G) before using the large-bore catheter (16G) needle.

(4) Once the IJ vein is cannulated, the Seldinger catheter-over-guidewire approach should be used to place the introducer. The guidewire minimizes damage to the vessel and should pass smoothly. Never force the guidewire against any resistance. If difficulty in threading the wire is encountered, reattach the syringe and attempt to aspirate venous blood to ensure that the needle tip is still located in the vessel.

(5) An instructional video on ultrasound-guided IJ vein access is available from the *New England Journal of Medicine* website (see reference) and is a helpful tool for clinicians and students alike.

c. An alternative IJ vein access is the posterior approach.

(1) The advantage of the posterior approach is that it minimizes the risk of carotid artery puncture. First, the external jugular vein is located, and the IJ vein is cannulated 1 cm superior to the point where the external jugular vein crosses the lateral edge of the sternocleidomastoid muscle.

(2) Another posterior approach is to puncture along the posterior edge of the sternocleidomastoid muscle, two finger widths above the clavicle. The needle should be pointing toward the posterior aspect of the upper portion of the manubrium sterni.

(3) The use of ultrasound allows the provider to find the optimal angle for access approach in which the carotid artery is as much to the side of the IJ as possible and not directly beneath.

2. Cannulation of the subclavian vein (see **Figure 60.1**) is associated with greater patient comfort. However, there is an increased risk of pneumothorax and inadvertent subclavian artery

cannulation, especially in patients on mechanical ventilation or with chronic obstructive pulmonary disease.

a. The vein lies just under the clavicle at the insertion site for the clavicular head of the sternocleidomastoid muscle. This is where the vein should be cannulated. The subclavian artery lies just beneath the anterior scalene muscle, which is just below the subclavian vein, with the lung just underneath the artery. For better landmark definition and separation of the vein from the pleura, a rolled-up towel can be placed between the scapulae.

b. There are two approaches to cannulating the subclavian vein: infraclavicular and supraclavicular. The infraclavicular approach is used more frequently.

(1) Infraclavicular approach. The needle is inserted under the clavicle approximately 1 cm lateral to the sternocleidomastoid muscle insertion point. The needle is then advanced horizontally, nearly parallel to the clavicle, toward the suprasternal notch.

(2) Supraclavicular approach. The vein is entered from above. The sternocleidomastoid muscle and the clavicle form an angle, and the needle is inserted at this point at a 45° angle. The vein should be cannulated no deeper than 2 cm below the skin surface.

c. If there is uncertainty on whether an artery or a vein has been cannulated, transduce pressure through the needle or obtain a blood gas sample to differentiate the vein from the artery before dilatation.

d. An instructional video is available from the *New England Journal of Medicine* website (see reference).

(1) The **femoral vein** may also be used for PA catheterization, with the advantages being ease of cannulation, easy compressibility, and the absence of pneumothorax risk.

(a) Palpate the femoral artery pulse at the level of the inguinal ligament. The femoral vein is usually located

2 cm medial to and 2 cm below the femoral artery. In some patients, the vein may lie closer to the artery. Sometimes, the Valsalva maneuver may make it easier to access the vein.

(b) Unfortunately, there is a high risk of bloodstream infection, associated with central venous access from femoral veins. It is recommended in the Centers for Disease Control and Prevention guidelines for the prevention of intravascular catheter-related infection that it not be used routinely for central venous access.

(2) As an alternative access route, the **right median cubital vein** or **basilic veins** can be considered.

(a) Access is usually obtained through the typical placement of a peripheral intravenous (IV) in the median cubital vein, or via the basilic vein. Access is then upsized to a 5-French sheath in a sterile manner. In the antecubital approach, a smaller pediatric PAC is utilized, given the small size of the peripheral veins.

(b) Placement may be technically more challenging because of venospasm. Further, the basilic, axillary, subclavian, and brachiocephalic veins must be navigated prior to reaching the RA, and this course may be tortuous. As such, the antecubital route is typically reserved for PA catheterization when the line is not intended to stay in place following the procedure, or for patients who have failed other access routes.

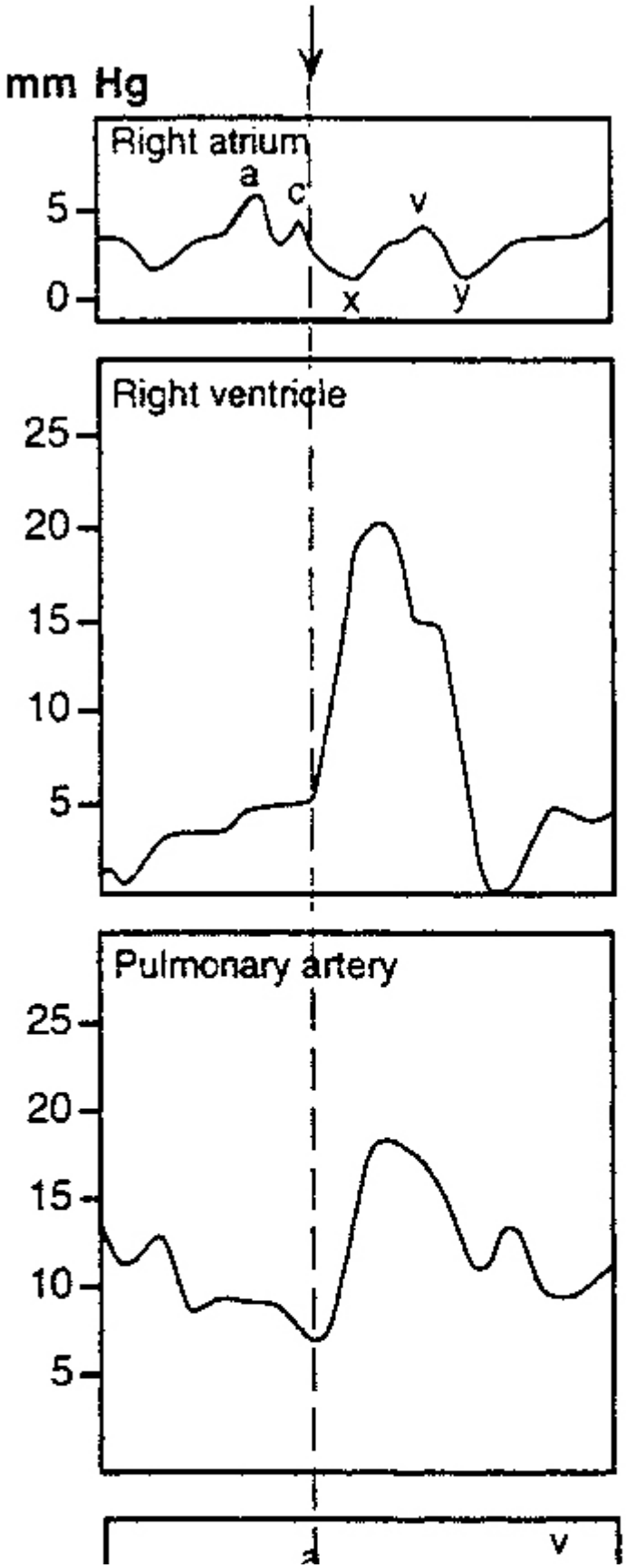
B. PAC insertion

1. After the introducer/sheath is placed and secured, the PAC can be inserted. Always test balloon inflation, flush the ports, and make sure the catheter is properly calibrated before beginning the procedure. After the PAC is tested, insert it through the protective sterile covering and then through the introducer. Keep the balloon deflated at this stage.

a. Ideally, **fluoroscopy and pressure waveforms should be used during PAC insertion for guidance**. The catheter should advance easily; if not, do not force the catheter, but make sure the introducer is properly positioned and flushed.

b. Once the catheter has been inserted 15 to 20 cm or after the RA tracing is seen, **inflate the balloon**.

c. Advance the catheter with the balloon up across the tricuspid valve. This may require turning the catheter clockwise as it is advanced. The RV tracing is visualized next, followed by the PA tracing, and, finally, the pulmonary capillary wedge pressure (PCWP) tracing (**Figure 60.2**).


mm Hg
Right atrium
a
c
v
x
y
5
0
Right ventricle
25
20
15
10
5
Pulmonary artery
25
20
15
10
5
v

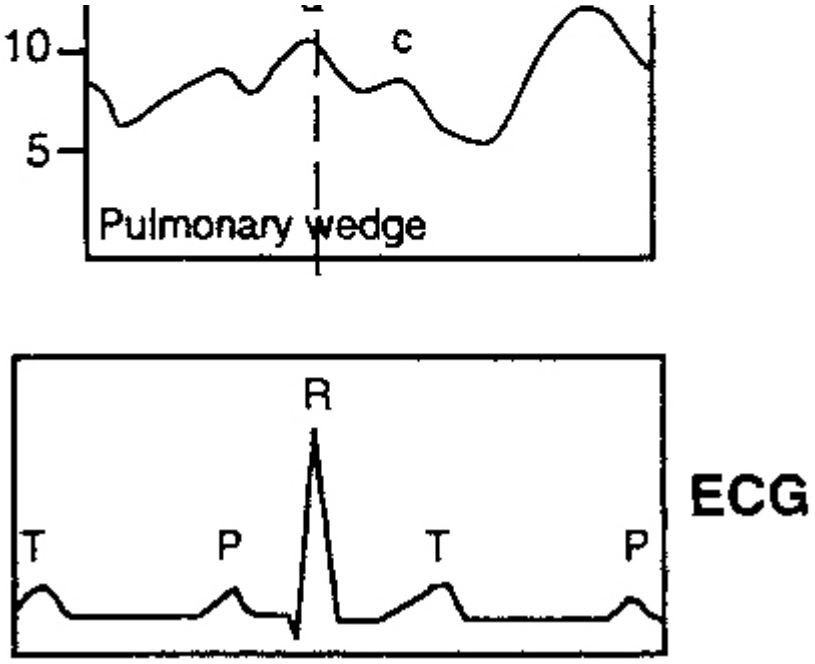


FIGURE 60.2 Waveforms. ECG, electrocardiogram.

d. Not infrequently, the RV tracing is accompanied by a few premature ventricular ectopic beats. Sometimes, ensuring that the balloon is inflated while in the RV may be useful to decrease the frequency of premature ventricular contractions (PVCs). In general, the PA tracing should be reached within 50 to 55 cm if the catheter is inserted from the IJ vein or subclavian vein or 65 to 70 cm if via a femoral or an arm approach. If the PA tracing has not been visualized by this point, the catheter is likely coiled in the RV. The balloon should be deflated and the catheter withdrawn. The process is repeated until proper placement is achieved.

e. Once the PCWP tracing is obtained, deflate the balloon and reobtain the wedge pressure by inflating the balloon with 1.5 cm^3 of air. If the PCWP tracing is obtained even when the balloon is deflated or with <1.5 cm^3 of air, the catheter has been advanced too far and needs to be pulled back. The pressure waveform should always be closely monitored when inflating balloon-tipped catheters to immediately identify this "overwedging." The likelihood of PA rupture and infarction

increases when catheters are overwedged. In general, wedging the catheter should be avoided in patients with severe PH.

2. It is easiest to float the catheter from the right IJ vein or subclavian vein. From the femoral veins, it is typically more difficult, **especially in patients with significant tricuspid regurgitation, RA, or RV enlargement**. Often, the femoral PAC needs to be inserted under fluoroscopic guidance and rotated in a continuous and clockwise motion, with the catheter tip resting just distal to the tricuspid valve until it begins to point upward. Forward motion is then applied to move the catheter into the PA. Alternatively, an S-shaped femoral Swan can be used. When using fluoroscopy, the camera should be in the anteroposterior position, and the balloon should be inflated under fluoroscopy.
3. Finally, check the catheter placement and check for pneumothorax after the procedure by obtaining a chest x-ray film. Catheter placement may be difficult in patients with low CO, severe tricuspid regurgitation, PH, or a dilated RA or RV.
4. Catheter advancement may be facilitated by a deep inspiration or, in more difficult cases, by a guidewire with a 0.021-in diameter (a "Swan wire"). The wire can be placed inside the distal lumen of the catheter, improving the stiffness and making the catheter easier to manipulate. The distal end of the guidewire should always be under manual control, and a hemostat can be placed on the end of the guidewire to ensure this.

V. COMPLICATIONS. See **Table 60.2**.

VI. TROUBLESHOOTING. See **Table 60.3**.

TABLE 60.3 Troubleshooting in Right Heart Catheterization

Problem	Solution
Arrhythmia	Catheter may be in the RVOT. Pull the catheter back or advance forward.
No PCWP tracing	Catheter tip is usually not advanced far enough, balloon has ruptured, or the catheter is coiled in the RV. Use fluoroscopy for

Problem	Solution
	guidance.
Continuous PCWP tracing	Balloon is inflated or the catheter is too far advanced ("overwedged").
Abnormal tracing	Catheter tip is up against a vessel wall or is too far advanced.
Damped tracing	Tubing is kinked, air or thrombus is in the catheter, or catheter tip is up against the vessel wall. Flush and/or withdraw the catheter.
Change in pressure tracing	Improper calibration, change in patient position or catheter location.

PCWP, pulmonary capillary wedge pressure; RV, right ventricle; RVOT, right ventricular outflow tract.

III. WAVEFORMS. See **Figure 60.2**.

A. RA. When interpreting hemodynamic data, it is helpful to align pressure tracings with simultaneous electrocardiography (ECG). RA systole occurs with the *p* wave (atrial depolarization) on the ECG and produces the *a* wave on the RA pressure (RAP) tracing. Atrial relaxation, the *x* descent, occurs with a decline in pressure. Tricuspid valve closure produces a slight upward deflection during the *x* descent, which is known as the *c* wave. The *c* wave follows the *a* wave, occurs within the PR interval, and correlates with RV systole. The *v* wave occurs near the end of the *t* wave on ECG and marks the rise in atrial pressure caused by atrial filling during early diastole. Finally, the *y* descent marks the opening of the tricuspid valve during RV diastole and emptying of the atrium. In the normal RA, the peak *a* wave is greater than the peak *v* wave.

B. RV. RV systole occurs with the QRS complex of the ECG (ventricular depolarization). With ventricular relaxation, the pressure declines and the tricuspid valve opens. During the continuous filling from the RA, a small *a* wave is produced that marks atrial contraction and occurs after the *p* wave and just before the QRS on the ECG. End diastole is the point just after the *a* wave and just before ventricular

contraction. The peak systolic and end-diastolic measurements are used for right ventricular pressures (RVPs).

C. PA. The normal pulmonary arterial pressure (PAP) tracing contains a *v* wave, which corresponds to RV systole and follows the QRS complex. During the relaxation period, pulmonic valve closure produces the incisura, a notch during pressure decline on the *v* wave. The trough of the pressure decline marks end diastole. Pulmonic arterial systolic pressure, end-diastolic pressure, and mean pressure are recorded.

D. The **PCWP tracing** is a transmitted left atrial pressure (LAP) and is considered an approximation for left ventricular end-diastolic pressure (LVEDP), that is, LV preload. The waveforms are similar to an RAP tracing, with the *a* wave corresponding to left atrial (LA) systole, the *x* descent to relaxation, the *v* wave to filling, and the *y* descent to emptying. However, in contrast to the RA, the *v* wave is greater than the *a* wave in the LA, and the *c* wave is not usually seen because of transmission through the pulmonary vasculature.

1. In the nonventilated patient, mean PCWP, the *a* wave, and the *v* wave should be obtained at end expiration—when intrathoracic pressures are equal to the atmospheric pressure (the "peak" of the waveform tracing).
2. In ventilated patients, the PCWP should be obtained at the nadir of the tracing (the "valley").

III. PITFALLS OF THE PULMONARY ARTERY CATHETER. Although the PAC remains the gold standard in monitoring hemodynamics, care should be taken to avoid errors in measurement and interpretation. Clinical decisions based on misleading PAC data may adversely impact the patient outcome.

A. Calibration and referencing. Before the PAC enters the body, it should be flushed to eliminate bubbles and calibrated/zeroed at the level of the patient's midthorax, which approximates the location of the RA, that is, phlebostatic level. Serial hemodynamic measurements should be performed with the reference point moved to match the phlebostatic level, which changes with patient's position.

B. Proper interpretation of PAC data is essential and must be carried out with an understanding of the clinical context.

1. A key to understanding the hemodynamics of PA catheterization is that RAP = RV diastolic pressure in the absence of tricuspid valve pathology and that RV diastolic pressure + 5 mm Hg should approximate PA diastolic pressure in the absence of pulmonic valve disease. Further, PA diastolic pressure = mean LAP (MPAP) in the absence of intrinsic pulmonary arterial or veno-occlusive disease, and LAP = LVEDP in the absence of mitral valve disease.

2. Thus, PCWP is an accurate measurement of LV filling pressure, except in the following circumstances:

a. Pulmonary arterial hypertension (PAH) disease (PCWP > LAP)

b. Mitral stenosis or obstructive LA myxoma (PCWP = LAP > LVEDP)

c. MR (may have large *v* waves on PCWP, which may make the mean PCWP unreliable; LAP > LVEDP)

d. Acute aortic insufficiency or a noncompliant ventricle (LVEDP > LAP)

e. Alterations in pulmonary alveolar and intrathoracic pressures (eg, in respiratory failure with high positive end-expiratory pressure) can also significantly alter the PCWP waveform.

IX. CARDIAC OUTPUT.

CO may be calculated via the **Fick equation** or **thermodilution** method.

A. Calculation of CO using the **Fick equation**:

1. Obtain patient's weight in kilograms.

2. Draw peripheral arterial blood gas to obtain systemic oxygen saturation (Ao_2%).

3. Draw blood gas from the distal lumen of the PAC (Vo_2%).

4. Draw hemoglobin (Hgb).

5. $CO = [Wt \times 3 \text{ mL } O_2/kg]/[(Ao_2\% - Vo_2\%) \times 1.36 \times Hgb \times 10]$

6. Oxygen consumption can be measured from a metabolic hood or a Douglas bag. It can also be estimated as 3 mL O_2/kg.

B. Measurement via **thermodilution** technique may be performed at the bedside but should be avoided in the setting of severe tricuspid regurgitation, intracardiac shunts, existing catheter thrombosis, and low CO.

1. Prefill syringes with 10 mL of room temperature indicator (usually normal saline), then connect the syringe to the distal port of the PAC, which should rest in the RA.
2. Check the position of the catheter. Make sure you can obtain the PCWP tracing with 1.5 cm^3 of air and no less. Then deflate the balloon, and ensure the catheter tip rests in the proximal PA.
3. After properly attaching the tubing to the thermistor, inject the contents of the syringe five separate times. Discard the highest and lowest values, taking the mean measurement of the remaining three values.

X. CLINICAL SCENARIOS.

See **Table 60.4**.

TABLE 60.4 Clinical Scenarios in Right Heart Catheterization

Clinical Scenarios	Data	Tracing
RV infarct	↑RAP, ↓CO, ↓MAP, RAP > PCWP, steep *y* descent, square root sign (morphology in RV tracing diastolic "dip and plateau")	**Figure 60.3**
Acute mitral regurgitation	↑PCWP, prominent *v* wave	**Figure 60.4**
Acute VSD	Oxygen saturation step-up from the RA to PA	
Noncardiac pulmonary edema	Normal to low PCWP, with abnormal chest x-ray	
Massive pulmonary embolism	↓MAP, ↓CO, ↑PAP, normal PCWP	
Pulmonary arterial hypertension (cor pulmonale)	↑RAP, ↑RVP, ↑PAP, prominent *a* and *v* waves, and normal PCWP. PAP and RV systolic pressure may reach systemic levels.	
Tamponade	Diastolic equalization of pressures (RAP = RV diastolic pressure = PCWP) ↑RAP, ↑RVP, ↑PCWP	**Figure 60.5**

Clinical Scenarios	Data	Tracing
	Paradoxical pulse, blunted *y* descent, prominent *x* descent on RA tracing	
Constrictive pericarditis	↑RAP, ↑PCWP, dip and plateau in RVP tracing, M- or W-shaped jugular venous pressure tracing	**Figure 60.6**
Tricuspid regurgitation	↑RAP, ↑RV EDP Blunted *x* descent, prominent *v* wave, steep *y* descent, and ventricularization of RAP	

CO, cardiac output; EDP, end-diastolic pressure; MAP, mean arterial pressure; PA, pulmonary artery; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVP, right ventricular pressure; VSD, ventricular septal defect.

A. Shock (**Table 60.5**). Four classes of shock are characterized: hypovolemic, cardiogenic, distributive, and anaphylactic.

TABLE 60.5 Interpreting Right Heart Catheterization Data in Shock

	MAP	PCWP	CO	SVR
Distributive	Low	Low	High	Low
Cardiogenic	Low	High	Low	High/normal/low
Hypovolemic	Low	Low	Low	High

CO, cardiac output; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

1. **Hypovolemic shock** is due to a profound decrease in venous return and ventricular preload and can be caused by hemorrhage, dehydration, increased positive intrathoracic pressure, and depressed vasomotor tone. Hemodynamic data consist of decreased mean arterial pressure (MAP), CO, and PCWP with increased systemic vascular resistance (SVR).
2. **Cardiogenic shock** results from failure of the cardiac pump to maintain adequate output and can be caused by a change in loading conditions (decrease in preload caused by tamponade or increase in preload caused by VSD), contractility (acute ischemia

or MI), an abrupt increase in afterload, valvular heart disease, or pulmonary embolism.

- **a.** Low MAP and CO but high PCWP and SVR characterize cardiogenic shock caused by LV dysfunction.
- **b.** Contrary to classic teaching, patients in cardiogenic shock from predominant LV failure can have normal to reduced SVR. This drop in SVR in the setting of an MI is most commonly seen after a large anterior wall MI and among the older patients and is likely mediated by profound nitric oxide release in the setting of acute myocardial injury.
- **c.** In general, predominant elevation of RAP is indicative of RV failure, and isolated elevation of the PCWP is indicative of LV failure.

3. **Distributive shock** is caused by profound systemic vasodilation, most often in the setting of infection or systemic inflammation.
   - **a.** The hemodynamic index characteristics of distributive shock are low MAP, PCWP, and SVR, but high CO.
   - **b.** A depressed CO as well as low MAP, PCWP, and SVR can characterize the late phase of distributive shock.
4. **Anaphylactic shock** caused by an allergic reaction causes profound systemic vasodilation. Although there are limited data describing hemodynamics in patients with anaphylactic shock, there appears to be a hyperkinetic phase, characterized by low SVR and high CO, as well as a later hypokinetic phase, dominated by profound hypovolemia with decreased CO.

B. RV failure (**Figure 60.3**; see **Table 60.4**) may be due to RV infarction, severe PH, pulmonary embolism, or increased preload caused by left-to-right intracardiac shunt.

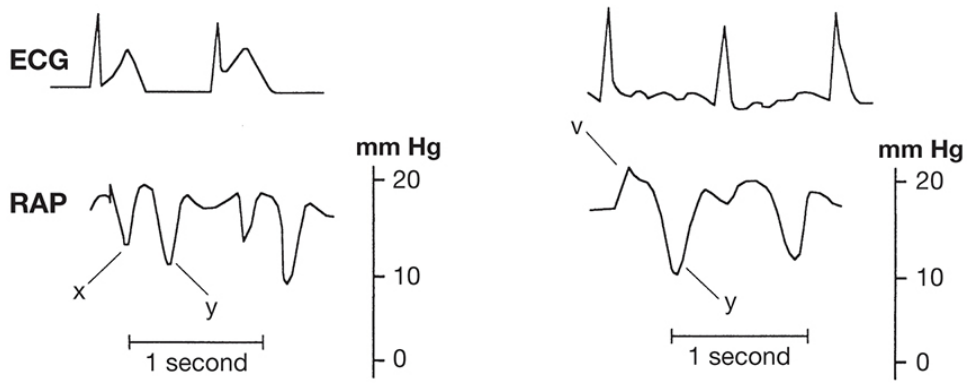


FIGURE 60.3 Right ventricular infarction without tricuspid regurgitation (left); right ventricular infarction with tricuspid regurgitation (right). ECG, electrocardiogram; RAP, right atrial pressure.

1. An RV infarct (see **Figure 60.3**) produces increased RAP and RV end-diastolic pressure, with low CO and MAP.
2. Because the RV dilates and becomes less distensible, a dip-and-plateau pattern on the RVP tracing is seen. On the RAP tracing, there is a steep *y* descent. In the setting of severe tricuspid regurgitation and RV infarction, the dip-and-plateau pattern is lost. A blunted *x* descent, prominent *v* wave, and steep *y* descent are then seen on RAP tracing.

C. Acute MR (**Figure 60.4**; see **Table 60.4**) may be due to papillary muscle dysfunction or rupture.

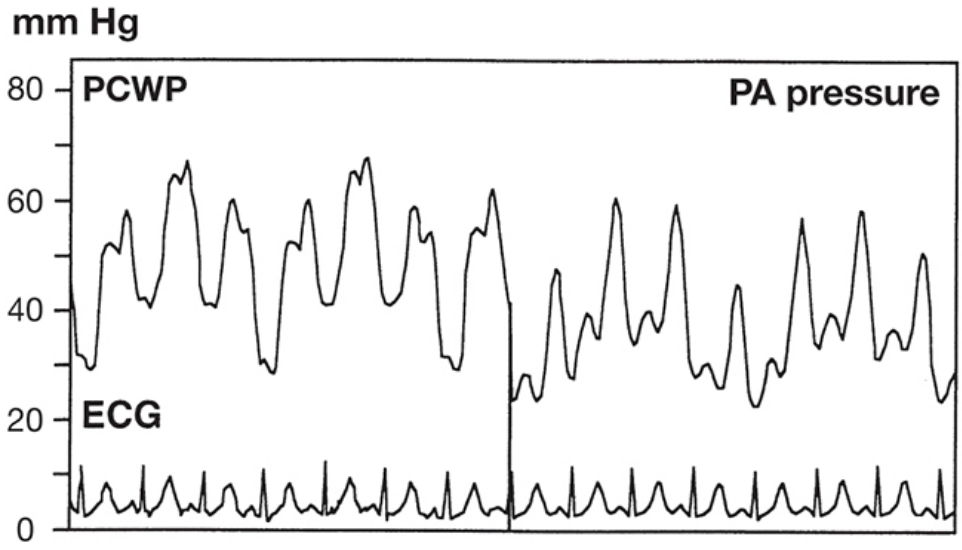


FIGURE 60.4 Acute mitral regurgitation. ECG, electrocardiogram; PA, pulmonary arterial; PCWP, pulmonary capillary wedge pressure.

1. In this setting, the LA is subjected to a sudden increase in pressure. Regurgitation produces a large *v* wave in the PCWP tracing that occurs after the *T* wave on ECG.

   A *v*-wave pressure that is twice the value of PCWP is considered abnormal.

2. In chronic MR, the *v* wave may be modest in amplitude because of chronic atrial dilatation.
3. Other causes of prominent *v* waves are severe tricuspid regurgitation and VSD.

D. Tricuspid regurgitation (see **Table 60.4**). The RA systolic wave may resemble the RV tracing. There is increased RAP and RV end-diastolic pressure, a blunted *x* descent, a prominent "*c*-*v*" wave, and a steep *y* descent on RAP tracing.

E. Cardiac tamponade (**Figure 60.5**; see **Table 60.4**). The hallmark of tamponade is diastolic equalization of pressures, where RAP = RVP = PCWP. The RA waveform is characterized by a deep *x* descent and absent *y* descent (because of the lack of RV filling at the beginning of diastole). In addition, RAP, RVP, and PCWP are increased.

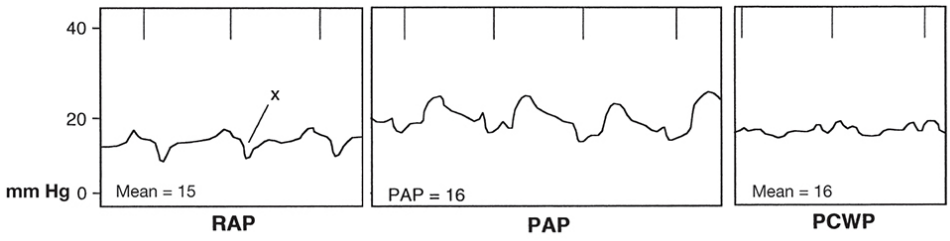


FIGURE 60.5 Cardiac tamponade. PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure.

F. Constrictive pericarditis (**Figure 60.6**; see **Table 60.4**) is characterized by brisk ventricular filling during early diastole and limited ventricular filling during late diastole. The constriction results in the elevation and equalization of RV end-diastolic pressure and LVEDP.

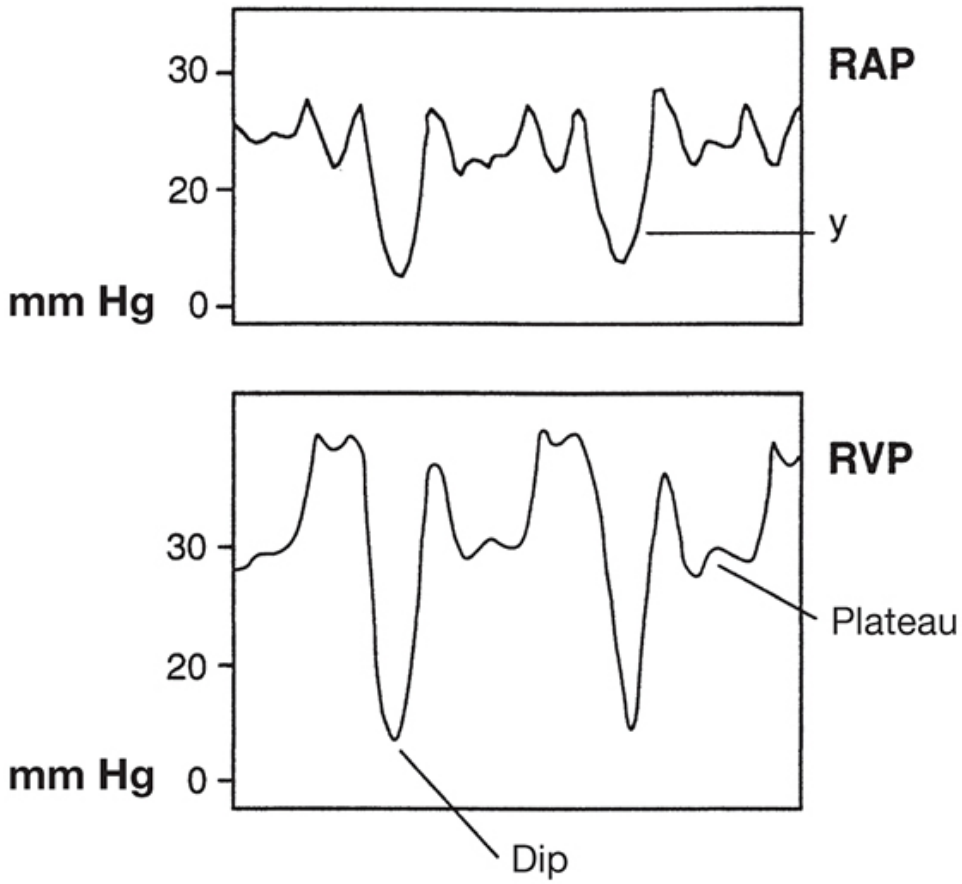


FIGURE 60.6 Constrictive pericarditis. RAP, right atrial pressure; RVP, right ventricular pressure.

1. The dip-and-plateau waveform is seen in constrictive pericarditis as well as restrictive cardiomyopathy, RV infarct, and massive pulmonary embolism.

G. Massive pulmonary embolism (see **Table 60.4**). There is ventricularization of the PA waveform with rapid end-systolic descent and a hardly visible, or absent, dicrotic notch caused by obstruction in the PA.

H. Restrictive cardiomyopathy (**Table 60.6**) includes a heterogeneous group of illnesses, such as hemochromatosis, amyloidosis, and endomyocardial fibrosis. This leads to impaired diastolic filling of the ventricles. There is a prominent *y* descent, but the dip-and-plateau waveform is less pronounced because of a pandiastolic hindrance to ventricular filling.

TABLE 60.6 Differentiating Diastolic Dysfunction

	Constrictive Pericarditis	RV Infarct	Tamponade	Restrictive Cardiomyopathy
Pulsus paradoxus	Rare	Occasional	Frequent	Rare
Right atrial waveforms	Prominent *y* descent	Prominent *y* descent	Prominent *x* descent	Prominent *y* descent
Equalization of diastolic pressures	Frequent	Frequent	Frequent	Rare
Dip and plateau (RV)	Frequent	Frequent	Absent	Frequent

RV, right ventricular.

I. PH (**Table 60.7**; see **Table 60.4**). PH is defined as an MPAP >20 mm Hg at rest. It can be caused by elevated pulmonary venous pressures resulting from LV dysfunction, left-sided valvular disease, and/or

volume overload (ie, elevated PCWP). It may also be caused by intrinsic pathology within the pulmonary arterial bed, that is, PAH.

TABLE 60.7 Definitions of Pulmonary Hypertension Based on Hemodynamics

Type of Pulmonary Hypertension	Right Heart Catheterization Hemodynamics
Pulmonary hypertension	Mean PAP >20 mm Hg
Precapillary pulmonary hypertension	Mean PAP >20 mm Hg PCWP <15 mm Hg PVR >2 Wood units
Isolated postcapillary pulmonary hypertension	Mean PAP >20 mm Hg PCWP >15 mm Hg PVR <2 Wood units
Combined pre- and postcapillary pulmonary hypertension	Mean PAP >20 mm Hg PCWP >15 mm Hg PVR >2 Wood units
Exercise pulmonary hypertension	Mean PAP/CO slope between rest and exercise >3 mm Hg/L/min

CO, cardiac output; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

1. PAH is defined as MPAP >20 mm Hg at rest with PCWP <15 mm Hg in addition to a pulmonary vascular resistance (PVR) >2 Wood units. Compensatory changes in the right heart to chronic PH or PAH result in elevations in RVP and PAP with prominent *a* and *v* waves.

J. Advanced HF evaluation. RHC is extremely important in patients who are undergoing advanced HF therapy workup. World Health Organization (WHO) Group II PH may result from left-sided heart disease and chronically elevated LVEDP, and if the pulmonary pressures remain chronically elevated, then it may lead to irreversible RV failure as well. This would become relevant as these patients may not be ideal candidates for heart transplant, as the RV from the donor heart may not be able to pump against the increased resistance from PA vasculature. Usually, a PA systolic pressure >60 mm Hg and PVR

>5 Wood units, transpulmonary gradient (TPG) >15 to 20 mm Hg are considered to be prohibitive for heart transplantation.

K. Vasodilator challenge. RHC with vasodilator challenge is important to help decide therapy in certain group of patients with PH. The baseline PAPs are obtained after which inhaled nitric oxide (or another vasodilator) is administered and then the pulmonary pressures are remeasured. A drop in the MPAP <40 mm Hg with a decrease by >10 mm Hg compared to baseline with no significant change in the CO/CI (cardiac index) is considered to be a positive response. These patients can be trialed on calcium channel blocker (CCB) for PH. It is important to keep in mind that the relative contraindications to performing a vasodilator challenge test would include left-sided heart disease (eg, aortic stenosis), elevated PCWP, or recent phosphodiesterase type 5 (PDE5) inhibitor use.

L. Exercise RHC. There are a certain subset of patients who may have dyspnea on exertion with relatively normal hemodynamics at rest and may benefit from an exercise RHC. It would be useful to perform the RHC via IJ or subclavian venous access, which would allow the lower body to be tested with exercise. An MPAP/CO >3 mm Hg/L/min and a PCWP/CO slope <2 mm Hg/L/min suggest an abnormality at the level of the pulmonary vasculature. PCWP/CO slope >2 mm Hg/L/min may suggest that the elevated pulmonary pressures are entirely driven by left-sided elevated filling pressures.

M. LV assist device (LVAD) ramp studies. The combined use of hemodynamics with echocardiography can help optimize the speed in patients with continuous-flow LVAD. The overall goal is to normalize the CO, PCWP, and RAP. Echo helps to ensure that there is no significant aortic insufficiency, MR, and the septum in the midline.

XI. FORMULAS. See **Table 60.8**.

TABLE 60.8 Normal Values and Formulas

Parameter	Formula	Normal Value
RA		0-8 mm Hg

Parameter	Formula	Normal Value
RV		Systolic 15-30 mm Hg Diastolic 0-8 mm Hg
PA		Systolic 15-30 mm Hg Diastolic 3-12 mm Hg Mean 8-20 mm Hg
PCWP	6-12 mm Hg	
CO	Fick equation: [Wt × 3 mL/kg] / [(AO_2% − VO_2%) × 1.36 × Hgb × 10]	4-8 L/min
CI	CO/BSA	2.8-4.2 L/min/m^2
SV	CO/HR	40-120 cm^3/beat
SVR	[(MAP − CVP) × 80] / CO	770-1,500 dynes s/cm^2
PVR	[(PAP − PCWP) × 80] / CO	20-120 dynes s/cm^2
MAP	2/3 Diastolic BP + 1/3 Systolic pressure	70-100 mm Hg
Shunt fraction (Q_p/Q_s)	[AO_2% − VO_2%] / [PVO_2% − PAO_2%]	>2.0 large defect 1.5-2.0 moderate defect

AO_2%, peripheral arterial oxygen saturation; BP, blood pressure; BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; Hgb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; PA, pulmonary artery; PAO_2%, pulmonary artery oxygen saturation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVO_2%, pulmonary vein oxygen saturation often assumed to equal AO_2 in left-to-right shunt; PVR, pulmonary vascular resistance; Q_p, pulmonary flow; Q_s, systemic flow; RA, right atrium; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; VO_2%, mixed venous oxygen saturation; Wt, weight in kilograms.

A. CO by Fick equation in L/min:

$$CO = [Wt \times 3\ mL\ O_2/kg] / [(Ao_2\% - Vo_2\%) \times 1.36 \times Hgb \times 10],$$

where Wt is weight in kilograms, Ao_2% is systemic arterial oxygen saturation, Vo_2% is mixed venous oxygen saturation, and Hgb is hemoglobin concentration.

B. CI in L/min/m^2:

$$CI = CO/BSA,$$

where BSA is body surface area in m^2.

C. Stroke volume (SV) in mL/beat:

$$SV = CO/\text{heart rate}$$

D. PVR in dynes × s/cm^5:

$$PVR = [(MPAP - PCWP) \times 80]/[CO],$$

where PAP is pulmonary arterial pressure and PCWP is pulmonary capillary wedge pressure.

E. SVR in dynes × s/cm^5:

$$SVR = [(MAP - CVP) \times 80] / [CO],$$

where MAP is mean arterial pressure and CVP is central venous pressure (can also substitute RAP for CVP).

F. Estimate of O_2 consumption = 125 mL/min/m^2 = 3 mL O_2/kg

G. O_2 content = (Ao_2% − Vo_2%) × 1.36 × Hgb × 10

H. CO = O_2 consumption/O_2 content

XII. INTRACARDIAC SHUNT. The existence of an intracardiac shunt can be evaluated by using a PAC and performing a saturation "run." Blood samples for oximetry are obtained from the PA as well as regions of the RV, RA, superior vena cava, and inferior vena cava. With the catheter positioned in the PA, CO by the Fick equation can be obtained. As the operator manipulates and pulls the catheter back under fluoroscopic and pressure guidance, a blood sample from each location is aspirated. A left-to-right shunt is suggested when a step-up, or increase, in the oxygen saturation in one chamber exceeds the oxygen saturation of a proximal compartment by more than 7% in the case of an atrial shunt or more than 5% in ventricular or great vessel shunts.

In a normal setting, the effective pulmonary blood flow (Q_p) should equal the systemic blood flow (Q_s) (ie, $Q_p/Q_s = 1$). However, with a left-to-right shunt, pulmonary blood flow is equal to systemic blood flow *plus the amount of shunt flow*. Conversely, in a right-to-left shunt, the effective pulmonary blood flow is decreased by the amount of shunt flow. The shunt fraction is the ratio of pulmonary to systemic flow, denoted by Q_p/Q_s. For an atrial septal defect, the mixed venous oxygen saturation is computed as the sum of 3 times the superior vena cava saturation plus the inferior vena cava oxygen saturation, and the total is divided by 4.

A. Calculation of left-to-right shunt

1. **Shunt fraction = pulmonary flow in L/min (Q_p)/systemic flow in L/min (Q_s)**
2. **Q_p = O_2 consumption / [10 × (PVo_2% − PAo_2%)],**
   where PVo_2% is pulmonary vein oxygen saturation and PAo_2% is pulmonary artery oxygen saturation.
3. **Q_s = O_2 consumption / [10 × (Ao_2% − MVo_2%)],**
   where Ao_2% is peripheral arterial oxygen saturation and MVo_2% is mixed venous oxygen saturation.
4. **Simplified calculation** using saturation only:
   $Q_p/Q_s = (Ao_2\% - MVo_2\%) / (PVo_2\% - PAo_2\%)$
   Important note: A shunt fraction of >1.5 often necessitates shunt closure.

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CHAPTER 61

Endomyocardial Biopsy

Matylda M. Mazur and Andres Carmona Rubio

I. INTRODUCTION. Endomyocardial biopsy (EMB) has evolved over the past 60 years. It is a technique that can be done safely when investigating a specific set of diagnoses and cardiac allograft rejection. Nevertheless, it is not without risk, and its implementation varies widely between centers.

Myocardial biopsies were historically performed surgically until 1958 when Konno and Sakakibara introduced a percutaneous EMB. Their technique was based on the use of a flexible bioptome with sharpened cusps, which allowed a biopsy by a pinching rather than a surgical cutting technique. Throughout the years, further modifications of the equipment along with significant progress in EMB sample analysis have resulted in great improvement in the diagnostic accuracy of EMB.

II. INDICATIONS AND CONTRAINDICATIONS. The major current indications for EMB are monitoring for allograft rejection after cardiac transplantation and evaluating for potentially treatable forms of myocarditis. EMB is less routinely used as a diagnostic tool for patients with systolic or diastolic dysfunction because of the availability of accurate noninvasive imaging techniques, such as cardiac magnetic resonance imaging (cMRI). The role of EMB in other disorders, such as arrhythmogenic right ventricular (RV) dysplasia, remains controversial because the risks of the procedure and its diagnostic accuracy must be considered in relation to limited proven effective therapy. The 2022 American Heart Association/American College of Cardiology/Heart Failure Society of America (AHA/ACC/HFSA) Guideline for the Management of Heart Failure not only recommends that EMB be considered in patients with heart failure when a specific diagnosis is suspected that would influence therapy but also concludes that biopsy should not be performed in the

routine evaluation of heart failure. Potential indications and contraindications for EMB are listed in **Tables 61.1** to **61.3**.

TABLE 61.1 Guideline and Consensus Statement Recommendations for EMB

Clinical Scenarios in Which EMB Should Be Considered
Acute cardiac rejection in patients after heart transplantation
Suspected myocardial infiltrative processes (ie, to determine treatment for light chain [AL] amyloidosis or transthyretin amyloidosis)
Rapidly progressive and unexplained cardiomyopathy or active myocarditis, especially if giant cell myocarditis suspected
Rapidly progressive clinical HF or worsening ventricular dysfunction that persists despite appropriate medical treatment
Clinical Scenarios in Which EMB Should NOT Be Considered
Patients with HF should not undergo routine EMB (limited diagnostic yield).

EMB, endomyocardial biopsy; HF, heart failure.
Derived from Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145:e895-e1032.

TABLE 61.2 Conditions Involving the Heart in Which EMB Can Establish the Diagnosis, Listed According to the Availability of Disease-Specific Therapy

Disease-Specific Therapy Available
Cardiac allograft rejection
Cardiac amyloidosis
Giant cell myocarditis
Hypereosinophilic syndrome
Cardiac sarcoidosis
Cardiac hemochromatosis
Lyme carditis
Fabry disease

Disease-Specific Therapy Not Available
Non-giant cell myocarditis
Arrhythmogenic right ventricular dysplasia
Anthracycline toxicity
Glycogen storage disease
Rheumatic carditis
Chagas disease

EMB, endomyocardial biopsy.

TABLE 61.3 Contraindications for EMB

Informed consent not obtained
Patient not cooperative (confused, agitated, etc)
Profound hemodynamic compromise
No cardiac surgery backup available
Coagulopathy (INR >1.5)
Severe tricuspid or aortic stenosis
Mechanical tricuspid or aortic prosthesis
Significant right-to-left shunt (risk of air embolus)
Thinning of myocardium after MI or in case of ARVD
RA or RV thrombus

ARVD, arrhythmogenic right ventricular dysplasia; EMB, endomyocardial biopsy; INR, international normalized ratio; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

III. IMAGING MODALITIES. Most centers perform EMB under fluoroscopic guidance, in a cardiac catheterization laboratory. Pre- and intraprocedural imaging techniques including real-time three-dimensional (3D) echocardiography, computed tomography, positron emission tomography (PET), and cMRI enable high-accuracy targeted EMB. In addition, intracardiac echocardiography, although used seldom, can be useful when attempting to biopsy cardiac tumors.

IV. PATIENT PREPARATION.

As with any other procedure, extensive patient education and informed consent are necessary before starting the procedure. Patients undergoing EMB should be informed that there is a very small chance (1% in experienced hands) of cardiac perforation, with potential urgent cardiovascular surgery and even death as a consequence.

Sedation is rarely needed but may help patients who are anxious to better tolerate the procedure. Monitoring of heart rate by continuous electrocardiographic telemetry, noninvasive blood pressure, and pulse oximetry is essential throughout the procedure. To reduce the risk of bleeding, an international normalized ratio (INR) is recommended to be ≤1.5 to 1.8 and the platelet of $\geq 50 \times 10^9$/L. The patient should be monitored for 2 to 4 hours after the procedure, as myocardial perforation with subsequent pericardial effusion may be delayed after EMB. The patient is placed in a supine position. Venous access is obtained through the internal jugular (most common), subclavian, brachial, or femoral veins. Ultrasound guidance and maneuvers to increase central venous pressure such as Valsalva, leg elevation with a wedge, and Trendelenburg position are helpful in obtaining venous access. Most centers use fluoroscopy as the imaging method of choice to guide EMB. However, echocardiography can also be used (either alone or concomitantly), particularly when radiation exposure needs to be minimized, such as in pregnant women.

V. EQUIPMENT

A. Sheath. Venous access is obtained using the Seldinger technique, and the sheath is always placed over a guidewire so as not to damage any vascular structures. A standard short sheath (11 cm, 7F, or 8F) is generally sufficient for the right internal jugular or any subclavian approach. The intermediate length sheath (24 or 35 cm) may be helpful to reduce venous angulation or to avoid damaging the vessel wall or a suture line when inserting the bioptome in patients with prior heart transplantation. For the left internal jugular approach, a longer sheath (40 cm, 7F) is used with a single- or double-curved tip based on operator preference and venous and cardiac anatomy. For a

femoral approach, a curved 7F, 85-cm-long transseptal sheath is used, because it can be easily positioned into the RV cavity.

B. Bioptome. There are two basic types of bioptomes: (1) independent and stiff, which does not require a long sheath but does rely on the operator's skill to be maneuvered safely into the RV, and (2) flexible, which requires a longer sheath advanced into the RV for positioning. Both resterilizable and disposable bioptomes are available. For internal jugular, brachial, and subclavian approaches, 50-cm bioptomes are used, whereas for femoral access, the bioptomes used are longer (up to 105 cm).

VI. TECHNIQUE. RV EMBs can be performed from either the right or left internal jugular, subclavian, brachial, or femoral veins. If necessary, a left ventricular (LV) EMB can be also obtained via the femoral or radial artery approach.

A. RV biopsy

1. Internal jugular vein approach. After standard preparation and local anesthesia, the required landmarks are identified anatomically and confirmed via ultrasound. A pilot puncture with a 22G needle can be made to localize the vein. The internal jugular vein is punctured with an 18G (or smaller) needle, preferably under ultrasound guidance, and the sheath is introduced using standard technique. The bioptome, with jaws closed and tip straightened, is advanced through the sheath under fluoroscopic and/or echocardiographic guidance across the atrial suture line (in allografts) until its tip lies against the lower third of the lateral right atrial wall. It is then rotated gently counterclockwise and simultaneously advanced into the RV cavity. During this procedure, the tip is gently unstraightened. Rotation is continued until the catheter reaches the apical half of the RV and the handle clamp points in the posterior direction. At this point, the tip of the bioptome rests on the interventricular septum. The position is confirmed by the inability to further advance the bioptome, the generation of premature ventricular contractions, and fluoroscopic appearance. Generation of premature atrial contractions or absence

of ventricular ectopy may indicate that the bioptome was advanced in the right atrium or the coronary sinus. If a long sheath reaching the RV is used and there is any doubt about its position, the bioptome can be withdrawn and the sheath can be connected to a pressure line to ascertain the correct position. This technique is useful, especially in patients with significantly dilated atria. Once in the desired position, the bioptome is withdrawn about 0.5 to 1 cm, the jaws are opened, and the bioptome is advanced again. When it touches the endocardium, the jaws are closed and the bioptome is gently withdrawn with its jaws closed under continuous fluoroscopic guidance. A small tug is often felt while withdrawing, but excessive tugging and multiple premature ventricular contractions should prompt consideration of repositioning. Usually, four to six biopsy specimens are obtained in different areas of the septum to reduce sampling error. Once the procedure is completed, the venous sheath is removed and hemostasis is achieved, usually by manual pressure.

2. **Femoral vein approach.** After standard preparation and local anesthesia, the required landmarks are identified anatomically and confirmed via ultrasound. The right (more common) or the left femoral vein is punctured with an 18G (Cook) needle, preferably under ultrasound guidance, and a 0.038-in. guidewire is advanced up to the right atrium. A long (85-cm) 7F sheath with a dilator is advanced over the wire, and on entering the right atrium, the dilator is withdrawn. The tricuspid valve is crossed with the help of the guidewire (a balloon-tipped catheter can also be used), and the sheath is advanced into the RV cavity toward the interventricular septum. Pressure tracing, the occurrence of ventricular ectopy, and fluoroscopy are used to confirm the position. The side port of the sheath may be connected to a slow continuous intravenous infusion to prevent clot formation inside the sheath, especially if a long procedure is anticipated. A long nonsteerable bioptome is advanced through the sheath and is used to acquire samples. Biopsies are taken in a manner similar to that of the internal jugular vein approach.

3. **Subclavian and brachial vein approach.** After standard preparation and local anesthesia, the required landmarks are identified anatomically and confirmed via ultrasound. The subclavian or brachial vein is punctured using an 18G (or smaller) needle, preferably under ultrasound guidance, followed by insertion of the sheath and the bioptome. The occurrence of ventricular ectopy and fluoroscopic images are used to confirm a position pointing toward the interventricular septum. Biopsies are taken in a manner similar to that of the internal jugular vein approach.

B. **LV biopsy.** While the RV remains a default EMB target site, in circumstances where the LV is predominantly affected or no venous access is available, the LV EMB is a safe alternative. It can be performed via either femoral or radial artery. The latter is associated with fewer vascular complications, earlier ambulation, and lower costs. However, radial artery thrombosis may occur if the inner vessel diameter is small (≤2.5 mm).

1. **Femoral arterial approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. The right (more common) or left femoral artery is punctured with an 18G (Cook) needle preferably under ultrasound guidance, and a short 8F sheath is inserted while a 0.035-in.-long exchange guidewire is advanced up to the ascending aorta. A regular length 7F pigtail catheter is advanced over the wire, and the aortic valve is crossed in a conventional manner. Afterward, the pigtail catheter is removed, while leaving the guidewire in the LV, and exchanged with an 8F long, curved guiding sheath. The tip of this sheath is directed toward the interventricular septum, distal to the mitral apparatus, away from the thinner posterobasal wall. The position of the sheath is carefully reconfirmed by obtaining fluoroscopic images in two angulations and pressure tracings, and 5,000 units of unfractionated heparin are given intravenously before insertion of the bioptome. A long, nonsteerable bioptome is then advanced through the guiding sheath, and biopsy samples are collected in a manner similar to the RV approach. It is important to note that

catheters must be aspirated and flushed after each biopsy because air can enter the sheath and clots can form in the sheath after removing the bioptome. Heparin is not reversed with protamine at the end of the procedure in an effort to minimize thrombus formation at the biopsy sites.

2. **Radial arterial approach.** Transradial LV EMB can be performed using either a standard sheath or a sheathless guide. The latter technique is preferable. Once radial access is obtained, the sheathless guide is mounted on its dilator and subsequently advanced over a 0.035-in. guidewire under fluoroscopic guidance. Once it reaches the ascending aorta, the dilator should be removed. To ascertain the correct positioning of the guide in the mid-cavity of the LV, a pigtail catheter can be used to cross the aortic valve. The position of the guide should be confirmed in the right anterior oblique and left anterior oblique planes. A hemostatic valve should be connected to the guide to allow for frequent bleed back and thorough flushing with saline with the use of a manifold to minimize the risk of air embolism. Subsequently, a 5.5-F 104-cm-long bioptome is advanced through the hemostatic valve and the guide catheter. Biopsies are taken in a manner similar to that of the femoral artery approach. Once the specimens are obtained, a radial hemostatic band should be positioned, the guide catheter removed over the 0.035-in. guidewire, and the hemostatic band secured.

VII. COMPLICATIONS. High-volume institutions were found to have a lower rate of major complications than low-volume centers. In general, EMB can be performed more safely in heart transplant recipients than in patients with native hearts, because of the scarred and thickened pericardium in transplanted patients.

A. **Mortality.** Procedure-related deaths have been reported to be <0.05% in contemporary series.

B. **Cardiac perforation and tamponade.** The reported incidence of cardiac perforation is 0.3% to 0.5%, which can rapidly result in tamponade. The risk can be minimized by careful monitoring of the

catheter position to ensure that biopsies are obtained from the thicker interventricular septum and by gentle catheter advancement and EMB procurement. Symptoms of chest pain during or after the procedure, shortness of breath, a pericardial rub, or altered hemodynamics should suggest potential perforation and should prompt urgent echocardiography to rule out a new pericardial effusion or tamponade. Patients in whom a new pericardial effusion is suspected or detected should be monitored in the hospital for evidence of increasing pericardial effusion or tamponade, and an echocardiogram should be repeated at intervals as necessary and before discharge. In patients early after heart transplantation, the atrial suture line also poses a higher risk of perforation. Very gentle advancement of the bioptome (and pulling back if any resistance is felt) and the use of a longer sheath to pass the suture line if needed will reduce this risk. Patients with suspected perforation should be closely monitored, and echocardiography, fluoroscopy, or cardiac computed tomography can be used to confirm the diagnosis. Emergent pericardiocentesis or cardiac surgery may be necessary if hemodynamic compromise develops. Both cardiac perforation and cardiac tamponade occur more frequently as a result of RV rather than LV EMB.

C. **Thromboembolism.** Right-sided thromboembolism during EMB is possible but does not cause any clinically significant sequelae if it occurs. The risk of arterial embolization during LV EMB is higher, owing to the longer sheath, and may have catastrophic consequences. Using heparin during a left-sided approach, aspirating air and flushing the sheath before inserting the bioptome minimize the risk of embolism.

D. **Arrhythmia.** Occasionally, sustained atrial or, less commonly, ventricular tachycardia is induced by EMB. These arrhythmias are sometimes terminated by touching the wall of the right atrium or RV with the bioptome. Bradyarrhythmic episodes or a bundle branch block induced by EMB is very rare. In heart transplant patients, due to denervation, bradyarrhythmias respond only to direct beta-receptor stimulants, not to atropine.

E. **Tricuspid valve (or mitral valve for LV biopsy) dysfunction.** The bioptome can damage the chordae or papillary muscle and produce significant valvular regurgitation. The risk of this complication is minimized by careful confirmation of bioptome position before sampling. The cumulative risk of this complication is greater in heart transplant patients because they undergo multiple serial EMB procedures.

F. **Damage to vena cava, coronary sinus, hepatic vein, and coronary arteries.** Gentle advancement of the bioptome, use of a longer sheath, retraction of bioptome whenever resistance is felt, and position confirmation with multiple fluoroscopic views may minimize these complications. Fistula formation from a coronary artery branch to the RV has occurred following EMB but is rarely of clinical significance.

G. **Local complications.** Hematoma, local infection, and injury to the lung (pneumothorax, incidence 0.9%) and nerves (recurrent laryngeal palsy and Horner syndrome) are possible but rare while achieving vascular access. Careful identification of anatomic landmarks under ultrasound guidance reduces the risk of these complications.

H. **Pain.** The EMB itself is usually painless, but some patients experience some mild degree of pain when the bioptome touches the heart or when a biopsy is taken.

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SUGGESTED READINGS

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CHAPTER 62

Temporary Mechanical Circulatory Support Devices

Ryan R. Keane, Zachary J. Il'Giovine, Andrew Higgins, and Ran Lee

I. INTRODUCTION. Patients in refractory cardiogenic shock (CS) and with acute coronary syndromes (ACSs) are often beyond pharmacologic intervention and require additional hemodynamic support with temporary mechanical circulatory support (tMCS). Knowledge of the indications and operation of tMCS has become vital to the practice of cardiovascular medicine, especially in the field of cardiac critical care. This chapter provides essential information necessary for the management of patients treated with intra-aortic balloon pump (IABP) counterpulsation, microaxial left ventricular assist devices (LVADs) such as the Impella devices, and extracorporeal membrane oxygenation (ECMO) therapy and briefly reviews other, less commonly used devices in contemporary management.

II. INTRA-AORTIC BALLOON PUMP COUNTERPULSATION. The IABP is inserted percutaneously through either the femoral or axillary artery, with the distal tip resting at the proximal portion of the descending aorta, distal to the branches off the ascending aorta. The IABP functions by inflating during diastole and deflating during systole, providing improved coronary perfusion by augmenting diastolic intra-aortic blood pressure. The principal functions of the IABP are to (1) **support hemodynamics** in individuals with CS and (2) **relieve medically refractory ischemia** in patients with severe coronary artery disease (CAD). The duration of support with IABP therapy is typically short, given the risk for complications with prolonged use, although axillary IABP use has

increased in the advanced heart failure (HF) population for patients awaiting transplant.

A. Indications

1. **CS.** Although there was no mortality benefit in patients with cardiogenic shock secondary to acute myocardial infarction (AMI-CS) who underwent timely percutaneous coronary intervention (PCI) in the SHOCK-IABP trial, the IABP is still a useful tool for improving coronary perfusion and reducing afterload in select patients in AMI-CS and HF-CS.
2. **Refractory angina or ischemia.** Patients with severe unrevascularized CAD with ischemic symptoms or hemodynamic instability refractory to medical therapy may benefit from IABP counterpulsation, particularly in severe left main disease.
3. **Mechanical complications of AMI.** Both **acute mitral regurgitation (MR)** and **ventricular septal rupture (VSR)** are mechanical complications of MI that rapidly progress to CS. An IABP can rapidly stabilize patients by reducing regurgitant volume and subsequent pulmonary edema in acute MR, and by reversing left-to-right shunting and pulmonary edema in a VSR. More recently, devices such as the Impella have also been used to stabilize VSRs, although again evidence is limited and there are limited head-to-head comparisons.
4. **Refractory arrhythmias.** Patients with ischemic cardiomyopathy in refractory **ventricular tachycardia (VT)** may hemodynamically improve with IABP counterpulsation to the point that they can tolerate a more definitive therapy, such as a VT ablation, LVAD, or transplant.
5. **Bridge to advanced therapies.** An IABP improves cardiac output (CO) and lowers filling pressures in patients with dilated and ischemic cardiomyopathy. It can be used for hemodynamic support before cardiac transplantation and is used by some institutions in an off-label axillary configuration to provide hemodynamic support while forgoing the need for bedrest. The 2018 update to the United Network for Organ Sharing (UNOS) allocation system gives listed patients meeting criteria for

hemodynamic CS a status 2 designation, which has led to increased utilization of the IABP in this patient population.

6. **Decompensated severe aortic stenosis (AS).** Small observational studies have demonstrated that IABP support improves hemodynamics in **patients with severe AS with CS.** However, great caution must be taken in patients with severe mixed aortic valve (AV) disease, as mild or moderate aortic regurgitation (AR) can be acutely exacerbated with IABP support.

B. Contraindications

1. **Aortic dissection.** Any type of aortic dissection (type A or type B; acute or chronic) precludes IABP use because of the potential for the balloon catheter to extend the dissection and to worsen ischemia of a peripheral vascular bed that may be involved by the dissection.
2. **Abdominal or thoracic aneurysm.** Using IABP with an abdominal or thoracic aneurysm can precipitate an acute aortic dissection, dislodgement of atheroemboli, or aortic rupture.
3. **Severe peripheral vascular disease.** The majority of the complications of IABP use are caused by vascular insufficiency in the accessed leg because of the **large size of the balloon sheath and catheter. This is especially prevalent in patients with iliofemoral peripheral artery disease (PAD).** In general, most IABP catheters requires an 8F or larger sheath, although there are some 7.5F catheters available.
4. **Descending aortic and peripheral vascular grafts**
   a. **Prosthetic descending aortic grafts and iliofemoral vascular grafts** are relative contraindications to IABP. Consultation with a vascular surgeon is recommended before attempting balloon pump insertion in these patients.
   b. **Iliac artery stents** are not a contraindication to IABP placement. However, passage of the guidewire and balloon catheter through the stent must be performed under direct fluoroscopic guidance.

5. **AR.** By inflating during diastole, the IABP can **worsen aortic insufficiency (AI)** when blood is displaced to the proximal aorta. Whereas severe AI is a contraindication to use, there is no consensus whether moderate AI is an absolute contraindication. Therefore, **careful monitoring** of patients with AI who require IABP support is recommended.
6. **Septic shock.** The afterload reduction caused by deflation in systole can lower the systemic vascular resistance (SVR) and thus **worsen the vasodilatory effects** of distributive shock. There is also a risk of device-associated infection in patients with bacteremia and septic shock.
7. **Coagulopathy or other intolerance to heparin**
    a. The balloon catheter is thrombogenic. Intravenous (IV) heparin is typically given while the IABP is in place to prevent the development of thrombi on the balloon surface. This is especially important at 1:2 or 1:3 inflation-to-beat-ratios where there is prolonged stasis of the balloon catheter itself. Patients with a contraindication to heparin, such as those with prior heparin-induced thrombocytopenia (HIT), can be **anticoagulated with alternative agents**, including direct thrombin inhibitors such as bivalirudin.
    b. In a very high bleeding risk patient, IABP placement is discouraged. However, if an IABP is used, a 1:1 inflation-to-beat ratio should be utilized, because anticoagulation is not absolutely mandated in this situation. A volume-wean strategy can be used to avoid the need for 1:2 or 1:3 ratios, which require anticoagulation.

C. IABP timing, triggering, and hemodynamic effects

1. **Augmented coronary perfusion**
    a. IABP inflation is timed to initiate just prior to the **dicrotic notch**. The IABP thus inflates during diastole and displaces blood to the proximal aorta, **augmenting aortic diastolic pressure** and thus increasing coronary artery perfusion

pressure. The augmentation of coronary perfusion pressure is more dramatic when systemic hypotension is present.

b. Doppler flow studies have suggested that peak coronary flow velocity is increased with IABP support. However, there is no improvement in coronary flow past critical coronary stenoses (unless the obstructions are first relieved with percutaneous revascularization). Also, collateral coronary flow does not increase with IABP support. Thus, with severe, nonrevascularized CAD, IABP relieves ischemia more through decreased left ventricular (LV) wall stress and decreased myocardial oxygen demand by reducing afterload than through increased coronary perfusion.

2. Decreased afterload

a. At the beginning of systole, the IABP rapidly deflates and creates negative pressure in the aorta. This reduces afterload, **reduces aortic end-diastolic pressure**, and improves ejection from the LV. This results in an augmentation of CO of approximately 0.5 to 1 L/min and decreases the mean pulmonary capillary wedge pressure (PCWP) approximately 20%.

b. The hemodynamic benefit of an IABP is a reduction in LV wall stress from decreased filling pressures and decreased afterload, which, in turn, improves stroke volume and CO (**Figures 62.1** and **62.2**).

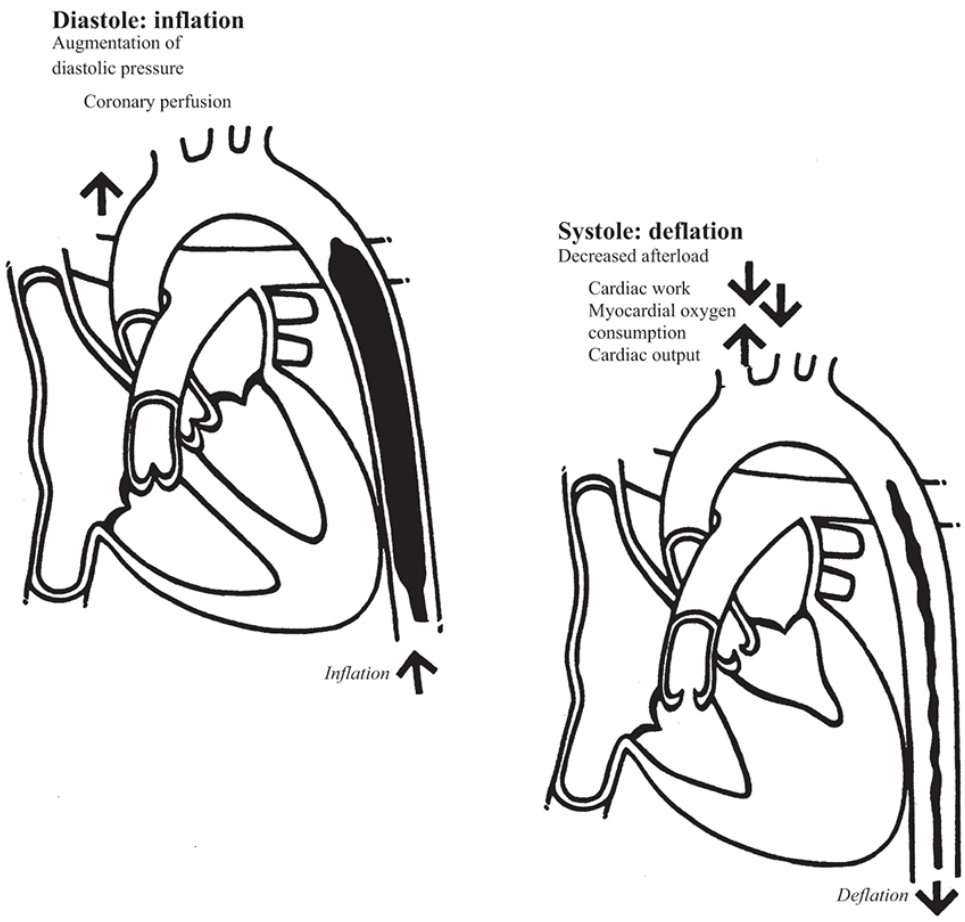


FIGURE 62.1 By inflating during diastole, the intra-aortic balloon pump increases coronary perfusion. Deflation of the balloon at the onset of systole decreases myocardial wall stress and oxygen demand and increases cardiac output. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

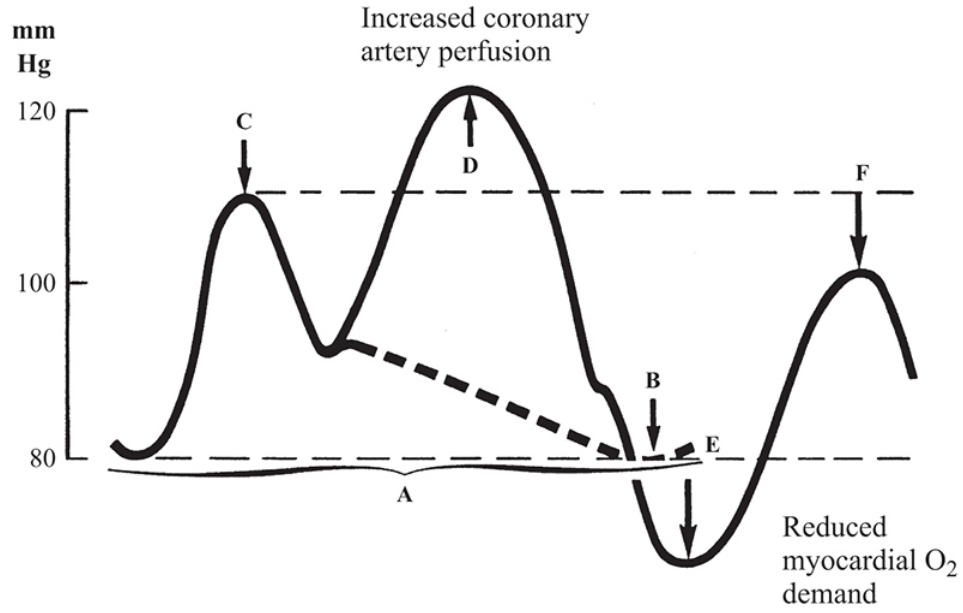


FIGURE 62.2 Proper timing of balloon function occurs when the balloon inflates on the downslope of the systolic pressure waveform and deflates before the onset of the next systolic waveform. The intra-aortic balloon pump inflation in diastole increases diastolic pressure to improve coronary artery perfusion and to increase mean arterial pressure. In addition, aortic end-diastolic pressure is reduced when the balloon deflates in end diastole to lower afterload and myocardial oxygen demand. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

D. IABP timing and triggering

1. **Triggering.** IABP inflation is triggered by either a surface electrocardiogram (ECG), arterial pressure waveform, paced rhythm, or an internal asynchronous mode, in that order of preference.
   a. With ECG gating, **proper IABP inflation** occurs immediately after the T wave such that the balloon inflates at the dicrotic notch (when the AV is closed).

b. For patients with poor surface electrocardiographic tracings, the balloon can be triggered from the central arterial pressure waveform. Pacing spikes can be used to trigger the balloon in patients who are 100% paced.

c. In cardiac arrest or when the other triggering mechanisms are not working correctly, an internal asynchronous mode can be used to trigger the balloon to inflate at a regular interval.

2. **Timing.** Optimal balloon inflation occurs during diastole (right at the dicrotic notch), and optimal deflation occurs prior to the onset of the next systolic waveform. Timing is adjusted by internal algorithms on the IABP console but can be manually adjusted as well. None of the four possible timing issues listed below are optimal, but **early inflation and late deflation** are considered hemodynamically dangerous, whereas late inflation and early deflation will only result in reduced IABP efficacy.

   a. Early inflation occurs when the balloon inflates prior to AV closure, resulting in increased afterload, LV wall stress, and myocardial oxygen demand. It can be corrected by delaying inflation until after the AV closes (**Figure 62.3**).

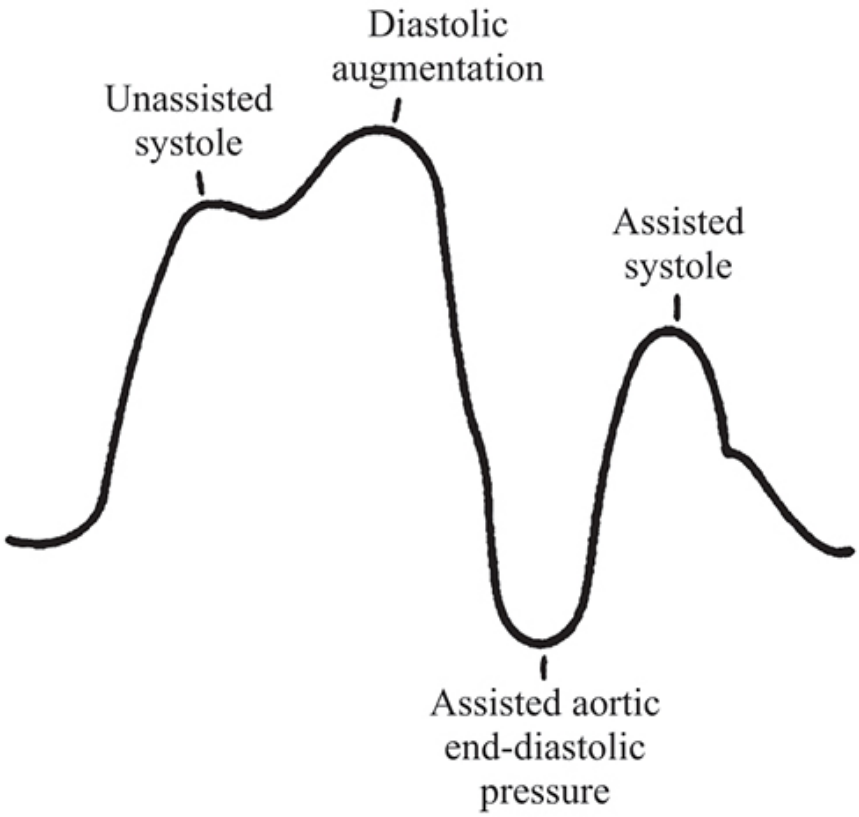


FIGURE 62.3 With early balloon inflation, the aortic valve closes prematurely, and left ventricular wall stress and myocardial oxygen demand are increased. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

b. Late inflation occurs when the balloon inflates too far after the dicrotic notch and AV closure. There is diminished diastolic pressure augmentation and suboptimal coronary perfusion. It is corrected by adjusting inflation to occur just before the dicrotic notch (**Figure 62.4**).

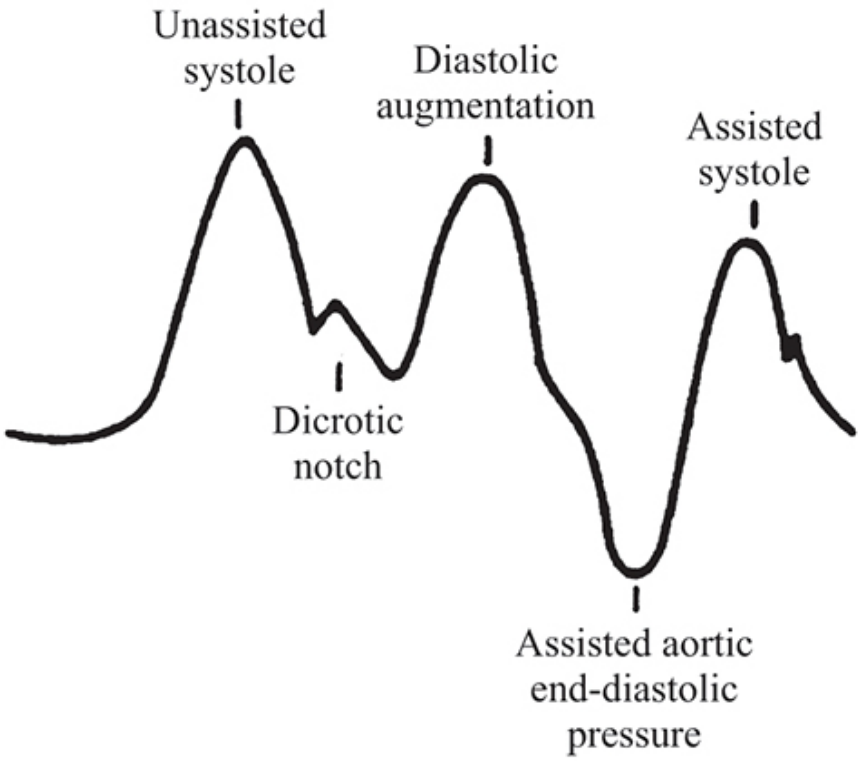


FIGURE 62.4 With late balloon inflation, there is suboptimal augmentation of diastolic aortic pressure and coronary perfusion. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

c. **Early deflation** occurs when balloon deflation occurs prior to isovolumic contraction, resulting in suboptimal diastolic augmentation and coronary perfusion (**Figure 62.5**).

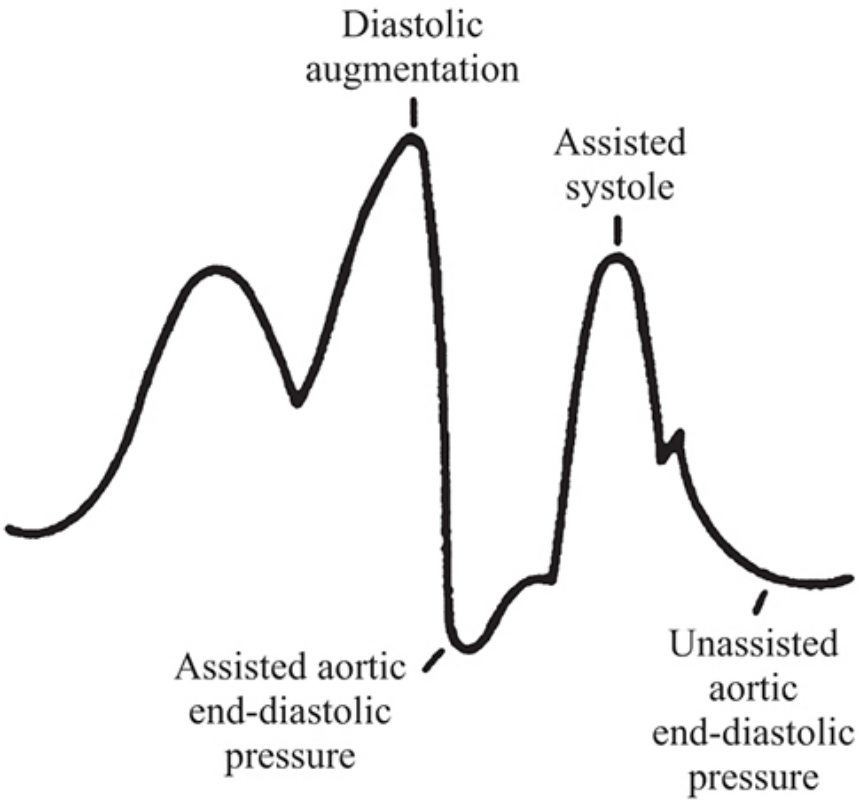


FIGURE 62.5 With early balloon deflation, there is suboptimal augmentation of coronary perfusion and afterload reduction. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

d. Late deflation occurs when balloon deflation occurs during the onset of systole as the AV is opening, resulting in increased afterload and impaired CO and thus increased myocardial oxygen demand (**Figure 62.6**).

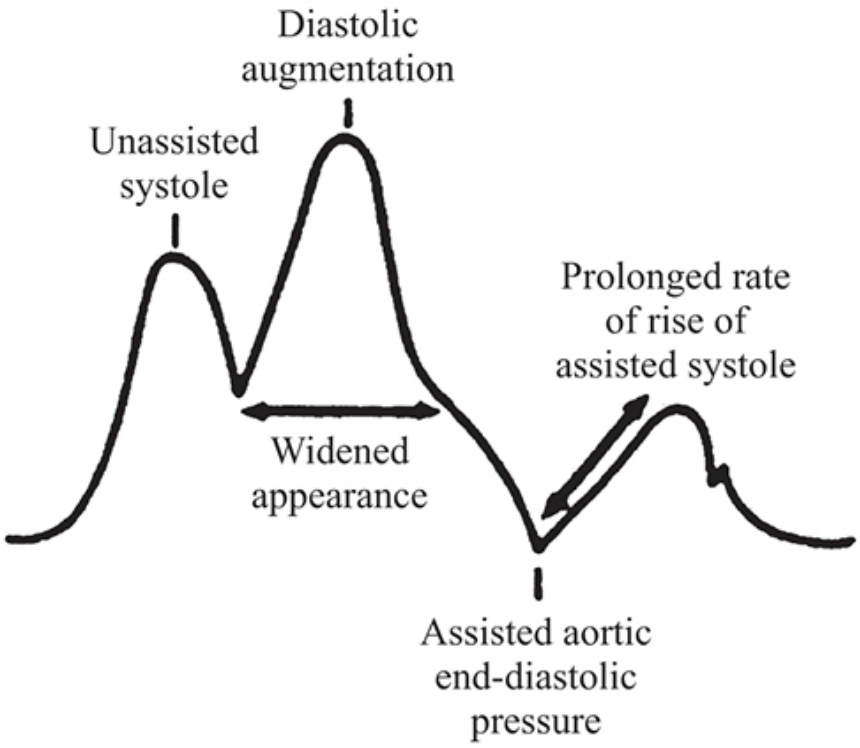


FIGURE 62.6 With late balloon deflation, there is no afterload reduction, and myocardial oxygen consumption is increased. (Courtesy of Datascope Corp. Copyright © 1992 Datascope Corp. All rights reserved.)

e. Tachyarrhythmias make maintaining adequate augmentation challenging, particularly once the heart rate exceeds 150 bpm. With rapid atrial fibrillation, variable systolic pressure waveforms caused by inadequate LV filling and rapid pulse rates make augmentation especially difficult. Adjusting balloon inflation to 1:2 can sometimes improve augmentation with tachyarrhythmias.

E. Technical considerations

1. Specific instructions for IABP insertion should be based on the manufacturer's recommendations and specifications. However, the following is a general description of IABP insertion technique.
2. **Balloon sizing** is based on the patient's height. The following is the recommended size for femoral configurations:
   a. 5 ft 4-in and above: 50 mL

b. 5 ft 0-in to 5 ft 4-in: 40 mL

c. <5 ft 0-in: 34 mL

3. Arterial access is obtained in the selected common femoral artery or axillary artery using the modified Seldinger technique, as well as ultrasound and fluoroscopic guidance for confirmation of needle and wire position. In general, an 8F or 9F introducer sheath is used for femoral access. The larger the sheath size, the easier guiding the 7.5F or 8F balloon catheter to the aortic knob will be, but at a slightly increased risk of vascular complications.
4. The balloon catheter is then flushed and deaired, without removing the wrapping holding the balloon in place.
5. A 0.025-in J-wire is then advanced through the sheath up to the aortic arch using fluoroscopy.
6. The balloon is then unwrapped and quickly loaded onto the catheter and then advanced to 1 cm below the aortic knob, typically at or slightly above the level of the carina. The tip closest to the femoral artery is confirmed under fluoroscopy to be completely out of the sheath.
7. The arterial lumen is then quickly flushed with normal saline and cleared of any excess blood. The helium tubing and ECG leads are then connected to the IABP console, and IABP inflation is initiated.
8. Balloon inflation and position are once again observed for a final time under fluoroscopy.

F. IABP monitoring

1. **Positioning.** A chest x-ray should be obtained immediately postinsertion and then daily and with any manipulation to confirm proper positioning has been maintained.
   a. For femoral IABPs, the patient should be maintained supine (<30°), and a leg brace used to keep the accessed leg still to prevent excessive movement and possible migration.
2. **Anticoagulation.** IV heparin should be started once the procedure is complete if feasible; goal anticoagulation is institution

dependent, but in general, an activated partial thromboplastin time (aPTT) of 50 to 70 seconds is considered therapeutic.

a. There is no robust evidence to support or refute the need for systemic anticoagulation for an IABP at 1:1 augmentation. **However, anticoagulation is mandatory** if the augmentation ratio is 1:2 or 1:3, typically done during weaning attempts.

3. **Laboratory monitoring.** Special attention should be paid to the hemoglobin and platelet count on daily labs to monitor for possible hemolysis (caused by shearing forces from inflation/deflation of the balloon).
4. **Limb perfusion.** Peripheral pulses in the affected limb should be monitored every 6 to 8 hours to ensure adequate perfusion.

G. Troubleshooting console alarms

1. **Loose connections** in either the gas drive line or arterial pressure tubing can cause alarms and are easily reconnected or exchanged.
2. **Poor augmentation** can be evaluated by the following:
   a. Issues with **timing** and **triggering** can be modified as outlined earlier.
   b. Positioning on chest x-ray
   c. The **inflation and deflation** of the balloon can be visualized by direct fluoroscopy to evaluate for **balloon kinking**.
   d. In patients with poor augmentation, despite appropriate placement and timing, should be closely evaluated for a concomitant vasodilatory process, such as **distributive shock.**
   e. In younger patients with high arterial compliance, augmentation may not be effective. This is in part due to the **Windkessel phenomenon,** where the elastance of the aorta dampens fluctuations in systolic and diastolic blood pressure.

H. Complications

1. **Vascular complications** from IABP insertion include limb ischemia, femoral and retroperitoneal hematomas, and access site bleeding. Overall rates of vascular complications are variable in the literature and range from <1% to 30%. Diabetes, female sex,

preexisting peripheral vascular disease, history of smoking, and catheter size are all independent risk factors that are strongly associated with the development of ischemic vascular complications from IABP use.

a. If **limb ischemia** develops in the accessed leg, the balloon catheter and sheath should be removed, and manual hemostasis should be obtained at the access site. Consultation with a vascular surgeon should be obtained for consideration of thrombectomy, bypass, or amputation.

b. **Bleeding** develops in 1% to 5% of patients and is generally treated by the application of manual pressure.

c. **Pseudoaneurysms are rare** but may require surgical repair or percutaneous injection of thrombin.

2. **Infection** is rare but should be considered in a patient who has continuous fever and/or bacteremia. This is particularly important in patients awaiting transplantation who may require prolonged IABP support (>14 days).

3. **Balloon rupture** should be considered if there is any amount of blood seen in the helium tubing.

a. Potential consequences of balloon rupture include helium gas embolism and balloon entrapment, as well as clotting/embolism and hemodynamic compromise.

b. The IABP should be immediately placed on standby and promptly removed to prevent thrombus/embolism and then replaced if still clinically indicated.

I. Weaning and removing the IABP

1. **Weaning** can be accomplished by either reducing the inflation ratio (most common) or reducing the balloon volume (usually used in patients who cannot tolerate anticoagulation). There is no standard practice for weaning an IABP. The following is a generalized protocol for illustration:

a. Anticoagulation must be started prior to switching to 1:2 or 1:3 to mitigate thromboembolic risk.

b. Baseline ECG, symptoms, labs, and invasive hemodynamics should be obtained.

c. The IABP is then switched to 1:2 for 1 to 2 hours and then an ECG, labs, and hemodynamics are rechecked, and the patient is reassessed.

d. If the patient passes this checkpoint, some providers will then switch the IABP to 1:3 for further weaning. Selection of the duration and thoroughness of weaning is largely based on patient selection. A patient with an IABP placed for severe CAD who has been revascularized likely does not need as prolonged of a wean as a patient with chronic HF-CS being titrated to IV afterload-reducing medications.

e. For a volume wean, the balloon volume is generally reduced from 100% to 75% to 50%.

f. If the patient completes the wean successfully, the IABP is switched back to 1:1 (or full volume), and heparin is paused.

2. **Withdrawal of the IABP** can be performed after heparin has been paused for ·4 hours (and/or once aPTT is normalized).

a. The IABP is placed on **standby.**

b. Gas drive line is disconnected.

c. The balloon catheter is then pulled back **until resistance is met.** This is the balloon getting trapped at the distal tip of the arterial sheath.

d. A hand is placed at the site of the arteriotomy site (not the skin puncture site), and the sheath and balloon are then withdrawn together as a single unit.

e. The puncture site is allowed to bleed for 2 beats to evacuate any potential thrombi. Manual pressure is then applied proximal to the puncture site (preferably right at the arteriotomy site) until hemostasis is achieved. A general rule is 3 minutes per French size (so 24 minutes for an 8F sheath).

f. A compressive dressing is then applied.

III. IMPELLA DEVICES. The Impella is a microaxial flow pump based on the principle of an Archimedes screw (**Figure 62.7**) manufactured by Abiomed. The currently approved Impella systems in the United States are the Impella CP and the Impella 5.5 for LV support, as well as the Impella RP/RP Flex for right ventricular (RV) support. For LV devices, the Impella catheter inlet area is placed retrograde across the AV into the mid-LV. A continuous impeller motor pump draws blood out of the LV and ejects it into the ascending aorta through the outlet area (**Figures 62.7** and **62.8**). Similarly, the Impella RP is placed across the tricuspid and pulmonic valve, with its inlet positioned in the vena cava/right atrium (RA) junction and its outlet positioned in the pulmonary artery (PA), thus directly bypassing the RV.

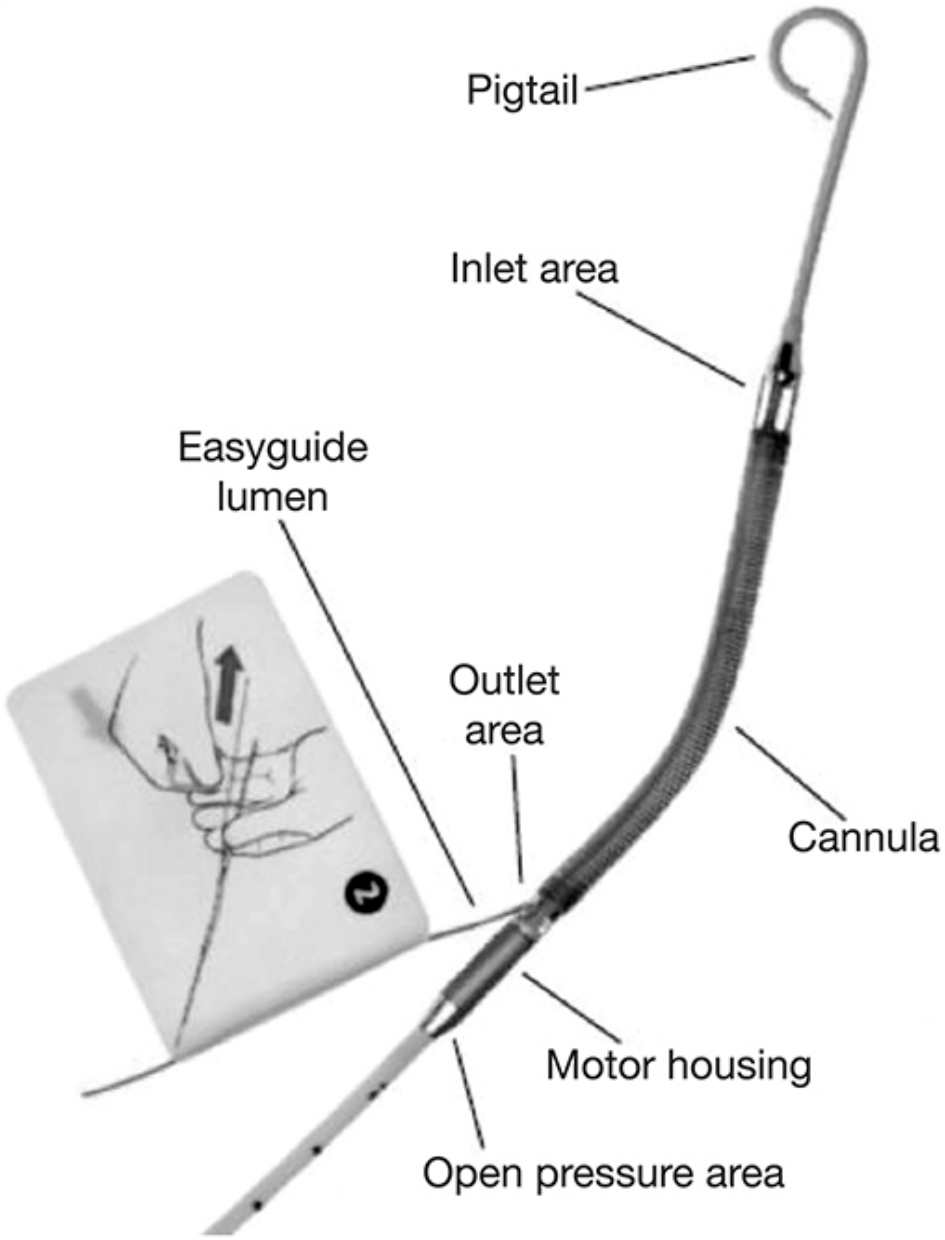


FIGURE 62.7 The Impella 2.5, CP, and 5.0 catheters have several components. The distal-most end is a soft pigtail with a monorail guidewire port (EasyGuide lumen). Blood is sucked through the inlet area distal to the aortic valve and ejected from the outlet area above the valve. The Impella LD and Impella RD have different structures and are not shown. (Image courtesy of Abiomed; used with permission.)

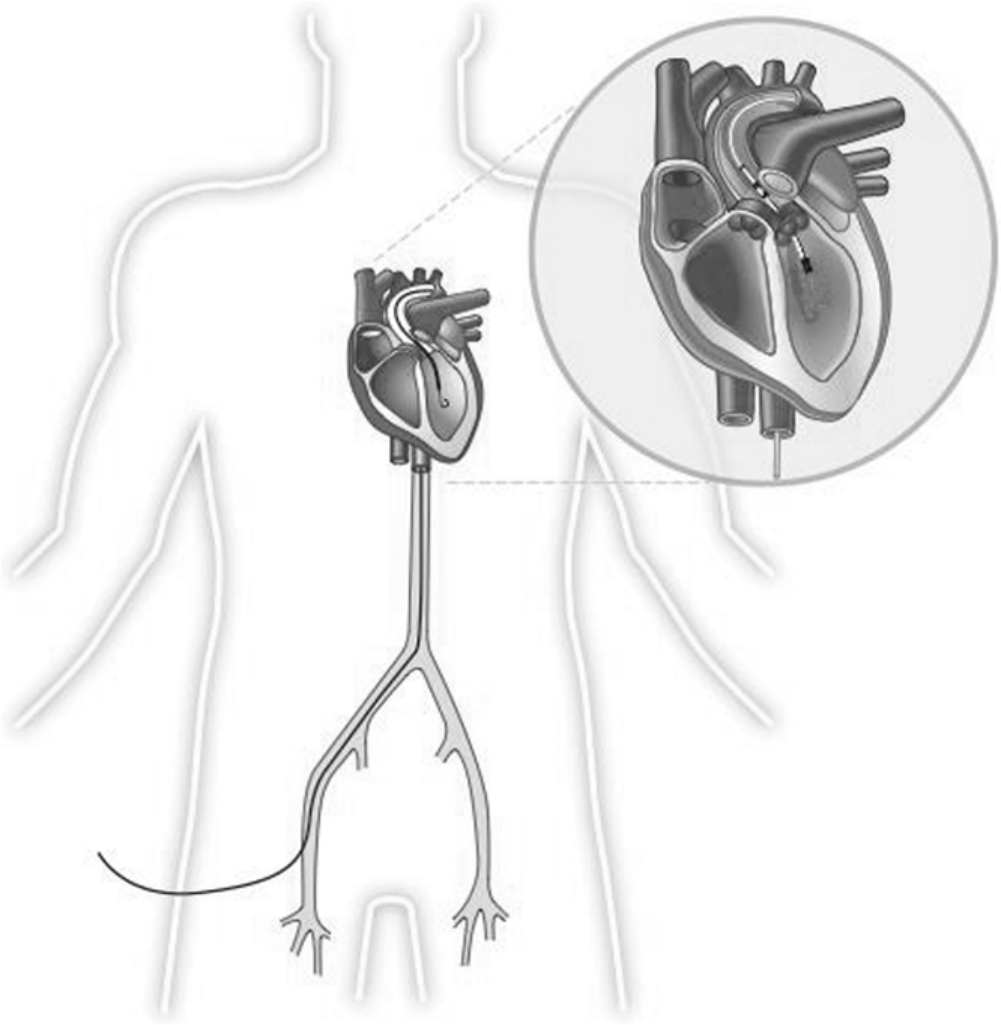


FIGURE 62.8 Impella catheter placement. (Image courtesy of Abiomed; used with permission.)

A. Type of Impella devices

1. **Impella CP** is placed percutaneously via the femoral artery and provides ·2 to 4 L/min of flow. Common applications include LV unloading during PCI and temporary support for CS. The advantages of the Impella CP are that it is easier to place in the cath lab, with drawbacks being a relatively higher risk of hemolysis to achieve high flows, increased potential for distal limb ischemia, as well as decreased mobility due to the mandatory bedrest.

2. The **Impella 5.5** is placed via surgical cutdown in the axillary artery and provides ·5 L/min of flow. The Impella 5.5 is growing in popularity for longer term support for patients in CS, especially among patients bridging to transplant or LVAD. Advantages of the 5.5 system include a relative lower risk of hemolysis to achieve the same or greater flow than the CP, as well as the opportunity for patient mobility, given its axillary insertion. Disadvantages include more difficult access (surgical cutdown by a surgical team) as well as increased bleeding with the cutdown.
3. The **Impella RP** is placed percutaneously in either the femoral vein or the jugular vein (with the newer **RP Flex** system) and affords the option as a temporary RV assist device (RVAD) for patients in isolated RV or biventricular failure.

B. Indications

1. **CS** is by far the most common indication for Impella support. There had been observational data to support its use prior to the DANGER-SHOCK trial in 2024, which demonstrated a mortality benefit to the utilization of Impella CP in patients with AMI-CS, with a concomitant increase in comorbid side effects. In addition, earlier trials evaluated Impella systems that are no longer in use, such as the Impella 2.5 or Impella 5.0, and thus may not accurately reflect contemporary practice. The Impella device allows for both optimal unloading of the LV and improved end-organ perfusion, leading to greatly improved forward flow. It can be a useful tool in improving hemodynamics and end-organ perfusion in appropriate patients.
2. **LV unloading** for patients on venoarterial (VA)-ECMO is an emerging strategy for the Impella device, as discussed in the "**Venoarterial Extracorporeal Oxygenation**" section.
3. **Impella-supported PCI** is another emerging area of interest, namely, with the Impella CP device as it can be inserted in the cath lab. For high-risk PCI, such as left main PCI, the improved flow from the Impella device is thought to provide improved end-organ perfusion in the case of a complication. In AMI-CS or STEMI, LV

unloading prior to PCI may improve outcomes, although this is currently under clinical investigation.

C. Contraindications

1. **Mechanical AV** is a contraindication to the Impella, as the Impella pigtail, inlet, and catheter must be advanced across the AV.
2. **Severe AS** is a relative contraindication to Impella insertion and is advised against for patients with an aortic valve area (AVA) of <1 cm^2.
3. **Moderate or severe AI** is a relative contraindication as Impella insertion will likely worsen regurgitant volumes and may further compromise hemodynamics. For patients with mild or moderate AI who do undergo Impella insertion, serial echocardiography should be performed to closely monitor for worsening AI.
4. **Severe PAD** of the target limb is an absolute contraindication to Impella insertion as this can lead to acute limb ischemia.
5. **Contraindications to anticoagulation** pose a relative contraindication to Impella insertion as systemic anticoagulation is preferred.
6. **LV thrombus** is an absolute contraindication to placement as the risk of embolization in the device and/or into the systemic circulation is prohibitively high.

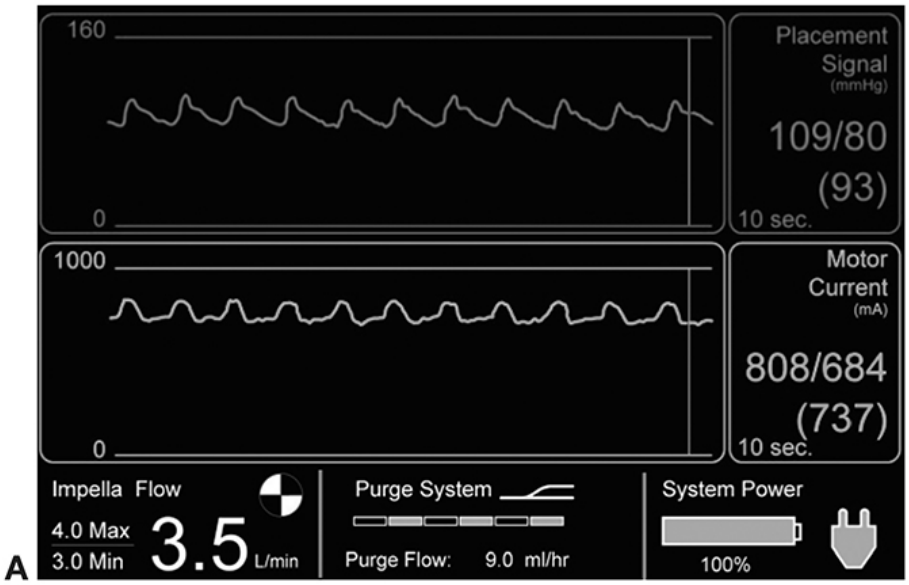
D. Hemodynamic effects

1. The Impella primarily provides a **reduction in left ventricular end-diastolic pressure (LVEDP)** and **improved CO** by emptying the LV and ejecting blood into the aorta and thus the systemic circuit.
2. Because it is ejecting blood into the aorta, the flow provided by the Impella is **afterload sensitive**, just like the LV. In patients supported by an Impella in CS, but with some degree of LV recovery, afterload reducing agents such as nitroprusside or short-acting oral agents can be started to allow continued forward flow and to provide a mechanism for weaning the Impella.
3. In addition, as the Impella primarily functions by **reducing LV preload**, the flow provided by the Impella is also somewhat

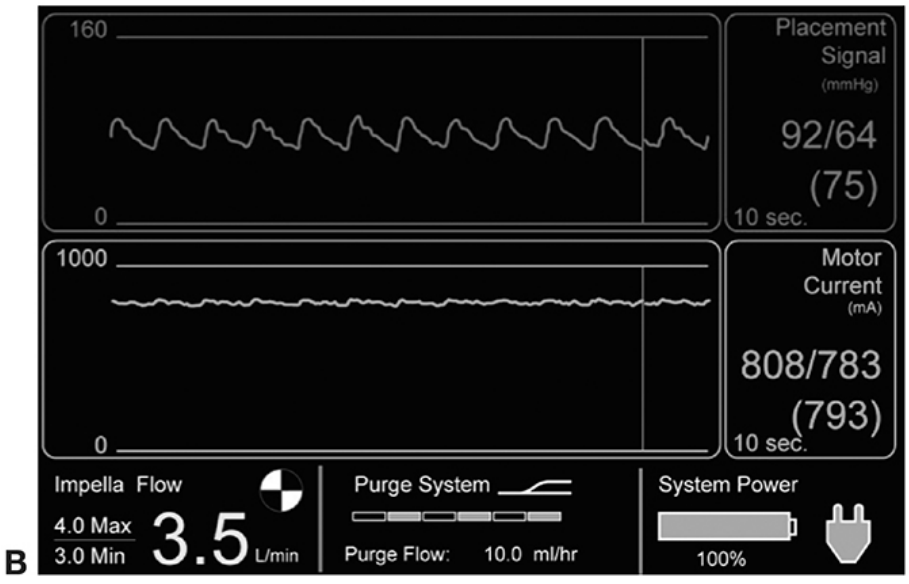
preload dependent and thus dependent on the RV CO. In patients with biventricular failure, attempting univentricular support with an Impella CP or Impella 5.5 can pose a challenge as forward flow may become limited by the degree of RV failure.

E. Understanding the Impella controller

1. A normal Impella console is shown in **Figure 62.9**, as well as several abnormal configurations.



A



B

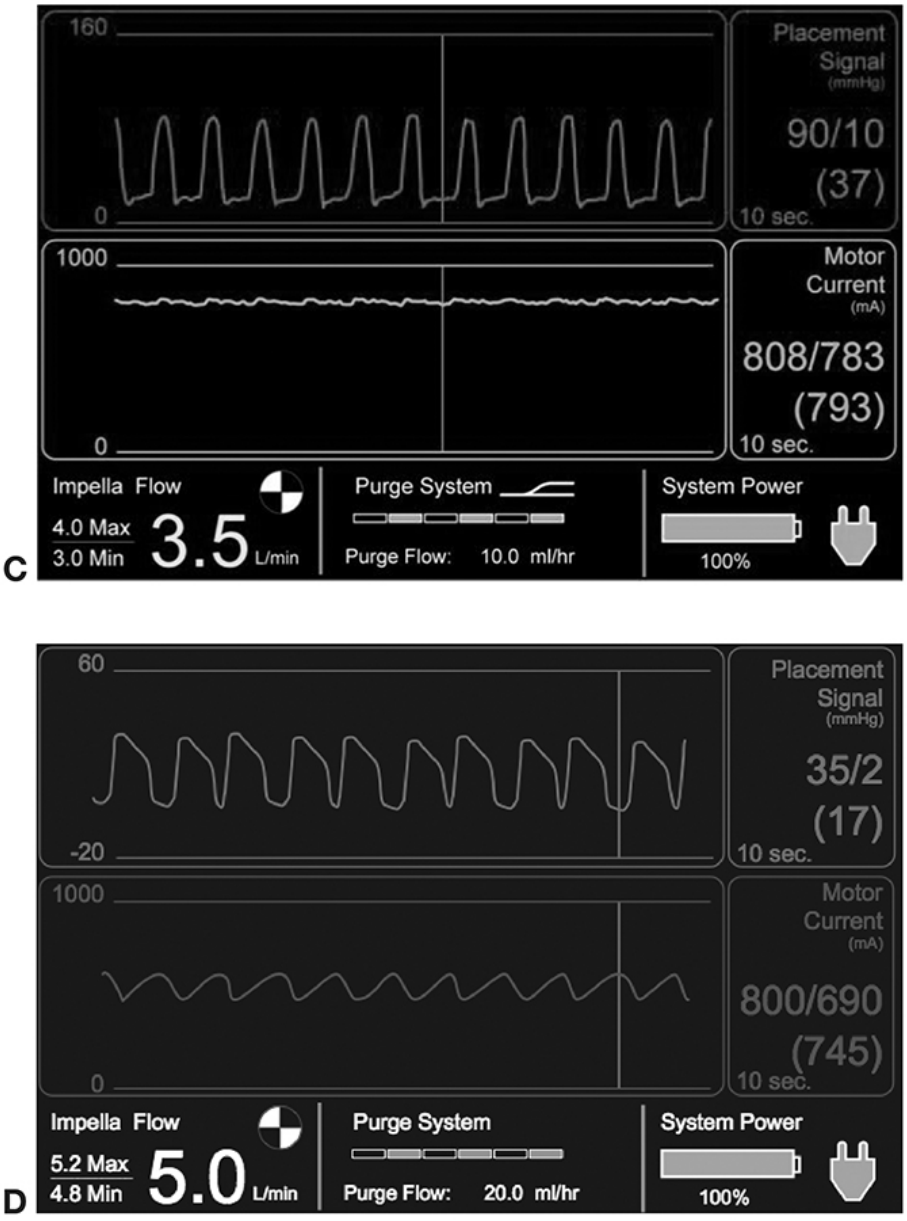


FIGURE 62.9 Impella console. **A.** Normal appearance of the console for an Impella 2.5 or Impella CP. **B.** Incorrect placement—device pulled back into aorta. **C.** Incorrect placement—device too far into the left ventricle. **D.** Normal appearance of the console of an Impella 5.0. (Images courtesy of Abiomed; modified with permission.)

a. Flow is directed by a performance ("P") level, which dictates the speed of the impeller motor (RPMs) and thus how fast blood is pulled through the Impella.

b. There is an aortic signal and a "placement" signal that represent pressure in the aorta and the LV, respectively. These are akin to aortic and LV pressure waveforms. While the aortic signal will generally correlate with a distal arterial line, the LV placement signal is computed and less reliable for measuring LVEDP.

c. The motor current should also appear to be pulsatile as blood flows across the Impella with LV systole.

d. The Impella also has a purge system that prevents blood from entering the motor housing; a heparinized dextrose solution is used to provide an adequate pH to prevent clot formation.

(1) Normal purge pressure ranges from 300 to 110 mm Hg; however, sudden increases in purge pressure should trigger an evaluation for an obstruction such as a thrombus in the motor housing or excessive purge solution viscosity.

(2) Low purge pressures would suggest a leak in the purge system itself or low purge solution viscosity.

(3) In individuals with contraindication to heparin use, sodium bicarbonate purge solution is an alternative.

F. Monitoring and postinsertion management

1. As this is not a potential bedside procedure, discussion of the technical aspects of Impella insertion are beyond the scope of this manual.
2. **Peripheral pulses** should be monitored frequently to ensure adequate perfusion in the affected limb, and the access site should be monitored closely for evidence of bleeding.
3. **Impella position** should be monitored by echocardiography immediately following insertion or with any clinical change or deterioration, such as new hypotension or a suction event. **Figure 62.10** shows both appropriate and inappropriate Impella positioning on echocardiography.

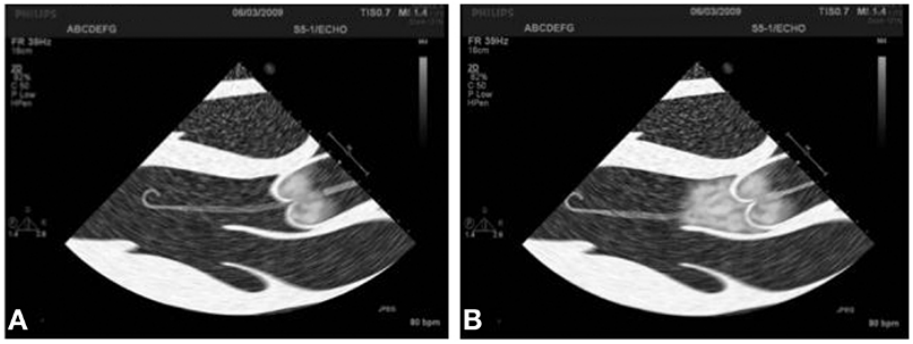


FIGURE 62.10 Correct (**A**) and incorrect (**B**) Impella catheter positions shown on transthoracic echocardiography. **A.** With the correct Impella position, there is a dense mosaic pattern of turbulence across the aortic valve near the catheter outlet area. **B.** In this example of an Impella placed too far in the left ventricle or entangled in a papillary muscle, the mosaic pattern crosses the aortic valve. (Images courtesy of Abiomed; modified with permission.)

a. The Impella catheter should be approximately 4.5 cm into the mid-LV cavity for the Impella 5.5 and 3.5 cm for the Impella CP, and the Impella outlet should be ·1 cm above the AV.

(1) The outlet flow is best observed with color-flow Doppler as a dense mosaic turbulent flow.

(2) Care should also be taken to ensure the Impella is not laterally displaced and tangled in the posterolateral papillary muscle.

b. Impella position can also be monitored on daily chest x-ray, although this is far less reliable to gauge appropriate positioning.

4. **Hemodynamic targets** are largely patient dependent and determined by the bedside clinician. As discussed earlier, the Impella is both preload dependent and afterload sensitive. In most patients with an Impella, a pulmonary artery catheter (PAC) and arterial line will provide useful information to help guide decision-making, including speed titrations, and to guide hemodynamic tailoring and weaning.

a. Slightly higher than normal filling pressures (RA ·10 mm Hg, PAD ·16 mm Hg) are important for preventing suctioning events. There is no "one-size-fits-all" range, and hemodynamics should be tailored to each individual patient.

5. **Anticoagulation** is essential to protect the Impella's internal impeller motor and to prevent thrombus formation on the outside of the Impella.
   a. **Systemic anticoagulation is preferred** in patients with an Impella. This is generally accomplished by utilizing both systemic heparin and purge heparin to achieve a goal partial thromboplastin time (PTT) or Xa level. Purge doses can be adjusted from full to half strength to prevent supratherapeutic heparin levels, just as the systemic heparin can be continually adjusted.
   b. In patients who are unable to receive systemic anticoagulation, heparin provided only through the purge system should be employed to prevent thrombus in the Impella motor system, although this will not prevent thrombus formation on the Impella catheter itself, although importantly some of this heparin still does become systemically absorbed.
   c. In patients who are unable to tolerate heparin of any kind (such as patients with HIT or individuals with intracranial bleeding), a bicarbonate purge solution can be used instead. Again, this will not prevent external thrombus.
6. **Hemolysis** monitoring is important, as red blood cells and platelets are easily destroyed by the impeller motor, particularly at higher settings or with thrombus formation.
   a. Any acute decrease in hemoglobin should trigger an evaluation for hemolysis with a lactate dehydrogenase (LDH) and haptoglobin, as well as a survey for a possible hematoma or access site bleeding. LDH and haptoglobin levels can be useful, particularly if there is an acute change in the trend.
   b. If labs are suggestive of hemolysis, the performance (P) level should be reduced, and the Impella purge pressure should be

checked to ensure there is no evidence of thrombus as a possible mediator of hemolysis.

G. Impella troubleshooting

1. **Suction alarms** can be related to decreased preload (eg, decreased intravascular volume or RV failure), improper Impella position (ie, against the LV wall, often resulting in VT), or entrainment of thrombus into the Impella inflow.
   a. **Decreased preload** can be managed by either repleting intravascular blood with IV crystalloid or colloid, decreasing performance level, or both.
   b. **Improper Impella positioning** should be evaluated by echocardiography. If the Impella is positioned too deep, it can be cautiously pulled back under live echocardiographic guidance by a qualified clinician.
      (1) **Extreme caution** should be employed when pulling back the Impella, as it can often have a delayed response to transmission of rotational torque and suddenly pull back into the aorta. Subsequently advancing the Impella back into the LV can be technically challenging, and repeated attempts at the bedside run the risk of aortic dissection. In these cases, patients often need to be taken back to the lab or operating room to have the Impella repositioned with the aid of a guidewire.
2. **Decreased device flow** may be due to increased afterload, in which case afterload reducing agents such as nitroprusside or oral vasodilators can be employed.
   a. A **loss of pulsatility** does not inherently mean cardiac arrest if Impella flow is still maintained. This may suggest worsened LV/aorta uncoupling, more dependence on the Impella device to sustain flow, and may suggest worsening LV function (or increased afterload).
   b. Inotropes can also be added to improve LV contractility and prevent potential clot formation in the LV or on the Impella.

3. **Position alarms** can be detected by the Impella console (called SmartAssist) utilizing the placement and LV signals and can suggest the Impella is either too deep into the LV or too far back into the aorta.
    a. **This should be confirmed on echocardiography prior to any repositioning maneuver.**
4. In patients requiring **cardiopulmonary resuscitation (CPR)**, the Impella should be turned down to P2 during CPR itself.
    a. If return of spontaneous circulation (ROSC) is achieved, Impella position should be immediately assessed by bedside echo or fluoroscopy, as well as on the controller.
    b. Once the position is confirmed to be appropriate, the P level can be increased based on clinical judgment.

H. Complications

1. **Hemolysis and thrombocytopenia** are caused by the constant rotation of the impeller motor and can lead to myoglobinuria and acute kidney injury (AKI).
2. **AV or aortic root injury** can occur during Impella placement or during repositioning attempts, which can result in severe AI or aortic dissection.
3. **Mechanical interaction** with the LV wall can result in VT, and acute or worsening MR can result from entanglement with the posterolateral papillary muscle.
4. **Device thrombosis** can result in both device failure and hemodynamic compromise, as well as **arterial embolization** such as a stroke or acute limb ischemia.
5. **LV free wall perforation** can also occur during device insertion.
6. **Limb ischemia** can occur in the accessed limb and is an indication for immediate removal and possible surgical intervention if ischemia persists after removal.
7. **Access site bleeding** is not uncommon and can pose challenges in regard to both duration of device therapy and anticoagulation.

IV. VENOARTERIAL EXTRACORPOREAL OXYGENATION. **VA-ECMO** is a form of mechanical circulatory support that pulls blood from the venous circuit via a centrifugal flow continuous pump, oxygenates the blood via an oxygenator, and then returns the blood to the arterial circuit via an arterial access point (**Figure 62.11**). Utilization of VA-ECMO for the management of critically ill patients has dramatically increased in the past decade and can provide substantial end-organ support for patients in CS. **Venovenous (VV) ECMO** is beyond the scope of this manual, although we briefly touch on hybrid configurations, such as **veno-arterial-venous (VAV) ECMO**.

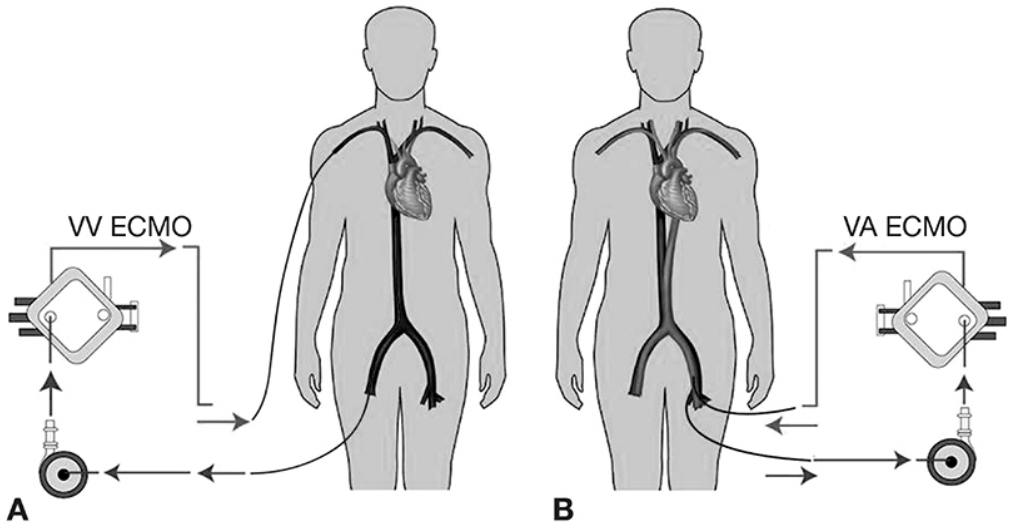


FIGURE 62.11 Venovenous (VV) and venoarterial (VA) ECMO schematic. **A.** In VV-ECMO, blood is drained from inferior vena cava (IVC) or right atrium (RA), passed through a pump, gas exchanger, and heater and returned back through the central venous circulation. **B.** In traditional VA-ECMO, blood is drained from the IVC or RA, passed through a pump, gas exchanger, and heater and returned back through the femoral arterial circulation. ECMO, extracorporeal membrane oxygenation.

A. Indications

1. **CS** is the most common indication for VA-ECMO deployment and can provide 5 to 6 L/min of flow, allowing for biventricular support and end-organ perfusion in refractory shock, as well as provide respiratory support to patients with refractory hypoxemia.

2. **Extracorporeal CPR** with VA-ECMO can be used in select patients to provide circulatory support following cardiac arrest, particularly in patients with a limited down time and reversible cause of cardiac arrest (such as ACS or ventricular tachyarrhythmias).
3. **Failure to wean from cardiopulmonary bypass** is a common indication for post–cardiac surgery patients and often serves as a bridge to recovery in the setting of postcardiotomy shock.
4. In both CS and cardiac arrest, patient selection is critical. The decision to place a patient on VA-ECMO is best made by a multidisciplinary **shock team**, generally composed of a cardiac intensivist, HF cardiologist, cardiac surgeon, and, possibly, an interventional cardiologist, with a clear **bridging strategy** in mind. VA-ECMO can act as a time-limited bridge to either an intervention (eg, PCI), advanced therapies (ie, transplant or VAD), or recovery.

B. Contraindications

1. **Active hemorrhage or inability to tolerate anticoagulation** is a contraindication as VA-ECMO requires systemic anticoagulation for the prevention of arterial embolization. **Extreme caution** should be used in patients with an increased predisposition to bleeding, such as thrombocytopenia, disseminated intravascular coagulation, and recent intracranial injury.
2. **Severe PAD** is a relative contraindication to VA-ECMO, given the high risk of limb ischemia with the large-bore cannulas used for VA-ECMO (generally 15-29F). In general, the placement of an **antegrade reperfusion cannula** in the arterial system is recommended and reduces of acute limb ischemia. In select patients, this can also be overcome by central cannulation in the axillary or subclavian artery.
3. **Severe AI** is a contraindication as the continuous retrograde flow against the AV can worsen regurgitant volumes and LV hemodynamics. However, individuals who still require VA-ECMO hemodynamic support with a primary AI lesion can have this mitigated via LV unloading with either atrial septostomy or LA

venting via ProTek Tandem trans-septal cannula to the LA and connected to the circuit in a VV-A configuration.

4. **Irreversible cardiac failure**, sometimes referred to as a "bridge to nowhere," is an absolute contraindication to VA-ECMO, as more harm will be done by the ECMO circuit than any possible derived benefit.

C. Hemodynamic effects

1. Deoxygenated blood is pulled from the RA via the venous (drainage) cannula through the oxygenator and returned to the arterial circulation via an arterial (return) cannula. Depending on where the arterial cannula is placed, some flow will be antegrade, and some will be retrograde. In the case of femoral arterial return, the ipsilateral lower extremity will be supplied by antegrade flow, and the contralateral limb and aortic circulation will be supplied by retrograde flow. With approximately ·5 L/min of flow, this affords adequate end-organ perfusion in the setting of poor CO and allows the LV to "rest."
2. However, the retrograde flow from the ECMO circuits also results in **increased LV afterload,** which decreases CO and increases LV wall stress and LV distention. At the extreme of severe LV dysfunction and high ECMO flow, there is a high risk of systolic AV closure, resulting in increased clot formation within the LV and on the AV, as well as worsening pulmonary edema.

D. LV unloading

1. As described earlier, the retrograde flow from the arterial return cannula will "mix" with blood ejected from the LV at a variable location within the aorta. Where exactly this "**mixing cloud**" occurs is dependent on both ECMO flow and native LV CO. In CS, where LV CO is compromised, the mixing cloud will be closer to the AV, ensuring adequate perfusion throughout the systemic circuit.
2. **Pharmacologic venting** can be accomplished with inotropes such as dobutamine or pressors such as epinephrine, both of which improve LV contractility.

3. **IABP counterpulsation** can also be used to provide afterload reduction in select patients.
4. **Impella devices** are a popular choice for LV unloading as they can provide robust flow to offload the LV in the setting of high ECMO flows.
5. **Left atrial-veno-arterial ECMO (LAVA-ECMO)** is a form of central ECMO that offloads the LV by draining the left atrium. A multistage fenestrated venous drainage cannula is placed in the left atrium via trans-septal puncture, allowing for biatrial drainage with arterial return. This can be useful in patients in whom a transaortic device is contraindicated, but care must be taken to ensure stable LA cannula position.

E. ECMO cannulation and configuration

1. Cannulation for ECMO is performed by a trained cardiothoracic surgeon, interventional cardiologist, or trained HF or critical care cardiologist.
2. For VA-ECMO, large-bore arterial and venous cannulae are placed using sterile Seldinger technique with serial dilations. Cannula size varies but ranges from 15F to 29F depending on the manufacturer and institutional preference.
    a. Various configurations of ECMO can be used, and access can be tailored to the patient based on their anatomy (eg, the axillary or subclavian artery may be preferred in a patient with severe PAD in the femoral vessels).
    b. The venous cannula is placed in the inferior vena cava (IVC) or RA if placed peripherally (ie, in the femoral vein). If placed in the right jugular, as in commonly seen in VV-ECMO, the cannula should terminate in the superior vena cava (SVC) or at the SVC/RA junction.
    c. The arterial cannula is shorter and is placed in the common femoral artery.

F. ECMO monitoring and parameters

1. **Flow rate** is modulated by changing the speed of the centrifugal pump (RPMs) and should be adjusted to provide adequate end-

organ perfusion without worsening LV strain and/or closing the AV.

2. **Oxygenation** should be monitored by monitoring oxygen levels at the most distal portion of the ECMO circuit. In VA-ECMO, the 100% FIO_2 is provided by countercurrent gas flow through the oxygenator (called the "sweep").
   a. In most cases, the **right radial artery** is the optimal point to measure patient oxygenation as this represents the distal portion of the ECMO circuit. Patients should be monitored routinely with a "patient gas" at the right radial artery and compared to a postoxygenator gas. The goal SpO_2 for the patient should be >90% to 92%.
   b. A preoxygenator gas can be hypothetically checked to monitor for peripheral oxygen extraction (ie, a surrogate for a central or mixed venous saturation), but this is not routinely done.
3. **Ventilation** (ie, CO_2 gas exchange) is also mediated by the sweep flow, with increased sweep flow allowing for more gas exchange.
4. The **ventilator settings** are generally minimized to provide lung "rest" with lung protective settings. This provides the added benefit of minimizing positive end-expiratory pressure (PEEP), which compromises preload and thus CO, as well as plateau and peak pressures. Importantly, **when weaning ECMO, the ventilator setting will need to be adjusted as native circulation becomes the dominant circulation again.**
5. **Tissue perfusion** is monitored by lactate levels, renal function, hepatic function, mean arterial pressure, and mental status. **Neurologic status** is crucial to monitor serially (every 2-4 hours with nursing), as patients are at increased risk for both hemorrhagic and embolic stroke while on VA-ECMO.
6. **Anticoagulation** is mandatory in patients on ECMO to prevent thrombus formation within the circuit and embolization. This is accomplished with systemic heparin, or with bivalirudin in patients unable to receive heparin. In VA-ECMO patients experiencing bleeding complications, anticoagulation can be

temporarily paused, but **flows must stay above minimum of 2.5 L/min** to reduce the risk of clot formation.

7. **LV contractility** is important to monitor to ensure the AV is opening to reduce the risk of thrombus formation. This is monitored by invasive arterial monitoring as well as by echocardiography.
   a. A reduction in pulsatility should prompt an assessment of the LV and AV to ensure adequate contractility and AV opening.
   b. If LV contractility is reduced and/or the AV is not adequately opening, an LV venting strategy should be considered as described earlier.
8. **Hemolysis and thrombocytopenia** should be carefully monitored in patients on VA-ECMO, as with an Impella or IABP.
9. **Invasive hemodynamics** with a PAC is recommended to help measure both RA and PA pressures, although a mixed venous from the PA port will not correlate with cardiac function as the blood flowing through the ECMO circuit is bypassing the native circulation.

G. ECMO troubleshooting

1. **Decreased preload** is intrinsic to venous drainage from the RA and is exacerbated in patients who are intravascularly depleted (either from volume removal with diuresis or dialysis or in patients with bleeding complications). This can result in "**chugging**" of the venous and arterial tubing, which can be treated by giving intravascular volume back in the form of blood, colloid, or crystalloid.
2. **Mixing cloud** monitoring is critical in patients on VA-ECMO. In patients with either an LV venting strategy or LV recovery, the mixing cloud can shift further downstream from the AV, particularly when weaning ECMO. If the patient has poor pulmonary gas exchange (either due to pulmonary edema, acute respiratory distress syndrome [ARDS], or high ECMO flows bypassing the pulmonary circuit), this can lead to regional hypoxia, called **north-south or Harlequin syndrome.**

a. For example, in a patient with LV recovery but with compromised pulmonary gas exchange, the blood ejected from the LV may meet the oxygenated ECMO blood in the middle of the aortic arch. This can result in reduced oxygen delivery to either the right or the right and left upper extremities and brain and thus hypoxic injury.

b. **North-south syndrome** can be corrected by (1) improving gas exchange through the native circulation; (2) increasing ECMO flows; (3) in the case of LV venting with an Impella, reducing Impella flows'; or (4) upgrading the ECMO circuit to a VAV-ECMO system with oxygenated return to a venous limb.

3. **Sedation** in patients on VA-ECMO can be very complicated. In general, patients should be kept on the minimal amount of sedation required to remain safe, with daily awakening trials and frequent assessments of neurologic status to ensure no acute change is missed.

a. In particular, analgesia with **fentanyl** presents a challenge. While favorable for its relatively short half-life to limit days on the ventilator, the tubing of the ECMO circuit is relatively lipophilic and will absorb a high portion of the fentanyl infused into the patient, resulting in higher doses being given.

b. However, over time, this fentanyl will diffuse back into the blood in the circuit and may prolong sedation even as infused doses are being weaned.

H. Complications

1. **Bleeding complications** are the most common serious complication of VA-ECMO and may occur in over one-third of patients. There are multifactorial causes of bleeding, including systemic anticoagulation, thrombocytopenia, and vascular access complications. These can range from minor blood loss at the access site, to retroperitoneal hematomas, to intracerebral hemorrhage.

2. **Thromboembolic** complications generally occur due to thrombus formation in the ECMO either at low flows or with inadequate (or

paused) anticoagulation.

a. The oxygenator should be visually inspected frequently for thrombus formation. Increase pressure across the oxygenator circuit is suggestive of significant thrombus formation.

b. The AV should be monitored for adequate opening as described earlier to minimize the risk of LV/AV thrombus.

c. As discussed earlier, neurologic status should be diligently monitored to ensure any change in baseline neurologic status is quickly identified.

3. **Limb ischemia** can be caused by either vessel occlusion by the cannula itself or distal thrombus formation. This risk can be mitigated using a **distal reperfusion cannula.** Vessel perforation, dissection, and other complications are rare but may occur due to the large caliber arterial catheter.

4. **Pulmonary hemorrhage** may occur with worsening LV distention and can result in worsening oxygenation and ARDS. This is avoided by minimizing ECMO flows as able and providing adequate LV venting in cases when ECMO flow is mandated to remain high at the cost of LV function.

5. **Infection** may occur due to the indwelling cannula themselves, or due to the various other indwelling lines required for support (eg, PAC, central line, dialysis catheter).

V. TEMPORARY RIGHT VENTRICULAR ASSIST DEVICES.

Isolated RV failure is less frequently encountered and even less frequently requires mechanical circulatory support. However, for patients with refractory RV failure and shock, there are several options available to provide RV support in select patients.

A. ProTek Duo

1. The ProTek Duo is a dual-lumen cannula that is inserted via the right internal jugular (RIJ) vein. The inflow sits in the RA, and the outflow sits in the main PA, providing improved RV CO, when connected to a TandemHeart or CentriMag pump. It can also be

connected to an oxygenator to provide extracorporeal oxygenation like VV-ECMO.

2. The RIJ access is favorable for allowing for patient mobility.
3. Common applications include AMI RV failure, massive pulmonary embolism, LVAD-associated RV failure, and biventricular failure.

B. Impella RP and RP Flex

1. As discussed earlier, the Impella RP and RP Flex (RIJ access) allow for ·4 L/min of flow through the RV.
2. The configuration and indications are like a ProTek Duo, but without the option for attaching an oxygenator.
3. The Impella console is used like an Impella CP or Impella 5.5, with performance levels dictating flow.
4. The same troubleshooting and monitoring principles described in the Impella section above apply.

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CHAPTER 63

Left Heart Catheterization

Nikolaos Spilias and Grant W. Reed

I. INTRODUCTION. In 1958, Dr Mason Sones and colleagues at the Cleveland Clinic performed the first selective coronary arteriography. Since then, left heart catheterization (LHC) has become one of the most widely performed cardiac procedures and is an important tool in diagnostic and interventional cardiology. More than 1 million cardiac catheterizations are performed yearly in the United States. Despite the advent of other diagnostic modalities, coronary angiography remains the gold standard for the diagnosis of significant coronary artery disease (CAD).

The COCATS 4 Task Force, composed of experienced specialists from academic and community-based practice settings, has defined certain criteria and training standards to achieve competency in cardiac catheterization. As in most areas of cardiovascular medicine, there are three levels of training. Level I training requires approximately 4 months of experience in the catheterization laboratory, during which the trainee should participate in a minimum of 100 cardiac catheterization procedures (at least 50 of them should involve coronary angiography and at least 25 should involve hemodynamic assessment of valvular, myocardial, pericardial, or congenital disease). Level II training generally requires a total of 6 months in the catheterization laboratory and participation in the performance of approximately 300 diagnostic procedures under direct supervision. Level III training must be performed during additional year(s) of fellowship, dedicated to cardiovascular interventional training. The goal of a cardiac catheterization training program is to provide the trainee with the required cognitive and technical skills, including detailed knowledge and understanding of the indications and contraindications of cardiac

catheterization, periprocedural care, analysis and interpretation of the angiographic and hemodynamic data, and prevention and management of potential complications.

II. INDICATIONS. The American College of Cardiology Foundation (ACCF) in collaboration with the Society for Cardiovascular Angiography and Interventions (SCAI) and other key specialty and subspecialty societies has created appropriate-use criteria (AUC) for performing diagnostic cardiac catheterization, based on review of common clinical scenarios where diagnostic catheterization is frequently considered. Common clinical scenarios were graded on a 1 to 9 scale and placed into the three categories of "appropriate use" (score 7-9), "uncertain use" (score 4-6), and "inappropriate use" (score 1-3). The SCAI has created an AUC calculator app to support clinical decision-making for diagnostic cardiac catheterization in individual patients (available at www.scai.org). A summary of the main indications and contraindications of LHC is provided in **Table 63.1**.

TABLE 63.1 Indications and Contraindications for Left Heart Catheterization

Indications
• Acute coronary syndrome
• Cardiogenic shock
• STEMI
• NSTEMI, UA
• Stable angina, uncontrolled by medications
• Abnormal stress test, especially with high-risk features
• Ventricular arrhythmias
• New-onset LV dysfunction
• Valvular heart disease
• Preoperative coronary assessment for cardiovascular surgery
• Preoperative risk assessment for noncardiovascular surgery

- Periodic surveillance for CAV after cardiac transplantation

Contraindications

- Active bleeding
- Severe coagulopathy
- Acute renal failure
- Active systemic infection
- Severe anemia
- Electrolyte abnormalities
- Acute decompensated heart failure (inability to lie supine)
- Hypertensive emergency
- Extensive comorbidities: risk of catheterization/revascularization outweighs benefits.

CAV, cardiac allograft vasculopathy; NSTEMI, non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

A. Suspected or known acute coronary syndrome (ACS)

1. **Cardiogenic shock due to suspected ACS.** A strategy of urgent angiography with the intent to perform percutaneous coronary intervention (PCI) is recommended for patients who present with severe heart failure (HF) or cardiogenic shock and findings of ACS and are suitable for revascularization.
2. **ST-elevation myocardial infarction (STEMI).** A strategy of immediate angiography with the intent to perform PCI is recommended in patients who present with STEMI in a PCI-capable facility. Immediate transfer to a PCI-capable facility for coronary angiography is recommended for patients with STEMI, if the time from the first medical contact to device (balloon) is less than 120 minutes. Coronary angiography is also recommended for patients with STEMI with evidence of failed fibrinolysis (“rescue PCI”). For stable patients who initially receive fibrinolytic

therapy, it is reasonable to proceed with coronary angiography within 24 hours, with the intent to perform PCI.

3. **Unstable angina/non–ST-elevation myocardial infarction (UA/NSTEMI).** An early invasive strategy, within 24 hours from presentation, is generally recommended for all patients presenting with UA or NSTEMI and especially for those with refractory angina, evidence of continued myocardial injury, hemodynamic or electrical instability, and high-risk patients (based on thrombolysis in myocardial infarction [TIMI] and GRACE scores). The most recent 2021 American College of Cardiology/American Heart Association (ACC/AHA) Chest Pain Guidelines emphasize the use of clinical decision pathways for patient risk assessment and the decision regarding further testing (noninvasive or invasive).

B. Chronic stable angina (or angina equivalent). The utility of an upfront invasive strategy with heart catheterization and subsequent revascularization in patients with chronic stable ischemic heart disease has been under question after the publication of the ISCHEMIA trial results. The study did not show survival benefit of an initial invasive approach in patients with chronic stable angina and objective evidence of at least moderate ischemia on stress testing compared to medical therapy alone. Of note, the majority of the patients were screened for the presence of left main stenosis with a coronary computed tomographic angiography (CTA) prior to enrollment and were excluded from the trial if significant left main stenosis (>50%) was identified. Nevertheless, the study showed significant symptomatic improvement in patients who underwent coronary angiography and subsequent revascularization (PCI or coronary artery bypass grafting [CABG]) compared to medical therapy alone during the first 3 months of follow-up. Coronary angiography is considered appropriate for patients with persistent, quality of life-limiting angina (Canadian Cardiovascular Society classes III and IV), which is refractory to medical therapy, patients with high-risk features on noninvasive testing (eg, ST depression >2 mm, especially in multiple leads or persisting into recovery, ST elevation >1 mm in leads without Q waves, drop in systolic blood

pressure (BP) of >10 mm Hg with exercise, development of ventricular tachycardia (VT), drop in left ventricular ejection fraction [LVEF] during stress, transient ischemic dilatation of the LV, or significant amount of myocardium at risk >10%), and patients with high pretest probability for severe CAD or left main disease based on clinical judgment.

C. **Abnormal coronary CTA.** Coronary CTA has been increasingly utilized in recent years in patients with suspected CAD. LHC is appropriate for patients who had a coronary CTA with evidence of left main stenosis or non–left main lesions of indeterminate significance (possibly obstructive), in whom the benefits of a more certain diagnosis and treatment outweigh the risks of the procedure.

D. **HF.** LHC is recommended for patients presenting with new-onset LV dysfunction, especially those who have concomitant angina or significant ischemia on noninvasive testing, for the delineation of coronary anatomy and detection of significant CAD (especially left main stenosis) as the cause of the cardiomyopathy. A left ventriculogram can also provide an estimate of LV function and regional wall motion, which can be particularly useful in cases of stress-induced cardiomyopathy (apical "ballooning," Takotsubo). While, in patients with ischemic cardiomyopathy, CABG has been shown to provide survival benefit compared to medical therapy alone (STICH trial), the recently published REVIVED trial did not show survival benefit or LVEF improvement with PCI compared to contemporary medical therapy in patients with LV dysfunction (LVEF <35%), extensive CAD, and the presence of myocardial viability on noninvasive testing. However, the study did not stratify patients based on the degree of myocardial ischemia, and it remains possible that patients with the most severe CAD were referred to CABG.

E. **Ventricular arrhythmias.** LHC is indicated for patients with life-threatening ventricular arrhythmias or survivors of cardiac arrest when there is high clinical suspicion of myocardial ischemia and especially if the initial rhythm is VT or ventricular fibrillation. Urgent angiography is also appropriate for patients with polymorphic VT,

when myocardial ischemia is suspected, in order to evaluate for the presence of obstructive CAD.

F. **Valvular heart disease.** Coronary angiography is indicated for patients older than 40 years (or younger if significant CAD risk factors are present) who are undergoing cardiac (valve repair or replacement, pericardiectomy, etc) or aortic surgery (ascending aorta or aortic root replacement) to detect significant CAD that may require CABG during the operation. LHC can also be useful for the assessment of the hemodynamic significance of aortic stenosis or LV outflow tract (LVOT) obstruction from hypertrophic obstructive cardiomyopathy (HOCM) with measurement of invasive gradients when noninvasive testing is inconclusive about the severity of disease. It can also help with the quantification of aortic and mitral regurgitation (MR) with aortography and left ventriculography, respectively.

G. **Preoperative evaluation for noncardiac surgery.** LHC is indicated for patients undergoing high-risk noncardiac surgery and have angina or a positive stress test with high-risk findings as part of preoperative risk stratification.

III. **CONTRAINDICATIONS.** The following are relative contraindications to elective LHC (**Table 63.1**).

A. **Active bleeding** or recent serious bleeding without identified or treated source (eg, gastrointestinal bleeding)

B. **Severe thrombocytopenia and coagulopathy.** In elective cases, an international normalized ratio (INR) of <1.8 is a cutoff that is often used for the femoral approach. If the patient is on heparin infusion, this is usually stopped 2 hours before the procedure. A platelet count of <50,000 substantially increases the risk of bleeding. After thrombolytic therapy, bleeding is more likely, and elective catheterization is best deferred for at least 24 hours; however, if the indication for the procedure is urgent, it is possible to proceed with caution 3 hours after administration of thrombolysis, with blood products prepared for support as necessary. The use of radial artery access for LHC substantially reduces bleeding complications and is

strongly recommended in patients at high bleeding risk or coagulopathy. This recommendation is especially true in patients presenting with ACS when anticoagulants and antiplatelet agents are frequently used.

C. **Renal failure.** Acute kidney injury is generally a reason to defer elective cardiac catheterization. For patients with end-stage renal disease (ESRD), dialysis is recommended within 24 hours after the catheterization. In patients with stable chronic kidney disease (CKD), catheterization may be performed with caution and appropriate preparation to minimize the risk of contrast-induced nephropathy (CIN) and worsening of renal function. It has been shown that a ratio of the volume of contrast to creatinine clearance greater than 3.7:1 correlates strongly with the risk of developing CIN in patients with moderate CKD. Limited use of contrast and adequate hydration before and after the procedure (3 mL/kg normal saline administered over 2 hours) are important to minimize the risk of CIN. LV end-diastolic pressure (LVEDP)-guided hydration can also be performed to reduce the risk for CIN (POSEIDON trial), where the LVEDP is measured in the beginning of the procedure and the rate of fluid administration is adjusted accordingly.

D. **Infection.** Active systemic infection and/or severe sepsis are reasons to defer elective cardiac catheterization. Local skin infection at the site of the potential access is also undesirable. Fungal infection in groin creases should be treated before elective cardiac catheterization from the femoral approach, especially in patients who are obese.

E. **Laboratory abnormalities.** Severe anemia (hemoglobin <7-8 g/dL) and electrolyte abnormalities (especially hypokalemia or hyperkalemia) should be corrected before an elective cardiac catheterization procedure.

F. **Decompensated HF.** The presence of acute decompensated HF increases the risk for complications during cardiac catheterization. It is best to medically optimize the volume and hemodynamic status of the patient before elective catheterization. At a minimum, the patient should be able to lie supine without significant orthopnea.

G. Uncontrolled severe hypertension. BP should be controlled before elective cardiac catheterization to maximize the safety of the procedure. Severe bleeding can occur at the femoral access site after sheath removal if the patient is very hypertensive, especially if BP is >180/100 mm Hg.

IV. PATIENT PREPARATION

A. Informed consent. A detailed discussion with the patient (and family) should outline the indication for the procedure, as well as the alternative diagnostic and treatment options. Specific mention of the serious risks/complications, such as death, myocardial infarction (MI), stroke, arrhythmia, bleeding, radiation exposure, and kidney failure, must be made. The possible need for emergency CABG should also be noted. The risk of serious complications should be individualized. Informed consent should be documented in the medical record prior to an elective or urgent case.

B. Precatheterization assessment. Before proceeding with a LHC, a detailed clinical assessment is necessary, including a comprehensive history, physical examination, and review of medications and allergies. Peripheral pulses of the upper and lower extremities should be palpated, and arterial bruits, if any, should be documented before the catheterization. In addition, an electrocardiogram (ECG) and laboratory data, including a comprehensive metabolic panel, complete blood count, and coagulation studies, should be obtained for all patients. Urine human chorionic gonadotropin should be checked in female patients of reproductive age.

C. NPO status. Fasting for at least 6 to 8 hours before the procedure is typically recommended, to minimize the risk of emesis and aspiration during the procedure.

D. Medications

1. **Antiplatelet agents.** When PCI is planned or anticipated, loading with aspirin 325 mg should be performed before the procedure if the patient is not already taking daily aspirin. Preloading with a P2Y12 inhibitor is reasonable, although there is no evidence that preloading decreases ischemic complications compared to loading

during or immediately after the PCI. In elective PCI cases, clopidogrel 300 or 600 mg loading dose is usually given, whereas ticagrelor 180 mg or prasugrel 60 mg is preferred in cases of ACS. Withholding P2Y12 loading in stable patients, until the coronary anatomy is defined, may prevent delays in case CABG is necessary.

2. **Anticoagulants.** For patients receiving warfarin or direct oral anticoagulants (DOACs) (apixaban, rivaroxaban, dabigatran, edoxaban), the operator should perform a careful evaluation of the bleeding and ischemic/thrombotic risks associated with the procedure and the patient. When femoral access is planned, the warfarin is typically discontinued at least 3 days prior to the procedure until the INR is <1.8. In patients at high risk for thrombotic complications (such as those with mechanical valves), bridging with low-molecular-weight heparin is often recommended. DOACs are generally discontinued at least 24 to 48 hours before the procedure depending on the bleeding risk and renal function. If the glomerular filtration rate (GFR) is reduced, DOACs should be discontinued at least 48 hours prior to the procedure. In patients who are at moderate or high risk for thrombotic complications (mechanical valve, atrial fibrillation, and history of stroke), continuation of OAC is reasonable when the procedure can be performed via the transradial approach. The anticoagulation interruption recommendations prior to LHC, based on the AHA scientific statement, are summarized in **Table 63.2**.

TABLE 63.2 Management of Oral Anticoagulation Prior to Cardiac Catheterization

	Estimated Glomerular Filtration Rate			
Oral Anticoagulant	**≥80 mL/min/1.73 m^2**	**50-79 mL/min/1.73 m^2**	**30-49 mL/min/1.73 m^2**	**15-29 mL/min/1.73 m^2**
Warfarin	Discontinue 3 d before the procedure for a target INR of <1.8 for femoral access and <2.2 for radial access.			

	Estimated Glomerular Filtration Rate			
Oral Anticoagulant	**≥80 mL/min/1.73 m^2**	**50-79 mL/min/1.73 m^2**	**30-49 mL/min/1.73 m^2**	**15-29 mL/min/1.73 m^2**
Dabigatran	≥24 h	≥36 h	≥48 h	Should not be used
Rivaroxaban	≥24 h	≥24 h	≥24 h	≥36 h
Apixaban	≥24 h	≥24 h	≥24 h	≥36 h
Edoxaban	≥24 h	≥24 h	≥24 h	≥36 h

INR, international normalized ratio.

3. **Hypoglycemics.** Generally, oral hypoglycemics are held on the morning of the procedure. Metformin should be held for 48 hours after the procedure in patients with CKD (GFR <60 mL/min/1.73 m^2) or patients at risk for CIN. The insulin dose needs to be adjusted accordingly, given the NPO status.
4. **Other medications.** The renin-angiotensin-aldosterone system (RAAS) inhibitors and diuretics may be discontinued prior to the procedure at the operator's discretion, to minimize the risk of kidney injury.

V. INTRAPROCEDURAL BEST PRACTICES

A. Choice of contrast. Nonionic, low-osmolar contrast (iohexol, iopamidol, ioversol), or iso-osmolar contrast agents (iodixanol) are standardly used. The iso-osmolar contrast agents may be preferred in patients with CKD to minimize the risk of CIN, although such benefit is not strongly supported by data. Effort should be applied by the operators to minimize contrast administration (ensuring good catheter engagement, avoiding excessive testing, using the minimum number of projections sufficient for the diagnosis). Biplane fluoroscopy may also be used to reduce the number of contrast injections and amount of contrast administered during the procedure. Automated contrast injection systems (ACIST) can be considered, as they have been associated with reduced contrast exposure, risk of acute kidney

injury, and radiation exposure to the operators compared to the traditional manifold.

B. Dye allergy

1. **Premedication.** If a patient has a history of allergic reaction to contrast dye (anaphylaxis, hives, urticaria), premedication with corticosteroids and antihistamines should be performed. Common regimens include 50 mg of oral prednisone administered 13, 7, and 1 hour (every 6 hours) prior to the procedure along with diphenhydramine 50 mg intravenously (IV) or orally 1 hour prior to the procedure. Alternatively, IV corticosteroids can be administered 1 hour prior to the procedure (hydrocortisone 100 mg IV once). With a history of possible life-threatening contrast allergy, it is also prudent to administer small quantities of contrast (1 mL) and observe the patient for a few minutes before proceeding.
2. **Treatment.** If a patient develops any signs of an allergic reaction, treatment should be administered promptly. If hives or rashes develop, treatment with IV diphenhydramine is usually sufficient. IV hydrocortisone is also often given, although its onset of action may not be immediate. In cases of oropharyngeal edema, bronchospasm, or hypotension, 0.3 mL of 1:1,000 epinephrine should be administered subcutaneously. With refractory symptoms, 10 mcg/min of IV epinephrine can be administered until symptoms abate.

C. Latex allergy has become increasingly recognized as a clinical entity, especially in patients and health care workers. True latex allergy can include urticaria, angioedema, laryngospasm, bronchospasm, and, in serious cases, anaphylaxis. Patients with latex allergy should be scheduled as the first case of the day to avoid latex dust from previous procedures. The vast majority of the catheterization laboratories are currently using latex-free equipment.

D. Heparin allergy or history of heparin-induced thrombocytopenia (HIT). Heparin and heparinized saline should be avoided. Direct thrombin inhibitors, such as IV bivalirudin, can be used instead.

E. Sedation and analgesia. Commonly used sedatives include the benzodiazepines midazolam 1 to 2 mg IV or lorazepam 1 to 2 mg IV. The opioids fentanyl 25 or 50 mg IV or morphine 1 to 2 mg IV are commonly used as analgesics. Diphenhydramine 25 or 50 mg IV can also be used for sedation. Continuous pulse oximetry should be performed to ensure that sedation is not excessive. In older patients, patients with dementia or other neurologic conditions, and patients with tenuous hemodynamics, minimizing the sedation is important.

F. Infection control. Sterile technique should be applied during patient preparation and throughout the procedure. Chlorhexidine-based preparations are commonly used over the access sites. Patient drapes that adhere to the skin around the access site are important in minimizing infection risk. The operators may use chlorhexidine/ethyl alcohol surgical hand antiseptic solutions or traditional surgical scrub with water and soap, along with sterile gowns, hats, and masks.

G. Monitoring and other equipment. Before performing a cardiac catheterization, it is essential to ensure that the monitoring equipment is fully functional. Continuous electrocardiographic monitoring, an automated BP cuff, and continuous pulse oximetry are mandatory. Resuscitation equipment should be readily available. Defibrillator pads should be placed on all patients with STEMI and those at increased risk for cardiac arrest (patients with reduced LV function undergoing PCI, left main PCI, etc). If a long procedure is anticipated, many operators prefer placement of a Foley or Texas urinary catheter.

H. Radiation safety. Every effort should be made to reduce radiation exposure to the laboratory personnel and the patient. The main source of exposure is scatter from the x-ray beam originating under the table. Lead aprons (with at least 0.5-mm-thick lead lining), thyroid collars, and leaded eyeglasses are mandatory to minimize radiation exposure. Lead caps should also be considered. Radiation badges are worn on the lead apron and outside the thyroid collar to monitor cumulative radiation exposure. A leaded acrylic shield should be used between the patient and the operator. Standing further from the table reduces radiation exposure by the inverse square of the distance. Fluoroscopy

and, in particular, cine acquisition time should be minimized. The image intensifier should be positioned as close as possible to the patient to reduce radiation scatter. Higher magnification should be used judiciously as it increases radiation exposure. “Coning down” on a region of interest with the use of collimators can also reduce the amount of radiation, as can the use of lung field collimators. Right anterior oblique (RAO) views produce less radiation scatter for the operator than left anterior oblique (LAO) views. Higher cine frame rates increase radiation exposure; the use of 7.5 frames/s for fluoroscopy and 10 or 15 frames/s for cine produces adequate image quality and less radiation exposure. Ultra-low radiation dose protocols are currently available (eg, in chronic total occlusion [CTO] procedures). In the rare situation that a pregnant patient needs catheterization, a lead apron should be placed under the patient’s lower back, closer to the x-ray source that is below the examination table.

VI. ARTERIAL ACCESS

A. Radial artery

1. The radial artery has been established as the preferred access site among most operators and catheterization laboratories, as it is associated with lower rates of bleeding and vascular complications, reduced mortality in patients presenting with ACS/STEMI, and enhanced patient comfort. The choice between the right or left radial artery depends on several factors, such as the quality of radial pulse, presence of internal mammary bypass grafts (ipsilateral radial is preferred), presence of hemodialysis fistula grafts (contralateral access is preferred), prior history of radial access difficulty or failure (due to occlusion, loop, small size, or severe tortuosity), and orthopedic issues that may prevent appropriate arm rotation/positioning. Transradial access failure may occur in 5% of the cases and is more commonly related to the inability advancing a guidewire or catheter to the ascending aorta (radial artery loop, accessory radial artery, severe subclavian and innominate tortuosity, spasm) and, less commonly, to unsuccessful

radial artery puncture/sheath placement due to small arterial size or significant disease/calcification. The use of a Wholey wire, a Glide wire, or a 0.014-in coronary guidewire may help traverse loops or an accessory radial artery; however, caution should be applied to avoid vascular injury or other complications. In cases of severe right subclavian/innominate tortuosity, turning the patient's head to the left followed by a deep inspiration may help straighten the innominate artery and facilitate delivery of the guidewire and/or catheter in the ascending aorta. Furthermore, a 75- or 85-cm R2P destination slender sheath (Terumo) can be used in these cases to facilitate catheter delivery and manipulation in the ascending aorta.

2. Prior to obtaining radial arterial access, the pulse should be palpated and the Allen or Barbeau test should be performed to assess for ulnar flow to the palmar arch. Local anesthetic (2-3 mL lidocaine 1%) is injected subcutaneously. The radial artery puncture site should be approximately 1 to 2 cm above the styloid process (**Figure 63.1**). Either a 22G angiocath needle using a "through-and-through" technique or a micropuncture needle (21-22G) using a "front wall" technique is inserted at about 45° into the radial artery while palpating the pulse. In cases where the pulse is not easily palpable or there is difficulty accessing the radial artery with the above technique, ultrasound (US)-guided puncture is recommended. Once access to the artery is obtained and brisk flow is observed, a 0.018-in guidewire is inserted, the angiocath (or needle) is removed, and the sheath is advanced using the modified Seldinger technique. The Glidesheath Slender (Terumo) is the preferred sheath due to its lower profile (outer diameter is 1 Fr smaller compared to the corresponding femoral sheath, while maintaining the same inner diameter) and hydrophilic properties. Typically, a 5-Fr sheath is placed for diagnostic cases, whereas a 6-Fr sheath is preferred for cases of possible PCI. A 6-Fr sheath may also be preferred in tall patients or patients with ascending aortic aneurysms, where longer (125 cm) diagnostic catheters may be necessary (longer diagnostic

catheters are available in 6 Fr). After sheath placement, the sheath is flushed with normal saline. Nitroglycerin (200 mcg) and/or verapamil (500-1,000 mcg) are usually injected to decrease radial artery spasm. IV heparin 3,000 to 5,000 IU should be given during the procedure to decrease the risk of radial artery occlusion.

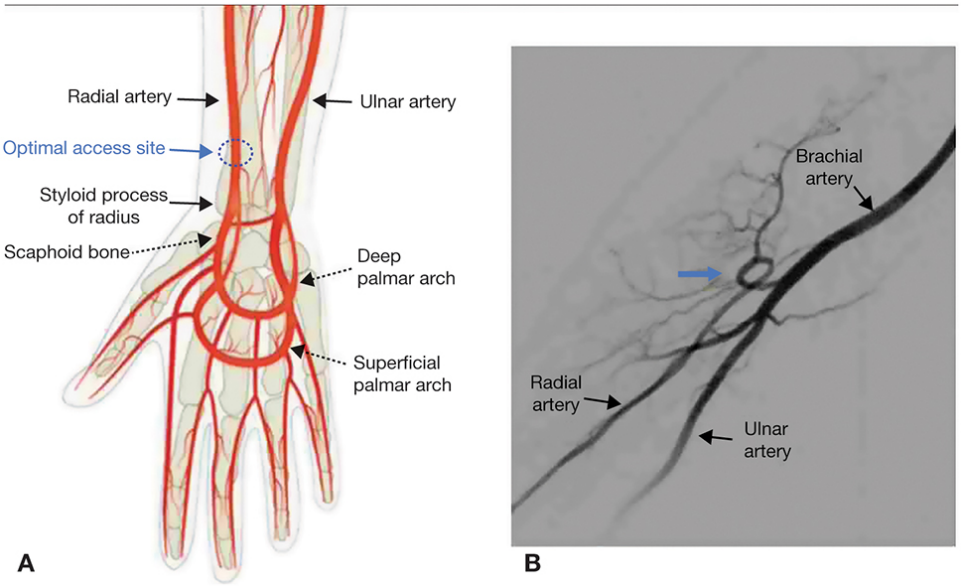

FIGURE 63.1 **A.** Arterial anatomy of the right wrist-hand. **B.** Example of a radial artery loop (blue arrow) at the level of the elbow.

B. Femoral artery

1. Despite the increasing use of radial access, femoral arterial access is still widely used for LHC, mainly in cases where the procedure cannot be successfully performed through the radial artery. Knowledge of the anatomy of the femoral artery and surrounding anatomic landmarks is extremely important for safe vascular access and prevention of complications. The common femoral artery (CFA) is the continuation of the external iliac artery below the inguinal ligament and bifurcates into the superficial femoral artery (SFA) and profunda femoris (PF) branch. In the majority of the cases (77%), the bifurcation is below the level of the femoral head. The lowest point of the inferior epigastric artery corresponds to the inguinal ligament, and arterial puncture above that point increases the risk for retroperitoneal bleeding. Puncture of the

CFA is ideally performed at the level of the mid-femoral head, 1 to 2 cm below the inguinal ligament (**Figure 63.2**). For a safe and successful CFA access, the routine use of fluoroscopy, US, and micropuncture technique is recommended. The FAUST study showed that US-guided CFA access resulted in improved first-pass success rate, reduced number of attempts, risk of venipuncture, and medial time to access. This strategy may be particularly beneficial in patients with peripheral arterial disease (PAD), obesity, and subcutaneous scarring/fibrosis from previous procedures.

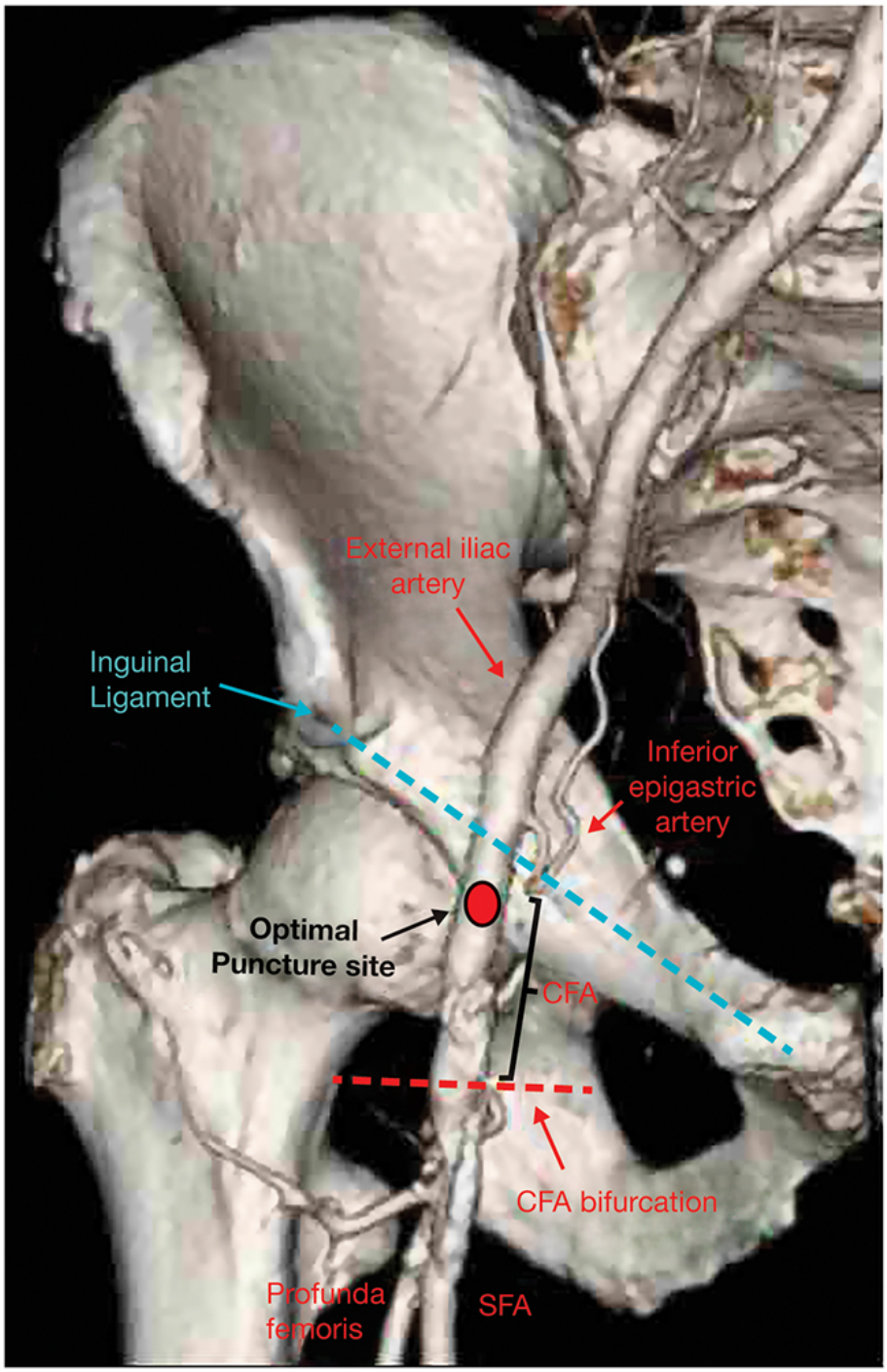

FIGURE 63.2 Computed tomographic angiography of the abdomen-pelvis three-dimensional reconstruction demonstrating the anatomic landmarks for right femoral artery puncture. CFA, common femoral artery; SFA, superficial femoral artery.

2. Anatomic landmarks such as the inguinal ligament can be located with palpation (between the superior-anterior iliac crest and the pubic tubercle). The femoral pulse is then palpated approximately 2 cm below the inguinal ligament, which represents the optimal site for arterial puncture. This method may be challenging in patients who are overweight and obese.
3. After palpation of the femoral pulse, fluoroscopy is used to mark the inferior border of the femoral head with a hemostat, which serves as a guide for the level of skin puncture. Fluoroscopy can also provide useful information about the presence of femoral artery calcifications. Using US, the CFA bifurcation is then identified, and the US probe is moved 1 to 2 cm proximal. US provides important information about the presence of atherosclerosis and vessel wall calcification and its distribution (anterior or posterior). After administration of subcutaneous lidocaine 1% to 2%, a 21G micropuncture needle is advanced through the skin at a 45° angle until the tip of the needle is visualized in the CFA and brisk continuous flow is observed. A 0.018-in wire is then advanced into the CFA, and the needle and wire positions are confirmed with fluoroscopy. The needle is removed, and a 4-Fr introducer sheath is placed over the wire. A limited femoral angiography can be performed through the introducer at this point, to ensure appropriate access location. If the entry site is too high or too low, the introducer is removed, and manual pressure is applied for 5 minutes before attempting again. If the location is acceptable, the 4-Fr introducer sheath is exchanged for the main sheath (usually 10 cm long) over a 0.035-in guidewire. The wire and dilator are removed, and the sheath is flushed with normal saline. Sheath size is determined by the procedure being planned: 4 or 5 Fr for diagnostic procedures and 6 or 7 Fr for coronary interventional procedures.
4. Alternatively, if a micropuncture kit is not available, an 18G Cook needle can be used to obtain femoral access, ideally with US and fluoroscopic guidance as above. Special caution must be taken not to enter the artery above the inguinal ligament because this

increases the risk of retroperitoneal bleeding. Arterial entry that is too low, below the CFA bifurcation, must also be avoided, because it can lead to pseudoaneurysm or arteriovenous fistula formation. In cases of severe iliofemoral tortuosity, disease, or calcification, a longer sheath (eg, 35 or 55 cm) can be placed over a long 0.035-in guidewire to straighten the artery, enhance catheter support and torquing ability, and avoid traversal of the calcified/tortuous segment during catheter exchanges. In patients with an abdominal aortic aneurysm (AAA) for whom a femoral approach is chosen, catheter exchanges should be performed over the wire, to avoid passing the wire through the aneurysm repetitively. The use of a wire with a softer tip (such as the Wholey wire) may prove less traumatic to the vessel, and a diagnostic catheter (eg, Judkins left [JR] 4) can be used to direct the guidewire through tortuosity. Special caution should be applied in patients who are obese, where the use of a longer sheath and a stiffer wire during sheath insertion may be considered (to avoid kinking in the subcutaneous tissue).

C. Distal radial artery. Distal radial access in the anatomic snuffbox or on the dorsum of the hand has recently gained popularity, especially in cases of left radial access, to engage a left internal mammary artery (LIMA) bypass graft. It may enhance patient and operator comfort as the arm is placed in a more natural position over the left groin (the wrist should be in the natural, relaxed rotation about 90° from the standard radial access position and slightly flexed toward the ulnar side). Distal radial access may be associated with lower rates of radial artery occlusion, although more data from prospective studies are needed to prove the potential benefits of this approach. Distal radial access is typically obtained with US guidance (to assess the size and precise location of the artery) and a 22G micropuncture needle for anterior wall puncture, followed by the modified Seldinger technique.

D. Ulnar artery. The ulnar artery is a safe and effective alternative access site when radial access cannot be successfully obtained. Although crossover from a failed transradial access to an ipsilateral ulnar access has been reported without increased risk for complications, ipsilateral ulnar access should be avoided in cases of

radial artery occlusion to prevent hand ischemia. Special caution should also be applied during hemostasis, due to less support/compression provided from the underlying ulnar bone. The compression device used for patent hemostasis (TR Band) may be left fully inflated for an extra 30 to 60 minutes to prevent hematoma formation.

E. Brachial artery. The brachial artery should be reserved for patients in whom the radial and/or femoral access is not feasible. It is very rarely used nowadays, due to a higher risk for hematoma formation and forearm/hand ischemia in case of a vascular complication. Percutaneous brachial access should be obtained with US guidance and a 22G micropuncture needle, ideally with the anterior wall puncture technique.

F. Prosthetic femoral grafts. In patients with prosthetic femoral grafts, it may be preferable to first place a small dilator and through this advance a stiffer 0.035-in wire (eg, Supra Core or Lunderquist) to facilitate sheath placement and avoid kinking at the arteriotomy. This technique is also useful in patients who are obese or those with significant subcutaneous scar tissue. If a synthetic graft is old, fluoroscopy can be performed to determine if the graft is heavily calcified, a sign that hemostasis may be challenging after sheath removal.

VII. ENGAGING THE CORONARY ARTERIES AND BYPASS GRAFTS

A. Catheters. The catheters commonly used for coronary angiography include the Judkins, Amplatz, and multipurpose systems. Catheters designed specifically for radial access such as the Tiger, Jacky, or Sarah can be used to engage both left (LCA) and right coronary arteries (RCA) without the need for catheter exchange. For the LCA, the size of the JL catheters ranges from JL 3.5 to JL 6. The number corresponds to the length in cm between the primary and secondary curves of the catheter. The Amplatz left (AL) catheters range in size from AL 1 to AL 3. Similarly, for the RCA, the Judkins right (JR) catheters range in size from JR 3.5 to JR 6. The modified version of the Amplatz right (AR) catheter is more commonly used than the

traditional AR catheter, and the size ranges from AR 1 to AR 3. Other catheters include the multipurpose catheters (multipurpose A1, A2, B1, and B2), which can be used for cannulating the LCA, RCA, and bypass grafts. For aortocoronary bypass grafts, the right or the left coronary bypass catheters may be used, although the JR 4 catheter may be adequate in some cases. The internal mammary artery (IMA) may be cannulated using either the IMA or the IMA special catheters, although again the JR 4 catheter may engage the LIMA graft successfully. The shapes of some of the commonly used diagnostic catheters are demonstrated in **Figure 63.3**. **Table 63.3** summarizes the preferred catheters for the engagement of coronary arteries and bypass grafts.

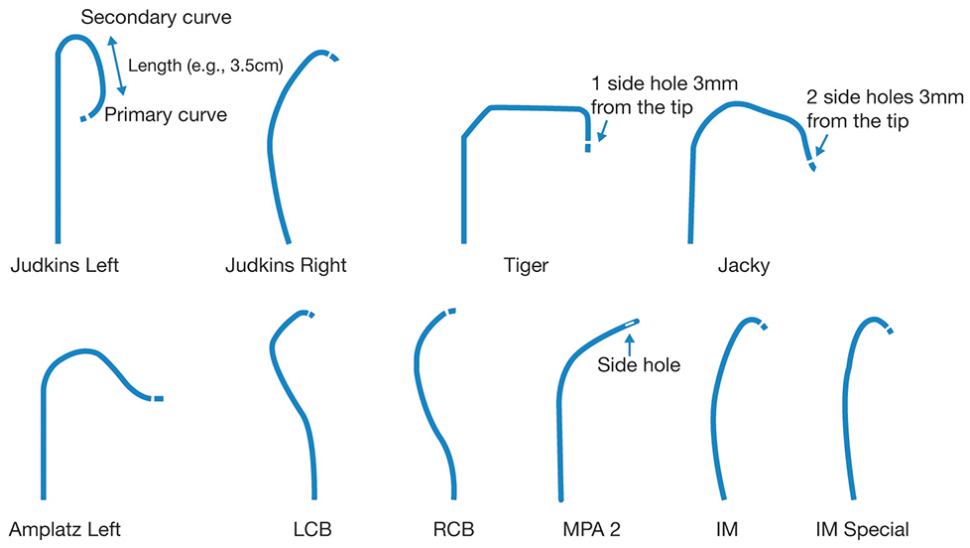

FIGURE 63.3 Commonly used diagnostic catheters for coronary artery and bypass graft cannulation. IM, internal mammary; LCB, left coronary bypass, MPA, multipurpose angiographic; RCB, right coronary bypass.

TABLE 63.3 Suggested Catheters for Coronary Arteries and Bypass Grafts

Coronary Artery or Graft	Catheters
LCA • Normal LCA origin and aorta size • Large ascending aorta	JL 3.5/4.0, Tiger 4.0, Jacky (radial) JL 5 or 6, Tiger 4.5, Sarah JL 3 JR 4, AR 2

Coronary Artery or Graft	Catheters
• Small ascending aorta • Anomalous left main from right sinus • Anomalous LCX from right sinus	JR 4
RCA • Normal origin • Anterior origin • Superior-anterior origin • Downward origin/course • Anomalous RCA from left sinus	JR 4, Tiger, Jacky (radial) AR 2, AL 1 AL 1 or Multipurpose (if downward course) Multipurpose (A or B) JL 3.5 or 4, AL 1, AR 2
LIMA or RIMA	IMA, IMA special, Bartorelli-Cozzi (from left radial), JR 4
SVG-RCA	JR 4, Multipurpose (A or B), RCB
SVG-left system	JR 4, LCB, AL 1, AR 2

AL, Amplatz left; AR, Amplatz right; IMA, internal mammary artery; JL, Judkins left; JR, Judkins right; LCA, left coronary artery; LCB, left coronary bypass; LCX, left circumflex; LIMA, left internal mammary artery; RCA, right coronary artery; RCB, right coronary bypass; RIMA, right internal mammary artery; SVG, saphenous vein graft.

1. **LCA.** Catheters are flushed with heparinized saline and advanced through the sheath over a 0.035-in J-tipped guidewire. Using fluoroscopic guidance in the LAO (30°-40°) projection, the left main coronary artery is cannulated, typically with a JL 3.5, TIG 4.0 or Jacky from the right radial, or a JL 4 from the left radial or femoral access sites. Generally, the size of the JL catheter is chosen based on the diameter of the ascending aorta (ie, JL 5 for patients with an ascending aorta diameter of 4 cm). The catheter tip should be coaxial to the left main coronary artery ostium upon engagement. If the catheter does not engage the left main ostium easily, torquing the catheter may help. With the JL catheters, unless the aorta is dilated and provides no hinge point for the JL catheter, counterclockwise rotation moves the catheter tip anteriorly and clockwise rotation moves it posteriorly (opposite in

dilated aortas, where the catheter does not make contact with the aortic wall). Care should be taken to prevent the catheter from engaging too deeply ("deep-seating") the left main coronary artery. The pressure waveform must be observed for **damping** (a decrease in the systolic pressure) or **ventricularization** (when the waveform looks like a ventricular pressure tracing) before even flushing the catheter, which may indicate the presence of significant ostial left main disease or the need to pull the catheter back in order to minimize the risk of iatrogenic dissection (**Figure 63.4**). Injection of contrast should be gentle with a gradual increase in pressure ("ramping"). Enough contrast should be injected to opacify the entire coronary artery and ensure reflux into the aorta. Diminished or absent reflux may indicate significant ostial disease. Injection should also be forceful enough for adequate blood displacement and "streaming" prevention, which can create the illusion of stenoses. Care should be taken to inspect the injection syringe for air bubbles before each injection and to hold the syringe upright while injecting to prevent air embolism.

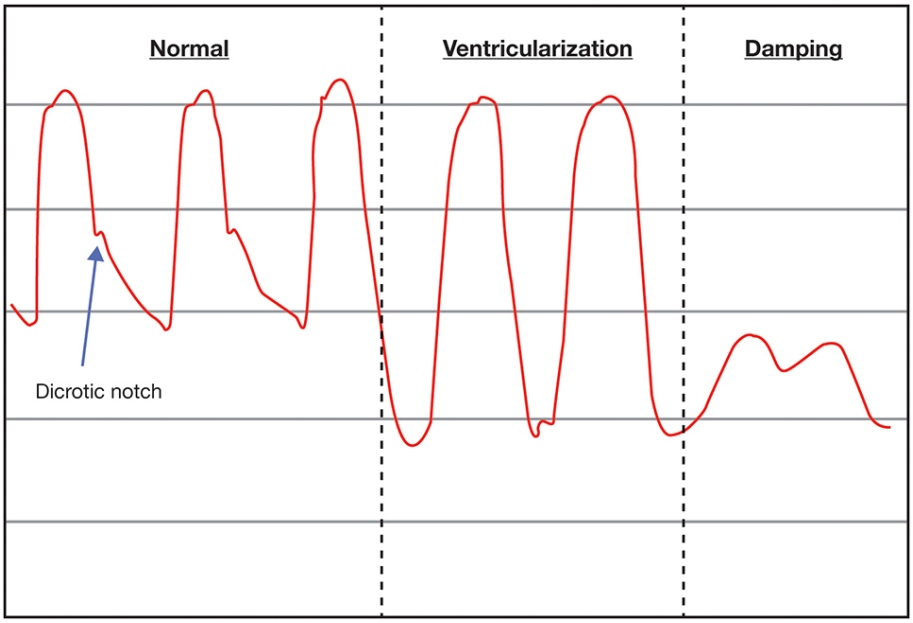

FIGURE 63.4 Arterial pressure waveform recorded from the catheter tip. Normal aortic pressure waveform with dicrotic notch

(left), ventricularization (center), and pressure damping (right).

2. **RCA.** Catheterization of the RCA is usually performed using a JR 4 in the LAO 30° projection. The RCA ostium is usually located anteriorly in the right sinus of Valsalva. As the catheter is slowly pulled back approximately 2 cm above the aortic valve, it is rotated clockwise (ie, anteriorly) to engage. If the pressure dampens upon engagement, ostial disease, spasm, or selective intubation of the conus (which arises separately 50% of the time) should be suspected. If the JR 4 does not easily engage the RCA, an anatomic variation of the RCA origin should be suspected, and a nonselective sinus angiogram can be performed for further evaluation. Care should be taken to avoid subselectively intubating the conus branch because of the risk of dissection or ventricular arrhythmia during contrast injection. If difficulty is encountered in engaging the RCA because of the orientation of the ostium, a 3DRC catheter can be useful. An Amplatz catheter (AL 1 or AR 2) can be useful for an anterior or upwardly ("Shepherd crook") RCA, and a multipurpose catheter can be useful for a downwardly angled ostium. In cases of a high and anterior RCA origin, less clockwise torque should be applied to the catheter so that it faces more anteriorly in the LAO projection.

3. **Bypass grafts**

   a. **LIMA.** Catheterization of the LIMA is done either in the posteroanterior (PA) or RAO projection; in the LAO projection, the LIMA overlies the left subclavian artery and is not adequately visualized. In femoral cases, the catheter (usually a JR 4 catheter or an IMA catheter) is pulled back from the ascending aorta into the aortic arch while applying counterclockwise torque so the catheter tip is pointing up until it enters the left subclavian artery (LAO 30° projection is helpful in separating the aortic arch branches and engaging the left subclavian). At this point, many operators will obtain an RAO 20° to 30° angiogram of the left subclavian artery to rule out a stenosis proximal to the LIMA and visualize the angle of LIMA origin. A wire (J-tipped guidewire or Wholey wire) is

then advanced into the subclavian artery. Next, the catheter is advanced over the wire into the subclavian artery (or exchanged for an IMA catheter if a JR 4 is used to enter the left subclavian), the wire is removed, and the catheter is slowly pulled back with a slight counterclockwise (ie, anterior) rotation until it engages the ostium of the LIMA. Movements around the ostium must be gentle to reduce the risk of dissection; frequent test injections may be helpful. Turning the head to the left or right and pulling the left arm caudally are maneuvers that can help engage the LIMA. If the ostium points downward at a sharp angle, the IMA or IMA special catheter provides better angulation and more coaxial engagement. If the ostium cannot be engaged successfully, a nonselective angiogram can be taken with the tip of the catheter as close to the ostium as possible. A BP cuff should be inflated above systolic pressure in the left arm to facilitate dye movement down the LIMA. If radial access is preferred, left radial access provides a direct route to engage the LIMA. A Bartorelli-Cozzi (B-C) catheter can be also used for LIMA engagement from the left radial approach. Special caution should be applied, as the B-C catheter tends to engage the LIMA more deeply than the IMA catheter.

b. **Right internal mammary artery (RIMA).** Catheterization of the RIMA is similar to that of the LIMA from the femoral approach. The catheter (either JR 4 or IMA) is placed in the innominate artery by pulling it back in the aortic arch while applying counterclockwise rotation. The wire is advanced to the right subclavian artery. Care must be taken to avoid the right carotid artery. The wire is removed, and the catheter is pulled back with a slight clockwise (ie, anterior) rotation until it engages the ostium of the RIMA. Right radial access provides a direct route to engage the RIMA.

c. **Saphenous vein grafts (SVGs).** Catheterization of SVGs depends on the specific type of graft. The grafts are anastomosed to the anterior surface of the aorta. The

orientation of SVGs from caudal to cranial is usually as follows: left anterior descending artery (LAD), ramus intermedius (RI), diagonal branches of LAD, and obtuse marginal (OM) branches of left circumflex coronary artery (LCX). In the LAO view, grafts to the RCA usually point to the patient's right (left side of the screen), whereas grafts to the left system are usually pointing toward the operator and to the left of the screen. In the RAO view, grafts to the left system point to the patient's left/anteriorly (right side of the screen). In some cases, the ostia of the vein grafts are marked by circular markers placed by the surgeon on the outer surface of the aorta. Injections into presumed vein graft stumps should be forceful enough to ensure that the graft is truly occluded, as opposed to poor opacification from an incompletely engaged catheter. A review of the operative note, previous catheterization procedures, and available chest CT scans is very important to determine the number, location, and type of grafts (eg, in situ vs free LIMA or RIMA, "Y" or sequential grafts). If a graft cannot be located or a stump identified, an aortogram can be performed (ideally with a power injector).

(1) **SVG to RCA.** The graft is engaged in the LAO 30° projection, by pulling back the catheter (usually JR 4) above the RCA ostium, while the tip is pointing to the left side of the screen. Often, the graft has a steep downward orientation from the aorta, and a multipurpose catheter can be useful in engaging the graft. Alternatively, a right coronary bypass (RCB) catheter or a modified AR catheter can be used.

(2) **SVG to LAD.** The graft to the LAD is most easily engaged in the RAO 30° view by moving the catheter slowly up and down until it engages the graft ostium. The grafts to the left system point anteriorly in the RAO projection (right side of the screen). JR 4, left coronary bypass (LCB), AL 1, and multipurpose catheters can be used to engage.

(3) SVG to LCX. Grafts to the LCX are engaged by pulling back the catheter from the SVG to the LAD, while remaining in the RAO projection. If the catheter does not engage the ostium of the graft easily, a slight clockwise rotation of the catheter is performed at an area cranial to the SVG to LAD. The technique is otherwise similar to that for engaging the graft to the LAD.

III. IMAGING THE VESSELS AND HEMODYNAMIC ASSESSMENTS

A. Normal coronary anatomy

The left main coronary artery originates normally from the left sinus of Valsalva and bifurcates into the LAD and LCX, although it sometimes trifurcates to provide an RI. The LAD courses along the anterior interventricular groove, supplying numerous septal perforators and a variable number of diagonal branches to the anterolateral wall of the LV before it continues to the apex. The LCX courses along the left atrioventricular (AV) groove, providing a variable number of OM branches to supply the lateral and posterolateral walls of the LV. The first marginal branch is also called the "high lateral" branch of the LCX, with subsequent branches called lateral or posterolateral branches depending on their destination. The LCX continues in the AV groove for a variable distance. In patients in whom the LCX is dominant, the LCX extends into the posterior AV groove and gives rise to the posterior descending artery (PDA) branch.

The RCA normally originates from the right sinus of Valsalva and courses along the right AV groove, providing atrial branches (to the right atrium) and acute marginal branches (to the right ventricle). A conus branch usually originates as the first branch from the proximal RCA to supply the right ventricular outflow tract; 50% of the time the conus artery has a separate ostium. It is usually unnecessary to visualize a separate conus branch, unless collaterals to the LAD are suspected (Vieussens ring). The RCA supplies the sinoatrial (SA) nodal branch in about 60% of the cases (otherwise, a left atrial branch of the LCX supplies the SA node). In a right dominant system, the distal RCA provides the PDA and continues in the posterior AV

groove, providing a variable number of posterior left ventricular (PLV) branches. **Dominance** refers to which artery provides the PDA, as this supplies the inferior wall of the heart and posterior portion of interventricular septum. In about 85% of patients, this will be the RCA; in 7%, the RCA and LCX will be codominant; and in another 8%, the LCX will be dominant. The PDA courses along the inferior interventricular groove, providing septal perforators to supply the inferior septum. After giving off the PDA, the posterolateral segment of the RCA provides a branch to supply the AV node, known as AV nodal artery, in 90% of the cases.

B. Basic principles

1. Several views of the coronary arteries are required to prevent overlap of vessel segments and to delineate the severity of stenoses. A general principle is that in an RAO view, the spine is on the left of the screen and conversely, in an LAO view, the spine is on the right of the screen. Cranial views bring the silhouette of the diaphragm into the field of view. The diagonal and OM branches tend to move in synchrony, because they supply the lateral aspect of the heart, whereas the LAD is located on the anterior portion of the heart.
2. Caudal angulation tends to move posterior vessels (such as the posterolateral branches of the RCA or the OM branches of the LCX) inferiorly. Cranial angulation tends to move posterior vessels superiorly and anterior vessels (LAD and diagonal branches) inferiorly.
3. **Panning** motion should be smooth, slow, and ideally minimal. It is best to wait for two to three systolic cycles after contrast injection and focus on proximal vessels before panning down the length of the artery of interest. It is important to pan to look for collaterals in cases of CTO of a coronary artery or ACS.

C. Basic angiographic views.

Table 63.4 summarizes the key angiographic views for the assessment of the coronary arteries and bypass grafts.

Key Angiographic Views for Specific Coronary Artery Segments

TABLE 63.4

	Projection	Artery Segments
LCA	RAO CAU	Proximal LAD Distal LAD Proximal and mid-LCX Obtuse marginals
	PA CAU	Left main shaft Proximal LAD Distal LAD Proximal and mid-LCX
	LAO CAU	Left main Left main bi- or trifurcation Proximal LAD (may be foreshortened) Ramus intermedius Proximal LCX Obtuse marginals
	PA CRA	Mid-LAD Diagonal origins Distal LCX
	LAO CRA	Left main ostium Mid- and distal LAD Diagonal origins Distal LCX branches Left PDA
	RAO CRA	Mid- and distal LAD Diagonal origins Distal LCX branches
RCA	LAO	Proximal RCA Mid-RCA
	PA (LAO) CRA	Distal RCA bifurcation Proximal and mid-PDA PLV branches
	RAO	Mid-RCA Mid- and distal PDA PDA length

CAU, caudal; CRA, cranial; LAD, left anterior descending; LAO, left anterior oblique; LCA, left coronary artery; LCX, left circumflex; PA, posteroanterior; PDA, posterior descending artery; RAO, right anterior oblique; PLV, posterior left ventricular; RCA, right coronary artery.

1. **LCA** (**Figures 63.5 to 63.10**). There is wide variation among operators in the sequence of views obtained. Many operators start with a PA view and focus on the left main coronary artery. The problem with a pure PA view is that there is significant overlap with the spine. Therefore, a few degrees of RAO angulation ("shallow RAO") can be used to get the coronaries off the spine. A steeper RAO angulation provides greater separation of the LAD from the LCX. A slight amount of caudal angulation can be used to decrease the foreshortening of the proximal circumflex in the straight RAO view and to place the diagonals below the LAD. Therefore, a **20° RAO, 20° caudal** is often the first view, displaying the entire left coronary system. This view also provides a good view of the proximal LCX and the origin of a RI branch, if present. The contour collimator (called the wedge or the shield) should be moved to the upper right of the screen over the lung fields to reduce radiation exposure. A PA view with **40° cranial** angulation is useful in viewing the mid- and distal portions of the LAD and diagonal branches. A **30° RAO, 30° cranial** view can be used to separate better the diagonals from the LAD, placing them above the LAD. The **50° LAO, 30° cranial** view is also good for separating the LAD from its diagonal branches, especially for vertically oriented hearts. This view is also helpful for the evaluation of a left-sided PDA branch and the ostium of the left main. Steeper degrees of LAO further separate the LAD from the LCX and move the LCX off the spine. The **50° LAO, 30° caudal** ("spider") view is useful for looking at the left main coronary artery and its bifurcation. The proximal LAD is typically foreshortened unless the heart has a horizontal orientation.

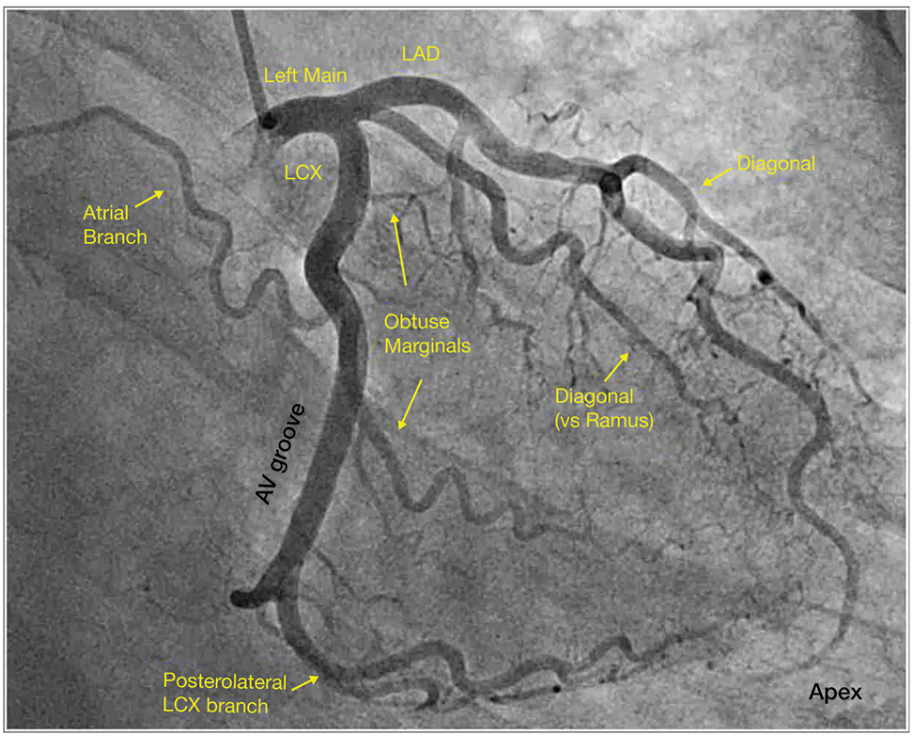

FIGURE 63.5 Right anterior oblique 20°, caudal 20° view of the left coronary artery and branches. LAD, left anterior descending artery; LCX, left circumflex artery.

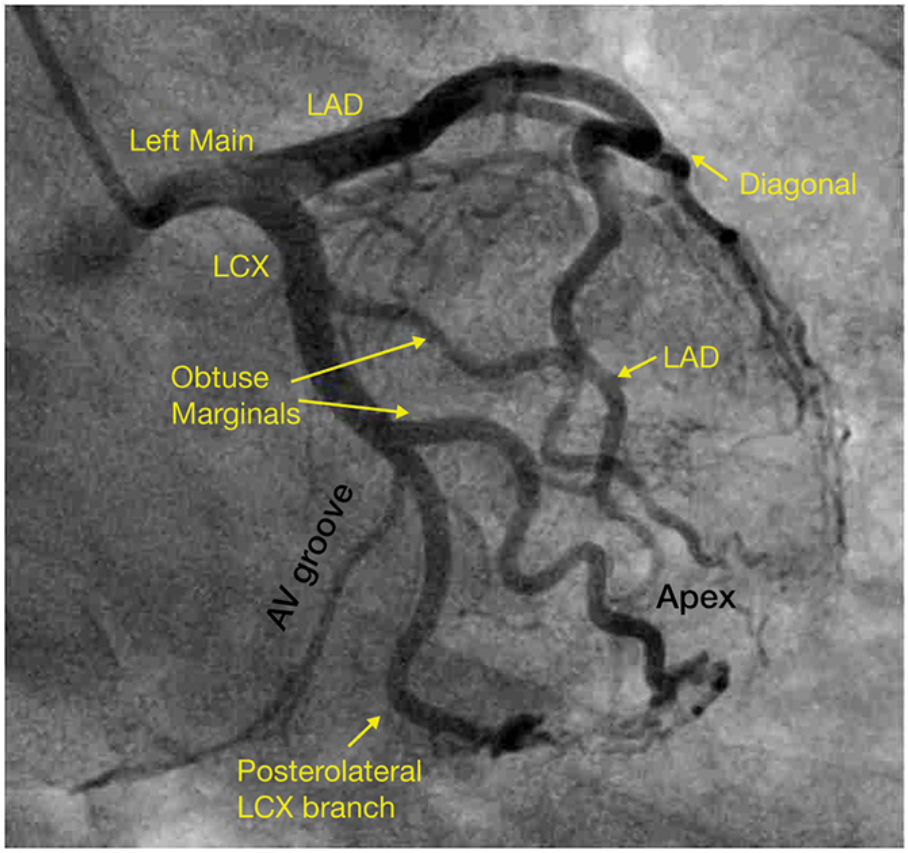

FIGURE 63.6 Posteroanterior, caudal 30° view of the left coronary artery and branches. LAD, left anterior descending artery; LCX, left circumflex artery.

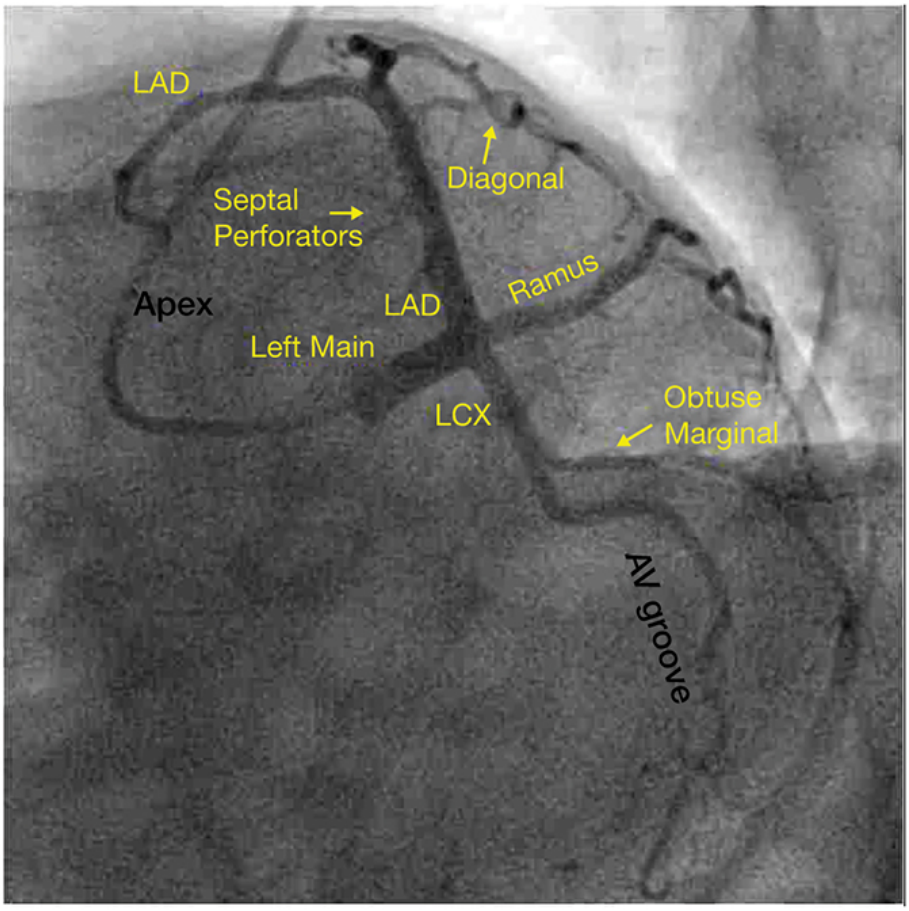

FIGURE 63.7 Left anterior oblique 50°, caudal 30° view of the left coronary artery and branches ("spider view"). LAD, left anterior descending artery; LCX, left circumflex artery.

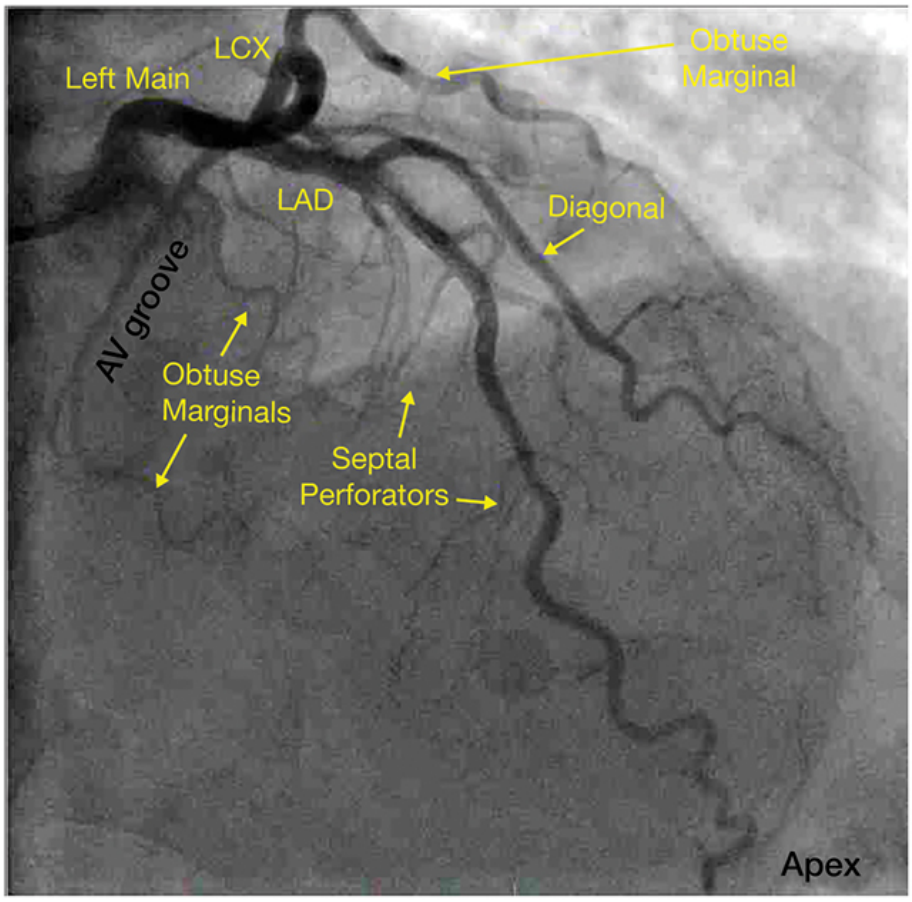

FIGURE 63.8 Posteroanterior, cranial 40° view of the left coronary artery and branches. LAD, left anterior descending artery; LCX, left circumflex artery.

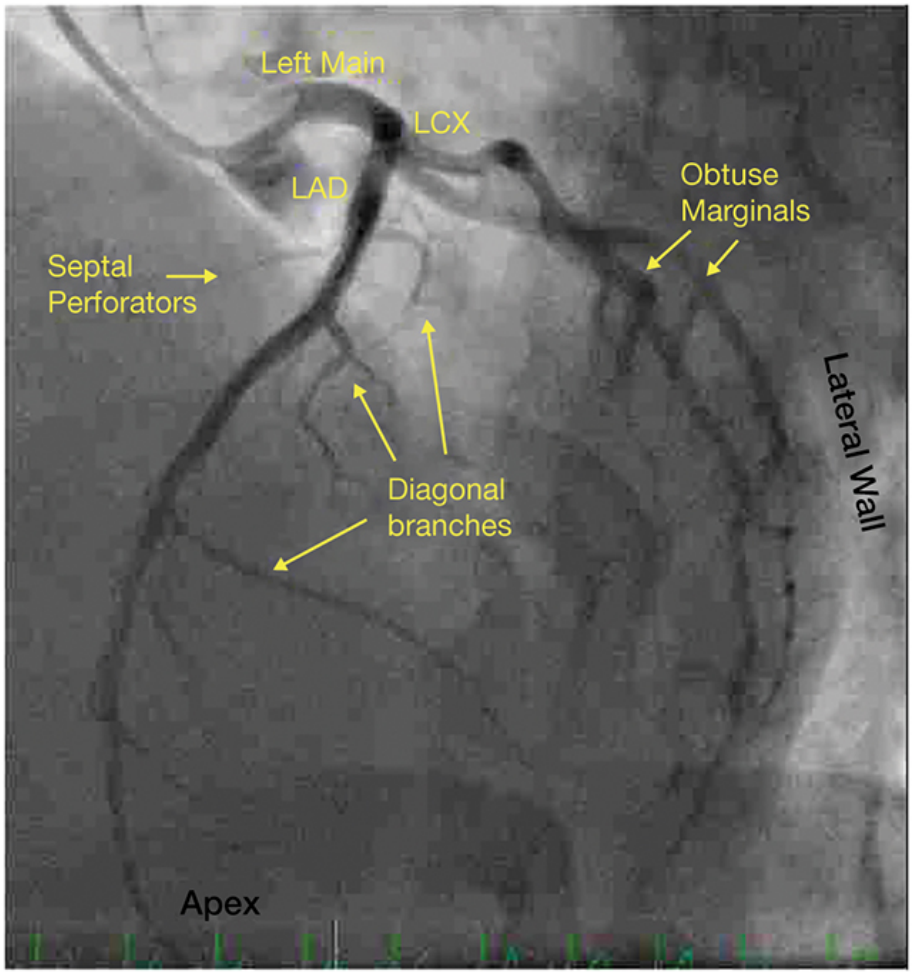

FIGURE 63.9 Left anterior oblique 50°, cranial 30° view of the left coronary artery and branches. LAD, left anterior descending artery; LCX, left circumflex artery.

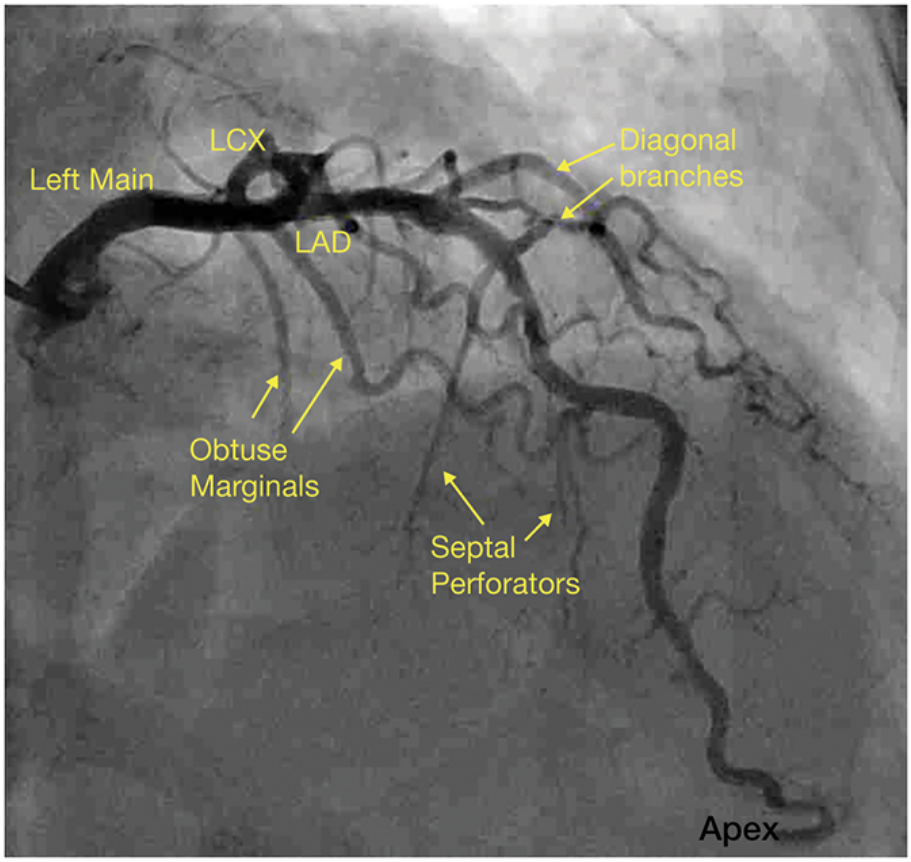

FIGURE 63.10 Right anterior oblique 30°, cranial 30° view of the left coronary artery and branches. LAD, left anterior descending artery; LCX, left circumflex artery.

2. **RCA** (**Figures 63.11 to 63.13**). The RCA is usually engaged in LAO 30° projection, which provides a good view of the proximal and mid-RCA. Cranial angulation is then added (25°-30°) for assessment of the PDA and PLV branches. The **PA with 30° cranial** can provide a useful view of the origins of the PDA and posterolateral branches at the distal RCA bifurcation. The **30° RAO** view provides a good view of the mid-RCA and the length of the PDA.

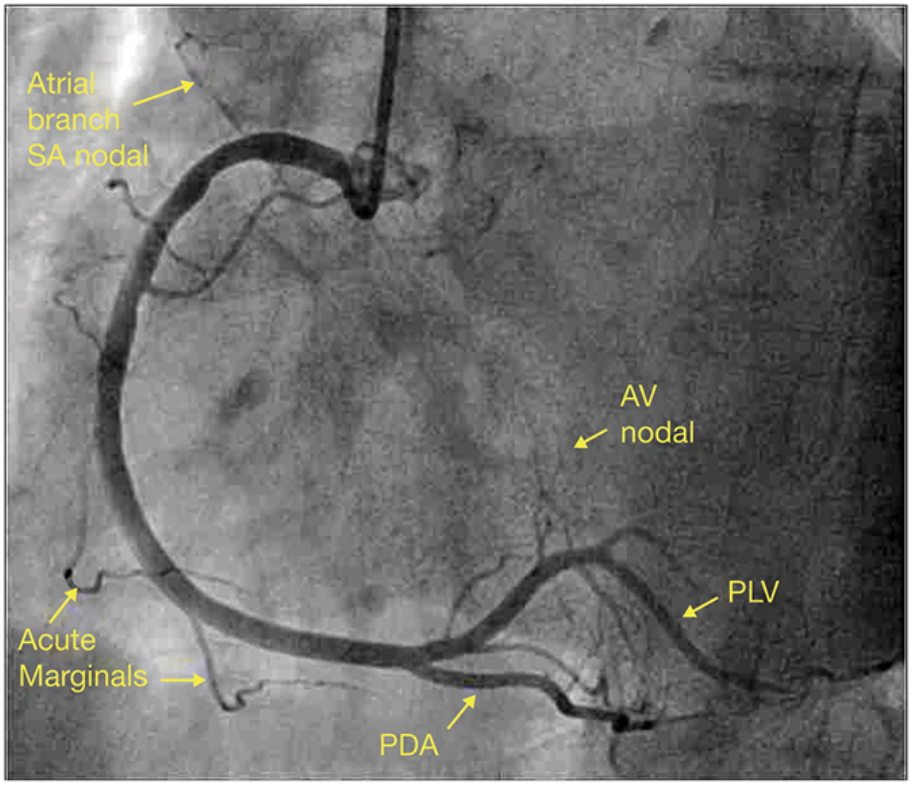

FIGURE 63.11 Left anterior oblique 30° view of the right coronary artery and branches. AV, atrioventricular; PDA, posterior descending artery; PLV, posterior left ventricular; SA, sinoatrial.

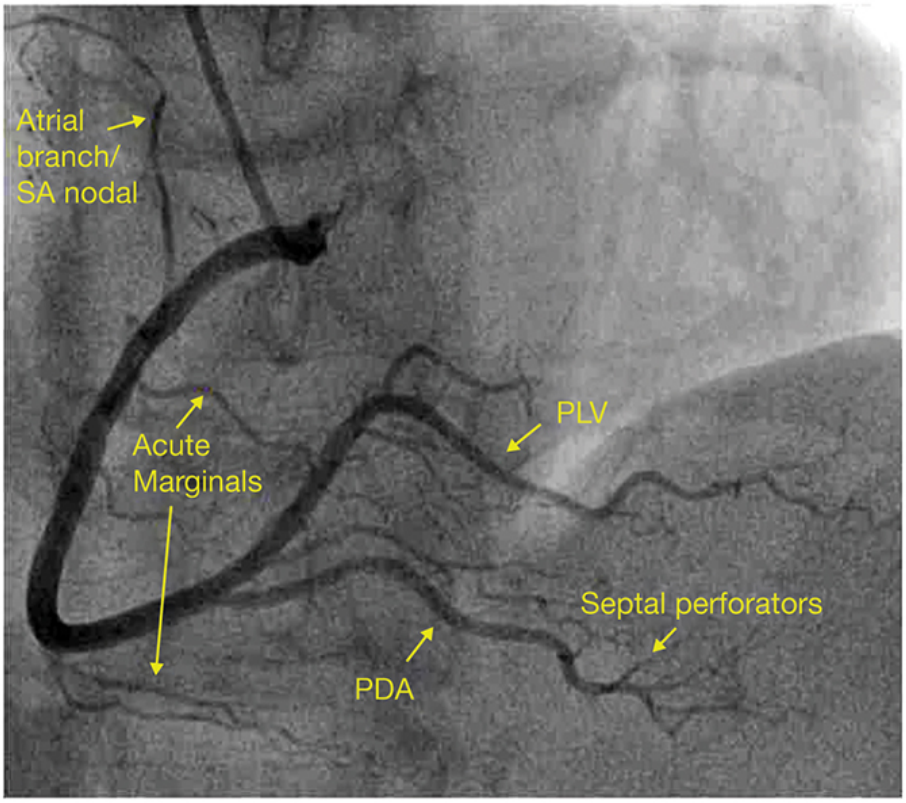

FIGURE 63.12 Posteroanterior , cranial 30° view of the right coronary artery and branches. PDA, posterior descending artery; PLV, posterior left ventricular; SA, sinoatrial.

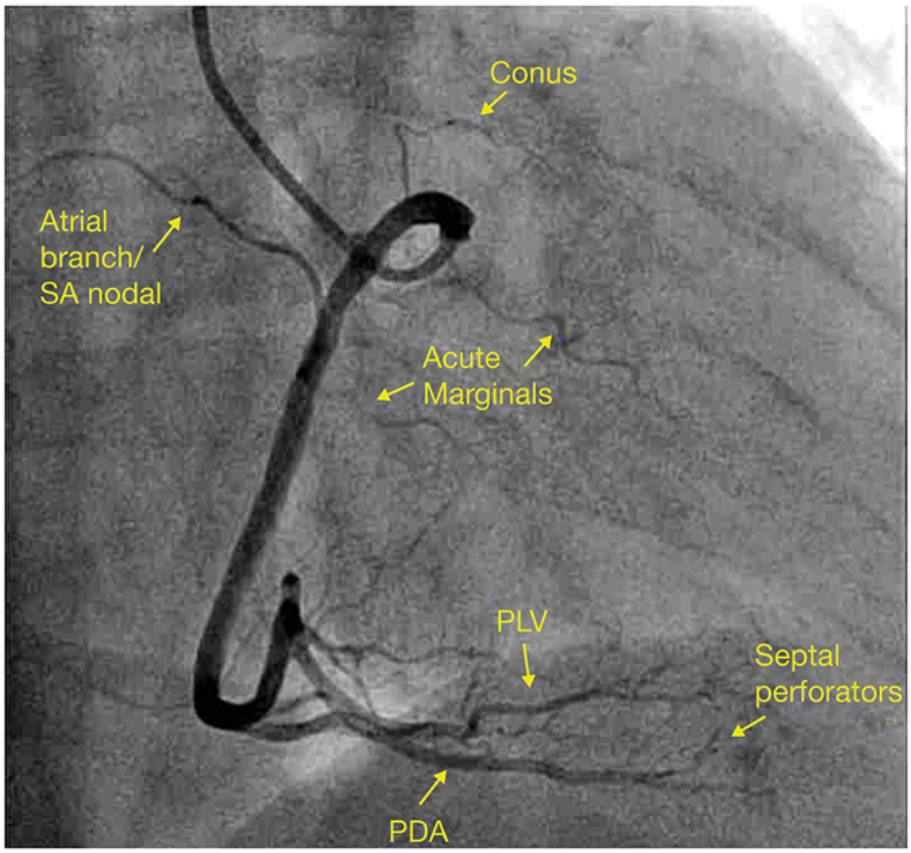

FIGURE 63.13 Right anterior oblique 30° view of the right coronary artery and branches. PDA, posterior descending artery; PLV, posterior left ventricular; SA, sinoatrial.

3. **Bypass grafts.** Typically, two orthogonal LAO and RAO views (with some cranial or caudal angulation depending on the vessel of interest) are used for the assessment of the bypass grafts. A particularly useful view (although rarely obtained) for the LIMA-LAD anastomosis is the lateral view (LAO 90°).

D. Congenital coronary artery anomalies. Coronary artery anomalies should be suspected if there is an absent coronary artery and a large area of myocardium without evidence of arterial supply in a stable patient. The most common anomaly is absent left main coronary artery trunk, in which the LAD and the LCX have separate ostia (incidence 0.47%). If the LAD is first cannulated, the LCX can be engaged with a counterclockwise rotation; sometimes, one size larger catheter may be needed. Likewise, if the LCX is first cannulated, clockwise rotation, perhaps with a smaller sized catheter (JL 3.5), is

usually needed to engage the LAD. Other common anomalies in order of occurrence are the LCX originating from the right sinus of Valsalva or the proximal RCA (0.45%) and the RCA originating from the ascending aorta above the sinus of Valsalva (0.18%). The RCA originating from the left sinus of Valsalva is the next most common anomaly, originating superior and anterior to the left main (0.13%). The origin of the left main artery from the right sinus is very rare (0.02%), but it can result in sudden death in cases of interarterial course between the aorta and the pulmonary artery. The left main artery can also course into the ventricular septum (most common), anterior to the pulmonary artery or posterior to the aorta. The 30° RAO view can help define the relationship between the coronary artery and the great vessels. If the course is septal, septal perforators can be seen originating from the left main. The Amplatz (left or right, depending on the cusp of origin) and multipurpose catheters are especially useful in cannulating anomalous coronary arteries.

Although not truly a congenital anomaly, every operator should be aware of **myocardial bridging**. This manifests as phasic compression of a coronary artery (usually the mid-LAD) that is present only during systole. There have been reports of bridging involving the diagonal branches of the LAD, the marginal branches of the LCX, and the distal RCA. Because most of the coronary blood flow occurs during diastole, myocardial bridges are rarely symptomatic. A phenomenon similar to bridging can occur in HOCM, in which septal perforators from the LAD become obliterated during systole.

E. Quantification of coronary stenosis. Given the three-dimensionality of the heart, it is important to always obtain at least two orthogonal views of each coronary artery. A single view can miss an eccentric lesion. The severity of a lesion is based on percent diameter stenosis compared with a “normal” reference segment. Lesions are generally classified based on the angiographic degree of stenosis as mild (0%-39%), moderate (40%-69%), or severe (≥70%). Fifty percent or greater stenosis of the left main artery is considered severe. When measuring the size of vessels and stenoses, it is useful to note that a 6F catheter has an external diameter of 2 mm. Formal quantitative

coronary angiography or the use of calipers can improve the measurement of coronary artery stenoses. Quantitative coronary angiography decreases the interobserver and intraobserver variabilities of grading stenosis severity.

F. Limitations of coronary angiography. Sometimes, the severity and clinical significance of a lesion are difficult to accurately assess based on angiography alone, particularly in the presence of diffuse disease. Angiography assesses the lumen of the artery; therefore, it can underestimate the presence of atheroma in cases of positive (outward) remodeling of the arterial wall (the Glagov phenomenon). Furthermore, angiography can only visualize arteries >200 mcm in diameter. Techniques such as hemodynamic assessment of angiographically intermediate lesions with fractional flow reserve or instantaneous wave-free ratio (iFR) and the use of intravascular US, especially in cases of left main or ostial RCA lesions, can provide more information about their severity and clinical significance. See Chapter 64 for more details on these adjunct methods of imaging and diagnosis.

G. Crossing the aortic valve

a. Normal aortic valve. The pigtail catheter is commonly used to cross native aortic valves if no significant stenosis is present. Bioprosthetic valves can also be crossed, but crossing mechanical valves (eg, St Jude, Björk-Shiley, Medtronic-Hall, On-X) with a catheter should be avoided due to the risk of catheter entrapment. The pigtail catheter should be viewed as a "6" in the ascending aorta in the RAO projection and then advanced to loop above the aortic valve to form a "9" shape. When pulled back very slowly, the catheter should fall into the commissure of the aortic valve, and it can then be rapidly advanced into the LV with the aid of the J-wire placed in the pigtail loop. Having the patient take a deep breath and hold it while the pigtail catheter is being unfolded can facilitate the passage of the catheter into the LV. Sometimes, the guidewire itself may be useful in crossing the valve, in which case the catheter is simply advanced over the guidewire into the LV.

b. Aortic stenosis. In cases of aortic stenosis, difficulty may be encountered in passing any catheter across the aortic valve. A 0.035-in straight-tipped wire along with a 5F AL 1 (or AR 2) diagnostic catheter can be used to cross the valve. Special care must be taken during this maneuver to avoid perforating the aortic cusps or causing trauma to the coronary ostia.

H. Left ventriculography

a. Setup. The pigtail catheter (commonly the angled version) is positioned in the mid-cavity of the LV and should look like a "6" in the RAO projection. If the pigtail catheter twists with each beat, this indicates that it is caught in the mitral valve apparatus and needs to be repositioned. The monitor should be observed for ectopy, and the catheter should be repositioned accordingly. First, the LVEDP should be measured on a 40 mm Hg scale. In patients with an elevated LVEDP (>25 mm Hg), a left ventriculogram is generally contraindicated. If the decision to proceed with the left ventriculogram is made, sublingual nitroglycerin should be given first, to lower the LVEDP. Digital subtraction can be used instead of cinefluoroscopy to obtain the left ventriculogram. This allows a smaller amount of contrast to be used, although it may not allow proper assessment of MR. With digital subtraction, the view must be carefully centered because panning should not be performed. The left ventriculogram is best avoided in patients with critical aortic stenosis, significant left main artery disease, or severe LV dysfunction. Ventriculography should not be attempted with a single end-hole catheter because of the risk of cardiac perforation, ectopy, and poor-quality images.

b. Views. The **30° RAO** view is used to look at the overall LV function. In particular, the anterior, apical, and inferior walls can be assessed. The RAO view is also useful to assess MR. The regurgitation is graded on a scale of 1 to 4; 1 represents trace MR, with mild left atrial opacification that clears with one beat; 2 represents a mild-to-moderate degree of opacification, although less than that of the LV; 3 represents moderate-to-severe opacification of the left atrium equal to that of the LV; and 4

represents severe MR, with complete opacification of the left atrium greater than that of the LV. The catheter itself can cause MR if it is caught in the mitral valve apparatus or if it induces premature ventricular contractions. The correlation between angiographic and echocardiographic MR is excellent. The **60° LAO** projection allows evaluation of the septum and the posterior and lateral walls. Ventricular septal defects are best identified in the LAO projection with slight cranial angulation. If biplane imaging capability exists, RAO and LAO views of the LV can be obtained simultaneously.

c. **Settings.** For a ventriculogram, the flow injector can be set at a rate of 10 to 12 mL/s for a total volume of about 25 to 30 mL, with a rate rise of 0.2 seconds (to minimize ectopy and to keep the catheter from moving abruptly) and a pressure of 600 psi. The exact settings will vary depending on the size of the heart and the need to limit contrast.

I. **Aortography.** Aortography is usually performed in the LAO projection, with the pigtail catheter about 2 cm above the aortic leaflets. Compared with a ventriculogram, a larger volume of contrast is needed to opacify the aorta. The flow injector is set to a higher total volume than for the left ventriculogram, usually about 30 to 45 mL (50:50 diluted contrast can be also used if limiting contrast is necessary) at a rate of 15 to 20 mL/s. No rate of rise is necessary, and a pressure limit of 900 psi is used. Aortic insufficiency can be identified with a grading system similar to that of MR, with 1 representing trace aortic insufficiency that clears from the LV with each beat, 2 representing mild LV opacification that takes more than one beat to clear, 3 representing moderate LV opacification equal to that of the aortic root, and 4 representing complete opacification of the LV greater than that of the aortic root. Diseases of the aorta such as aneurysms or dissection can be identified. An aortogram can aid in visualization of anomalous coronary arteries or grafts that are difficult to engage; however, the absence of filling of a bypass graft on an aortogram does not exclude its presence or patency. The aorta must be completely opacified to ensure that grafts are seen. Left

coronary grafts are best seen in the RAO projection, and right coronary grafts in the LAO projection.

J. Pharmacologic testing. When coronary artery spasm is suspected as the cause of episodic angina, acetylcholine provocation testing can be performed. Incremental doses of intracoronary acetylcholine (starting with 10 mcg, increasing the dose by 10 mcg every few minutes for a maximum of 50 mcg for the RCA and 100 mcg for the LCA) are administered as slow bolus through the coronary catheter. The patient is monitored for the development of chest pain and ST-segment changes on the 12-lead continuous ECG monitor. Acetylcholine injection can result in a transient complete AV block, especially when RCA is injected. If the patient develops typical chest pain or ST elevation on electrocardiographic monitoring, a coronary angiogram is performed immediately to assess for epicardial spasm. A positive response consists of a focal area of spasm that is relieved by intracoronary nitroglycerin (a usual dose of 100-200 mcg) in the setting of chest pain and ST elevations in the corresponding myocardial territory. Physiologic diffuse spasm may also occur and can be managed with nitroglycerin and verapamil (100-200 mcg).

Intracoronary vasodilators, such as nitroglycerin, can be used in cases where ostial disease is suspected (especially of the RCA), in order to rule out catheter-induced spasm.

IX. POSTCATHETERIZATION CARE

A. Radial sheath removal and hemostasis. Radial artery hemostasis is generally achieved using one of the compression bands, such as TR Band (Terumo). The band is secured and inflated around the arteriotomy site, and the sheath is slowly removed simultaneously as the band is inflated. The band pressure is adjusted to the minimum pressure needed to obtain hemostasis so that distal flow is not obstructed, a term called “patent hemostasis.” This technique lowers the risk of radial artery occlusion after the procedure. Palpating a radial artery pulse distal to the band and monitoring flow with the use of a pulse oximeter placed on the thumb are important steps used to ensure adequate palmar arch flow during compression. The band is

gradually deflated over a period of time (beginning typically 60-90 minutes after placement) to ensure hemostasis has occurred. Careful monitoring of the upper extremity for the development of hematoma should be performed.

B. Femoral sheath removal and hemostasis

1. **Manual compression and compression devices.** After the completion of the procedure, the femoral sheath is removed, and direct manual pressure is applied over the pulse. Pressure is held for approximately 20 minutes (about 3 minutes per Fr sheath size) until there is no bleeding. Manual compression remains an important technique because of the low cost, good safety profile (complication rate <0.23%), and ability to be employed despite femoral artery dissection, significant peripheral vascular disease, or a low stick. The amount of pressure should be enough to stop the bleeding and allow adequate blood flow to the distal extremity. Pedal pulses should be periodically checked. Compression devices such as the FemoStop (Abbott Cardiovascular) are available but are not widely used due to cost and potential complications (skin abrasion or tissue necrosis, compression nerve injury, femoral artery, and/or vein thrombosis). In patients with severe aortic stenosis or significant left main disease, laboratory personnel should be prepared to rapidly manage a vagal episode, which can be life-threatening in these situations. Adequate administration of analgesia before sheath removal decreases the risk of a vagal reaction. Bed rest is generally required for 4 to 6 hours after femoral sheath removal. During the postprocedural observation period, the heart rate (HR), BP, urine output, distal pulses, and the access site should be monitored (for bleeding, or hematoma). Before discharge, it is best to have the patient ambulate under observation. Specific discharge instructions should include avoidance of excessive straining or lifting weights for 5 to 7 days, as well as education on the possibility of late access site bleeding or hematoma formation.
2. **Arteriotomy closure devices.** Femoral artery closure devices have been increasingly used, due to the advantages of immediate

hemostasis without the need for manual compression, enhanced patient comfort, early ambulation, and early/same-day discharge. There are two broad categories of arteriotomy closure devices, based on the mechanism of achieving hemostasis: active approximation and passive approximation. Prior to closure device deployment, a femoral sheath angiogram should be performed to ensure that the arteriotomy site is at an appropriate level of the CFA. The use of closure devices should be avoided in cases of high (external iliac) or low (below the bifurcation) arteriotomies. Although the use of arteriotomy closure devices is generally safe and effective, there is a significant learning curve for the operators. Specific complications, including device embolization, vessel closure, and access site infection, are rare but potentially serious. Sterility should be maintained during the deployment of vascular closure devices to minimize the risk of infection. Several arteriotomy closure devices have been approved by the Food and Drug Administration (FDA). The most commonly used closure devices are Perclose ProGlide (Abbott Vascular), StarClose (Abbott Vascular), Angio-seal (Terumo), and Vascade (Cardiva Medical Inc).

3. The **Perclose ProGlide** is an active approximation percutaneous suture device that allows early ambulation (usually 2 hours after sheath removal). The device contains two small needles with an attached suture (nonbioresorbable), which are pushed through the arterial wall into the receiving plates of the device inside the vessel. The two ends of the suture are externalized, and a preformed knot is tightened on the external surface of the artery, creating a seal. The device is currently available in 6, 8, and 10F sizes. The Perclose also allows for preclosure in large-bore access (eg, prior to Impella sheath insertion or transcatheter aortic valve replacement [TAVR]).
4. The **Angio-seal** is an active approximation closure device, composed of a bioresorbable polylactic polymer plug and collagen sponge. It is available in 6 and 8F sizes. A special sheath is advanced over a guidewire, an intravascular anchor is pulled

against the arterial wall at the arteriotomy site, and the collagen plug is pressed against the adventitia of the artery, creating a mechanical seal. No manual pressure is required, and ambulation can begin after 2 hours. Repeat arterial puncture should be avoided at the same site for about 45 to 60 days.

5. The **StarClose Vascular Closure System** is an active approximation percutaneous vascular closure device. It is composed of a nitinol clip with two major and four minor tines that is delivered through a sheath and pinches the arterial surface at the arteriotomy site in a circular manner, creating a purse string closure of the vessel that employs a nitinol clip.
6. The **Vascade Vascular Closure System** is a passive approximation closure device, composed of a bioresorbable collagen patch. A footplate is pulled against the inner wall of the artery at the arteriotomy site, while a collagen plug is deployed in the track above the access site, creating an external seal when the device is removed.

X. COMPLICATIONS

A. Death. The risk of death during LHC is very low (0.1% or less). This risk is higher in patients undergoing urgent catheterization for ACS. In addition, older patients, patients with left main CAD, severe aortic stenosis, or severe LV dysfunction are known to be subgroups with a particularly increased risk.

B. MI. There is a 0.05% risk of MI from LHC. MI can result from coronary dissection, disruption of a preexisting atheromatous plaque, or a large air embolus or thrombus. Patients presenting with ACS have a higher risk of procedural MI.

C. Stroke. The stroke risk during LHC is about 0.05%. Causes include embolization of atheromatous material, thrombus formation on the surface of the catheters, or inadvertent air embolization. The presence of extensive aortic atheroma increases the risk, as dislodgement of atheromatous debris from the aorta can lead to a stroke. This risk can be minimized by exchanging catheters over the wire and limiting catheter manipulation in the ascending aorta.

D. **Coronary artery dissection.** Engagement of the coronary arteries can rarely cause dissection. It is most often due to the injection of contrast through a catheter that is not coaxial to the coronary artery, especially in cases of significant ostial disease, or placement of the catheter too deeply into the coronary artery. The BP waveform should be carefully inspected for pressure damping or ventricularization upon catheter engagement and prior to every contrast injection. Special caution should be applied with the Amplatz catheters. In cases where extensive coronary artery dissection occurs, especially of the left main, emergency CABG may be required, which is associated with significant morbidity and mortality in that setting.

E. **Coronary artery spasm.** Engagement of the coronary arteries, in particular the RCA, can cause spasm. This is best treated with withdrawal of the catheter. Subsequent reengagement and administration of intracoronary nitroglycerin (100-200 mcg) may also be necessary for more rapid resolution of spasm.

F. **Renal failure.** Contrast dye can precipitate renal failure in any patient, although certain patients (those with preexisting CKD, diabetes, proteinuria, or dehydration) are at higher risk. Adequate prehydration with normal saline (3 mL/kg administered over 2 hours) can reduce the risk of CIN. Every effort should be made to minimize the use of contrast. Biplane cineangiography can help limit the total amount of contrast used. LVEDP-guided hydration can also be performed to reduce the risk for CIN, where the LVEDP is measured in the beginning of the procedure and the rate of fluids is adjusted accordingly.

G. **Arrhythmias.** There is about 0.5% risk of VT or fibrillation during cardiac catheterization. If ventricular fibrillation or hemodynamically unstable VT occurs, immediate defibrillation should be applied. Contrast injection in the RCA can rarely cause transient bradycardia due to vagally mediated reflexes (can be managed with having the patient cough or with IV atropine administration).

H. **HF.** In patients with severe LV dysfunction and especially those with very high LVEDP, the use of contrast should be minimized to reduce the risk of CIN and development of pulmonary edema.

I. **Vagal reaction.** If a patient develops sudden hypotension and/or bradycardia, a vagal reaction should be suspected. It is a common occurrence when local anesthetic is being administered or when the sheath is being removed, as a response to pain. Adequate sedation and analgesia can help prevent such reactions.

J. **Vascular**

1. **Radial.** Radial artery occlusion is the most common vascular complication (incidence ranges from 2% to 10%) of transradial catheterization but is rarely associated with major clinical consequences such as hand ischemia, given the dual blood supply to the hand. The intraprocedural administration of IV heparin 5,000 IU (or 50 IU/kg), use of smaller sheath size, and ensuring patent hemostasis with the TR Band after sheath removal can minimize the risk of radial artery occlusion. A forearm hematoma may occur from injury to side branches during wire or sheath/catheter advancement from the wrist. Although it is very rarely associated with significant complications, it should be closely monitored for the development of compartment syndrome. If significant forearm hematoma occurs, inflation of a BP cuff above the elbow and at 10 to 20 mm Hg below the systolic pressure for 15 to 30 minutes should be performed and the forearm/hand should be monitored closely.

2. **Femoral**

a. **Pseudoaneurysms, arteriovenous fistulas, arterial thrombosis, and peripheral emboli** are possible vascular complications. Careful technique can minimize these risks. In particular, paying attention to puncture location and obtaining adequate hemostasis after sheath removal are the best ways to decrease vascular complications. Auscultation for femoral bruits should be performed before and after the procedure, in cases of femoral access. A new bruit may indicate the formation of a pseudoaneurysm or AV fistula. Vascular US is an essential part of managing groin complications. In cases of pseudoaneurysm, US-guided compression and/or percutaneous thrombin injection are sufficient in most cases, although

surgical repair may be rarely required. Small pseudoaneurysms (<2 cm) tend to close spontaneously but should be followed by serial US examinations. An arteriovenous fistula that does not close spontaneously in 2 to 4 weeks may require surgical repair.

b. **Access site bleeding** is an important complication of femoral access. Adequate manual compression is usually sufficient to achieve hemostasis after sheath removal. If there is significant oozing around the sheath insertion site at the conclusion of the procedure, placement of a sheath 1 Fr larger can be considered. If IV heparin is administered during catheterization or coronary intervention, an activated clotted time (ACT) should be checked prior to sheath removal. ACT should be less than 150 seconds for arterial sheath removal and less than 180 seconds for venous sheath removal. IV protamine (1 mg/100 IU heparin) can also be given to reverse heparinization, but this is not a widely preferred strategy and exposes the patient to potential allergic reactions (mainly hypotension).

c. A very serious complication of femoral arterial access is **retroperitoneal bleeding**, which can occur when the arterial puncture site is above the inguinal ligament. Severe back or flank pain, especially associated with tachycardia and/or hypotension after a femoral catheterization procedure, are alarming symptoms and signs that should raise the suspicion of retroperitoneal bleeding/hematoma. An unexpected drop in hemoglobin should also raise this possibility. Patients who are obese can develop a large retroperitoneal hematoma without obvious external signs. A noncontrast CT scan of the abdomen and pelvis can be performed for a definitive diagnosis in stable patients. For hemodynamically unstable patients, aggressive resuscitation with IV crystalloids and/or blood products should be performed, and the patient should be urgently taken to the catheterization laboratory. Iliofemoral angiogram should be performed from the contralateral femoral or left radial access, and the team should be prepared for possible peripheral

intervention (balloon tamponade, covered stent placement) and vascular surgery consultation.

K. Infection. There is a risk of infection, as with any invasive procedure. This risk can be minimized with proper attention to sterile technique. There is usually no need for prophylactic antibiotics; however, some operators may give perioperative antibiotics after the use of a percutaneous vascular suture device in patients who are at high risk for infection, such as patients who are obese or those with diabetes.

L. Neuropathy. There is a slight risk of damage to the femoral nerve from inadvertent puncture. Femoral hematoma (or retroperitoneal bleeding) can also cause compression of the femoral nerve. Function usually improves with time, but complete recovery can take several months.

M. Allergy. As discussed above, contrast dye can cause adverse reactions, ranging from hives to anaphylaxis. Severe anaphylactoid reactions to contrast dye occur in about 0.1% of cases, with the rate being lower with the use of the newer, nonionic contrast agents. Local anesthetics (lidocaine) can also cause reactions because of specific allergies to the amide or ester component or to the preservative.

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CHAPTER 64

Percutaneous Coronary Intervention

Kara Denby and Laura Young

I. INTRODUCTION

A. Coronary atherosclerosis may result in a flow-limiting stenosis that leads to myocardial ischemia and/or myocardial infarction (MI) and remains the leading cause of morbidity and mortality worldwide. Andreas Gruentzig is considered the father of the modern percutaneous treatment of coronary artery disease (CAD), performing the first percutaneous transluminal coronary angioplasty (PTCA) in 1977. With the advent of coronary stents and other therapeutic coronary devices, these procedures are now more broadly termed *percutaneous coronary intervention* (PCI). It is estimated that nearly 1 million PCI procedures are completed in the United States and approximately 2 million worldwide annually.

B. The field of interventional cardiology continues to evolve rapidly, as a result of ongoing advances in equipment technology, treatment strategies, and adjunctive medications. These advances have been paralleled by a concomitant improvement in the safety and efficacy of PCI. Continuing basic and clinical research encompassing all areas of interventional cardiology continues to redefine the standard of care paradigm.

II. PERCUTANEOUS CORONARY INTERVENTION INDICATIONS

A. Central tenet. Although there is no substitute for sound clinical judgment, PCI is generally reserved for patients in whom there is an objective demonstration of substantial myocardial ischemia or symptoms as well as angiographic demonstration of obstructive coronary disease. PCI may not be indicated for asymptomatic or

mildly symptomatic patients who have only a small area of viable or jeopardized myocardium, have no objective evidence of myocardial ischemia, have other life-limiting disease processes, or have lesions that have a low likelihood of success (**Tables 64.1 and 64.2**).

TABLE 64.1 Standard PCI Evaluation

History
• Symptoms (angina, dyspnea, paroxysmal nocturnal dyspnea, syncope)
• Previous MI
• Previous cardiac interventions (PCI, CABG)
• Comorbidities (diabetes mellitus, hyperlipidemia, hypertension, tobacco use, bleeding diathesis, etc)
Medications (glucophage, statins, aspirin, thienopyridines, etc)
Allergies (contrast dye, latex, antiplatelet agents, etc)
Physical examination (murmurs, jugular venous pressure, pulses, bruits, edema)
Laboratory data (creatinine, potassium, hemoglobin, platelets, INR)
Other tests (ECG, echocardiogram, stress tests)
Informed consent including risks, benefits, alternatives

CABG, coronary artery bypass grafting; ECG, electrocardiogram; INR, international normalized ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 64.2 Considerations for PCI

Review clinical and angiographic risk factors.
Develop strategy and anticipate problems.
Surgical backup
Access
Anticoagulation and antiplatelet therapy
Consider diagnostic adjuncts (eg, pulmonary artery catheter, temporary venous pacing wire).

Consider therapeutic mechanical adjuncts (eg, IABP, temporary percutaneous ventricular assist devices).
Guidewire
Device (eg, atherectomy, angioplasty, stent)
Closure of vascular access site
Post-PCI destination (telemetry ward, CICU)

CICU, cardiac intensive care unit; IABP, intra-aortic balloon pump, PCI, percutaneous coronary intervention.

B. ST-segment elevation myocardial infarction (STEMI). Primary PCI should be the preferred treatment strategy for patients presenting with STEMI to a facility experienced with and capable of performing PCI. Randomized trials have demonstrated that clinical outcomes are improved when patients with STEMI are emergently transferred to centers able to perform primary PCI as opposed to being treated with thrombolytics. Patient should preferentially be treated with PCI if the delay from the time of hospital presentation to PCI is <120 minutes. If the delay exceeds 120 minutes, treatment with thrombolysis is recommended. For patients with late presentations (symptoms >24 hours) with hemodynamic stability and without evidence of ongoing ischemia, it is not recommended that PCI be performed. If late STEMI presentation is complicated by ischemia, acute severe heart failure, or life-threatening arrhythmias, PCI may be performed to improve clinical outcomes. **For a more thorough discussion of the management of STEMI, refer to** Chapter 1.

C. Non–ST-segment elevation acute coronary syndrome (NSTEACS). Unstable angina and non–ST-segment elevation myocardial infarction (NSTEMI) are considered part of the spectrum of NSTEACS. Given that individual patients presenting with unstable angina/NSTEMI are at widely varying risk for subsequent morbidity and mortality, early and aggressive risk stratification including cardiac catheterization with subsequent percutaneous or surgical revascularization (rather than noninvasive stress testing) is recommended. This recommendation is supported by a number of clinical trials comparing an early invasive to delayed conservative

strategy. Risk stratification can be aided by using validated scoring systems (eg, GRACE or thrombolysis in myocardial infarction [TIMI]). **For a more thorough discussion of the management of NSTEACS, refer to** Chapter 2.

D. Chronic stable angina. A significant proportion of all PCI procedures are performed in the elective setting for chronic stable angina. Whereas recent trials have continued to question the mortality benefit of PCI or coronary artery bypass grafting (CABG) over optimal medical therapy in stable CAD, revascularization still remains the most effective treatment strategy for patients with refractory angina. **For a more thorough discussion of the management of stable CAD, please refer to** Chapter 6.

III. PERCUTANEOUS CORONARY INTERVENTION CONTRAINDICATIONS.

The only absolute contraindication to PCI is **significant active bleeding**, given the absolute need for procedural anticoagulation and continued dual-antiplatelet therapy (DAPT). Relative contraindications include a bleeding diathesis, unsuitable or high-risk coronary anatomy (eg, chronic total occlusion [CTO] in the absence of ischemia or diffuse distal disease), and a short life expectancy because of a comorbid condition.

IV. PROGNOSIS

A. A patient's clinical status and coronary angiogram are powerful predictors of outcome. Certain clinical and angiographic variables have repeatedly been associated with adverse events (**Table 64.3**).

TABLE 64.3 Clinical and Angiographic Predictors of Adverse Outcomes

Clinical Predictors
• Older age
• Unstable angina
• Acute MI
• Cardiogenic shock

- CHF
- Left ventricular function
- Multivessel coronary disease
- Diabetes mellitus
- Renal impairment
- Peripheral vascular disease
- Small body size

Angiographic Predictors

- Thrombus
- Bypass graft
- Left main trunk
- Lesion >20 mm in length
- Excessive tortuosity of proximal segment
- Extremely angulated lesions >90°
- Total occlusion >3 mo old and/or bridging collaterals
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions
- Unprotected left main trunk

CHF, congestive heart failure; MI, myocardial infarction.

B. Lesion complexity can be assessed using one of many calculators, with the SYNTAX score being the most widely used and validated. This scoring system is used to objectively measure the anatomic complexity of CAD in patients with multivessel disease. It is an independent predictor of long-term major adverse cardiac and cerebrovascular events and death.

V. EXPERIENCED OPERATORS/CENTERS

A. Procedural volume is an important predictor of PCI complications.

B. Elective PCI should be performed in high-volume centers (>200 interventions per year, with an ideal minimum of >400 cases per year) by operators with an acceptable annual volume (>75 cases per year) at institutions with fully equipped interventional laboratories, experienced support staff, and an on-site cardiovascular (CV) surgical program. Elective PCI should not **be** performed by low-volume operators (<75 cases per year) in low-volume centers (<200 cases per year), regardless of the availability of on-site cardiothoracic surgery, because of the increased risk of suboptimal outcomes. Referral to a larger regional center is recommended in this situation.

C. Primary PCI for STEMI should be performed in similarly experienced/skilled centers by operators who perform >75 elective cases per year and intervene in at least 11 STEMI cases per year. In cases of STEMI, there is an inverse relationship between the number of primary angioplasty procedures performed by an operator and in-hospital mortality. The data suggest that both door-to-balloon time and in-hospital mortality are significantly lower in institutions that perform a minimum of 36 primary angioplasty procedures per year.

VI. SURGICAL BACKUP.

Emergency surgical intervention is a rare event and is required in 0.3% to 1.0% of cases of PCI, usually because of complications that cannot be addressed percutaneously or to provide urgent hemodynamic support. The most common reasons for emergency CABG surgery are dissection resulting in acute vessel closure, perforation, device entrapment, or aortic dissection. Emergency CABG after PCI has a mortality rate of 15% and periprocedural MI rate of 12%. The internal mammary artery may not be harvested during these emergent procedures. Registry data suggest that primary PCI for STEMI can be safely and effectively performed in centers that do not perform elective PCI and do not have on-site cardiac surgery capabilities if they utilize experienced operators (>75 total PCI per year and ≥11 primary PCIs for STEMI per year) with a predetermined transfer plan to a nearby center with on-site surgical backup.

II. VASCULAR ACCESS, SHEATHS, GUIDES, AND GUIDEWIRES

A. Vascular access and sheaths

1. **Radial access** is now the recommended approach for all patients undergoing PCI for acute coronary syndrome (ACS) due to a reduction in death, vascular complications, and bleeding. It is also recommended for patients with stable ischemic heart disease undergoing PCI for a reduction in access site bleeding and vascular complications. Radial access is contraindicated with ipsilateral arteriovenous (AV) fistula. The average radial artery can accommodate 6 to 7 Fr sheaths. A long sheath (75 cm) may be considered to overcome tortuosity of the innominate or subclavian artery. Radial artery occlusion rates range from 3% to 5%. Ulnar access has been utilized but should not be used if the radial artery is occluded. Hemostasis may also be more difficult with the ulnar artery, given the greater depth and incompatibility of hemostasis devices.
2. **Femoral access** may be required/preferred with severe tortuosity of the innominate/subclavian arteries, arterial vasospasm, or if larger bore sheaths are required. Femoral access should be obtained with ultrasound (reduces the number of attempts) and fluoroscopic guidance. Micropuncture technique is strongly preferred to enhance safety. The femoral artery should be accessed over the femoral head (to allow compressibility), above the bifurcation (to reduce the risk of pseudoaneurysm), and below the inferior epigastric artery. Femoral angiography should be obtained at an ipsilateral angle of 30° to 40°. Typical sheath sizes range from 6 to 8 Fr. Often, long sheaths (23 or 35 cm) may be used to overcome tortuosity of the iliac arteries.

B. Guiding catheters

1. Larger guide sizes (7 or 8 Fr) provide extra support that may be required for interventions in tortuous or calcified coronary lesions and also permit simultaneous kissing balloons/stents. For the majority of cases, a 6-Fr system is typically adequate.
2. The **EBU and XB** (extra backup) and **Amplatz** guiding catheters provide excellent support for interventions and can be useful in

cases of acutely angled left circumflex artery (LCx), anomalous LCx originating from the right sinus, very anteriorly originating right coronary artery (RCA), or a tortuous/calcified RCA. The Amplatz guiding catheters are also at slightly higher risk of ostial/proximal artery dissection; thus, care must be taken to prevent deep intubation of the guiding catheter.

3. The **three-dimensional (3D) right** guiding catheter is another highly supportive guide, designed for RCA interventions from the right radial approach.
4. Other shapes/types of catheters may be used depending on the ostial takeoff and course of the vessel and the degree of support required.

C. Guidewires

1. The coronary lesion is initially crossed with a 0.014-in diameter coronary wire, which serves as a "rail" for devices such as balloons and stents. Wire choice is based on parameters including tip strength (soft vs penetrating), coatings (hydrophilic vs hydrophobic), and support. Wires are available in 180 to 190 and 300 cm lengths to facilitate either rapid exchange or over-the-wire systems.
2. **Workhorse wires** are soft-tipped wires that are used for the majority of the intervention. Common workhorse wires include Runthrough, Sion Blue, Prowater, and BMW wires.
3. **Hydrophilic or polymer-jacketed wires** are designed to be slippery and are helpful in tight lesions or highly tortuous lesions. These include wires such as Whisper, Sion black, and Pilot.
4. **Support wires** include wires with good body support (BHW, Grandslam, Ironman) or special curves at the distal end of the wire (Wiggle wire) that help support the delivery of equipment.
5. Other specialty wires are used in CTO interventions and include wires with very high gram tip loads and/or tapered tips. Stiff tips are helpful for penetrating tough lesions but increase the risk of vessel dissection or perforation.

III. DIAGNOSTIC ADJUNCTS

A. Intravascular imaging provides additional anatomic information that can help guide diagnostic and interventional procedures. Angiography alone often over- or underestimates the severity of lesions. It is especially recommended for procedural guidance in cases of left main or complex coronary artery stenting to reduce ischemic events.

1. **Intravascular ultrasound (IVUS)** provides better anatomic information by generating a cross-sectional tomographic image of both the lumen and the vessel wall. This complementary imaging modality can be invaluable when repeated angiographic views fail to determine the mechanism and/or significance of a coronary lesion. This has been shown especially useful in indeterminate left main lesions with a cutoff of minimum lumen area (MLA) of ≥6 to 7.5 mm^2 considered safe for PCI deferral. IVUS has proven helpful in planning pretreatment strategy prior to stent deployment (eg, need for calcium modification with atherectomy or lithotripsy), determining appropriate stent sizing and length, and assessing the adequacy of stent deployment and any associated complications (eg, underexpansion, malapposition, and medial edge dissections). IVUS can also be helpful in assessing the mechanism of in-stent restenosis (ISR) (eg, neointimal hyperplasia [NIH], neoatherosclerosis, underexpansion, or stent fracture), which will help guide treatment strategy.
2. **Optical coherence tomography (OCT)** images are acquired using near-infrared light during an automated pullback. This requires a contrast injection to clear the vessel of blood and should, therefore, be used cautiously in patients with renal dysfunction. In comparison with IVUS, OCT provides higher image resolution at the expense of a shallower depth of penetration. The superior image quality allows for better evaluation of plaque morphology to guide prestent treatment strategy. It similarly provides high-quality poststent evaluation to assess for malapposition, underexpanion, or medial dissection. OCT is highly useful in ACS, with visualization of lipid pools,

thin-cap fibroatheromas, and thrombus. It is also able to identify culprits in patients with myocardial infarction with nonobstructive coronary arteries (MINOCAs), with plaque erosion and spontaneous coronary artery dissection being readily identified. OCT may also be more helpful in cases of ISR than IVUS, given the superior image resolution. Studies comparing OCT with IVUS have shown noninferiority.

B. Coronary physiology is also helpful for diagnosis and guidance in interventional procedures. These techniques can assess the hemodynamic significance of an indeterminate stenosis or assess the function of the microvasculature.

1. **Fractional flow reserve (FFR)** is the ratio of distal coronary pressure to aortic pressure (*P*d/*P*a) during maximal hyperemia. This measurement is obtained by a specialized 0.014-in pressure wire that is advanced beyond the lesion of interest and into the distal vessel. Hyperemia is typically achieved with a vasodilator such as adenosine (intravenous [IV] infusion 140 mcg/kg/min or intracoronary 36-64 mcg). A normal coronary artery would have an FFR of 1.0. An FFR of <0.80 is consistent with a hemodynamically significant obstruction with accuracy >90%. This measurement is obtained by specialized 0.014-in pressure wires. Studies have shown a superiority of FFR-guided PCI over angiography-guided PCI of intermediate lesions with a decrease in stents deployed as well as decreased morbidity and mortality.
2. **Instantaneous wave-free ratio (iFR)** is another measure of hemodynamic significance across a lesion; however, this is obtained as a resting *P*d/*P*a. Measurements for iFR are obtained during the "wave-free period." This is a period of diastole in which equilibration occurs between pressure waves from the aorta and distal microcirculation. iFR values <0.89 are consistent with a hemodynamically significant lesion. Studies have shown a good concordance of iFR with FFR, and iFR testing has become more common, given that it can be obtained without the use of vasodilators, which may improve patient comfort and reduce cost and procedural time. Other resting indices have been developed

that are felt to have similar predictive value (eg, resting full-cycle ratio [RFR], diastolic pressure ratio [dPR]).

3. **Coronary flow reserve (CFR)** is a measurement of epicardial and microvascular resistance. This is typically used in the setting of nonsignificant epicardial disease, with the goal of assessing microvascular function as a cause of angina or ischemia. This can be done with either a Doppler-based wire (ComboWire) or thermodilution (PressureWire X). With both of these, measurements of flow are obtained at rest and then with maximal hyperemia. CFR is the ratio of hyperemic to resting flow, and normal is considered a CFR of 3 to 5 (a normal circulation should be able to augment flow 3-5 times with hyperemia). The cutoff for abnormal CFR is <2.0 or <2.5. Unfortunately, CFR measurements may be influenced by different hemodynamic states. With CFR, typically either a hyperemic microvascular resistance (HMR) or an index of microvascular resistance (IMR) is obtained. These measurements assess microvascular function and are less affected by changes in hemodynamic states. The assessment of microvascular dysfunction is currently a rapidly growing field.

C. Pulmonary artery catheter (physiologic). A balloon-tipped Swan-Ganz catheter advanced into the pulmonary artery allows measurement of right and left heart filling pressures as well as the cardiac output. This information can be helpful in patients presenting with cardiogenic shock, during high-risk PCI in the setting of severe left ventricular (LV) dysfunction, when there is a question of pericardial tamponade, or when the cause of hemodynamic deterioration is unclear.

IX. THERAPEUTIC DEVICES

A. Balloons

1. **Semi-compliant balloons** are typically made from polyvinyl chloride (PVC), nylon elastomer, latex, or silicone rubber and can be easily deformed with internal pressure (expand with lower pressures). They are most often used for pretreatment of coronary

lesions. They are lower profile and, when inflated, do not expand uniformly.

2. **Noncompliant balloons** are typically made of nylon or polyethylene terephthalate (PET), which is a very low-compliance material. They are designed to expand uniformly over their longitudinal axis and generally cannot expand past a predetermined size. This allows for a higher pressure inflation without significant size growth. Ultra-high pressure balloons are also under investigation. They are often used for more recalcitrant lesions or postdilation of implanted stents.
3. **Cutting balloons** were designed to create a "controlled dissection" but using longitudinally mounted atherotomes (blades) that cut into plaque and the vessel wall, allowing vessel expansion at lower pressure inflations. An advantage of cutting balloons is that they have significantly less slippage than traditional balloons. An additional use of the cutting balloon is for creating fenestrations in an intramural hematoma.
4. **Plaque-modifying balloons** are specialty balloons that have nitinol cages around them that are intended to prevent balloon slippage and score the plaque (examples include AngioSculpt, Chocolate). A newer balloon utilizes a single-side nitinol integral wire on one side while the guidewire is on the other (mimicking a buddy wire inflation), which is also used to score the plaque (Scoreflex).
5. **Drug-coated balloons** are not yet approved in the United States, but there are ongoing trials. They have had successful trials and been approved in Europe for over a decade and may be a viable treatment option for small vessels, bifurcations, and multilayer ISR.

B. Stents

1. **PTCA.** The coronary balloon remains the backbone of endovascular intervention, although it is almost never used as a stand-alone therapy. The initial gain in the coronary lumen achieved by balloon inflation often results in localized dissection of the intima +/− media. These dissections attract platelet-rich

thrombus and later intimal hyperplasia with a historically abrupt vessel closure rate of 4% to 7%. This has been reduced by the use of contemporary antithrombotic therapies. Restenosis rates are in the 30% to 50% range, with balloon angioplasty as a stand-alone therapy.

2. **Bare-metal stents (BMSs)** are made of either stainless steel or a metal composite and were the first coronary stents, introduced in 1986. The introduction of stents reduced the high incidence of abrupt closure, requiring emergency CABG, and high restenosis rates. Significant evolution of stent design, high-pressure implantation of stents, and advances in periprocedural antithrombotic regimens led to a rapid reduction in procedural complication rates and marked improvement in the ease of stent delivery. However, restenosis rates secondary to NIH remained high (especially in patients with small reference vessel size, smaller postprocedural luminal diameter, long lesion length, diabetes, left anterior descending artery [LAD] location, or with untreated edge dissections), with BMS prompting further development of stent technology. Currently, BMSs are not the first line for coronary revascularization.
3. **Drug-eluting stents (DESs).** Given the high rates of restenosis with BMS, DESs were developed and designed to elute an antiproliferative agent, such as sirolimus, paclitaxel, zotarolimus, or everolimus, that targets and arrests cell division during the mitotic growth phase and prevents excessive tissue growth. The use of polymers on the surface of the stent allows controlled, local drug delivery that has dramatically reduced NIH and thereby ISR. The “first-generation” DES was introduced in 2003 and rapidly became the first-line stent. Early studies raised concerns about higher rates of stent thrombosis (ST) in DES compared with BMS, but this has improved with second-generation DES (zotarolimus- or everolimus-eluting stents). Implantation of a DES is recommended as the first line for all interventional coronary procedures.

4. **Bioresorbable polymer DES** is a newer iteration of DES, given concerns about permanent polymers leading to incomplete endothelialization, persistent inflammatory reactions, loss of native vessel curvature and vasoregulation, and neoatherosclerosis. Bioresorbable polymers are absorbed over time leaving only the metal stent scaffold.
5. **Bioabsorbable vascular scaffolds** were developed to incorporate the early benefits of DES—mechanical support to the artery to prevent elastic recoil and allow healing as well as controlled antiproliferative drug delivery to prevent ISR—while leaving no permanent metallic scaffold in the artery, which was postulated to allow a return of normal vascular physiology and access to the vessel, should future surgical revascularization be required. Unfortunately, bioabsorbable vascular scaffolds were plagued by increased ST, target vessel revascularization, and target vessel MI and have subsequently been removed from the market.
6. **Covered stents** use a material such as polytetrafluoroethylene or electrospun polyurethane, which covers the stent struts and seals off the vessel wall from the stent lumen. These are typically used as a bailout strategy in vessel perforations that cannot be resolved with prolonged balloon inflations, or to exclude coronary artery aneurysms. They initially showed promising results in vein graft lesions, but with long-term data, restenosis and major adverse cardiac event (MACE) rates were unfavorable, leading to their withdrawal.

C. Atherectomy devices

1. **Rotational atherectomy** uses a diamond-coated burr that is advanced over a 0.009-in wire to the coronary lesion. Rotational atherectomy increases the change of procedural success in comparison with balloon angioplasty alone. Rotational atherectomy is most often used in severely calcified lesions (especially long segments) and balloon undilatable/uncrossable lesions to ensure adequate expansion of the vessel prior to stenting. During atherectomy, microparticles are generated and may attenuate the downstream coronary microcirculation, leading

to transient myocardial stunning, periprocedural MI, and LV dysfunction in the region of the target vessel. To counteract this effect, vasodilators (verapamil, nitroprusside, or adenosine) are often administered. Rotational atherectomy is contraindicated in patients with thrombus or dissection with a relative contraindication in severely reduced LV systolic dysfunction or highly tortuous vessels (1% perforation risk). In the RCA, backup pacing or aminophylline is frequently required due to bradycardia related to ischemia of the AV nodal branch.

2. **Orbital atherectomy** uses an orbiting crown to ablate plaque into very small microparticles. The device differs from rotational atherectomy in that the orbiting crown allows for differential depth of plaque ablation by changing the speed of rotation or speed of device pullback. This is helpful, in that the same device can ablate vessels of different size. In addition, it can ablate in both directions, which can be especially helpful in ostial lesions (ablation on pullback rather than advancement). Orbital atherectomy has the same contraindications as rotational atherectomy.
3. **Excimer laser coronary atherectomy** (ELCA) works by using ultraviolet light (308 nm) at a rate of 25 to 40 pulses/s from a high-energy, metastable, dimeric molecule of xenon and chloride. This provides 45 mJ/mm^2, which can ablate 0.5 mm of tissue per second, and reduces the target tissue to gas and subcellular debris. The size of the lumen created is equivalent to that of the catheter (0.9 mm diameter). This device is approved for CTOs, moderately calcified stenoses (not effective with highly calcified lesions), balloon uncrossable/undilatable lesions, ostial lesions, bypass grafts, ISR, and long diffuse disease. It should be avoided in highly tortuous vessels due to perforation risk. Long-term data have not shown a significant benefit, and thus, it is not recommended as first-line strategy.

D. Thrombectomy devices

1. **Manual aspiration thrombectomy catheters** can be used to remove intracoronary thrombus. However, large-scale clinical

trials have not demonstrated a significant benefit from its routine use. Early trials suggested a possible benefit in STEMI; however, more recent randomized controlled trials (RCTs) did not show a benefit, and there was an increased risk for stroke (hazard ratio [HR] 2.0).

2. **Continuous mechanical aspiration thrombectomy catheters** are new to the market, and the recent CHEETAH study demonstrated safety with no recorded stroke. However, this was a single-arm prospective trial, and further investigation is warranted.
3. **Rheolytic thrombectomy catheters** are flexible catheters that contain a hypotube through which six high-speed saline jets create a low-pressure area at the tip (approximately −760 mm Hg), serving to macerate and aspirate the thrombus back into the catheter lumen in accordance with the Venturi-Bernoulli principle. There are drawbacks to rheolytic thrombectomy in the coronaries, including transient ST elevation, AV block with the treatment of inferior territory, and perforation in small vessels. Unfortunately, prospective randomized data demonstrating a clinical benefit are lacking; some trials even suggest worse outcomes in those undergoing rheolytic thrombectomy.

E. Embolic protection devices

1. **Filters** are collapsible microporous polyurethane net attached to a nitinol ring anchored distally to a 0.014-in guidewire that can be advanced across high-risk saphenous vein grafts (SVGs) and deployed downstream of the lesion. When deployed, these porous devices allow blood to flow through while filtering any debris larger than 80 to 100 mcm. Advantages are ease of use and avoidance of prolonged ischemia. Potential disadvantages are incomplete sealing, passage of smaller particles through the filter pores, overloading of the device, and spillage during device retrieval. Studies have shown a reduction of a primary end point of death, periprocedural MI, and target lesion revascularization (TLR) at 30 days. It is currently a class IIa recommendation to use an embolic protection device with PCI of SVG.

X. SAPHENOUS VEIN GRAFT INTERVENTIONS

A. **Saphenous vein bypass grafts** are frequently used in CABG surgery. However, 15% to 20% occlude the first year, and by 10 years, 50% of SVGs are occluded, and another 25% are severely degenerated. Redo CABG is a high-risk surgery with high rates of morbidity and mortality, and if the internal mammary artery was utilized during the prior surgery, the risk of reoperation is further increased while the potential for benefit greatly diminishes. Patients with no prior arterial conduits used, multiple failed SVGs, multivessel disease, and depressed LV systolic function are potential candidates for redo surgery, but patients not meeting those criteria often undergo PCI instead.

B. **Early postoperative ischemia** (within 30 days) usually reflects graft failure (often secondary to thrombosis) or incomplete revascularization, and urgent coronary angiography is indicated. Emergency PCI of the graft, even across suture lines, can often be safely performed within days of surgery. Intracoronary thrombolysis should be used with caution, with a preference for mechanical thrombectomy if there is a large thrombus burden. Given that SVG flow is pressure dependent, an intra-aortic balloon pump use should be strongly considered in patients who present with cardiogenic shock.

C. **Recurrent ischemia 1 to 12 months** after CABG surgery usually reflects perianastomotic graft stenosis. Distal anastomotic stenoses respond well to balloon inflation only without subsequent stenting. Midshaft vein graft stenoses are usually due to intimal hyperplasia.

D. **Recurrent ischemia >1 year** after CABG surgery usually reflects the development of atherosclerosis within the graft.

E. **Distal embolic protection devices** should be utilized whenever possible in SVG interventions. SVGs have a greater plaque burden than native coronary arteries, and aspirates are typically composed of atherosclerotic rather than thrombotic elements. With SVG interventions, there is a very high risk for atheroembolization, with 15% of patients having a creatine kinase-muscle/brain (CK-MB) more than 5 times normal postprocedurally. The use of these devices

is discussed in Section XI. In situations of poor reflow after SVG PCI, copious administration of intracoronary adenosine and/or nitroprusside is recommended, with the goal of improving microvascular flow. It should also be noted that poor reflow may be seen due to a plaque-burdened filter, which should resolve with aspiration of the filter followed by filter retrieval.

XI. MEASUREMENT OF SUCCESSFUL PERCUTANEOUS CORONARY INTERVENTION

A. Angiographic success is defined as a residual stenosis <50% with PTCA or <20% with stenting with TIMI 3 flow and is achieved in 96% to 99% of patients. However, there are limitations with utilizing angiography exclusively.

B. Intravascular imaging can also be used to assess the results after PCI. With IVUS, stent optimization is defined as (1) an MLA of >5.0 or 90% of the MLA at the distal reference, (2) plaque burden <50% within 5 mm of the proximal or distal stent edges, and (3) no edge dissection that involves the media with length >3 mm. With OCT, stent optimization is defined as (1) >80% expansion (preferably ≥90%) as compared with the reference vessel, (2) no stent malapposition ≥0.3 mm from the wall for longer than 3 mm in length, and (3) no medial dissection that is greater than one quadrant arc.

C. Procedural success is defined by the criteria above, without major in-hospital complications (eg, death, CABG, or MI). **Clinical success** is defined as procedural success with relief of the symptoms and signs of myocardial ischemia.

XII. IMMEDIATE COMPLICATIONS OF PERCUTANEOUS CORONARY INTERVENTION

A. The incidence of serious complications (death 0.5%-1.4%, periprocedural MI, and emergency CABG surgery 0.2%-0.3%) has consistently decreased over the past 20 years with the advances in stent technology, new and more effective antiplatelet therapies, improved equipment, and increasing reliance upon evidence-based strategies.

B. Abrupt closure is one of the most feared MACE and typically occurs within 6 hours of intervention. The most common cause of abrupt

closure is suboptimal stent expansion or dissection followed by thrombus, spasm, and side branch occlusion. In the mid-1980s, the risk of abrupt closure approached 5%. The common use of periprocedural contemporary antithrombotic therapies and stent deployment has reduced this risk to <1% in modern practice. The risk is further decreased with the use of intravascular imaging, which is able to identify these risk factors and prompt further therapy before the patient leaves the catheterization laboratory. Risk factors for abrupt closure include presentation with acute MI, poor coronary flow postintervention (eg, TIMI I-II), complex lesion morphology (eg, class C lesions), and suboptimal result as judged by angiography or intravascular imaging.

C. **Atheroembolism and thromboembolism** probably occur to varying degrees in all interventions but are most frequently encountered in cases involving degenerated vein grafts, in patients presenting with ACSs, and in cases using orbital/rotational atherectomy. Distal embolization can result in "no reflow" (decreased coronary flow due to microvascular occlusion or dysfunction), abrupt closure, and periprocedural MI. Thromboembolism may be minimized by thrombectomy catheters; however, the most effective measure is effective anticoagulant and antiplatelet therapy. The prevention of atheroembolus, most often encountered during vein graft intervention, is frequently addressed with the use of a distal embolization protection to trap and remove the debris before it reaches the distal vascular bed. Intracoronary administration of vasodilators such as adenosine (36-72 mcg repeatedly), nitroprusside (50-200 mcg), and verapamil (200 mcg) has been shown to prevent and manage no reflow but has no effect in preventing CK-MB elevation.

D. **Coronary perforations** occur in 0.19% to 1.46% of all PCI procedures and increase the in-hospital mortality risk at least 5-fold. They are typically characterized using the Ellis classification system: type I: extraluminal crater without extravasation; type II: pericardial or myocardial blush without contrast jet extravasation; and type III: extravasation through frank (>1 mm) perforation; type III cavity

spilling: perforation into an anatomic chamber, coronary sinus, and so on. Contrast extravasation is typically evident in the majority of cases at the time of PCI; however, up to 20% of cases can present several hours after the procedure and are frequently due to hydrophilic wire perforation of a small vessel. Treatment usually requires prolonged balloon inflation and reversal of anticoagulation. Transthoracic echocardiography should be immediately performed in the setting of clinical instability in order to evaluate for the presence of a pericardial effusion and/or tamponade, in which case urgent pericardiocentesis is required. Covered stents, coils, or surgical repair may be required for definitive management.

E. **Coronary dissection** is much less common in the stent era as compared with the balloon angioplasty era. However, major dissections may still occur and lead to obstruction of coronary flow, vessel occlusion, and hemodynamic collapse. The first step in treating dissections is maintaining wire position across the dissection, followed by balloon dilation and/or stenting. Nearly all dissections should ultimately be treated with stent implantation. If the wire position is lost, it is imperative to confirm the true luminal position (usually with IVUS) before using balloon dilation or stent implantation.

F. **ST** is defined as early (<30 days), late (30 days to 1 year), and very late (>1 year). It may be the result of stent-, procedure-, patient-, and antiplatelet therapy–related factors, and minimizing the risk of ST requires a conscious consideration of each of these factors. Compared with thrombosis of native coronary arteries, ST is associated with a higher thrombus burden and less frequent procedural success, all of which result in a much higher rate of death, recurrent MI, and recurrent ST.

1. **Stent-related factors** are primarily due to delayed endothelialization. In BMS, endothelialization occurs in 2 to 4 weeks, but due to the elution of antiproliferative agents, there is delay of endothelialization in DES. Prolonged DAPT has decreased rates of ST, and the overall rates of ST are similar between DES and BMS.

2. **Procedure-related factors** include incomplete stent apposition to the plaque/vessel wall, inadequate stent expansion (undersizing), and stent-edge dissection. Thus, ST rates may be reduced when stent optimization is done with intravascular imaging. Additional risk factors for ST include long lesion length, small artery diameter, and complex lesion morphology.
3. **Patient-related factors** include diabetes mellitus, impaired LV function, and renal disease. Premature cessation of DAPT, holding of antiplatelet agents (eg, prior to procedure, secondary to bleeding), or poor response to clopidogrel (seen in up to 15% of patients) may also increase the risk of ST.

G. **Vascular access site complications** remain the most common complication of PCI and occur in up to 5% of patients. The most common are blood transfusion (3%), AV fistula (<2%), pseudoaneurysm (up to 5%), acute arterial occlusion (<1%), and infections (<0.1%). Shorter anticoagulation regimens, weight-adjusted heparin, use of bivalirudin, early sheath removal, vigilant monitoring of activated clotting times (ACTs), smaller sheaths, avoidance of routine venous sheath insertion, and widespread adoption of radial artery access have all contributed to a reduction in vascular access site complications.

H. **Contrast-induced nephropathy** defined as an increase in creatinine (Cr) >0.3 above baseline occurs in 3% to 7% of patients, and the risk increases 10-fold for patients with serum Cr >2.0 mg/dL, especially in the presence of diabetes mellitus. Data regarding methods to prevent renal failure are not definitive, but the most proven benefit is seen with conservative contrast utilization. In addition, the use of biplane imaging can significantly reduce the amount of contrast required. There is some evidence to support periprocedural hydration with saline infusion. However, numerous studies have shown no benefit for the administration of *N*-acetylcysteine, sodium bicarbonate, and ascorbic acid

I. **Contrast-mediated reactions** may also occur and can be life-threatening. Anaphylactoid reactions occur in 1% to 2% of patients receiving iodinated contrast. These reactions can be severe in 0.10%

to 0.23% of patients. The risk of a severe reaction can be effectively decreased by using nonionic contrast, preprocedural corticosteroids, given the evening before and the morning of the procedure, and the use of H_1- and H_2-blockers. If a patient presents for emergent PCI (ie, STEMI) without having undergone preprocedural steroid preparation, the emergent administration of hydrocortisone 100 mg IV and diphenhydramine 25 to 50 mg IV is reasonable and is shown to be safe in small series. In patients undergoing an elective procedure, caution is prudent, and a full premedication regimen is recommended prior to proceeding.

III. LONG-TERM COMPLICATIONS

A. Post-PTCA restenosis is very common and occurs in 30% to 40% of cases by 6 months. Given that most lesions are now treated with stents, this rate has significantly decreased.

B. ISR is the most common occurring late complication, with the most common causes being NIH, neoatherosclerosis, or stent fracture.

1. Rates of restenosis with BMS ranged from 17% to 32% at 1 year, first-generation DES improved that the rate to 9% to 10%, and second-generation DES has reduced ISR to 5% to 6% at 1 year.
2. In the BMS era, the cause of ISR was almost exclusively NIH, and the most common pattern was diffuse restenosis. With DES, the etiology is more variable and the pattern is more typically focal, often involving the stent edge. The cause of ISR is best diagnosed by intravascular imaging, which will help to guide the treatment strategy.
3. **Predictors of restenosis** include diabetes, unstable angina, acute MI, prior restenosis, small-vessel diameter, total occlusion, long lesion length, SVG, proximal LAD artery, higher percent stenosis after the procedure, and smaller minimal luminal diameter after the procedure.
4. **Treatment of ISR** depends on the etiology and number of existing stent layers. If there is only one stent layer, most often, the preferred strategy is to place a second stent layer (especially if the first layer is BMS). Exceptions to this include small-vessel size or

bifurcation lesions. If there are already two stent layers, it is not recommended to place a third layer. Options for treatment include balloon angioplasty, brachytherapy, or drug-coated balloon (only available currently in trials in the United States).

5. **Brachytherapy** modulates vascular biology by delaying or disrupting the formation of neointima by damaging components of the cell cycle. This is accomplished by delivery of a temporarily implanted radiation source in the vessel of interest. ISR rates following brachytherapy are about 18% to 20% at 1 year. There is a late catch-up phenomenon with increased ISR recurrence by 3 to 5 years. Brachytherapy fell out of favor with the introduction of DES, but interest has again increased due to the large number of patients with multiple stent layers and recurrent ISR. Brachytherapy is unfortunately only available at select centers.

IV. PHARMACOLOGIC THERAPY

A. Antithrombins prevent the generation of thrombin and/or inhibit the activity of thrombin. An antithrombin such as unfractionated heparin (UFH), bivalirudin (direct thrombin inhibitor [DTI]), or enoxaparin (low-molecular-weight heparin [LMWH]) should be used during all coronary interventions to prevent thrombus formation on the equipment. This principle applies even to patients with a high international normalized ratio (INR). Maintenance of appropriate levels of anticoagulation is imperative to safely navigate the path between thrombosis and bleeding complications. The following provides a brief overview of the anticoagulant agents used during PCI. For specific data regarding their use during ACS, refer to Chapter 2.

- **UH**
- **Bivalirudin**
- **LMWH**

B. Warfarin does not have a role during PCI; however, in patients on warfarin, it is a relative contraindication to proceed with PCI with INR >1.6. If PCI must be performed emergently, radial approach is strongly preferable due to the decreased risk for bleeding.

C. **Glycoprotein IIb/IIIa (GPI) inhibitors** (abciximab, eptifibatide, tirofiban) are IV medications that inhibit platelet aggregation and thrombus formation by preventing the binding of fibrinogen or circulating von Willebrand factor on the platelet surface. GPI receptor inhibition prevents these receptors from binding to fibrin and forming the platelet-fibrin cross-linking that is required for thrombus formation. GPI receptor occupancy >80% prevents the development of thrombus. The use of GPI versus heparin alone during PCI was shown to be superior in the era of aspirin-only PCI; however, they have largely fallen out of favor for routine use as they do not add a significant incremental benefit to DAPT and are associated with increased bleeding risk. They are typically reserved for patients who remain unstable, have a large thrombus burden on angiography, or have very high-risk clinical features. For specific recommendations regarding the use of GPIs during ACS, refer to Chapter 2.

1. **Abciximab** is a human-murine chimeric antibody fragment that binds the GPI receptor with high affinity, resulting in a slow dissociation rate (noncompetitive inhibition). It is rapidly cleared from the plasma, allowing platelet aggregation to return to normal in 12 to 36 hours. Rapid reversal of platelet inhibition in the event of bleeding requires discontinuation of the abciximab infusion, waiting 30 minutes for plasma clearance, and platelet infusion (12 units) so as to provide functional platelets. Profound thrombocytopenia occurs in 0.4% to 1.1% of patients. Platelet counts should be measured within the first 2 to 4 hours and the following day.
2. **Eptifibatide** and **tirofiban** are competitive inhibitors of GPI receptor. They both have short plasma half-lives (2.0-2.5 hours), with platelet aggregation normalizing in 30 minutes to 4 hours. With bleeding, the infusion should be discontinued. Unlike abciximab, the effect cannot be reversed and platelets remain inhibited until plasma drug levels fall. However, rates of profound thrombocytopenia are much lower (0%-0.3%) than with abciximab.

D. **Antiplatelet agents** are the backbone of therapy for preventing thrombus formation during PCI and for secondary prevention to prevent subsequent events.

1. **DAPT duration in ACS** is recommended for at least 12 months due to established benefits in reducing MACE as compared with aspirin alone. In the DAPT trial, longer duration of DAPT (additional 18 months) was associated with a decreased rate of MI, but at the expense of higher bleeding rates, though other subsequent trials have not shown this benefit.
2. **DAPT duration in non-ACS** is typically shorter, with a DAPT duration of 4 to 6 weeks for BMS and a DAPT duration of 6 months for DES likely being adequate. There has been much interest in shorter duration of DAPT to minimize bleeding risks. The 2019 STOPDAPT-2 trial showed superiority of 1-month DAPT followed by clopidogrel monotherapy compared with 12 months in regard to a composite end point of CV death, MI, ischemic or hemorrhagic stroke, definite ST, and major bleeding (2.4% vs 3.7%). In the 2021 EVOLVE Short DAPT trial, a DAPT duration of 3 months was noninferior to 6- and 12-month durations. Another study, the 2021 XIENCE Short DAPT trial, showed DAPT duration of 1 month to be noninferior to longer protocols in high bleeding risk patients. Recent trials have also shown reduced bleeding associated with clopidogrel as compared with aspirin monotherapy.
3. **Triple therapy** may be necessary when patients require anticoagulation (eg, mechanical valves, atrial fibrillation, deep venous thrombosis/pulmonary embolism [DVT/PE]). The most common recommendation is 1 to 2 weeks of triple therapy followed by anticoagulation with clopidogrel monotherapy. The higher potency $P2Y_{12}$ inhibitors should not be utilized for triple therapy due to excessive bleeding risk.
4. **Aspirin** is a thromboxane A2 inhibitor and is the cornerstone of antiplatelet therapy. Aspirin impairs platelet aggregation by irreversibly inhibiting platelet cyclooxygenase, thereby limiting thromboxane A2 production. A 325-mg loading dose of aspirin

should ideally be given at least 2 hours before PCI and be continued indefinitely at 81 mg daily maintenance therapy following the procedure. Data from prior trials do not support an ischemic benefit of higher doses of aspirin while bleeding complications are much higher with higher doses. Secondary prevention trials have shown aspirin to reduce death, MI, and stroke by 27%.

5. **Adenosine diphosphate receptor antagonists** (clopidogrel, prasugrel, ticagrelor, cangrelor, ticlopidine) inhibit adenosine diphosphate–induced platelet aggregation by the $P2Y_{12}$ receptor. These agents are typically added as a second antiplatelet agent in patients with ACS or who are undergoing PCI. Multiple landmark trials showed clear benefit for DAPT as compared with conventional anticoagulation therapy, and this has become the standard of care. Trials have also shown the higher potency agents (prasugrel and ticagrelor) to be superior to clopidogrel in ACS; thus, these agents are preferentially used for patients presenting with ACS.
   a. **Clopidogrel** is the most commonly used $P2Y_{12}$ inhibitor for elective PCI, long-term DAPT, and in cases where anticoagulation is required. The recommended pretreatment dose is 600 mg, followed by 75 mg daily for maintenance. In the ARMYDA-4RELOAD trial, no benefit was found in giving an additional loading dose to patient undergoing elective PCI, but there was a benefit (reduction in MACE at 30 days) in those with NSTEACS. Some concerns have been raised regarding clopidogrel nonresponsiveness (defined as platelet inhibition <20%), which is associated with worse MACE rates. However, routine testing for clopidogrel nonresponsiveness has not been shown beneficial and is thus not recommended. For true nonresponders who have recurrent events, transitioning to a higher potency $P2Y_{12}$ agent is recommended.
   b. **Prasugrel** is a prodrug that requires conversion to an active metabolite. It became popular after the TRITON-TIMI 38 trial showed a reduction in MACE in patients with ACS who were

treated with prasugrel as compared with clopidogrel. However, this was at the risk of increasing major and life-threatening bleeding (1.03% vs 1.68%, $P = .03$; 1.4% vs 0.9%, $P = .01$). Some subgroups in particular had worse net outcomes, including patients with prior stroke, transient ischemic attacks, patients >75 years of age, and patients weighing <60 kg. Thus, prasugrel is contraindicated in these groups. In addition, prasugrel was studied with a loading dose after the definition of coronary anatomy with angiography, and for this reason, it is not recommended to preload with prasugrel. After decision to proceed with PCI, use a loading dose of 60 mg followed by maintenance of 10 mg daily.

c. **Ticagrelor** is a reversible $P2Y_{12}$ inhibitor that is an active drug that does not require hepatic conversion. It has the most rapid onset, greatest inhibition, and least individual variability of the oral $P2Y_{12}$ agents. It became popular after the PLATO trial where it was shown to have decreased MACE and decreased ST compared with clopidogrel. There was, however, a higher incidence of major bleeding in the ticagrelor group (4.5% vs 3.8%, $P = .03$). Ticagrelor was administered upstream of angiography in contrast to prasugrel and thus should be administered with a preloading dose of 180 mg. Maintenance dosing is 90 mg twice daily. Ticagrelor is contraindicated in patients with severe hepatic dysfunction.

d. **Cangrelor** is an IV reversible $P2Y_{12}$ inhibitor that was approved as an adjunct to PCI in patients who have not been treated with a $P2Y_{12}$ agent and who are not being given a GPI. Major advantages of cangrelor when compared with other antiplatelet agents are its rapid onset of action and rapid return of platelet function after its discontinuation. Trials assessing the efficacy of cangrelor compared to clopidogrel showed superiority in regard to MACE with its use. There was an increase in mild bleeding associated with cangrelor, but not with major bleeding.

e. **Ticlopidine** has fallen out of favor due to poor tolerance, with 20% of people discontinuing due to adverse effects. Thrombotic thrombocytopenic purpura occurred in 1% to 3% of patients as well, which limited its use.

E. Intracoronary vasodilators work to dilate the epicardial coronary vessel as well as the distal microcirculatory bed. PCI can result in no reflow defined as a reduction in coronary flow without an obstructive lesion. The most probable causes of no reflow are microvascular spasm and distal embolization. Potent microvascular vasodilators, such as adenosine (36-72 mcg), nicardipine (100-200 mcg), nitroprusside (50-200 mcg), or verapamil (200 mcg), often restore normal flow. Nitroglycerin is a logical choice for relieving epicardial spasm but has no effect on the microvasculature. Immediately before SVG intervention, verapamil pretreatment has been shown to prevent no reflow but has never been shown to reduce the risk of CK-MB elevation.

XV. SUPPORTIVE ADJUNCTIVE THERAPY.

Refer to the Chapter 62 on Mechanical Circulatory Support Devices.

VI. POST–PERCUTANEOUS CORONARY INTERVENTION MANAGEMENT

A. Access site care

1. The femoral or radial access site should be examined for hematoma, pseudoaneurysm (systolic bruit), and AV fistulas (continuous murmur). A pulsatile mass also suggests a pseudoaneurysm. Ultrasound studies can confirm the diagnosis of pseudoaneurysm or AV fistula. Suprainguinal tenderness, back pain, lower quadrant abdominal pain, or unexplained hypotension should make one suspicious for retroperitoneal hemorrhage. Hemoglobin is not expected to drop >2 g/dL with PCI, and a greater drop should be concerning for bleeding. Distal pulses should be examined as well. Pulselessness, pain, pallor, paresthesias, and a cool extremity suggest an acute arterial occlusion.

2. **Pseudoaneurysms** <2 cm often close spontaneously; those 2 to 3 cm can often be closed by external, ultrasound-guided compression (90% success rate); and those >3 cm generally require surgical correction. Thrombin injection may also be utilized with very high success rate if the pseudoaneurysm has a thin neck.
3. **AV fistulas** are typically small and inconsequential, rarely causing high-output failure. Indications for ultrasound-guided compression (success rate >80%) or surgical closure include significant shunting, extremity swelling/tenderness, congestive heart failure, or DVT.
4. **Retroperitoneal hemorrhage** can be treated by supportive care (eg, transfusions, close observation, and bed rest) in >80% of cases. Anticoagulation should be reversed, and frequent hemodynamic monitoring in an experienced intensive care unit is required. If the patient is hemodynamically unstable, evaluation by computed tomography (CT) should be deferred and the patient should be treated empirically for retroperitoneal bleed. If the bleeding does not spontaneously stop, the patient may require vascular surgery consultation. Other options include balloon tamponade or coil embolization if a small side branch is the culprit.
5. **Acute arterial occlusion** may be due to dissection or thromboembolism. Both typically require angiography of the affected extremity with access from another extremity. Dissection typically requires prolonged balloon inflation and possible stenting or surgical repair. Stenting of the common femoral artery is discouraged because it is a flexion point, a frequent anastomotic site for bypass grafts, and risks jailing or injury to the profunda. Thromboembolism can be treated with surgical or percutaneous mechanical thrombectomy.

B. **Monitoring for myocardial ischemia.** A 12-lead electrocardiogram (ECG) should be obtained before and after PCI in order to have a baseline. The patient should be monitored in a cardiac ward that has continuous electrocardiographic monitoring and nurses familiar with

routine post-PCI care. Mechanisms for elevated cardiac biomarkers or ECG changes include distal embolization, side branch occlusion, dissection, and spasm. Troponin levels are not routinely measured after PCI. It is not uncommon for patients to experience some chest discomfort following PCI, the so-called stretch pain.

C. Monitoring for contrast-induced nephropathy. Nonsteroidal anti-inflammatory drugs, cyclosporine, and metformin should be withheld for 24 to 48 hours beforehand and 48 hours afterward. Periprocedural IV hydration should be used as tolerated, and renal function (serum Cr) should especially be monitored in patients with previously known renal dysfunction.

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CHAPTER 65

Percutaneous Structural Heart Disease Procedures

Anirudh Kumar and Amar Krishnaswamy

I. INTRODUCTION. The past decade has witnessed a remarkable rise in the number of novel percutaneous, catheter-based procedures using new concepts and technologies for the treatment of structural heart disease. Currently, percutaneous catheter-based therapy is available for several valvular disorders, including aortic stenosis (AS), mitral stenosis (MS), mitral regurgitation (MR), tricuspid regurgitation (TR), and prosthetic paravalvular leaks (PVLs), as well as other structural cardiac disorders such as hypertrophic obstructive cardiomyopathy, patent foramen ovale (PFO), and atrial septal defects (ASDs). Whereas a comprehensive review of structural cardiac interventions is beyond the scope of this chapter, we provide an overview of the major devices and relevant clinical studies that have been performed.

II. PERCUTANEOUS TRANSCATHETER MITRAL VALVE REPAIR

A. Background. MR is one of the most common valvular disorders, encountered in about 9% of the population aged >75 years. Surgical mitral valve repair (MVRe), when feasible, produces excellent outcomes, including lower operative mortality, improved long-term survival, and reduced incidence of endocarditis and thromboembolic complications, compared with mitral valve replacement (MVR).

A number of percutaneous MVRe techniques have been developed that are analogous to surgical procedures. Percutaneous mitral annuloplasty leverages the close relationship of the coronary sinus (CS) to the posterior mitral annulus. The **Carillon** (Cardiac Dimensions) device, which has been granted Conformité Européenne (CE Mark) approval, is deployed in the CS and serves to "cinch" the

annulus, resulting in improved mitral valve (MV) leaflet coaptation. There are also numerous other devices in various stages of preclinical and clinical development.

The **MitraClip** (Abbott Vascular) remains the most widely tested system in humans. The technique is based loosely on the surgical Alfieri stitch, which brings the anterior and posterior leaflets in close apposition using a suture and creates an anatomic "double-orifice" MV. In the United States, transcatheter MVRe is currently indicated in symptomatic patients with severe degenerative MR who are considered to have prohibitive surgical risk and, following the positive results of the COAPT trial, in patients with severe functional MR. More recently, the **PASCAL** Precision Transcatheter Valve Repair System (Edwards Lifesciences) was granted U.S. Food and Drug Administration (FDA) approval for similar indications.

B. Procedure. The MitraClip system uses a steerable 24F guide catheter that is introduced through the femoral vein and subsequently advanced to the left atrium (LA) via transseptal puncture (**Figure 65.1**). Through this guiding catheter, a delivery system containing the V-shaped clip is introduced in the LA and positioned with the arms of the clip perpendicular to the MV line of coaptation using transesophageal echocardiography (TEE) guidance. The clip is advanced to the left ventricle (LV) in an open position and retracted to grasp the anterior and posterior MV leaflets at the desired location. After confirmation by TEE of the clip position, the clip can be locked. If satisfactory (by TEE), the clip can be released; otherwise, it can be reopened and the process repeated. If necessary, multiple clips can be deployed to achieve a satisfactory result. Care must be taken in this situation to not impede forward flow across the valve and trade MR for functional MS.

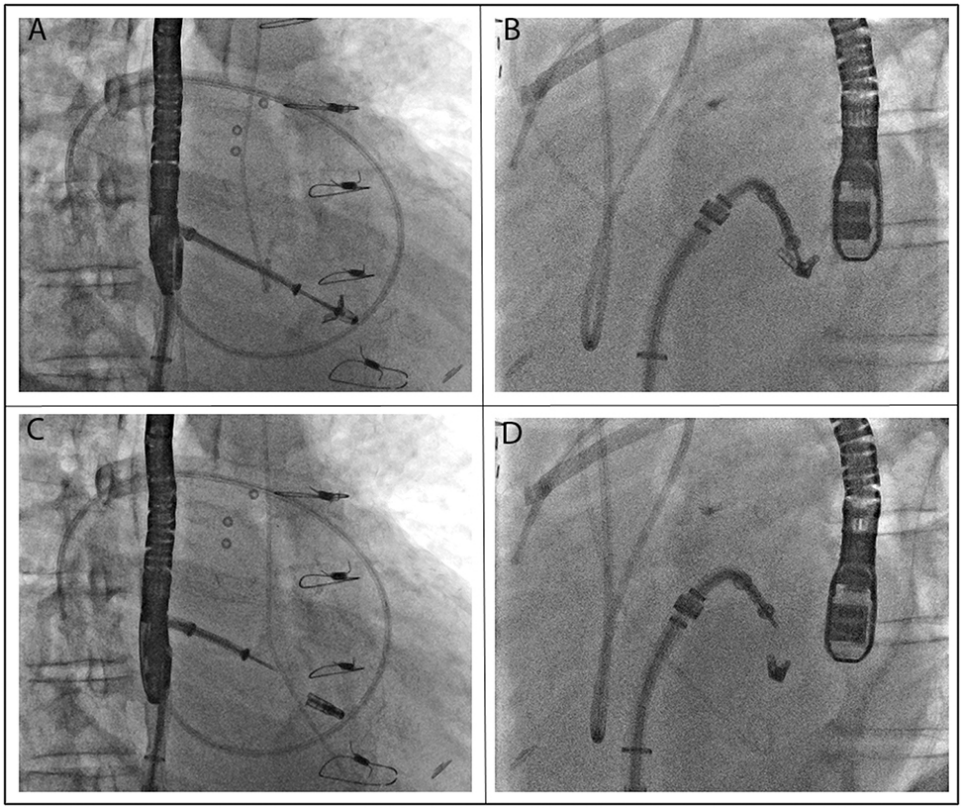

FIGURE 65.1 Percutaneous transcatheter mitral valve repair. **A.** Right anterior oblique projection of the optimal positioning of the MitraClip device. **B.** Left anterior oblique projection of the optimal positioning of the MitraClip device. **C.** Right anterior oblique projection of MitraClip after its release from the delivery catheter. **D.** Left anterior oblique projection of MitraClip after its release from the delivery catheter.

C. Complications. Routine complications associated with vascular access like major or minor bleeding are the most commonly encountered complications. Recurrent MR and the requirement for MV surgery are the prime limitations of the current technique, especially in ischemic MR or in the presence of a significant annular calcification. Partial clip detachment is the most important mechanical problem encountered with the procedure, and treatment with subsequent clip placement or surgical intervention is dependent on the mechanism of leaflet detachment. These are generally not symptomatic and are treatable with MV surgery or placement of an additional clip. Iatrogenic MS is a significant complication that may

arise as a result of this procedure, though its clinical relevance remains unknown.

D. Outcomes. Data from the pivotal EVEREST II trial, which randomized 279 patients to MitraClip versus surgical repair in a 2:1 manner, demonstrated freedom from the combined end point (death, MV surgery within 90 days, or MR >2+ at 1 year) of 72.4% and 87.8% in the two groups, respectively, demonstrating noninferiority of the MitraClip to conventional surgical treatment. Nevertheless, the MitraClip arm had a higher incidence of residual significant MR and subsequent need for MV surgery and thus surgical MVRe remains the gold standard for patients able to undergo open-heart surgery. Currently, clinical trials are undergoing studying patients with degenerative MR at both intermediate and low surgical risks.

The initial studies of the MitraClip concentrated on patients with degenerative MR. Recently, the COAPT trial studying patients with moderate-to-severe functional MR and heart failure randomized 614 patients to MitraClip versus medical therapy alone. This study demonstrated significant benefit in the MitraClip arm in both heart failure hospitalizations (35.8% per patient-year vs 67.9% per patient-year) and 2-year mortality (29.1% vs 46.1%). Moreover, significant benefit was demonstrated among patients in the medical therapy arm who subsequently crossed over to the MitraClip arm.

III. PERCUTANEOUS MITRAL BALLOON VALVULOPLASTY

A. Background. Although there has been a significant reduction in the prevalence of rheumatic heart disease in Western countries, it still represents a major public health concern in the developing world. MS is one of the most common presentations of rheumatic heart disease. It continues to represent a major clinical problem in the United States, primarily because of outmigration from developing countries or the occurrence of restenosis after previous surgical commissurotomy. Stenosis of the valve may occur because of commissural fusion, leaflet thickening, and/or chordal shortening and fusion.

Before the advent of percutaneous mitral balloon valvuloplasty (PMBV), symptomatic MS was treated using surgical commissurotomy. Since the introduction of the percutaneous procedure in the early 1980s by Inoue and colleagues, PMBV has evolved to become the first line of therapy for appropriately selected patients with MS. The technique works similarly to commissurotomy, resulting in the opening of the fused commissures.

B. Procedure. The Wilkins splitability score is the most widely used echocardiographic parameter to determine the safety and feasibility of PMBV, and this takes into consideration leaflet mobility, leaflet thickening, subvalvular thickening, and valve calcification (each scored 0-4 points). Multiple investigators have shown that patients with a score of 8 or less have the greatest freedom from death and valve surgery and the largest improvement in MV area with PMBV.

Selection of the appropriate balloon size is one of the most important steps for accomplishment of a successful PMBV. A good rule of thumb is to use the following formula to determine the maximum balloon dilation size: Balloon size (mm) = patient height (cm)/10 + 10 mm. Transseptal puncture is performed, most commonly with TEE guidance, via a sheath placed in the femoral vein. Once the sheath has entered the LA, it is exchanged for the Inoue balloon catheter.

The balloon catheter is slowly advanced into position in the LV. The Inoue balloon consists of three portions with slightly different compliances. As pressure is added to the balloon, the distal portion inflates first followed by the proximal portion. As soon as the distal portion is inflated, the balloon is pulled until resistance is felt. With the addition of more pressure, the proximal portion is inflated, which fixes the balloon in the middle waist portion of the valve. The middle waist has the least compliance and dilates only when substantial pressure is added to the balloon, thereby securing the balloon across the valve prior to the dilation of the annulus.

In our institution, we routinely use TEE to guide the valvuloplasty in order to assess the result of balloon inflation (in addition to simultaneous LA-LV gradient measurement) and, more importantly,

to evaluate the degree of MR. Substantial increases in MR should preclude further inflation. In addition, the procedure should be aborted in the presence of left atrial appendage (LAA) clot.

C. Complications. The most common serious complications include hemopericardium or severe MR. Perforation of cardiac chambers, which occurs at a rate of 0% to 2%, may happen while manipulating the catheters in the heart. Whereas an increase in MR may routinely be noted after the PMBV, it rarely requires a surgical intervention.

D. Outcomes. Immediate postprocedural success with a final valve area >1.5 cm^2 without moderate or severe MR is the best predictor of long-term outcome. The best results are obtained in young people with favorable anatomic characteristics. Randomized clinical trials have demonstrated that long-term results of PMBV in young patients are as good as open commissurotomy and are better than closed commissurotomy. In patients with optimal morphology, freedom from restenosis has been reported as 92% at 5 years, 85% at 10 years, and 65% at 15 years. Repeat PMBV has been recommended as first-line therapy in patients with symptomatic mitral restenosis after PMBV or commissurotomy in whom the mechanism of restenosis is commissural fusion.

IV. BALLOON AORTIC VALVULOPLASTY

A. Background. Degenerative or calcific AS is one of the most common valvular disorders encountered in Western countries. With the rapid development of transcatheter aortic valve replacement (TAVR), which has emerged as a favorable option for definitive valve replacement in patients with suitable anatomy, the use of balloon aortic valvuloplasty (BAV) is reserved for fairly specific clinical indications.

In patients with severe AS who are hemodynamically unstable and for whom urgent aortic valve replacement (AVR) is not feasible, BAV may serve as a "bridge" to valve replacement. Similarly, we have also seen significant functional improvement in patients after BAV so that patients unable to undergo AVR initially have improved to a point that TAVR or surgical aortic valve replacement (SAVR) could be

performed safely. In patients with symptomatic severe AS who require urgent noncardiac surgery, BAV may be considered a temporizing measure in the hope of reducing the risks of perioperative hemodynamic changes associated with anesthesia.

A number of patients with severe AS have other comorbidities, such as chronic obstructive pulmonary disease or liver or kidney disease, that make it difficult to discern the degree to which AS contributes to their symptoms. In such cases, BAV may provide a therapeutic answer; improvement of symptoms points to AS as the driver of symptoms and may push for a more definitive valve replacement option. Finally, in patients without any option for either TAVR or SAVR, BAV may be considered a palliative measure.

B. Procedure. The femoral retrograde approach is the most commonly utilized method for BAV, although, in patients with severe iliofemoral disease, the procedure can be performed in an antegrade manner via venous access and transseptal puncture. A Swan-Ganz catheter is placed in the pulmonary artery for continuous hemodynamic monitoring and assessment of cardiac output. A temporary pacemaker is placed in the right ventricle to perform rapid pacing (180 beats/min) during balloon inflation to reduce cardiac output and minimize balloon movement in the annulus. After crossing the aortic valve using a 5F Amplatz left (AL) 1 diagnostic catheter and a straight wire, a stiffer wire is inserted and positioned in the LV. BAV is typically performed using balloons ranging from 18 to 25 mm in diameter. The balloon is sized based on the annulus diameter on transthoracic echocardiography (TTE) or gated computed tomography (CT); the maximum balloon size is 10% larger than the annulus, and we routinely begin dilation at smaller sizes and assess the hemodynamic result prior to increasing the balloon size. Procedural success with BAV is typically defined as a 50% reduction in mean aortic valve gradient and a 25% increase in aortic valve area (AVA); most patients usually experience almost a 50% increase in AVA.

C. Complications. While BAV can be performed relatively safely, the 30-day mortality associated with the procedure may be up to 10% and

as high as 50% at a median follow-up period of 6 months depending on the clinical context of the index procedure, usually due to persistent heart failure. Other complications include stroke and peripheral vascular complications; the need for permanent pacemaker implantation, cardiac tamponade, and cardiac arrest are rare.

D. Outcomes. Despite a modest improvement in valve area, a significant improvement in functional status may be noted after BAV. However, the benefit of BAV gradually disappears over the course of the next few months. The poor functional status of the patients, as well as only moderate, transient effects of the technique, is primarily responsible for the overall grim long-term results of stand-alone BAV. Extensive data indicate that stand-alone BAV does not change the natural course of AS, even after repeated procedures. Despite this, BAV holds an important place in the treatment of patients with severe AS.

V. TRANSCATHETER AORTIC VALVE REPLACEMENT

A. Background. The interest in percutaneous aortic valve implantation began in the early 1990s. The first human experience was reported by Cribier et al in 2002. Since then, rapid advancements in the design of the stented valve and delivery catheters and improved facility in implantation techniques have led to a consistent improvement in the postprocedural outcomes and have heralded a new era in the treatment of valvular AS.

The procedure involves implantation of a tissue pericardial valve that is mounted within a stent. The key to TAVR success is a careful selection of patient population for the procedure and a judicious use of preprocedural and intraprocedural imaging modalities, including fluoroscopy and aortic angiography.

In a study of the application of TAVR to patients with low surgical risk, both balloon-expandable and self-expanding devices led to favorable short- and intermediate-term outcomes compared to surgical AVR. Focus of management of patients with severe AS has shifted to a “lifetime management approach” that balances the pros and cons of percutaneous and surgical approaches to AVR.

B. Procedure. There are a number of valves available worldwide for TAVR, but only two are currently available in the United States and have been studied within randomized controlled trials: the balloon-expandable Edwards SAPIEN 3 Ultra valve (Edwards Lifesciences) and the self-expanding Evolut FX system (Medtronic Inc) (**Figure 65.2**). The largest human experience is with the Edwards Lifesciences series of balloon-expandable aortic valves. The valve consists of a tubular stainless-steel stent with a fabric valve cuff and contains valve leaflets derived from bovine pericardial tissue. This valve is available in four sizes: 20, 23, 26, and 29 mm. Valve sizing takes into consideration the annular area measured using three-dimensional (3D) imaging (CT or TEE) as well as various aortic root characteristics. Although the valve was implanted initially using the transvenous access and subsequent transseptal puncture, it is now routinely implanted using either a retrograde transfemoral (TF) approach or an antegrade transapical approach. The newest iteration of the commercially available SAPIEN series, the S3, is delivered via a 14F (20-, 23-, 26-mm valves) or 16F (29-mm valve) expandable sheath.

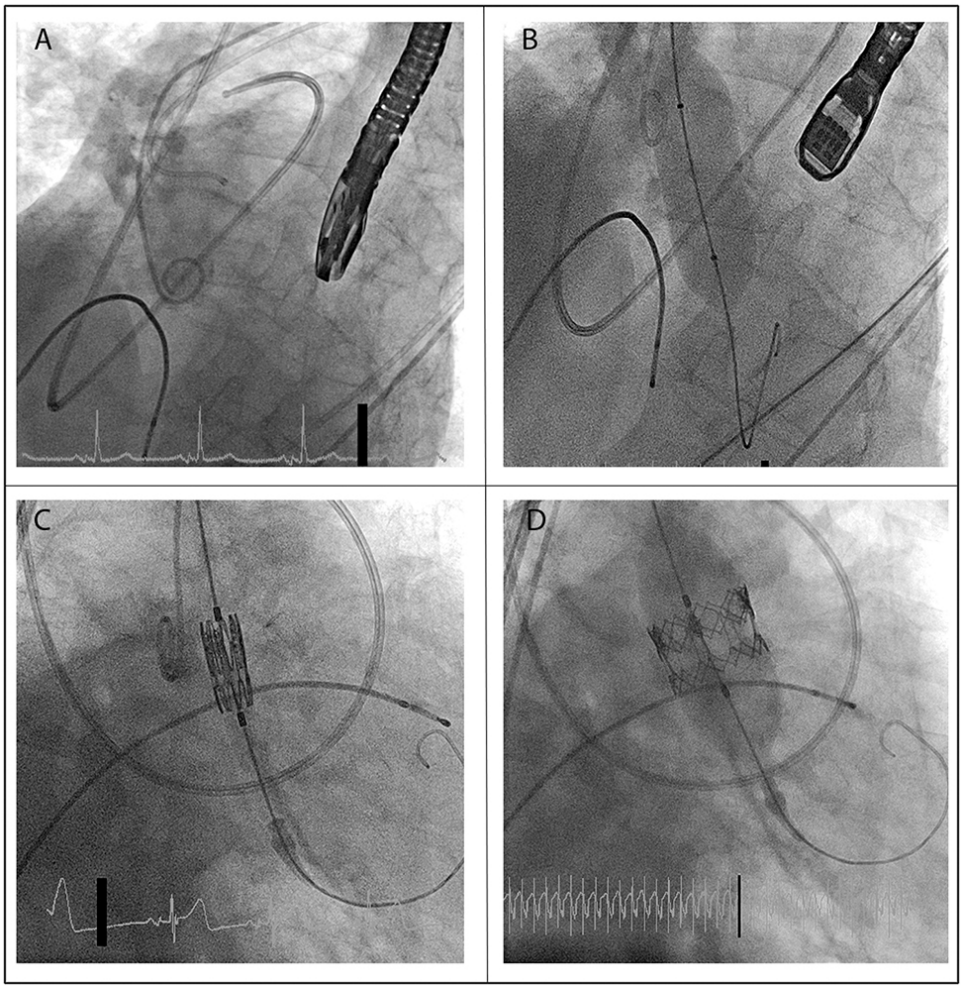

FIGURE 65.2 Transcatheter aortic valve replacement. **A.** Proper positioning of various catheters and devices for valve replacement: a transesophageal echocardiography probe in the esophagus, a Swan-Ganz catheter in the pulmonary artery, a pigtail catheter in the aortic root, an AL 1 diagnostic catheter in the ascending aorta (prior to valve crossing), and a temporary pacemaker wire in the right ventricle. **B.** Aortic valvuloplasty being performed using a standard balloon. **C.** Proper positioning of the crimped Edwards SAPIEN prosthesis across the aortic valve. **D.** Deployment of the valve using balloon inflation after initiation of rapid pacing.

The preprocedural assessment consists of TTE, iliofemoral contrast angiography or iliofemoral CT, 3D annulus imaging using CT angiography, TEE, or magnetic resonance imaging and coronary angiography. Appropriate patient selection, which includes the

anatomic characteristics of the aortic annulus and iliofemoral system, is imperative to procedural success.

1. **TF-TAVR.** TF-TAVR is usually performed under general anesthesia or conscious sedation in a catheterization laboratory or hybrid operating room equipped with multimodality imaging equipment. A transvenous pacing wire is introduced into the right ventricle through the venous access port to enable rapid pacing (180 beats/min) in order to minimize cardiac output and valve movement during valve deployment. BAV can be performed using the standard technique with a balloon that is slightly smaller than the size of the planned valve prosthesis to facilitate valve crossing, though this is typically not necessary.

   Once the TAVR prosthesis is suitably positioned, the valve is deployed. This requires rapid pacing for the balloon-expandable valves and is recommended though not necessary for self-expanding valves. The final positions of deployment as well as the degree of paravalvular aortic regurgitation are assessed using echocardiography, hemodynamics, and aortography.

   Inappropriate positioning may require a second valve deployment. Excessive paravalvular aortic regurgitation may be treated using further balloon dilation or deployment of a second valve. Echo and angiographic assessment for complications (including pericardial effusion, aortic root trauma, and coronary occlusion by the valve) are imperative prior to closure of the femoral access. Similarly, angiography of the iliofemoral system is necessary to evaluate for vascular trauma that might require endovascular or open surgical repair prior to completion of the procedure.

2. **Alternate access for TAVR.** Given the high incidence of peripheral arterial disease in patients with severe AS, several alternative access sites have been investigated and include the **transapical, transcarotid, transsubclavian, transaortic, and transcaval approaches**. The result of TAVR from these access sites carries a higher risk than traditional TF-TAVR, and outcomes are not as good.

C. Complications. Procedural success has improved with device improvements with each iteration. After an initial learning curve, excellent procedural success rates with minimal intraprocedural mortality have been reported. Vascular access complications are encountered more often (<10%) than with other interventional procedures because of the large sheath sizes used for TAVR. Complications associated with limited thoracotomy are expected after alternate access TAVR. Malposition of the aortic prosthesis may be encountered in <1% to 3% of cases. Periprocedural strokes have been reported in 2% to 3% of patients undergoing TAVR with the newest generation Edwards S3 valve and about 3% with the Evolut prosthesis.

D. Outcomes. The Placement of Aortic Transcatheter Valves (PARTNER) 1 trial was the first multicenter randomized controlled trial of TAVR and provided two important randomized comparisons. The PARTNER 1B cohort showed a significant reduction in mortality (30% vs 50% at 1 year and 72% vs 94% at 5 years) in 358 inoperable patients with severe symptomatic AS after randomization to TAVR with balloon-expandable valve (Edwards SAPIEN) versus standard therapy, including BAV. The PARTNER 1A cohort showed that outcomes of surgical AVR and balloon-expandable TAVR are comparable in high-risk patients, with no difference in 5-year rates of mortality and major clinical outcomes (including stroke, cardiac death, and myocardial infarction [MI]). A randomized control trial of self-expanding valves (CoreValve) showed superiority to surgical AVR in mortality at 1 year (14% vs 19%), although the STS score was lower in this cohort compared with the PARTNER cohort (7.4% vs 11.7%). The PARTNER 2 trial showed that balloon-expandable TAVR (Edwards SAPIEN XT) had comparable primary composite end points of all-cause death or disabling stroke (19% vs 21%) at 2 years to surgical AVR in intermediate-risk patients, with a suggestion that TF-TAVR patients fared better than SAVR. The S3 intermediate-risk trial compared approximately 1,000 patients at intermediate surgical risk who underwent TAVR (88% TF approach) with a propensity-matched SAVR group from the PIIA trial. At 1 year, the

TF-TAVR group demonstrated superiority over surgery with regard to the major end points of death (7.4% vs 13.0%, $P < .001$) and stroke (4.6% vs 8.2%, $P = .004$). Most recently, both valves were studied in the low-risk surgical group and found to be noninferior to surgical AVR. The Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients trial randomized 1,403 patients with a mean age of 74 years and found an estimated incidence of the primary end point, defined as a composite of all-cause mortality or disabling stroke at 24 months, in 5.3% of patients undergoing TAVR versus 6.7% of patients undergoing SAVR ($P > .999$ for noninferiority). The PARTNER 3 Trial randomized 1,000 patients with a mean age of 73 years and found the incidence of the composite endpoint, defined as all-cause mortality, stroke, or rehospitalization, to be significantly lower at 12 months among patients who underwent TAVR in comparison to SAVR (8.5% vs 15.1%; $P < .001$ for noninferiority; $P = .001$ for superiority).

VI. PATENT FORAMEN OVALE CLOSURE

A. Background. PFO is a remnant of fetal cardiac circulation and is found in 27% to 33% of adults. Although generally believed to be an "innocent bystander," PFO has been associated with stroke, migraines, platypnea-orthodeoxia, and decompression sickness among divers. PFO arises when the septum primum and septum secundum fail to fuse despite some degree of overlap. Atrial septal aneurysms and prominent Chiari networks have been associated with PFO. Percutaneous PFO closure is currently recommended in patients with platypnea-orthodeoxia, divers with decompression sickness, and patients with cryptogenic stroke younger than 60 years of age. Although several observational studies have shown the benefits of PFO closure in the prevention of migraine, these findings have not been confirmed in major randomized trials.

All PFO closure devices have a similar design, usually consisting of two atrial disks connected by a short neck. Under fluoroscopic and intracardiac echocardiography (ICE) guidance, the device is placed such that the two atrial disks lie on either side of the interatrial septum, with the neck positioned in the PFO tunnel. A large part of

the atrial shunt is eliminated as a result of physical obstruction to flow. Most of the residual shunt is eliminated over the course of a few months after the procedure, as the device becomes endothelialized. Dual-antiplatelet therapy is generally recommended for the first 6 months after closure to minimize the risk of thromboembolism prior to device endothelialization.

B. Procedure. Several devices for transcatheter PFO closure have been tested in humans, including the Cardioform Septal Occluder device (WL Gore & Associates) and the Amplatzer cribriform ASD occluder device (AGA Medical) (**Figure 65.3**). Because these devices are FDA approved only for ASD closure, use for PFO closure is "off-label." Sizing of the devices may vary based on the degree of associated atrial septal aneurysm; significant aneurysm generally requires a larger device.

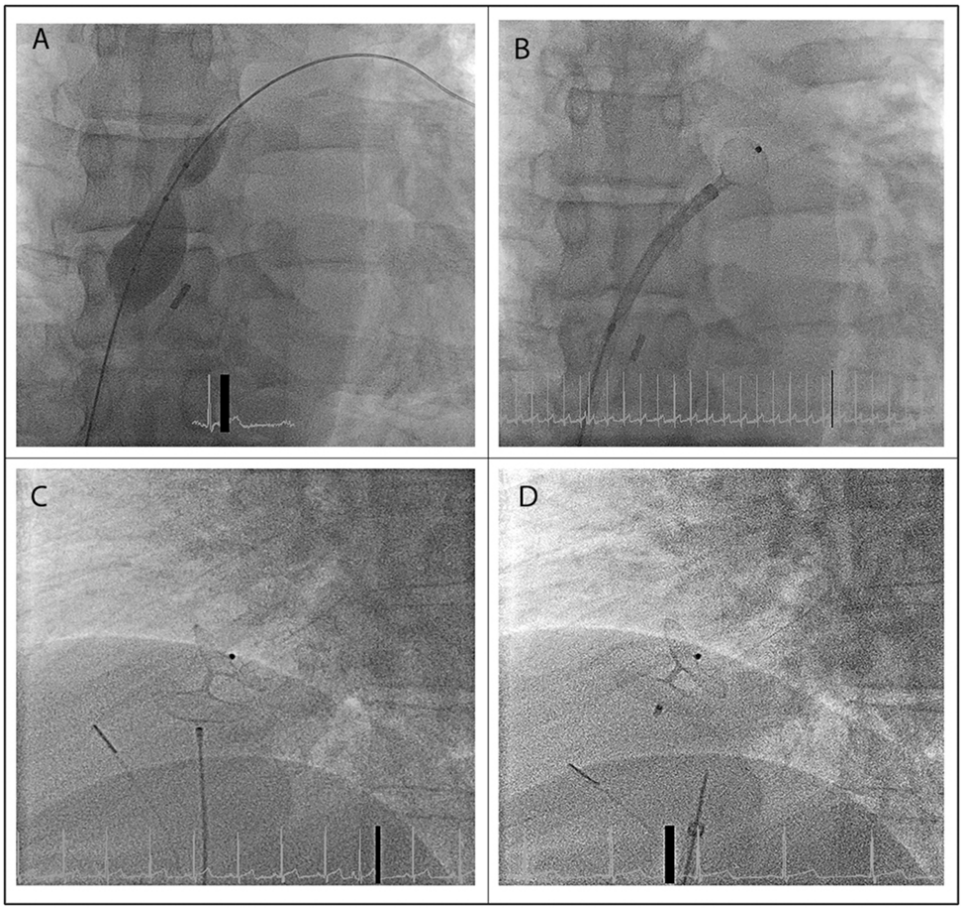

FIGURE 65.3 Patent foramen ovale (PFO) closure using Amplatzer device. **A.** Balloon sizing of the PFO tunnel after crossing the PFO using a wire. The intracardiac echocardiography probe is visible next to the balloon. **B.** Deployment of the left atrial disk of the Amplatzer occluder device. **C.** Deployment of the right atrial disk of the Amplatzer occluder device. **D.** Device in place after its release from the delivery catheter.

Briefly, the procedure involves placement of an 8F to 12F vascular sheath (depending on device size) in one femoral vein and a 9F sheath in the contralateral femoral vein for ICE. The ICE catheter is parked in the right atrium for procedural visualization. The PFO is usually crossed using a wire and a Goodale-Lubin (GL) catheter or multipurpose A catheter under ICE and fluoroscopic guidance. Through the GL catheter parked in the left superior pulmonary vein, the wire is exchanged for a stiffer wire over which the closure device delivery system is advanced. The LA disk of the device is deployed and the system slowly retracted. This action facilitates apposition of the septum primum to the septum secundum and effectively closes the PFO. The right atrial disk is then deployed. After confirmation of the positioning and stability using ICE and fluoroscopy (and sometimes right atrial angiography), the device is released from the delivery catheter.

C. Complications. Transcatheter PFO closure is generally associated with a high procedural success rate and without significant risk of complication. Rare complications including device migration or embolization, symptomatic air embolism, and atrial fibrillation (AF) or chamber perforation with cardiac tamponade may occur intraprocedurally. Later complications associated with the procedure include thrombus formation (more common with CardioSEAL than Amplatzer), device erosion, or formation of a new ASD.

D. Outcomes. Initial studies investigating PFO closure for the prevention of cryptogenic stroke were largely negative. The Migraine Intervention with StarFlex Technology study failed to demonstrate any significant difference in migraine cessation between the closure and the "sham" arms. The Closure of Patent Foramen Ovale versus Medical Therapy after Cryptogenic Stroke (RESPECT) trial

randomized 980 patients with cryptogenic stroke to PFO closure versus medical therapy alone. The initial results of the RESPECT trial showed no difference in the primary composite end point of recurrent nonfatal ischemic stroke, fatal ischemic stroke, or early death on the primary intention-to-treat analysis, but there was statistical evidence of benefit to PFO closure in the secondary as-treated and prespecified per-protocol analysis with a reduction in event rate of 0.43 versus 1.38 events per 100 patient-years. Long-term results of the RESPECT study demonstrated a significant decrease in risk of recurrent cryptogenic stroke of 4.3% versus 1.5% with PFO closure.

VII. ATRIAL SEPTAL DEFECT CLOSURE

A. Background. ASD is one of the most common adult congenital heart diseases encountered in the U.S. population. Although ASDs generally remain asymptomatic till early adulthood, they are associated with several clinical presentations, including right ventricular failure, atrial arrhythmias, pulmonary hypertension, and paradoxical embolism.

Patients with hemodynamically significant ASD should undergo elective closure either surgically or with the transcatheter technique, although, in recent years, the transcatheter approach has become the first line of therapy in patients with appropriate secundum ASD anatomy. The hemodynamic significance of an ASD is determined by the presence of right ventricular enlargement in the presence of defect diameter >1 cm or the presence of significant left-to-right shunting with an elevated shunt ratio (Q_p:Q_s >1.5).

The principle of ASD closure is similar to that of PFO closure, entailing implantation of an occlusion device with atrial disks lying on either side of the interatrial septum and the central waist residing in the ASD. Because of significant variations in size and anatomy of ASD, transcatheter ASD closure is technically more challenging than PFO closure.

B. Procedure. Several devices have been used for percutaneous ASD closure. The Amplatzer atrial septal occluder (AGA Medical) has the

largest reported human experience. The other major device available is the Cardioform (WL Gore & Associates).

The procedural approach to percutaneous ASD closure is similar to the percutaneous PFO closure approach as described above. A few important differences exist that are worth considering.

1. Because of a significant variation in the size of ASD and the shape of the defect, proper invasive balloon sizing (by ICE and fluoroscopy) is needed. Both oversizing and undersizing of the device may be hazardous and may lead to complications like device erosion or device embolization.
2. Device deployment and orientation during transcatheter ASD closure poses greater technical challenges than during PFO closure. The technical complexities are more frequent when ASDs are associated with other structural anomalies like atrial septal aneurysms or in cases of inadequate rim capture. It is imperative to demonstrate an adequate rim surrounding the defect for percutaneous closure.
3. Multiperforated septa demonstrate a particularly greater challenge to complete closure. In these cases, specific devices like the Amplatzer cribriform occluder or multiple devices may be needed to achieve a good clinical result.
4. The Amplatzer device is sized based on the defect size (ie, 16-mm device for a 16-mm ASD) and can be used to close defects 2 to 38 mm in diameter. The Cardioform device is sized 1.7 times the size of the defect (ie, 30-mm device for a 15-mm ASD) and can be used to close defects 2 to 17 mm in diameter.

C. Complications. As in transcatheter PFO closure, procedural success in experienced hands is high and complications are rare. Potential complications include device embolization, perforation as a result of device erosion into the atrial wall, residual shunting, or atrial arrhythmias. ASD device mismatch is encountered in 2% to 5% of cases. Other rare complications include vascular access complications, sizing balloon rupture, and entrapment of right atrial structures. Chest discomfort or new onset of arrhythmia may be clues

to device erosion or embolization and should prompt urgent echocardiographic evaluation.

D. Outcomes. Most patients demonstrate improved functional class and exercise capacity after a successful closure. Several observational studies have demonstrated an improvement in overall long-term survival. Timely ASD closure prevents the development of right heart failure and pulmonary hypertension. There has been evidence of reduction in the size of enlarged cardiac chambers with normalization of intracardiac pressures after successful ASD closure.

III. VENTRICULAR SEPTAL DEFECT CLOSURE

A. Background. Although isolated ventricular septal defects (VSDs) are a relatively common form of adult congenital heart disease, congenital VSDs of hemodynamic significance are rare, with a prevalence of 0.03% in the adult U.S. population. More commonly, VSDs are acquired as a result of complications of MI, cardiovascular surgery, or chest trauma. Postinfarction ventricular septal rupture (VSR) is associated with >90% mortality if left untreated. The postinfarction or traumatic VSRs may be located in the posterobasal (inferior infarct) or apical (anterior infarct) portions of the muscular ventricular septum and are typically irregular with multiple ruptures in necrotic myocardium that are prone to rupture or expansion. This presents significant challenges with respect to surgical as well as transcatheter repair.

Percutaneous VSD/VSR closure involves devices that are similar to those described for ASD closure. The device is positioned under fluoroscopy and echocardiographic guidance (TEE and/or ICE as needed) such that the two disks lie on either side of the ventricular septum and the waist lies in the septal defect. The width of the connecting waist determines device sizing.

B. Procedure. The only available device that is approved for closure of congenital muscular VSDs is the Amplatzer muscular VSD occluder device (AGA Medical). There is a specially designed Amplatzer postinfarction muscular VSR occluder device, which is currently under investigation in the United States. It is similar to its congenital

counterpart, except for a longer waist, large disk diameter, and a larger waist diameter. In patients with postinfarct VSR, it may be necessary to use an atrial septal occluder, as the distance between the disks of the VSD occluder device may be too large. Again, this would be considered an "off-label" usage.

VSD closure can be achieved via the retrograde approach from the LV or via the femoral or jugular vein. The VSD is crossed using a diagnostic catheter and wire, with the wire then externalized to the artery (if approached from the right ventricle) or vein (if approached from the LV) to create a continuous arteriovenous (AV) loop. A delivery catheter containing the device is subsequently delivered over the loop. Under fluoroscopic and echocardiographic guidance, proper alignment and position are confirmed, and the device is subsequently deployed.

C. Complications. The major complications of transcatheter VSD closure include device embolization, air embolism, residual shunting, defect enlargement, complete heart block requiring pacemaker implantation, arrhythmias, valvular regurgitation because of impingement, and intravascular hemolysis.

D. Outcomes. The results of transcatheter closure of congenital VSDs are encouraging; however, the closure of postinfarction VSR has yielded disappointing results in several studies. Although surgery has been recommended as the gold standard for the repair of postinfarction VSD, emergent surgical repair carries an operative mortality of about 50%. This often leads surgeons to recommend delaying the surgery for at least 2 weeks after the initial ischemic event to improve the tissue integrity for sutures/patches and results in a lesser operative mortality and improves the chance of success. Because of this, several centers have attempted transcatheter VSR closure in patients who are either not surgical candidates or too unstable to survive the "waiting period." Data from observational studies have reported variable success, with mortality rates ranging from 20% to 100%.

IX. LEFT ATRIAL APPENDAGE OCCLUSION

A. Background. AF is associated with 15% of all ischemic strokes. Autopsy studies have shown that up to 90% of the thrombi in nonvalvular AF originate in the LAA. Although warfarin has been demonstrated to reduce the rate of stroke in patients with AF, there are several limitations, including risk of bleeding, pharmacologic interactions, and need for prothrombin time (international normalized ratio) monitoring. In several patients, the use of warfarin may be contraindicated, necessitating another method of stroke prevention.

Surgical amputation and exclusion of the LAA have been demonstrated to reduce the risk of stroke after MV surgery, without any significant impact on the rate of postoperative AF. Given the favorable location of the LAA for percutaneous closure, a number of methods have been developed.

B. Procedure. The two devices with the most significant human experience available for left atrial appendage occlusion (LAAO) are the Amplatzer Cardiac Plug (ACP) (AGA Medical) and the WATCHMAN device (Atritech Inc). The WATCHMAN and ACP devices have CE Mark approval, whereas only the WATCHMAN is commercially available in the United States. The size and shape of the LAA is most commonly assessed using TEE, although modified discrete cosine transform analysis is often helpful in sizing and understanding the morphology.

The devices are generally implanted using 14F femoral venous access. A transseptal puncture is performed under fluoroscopic and TEE guidance. The device delivery system allows for collapse, repositioning, or removal of the device in case of unsatisfactory result. Adequacy of the LAAO (defined as mild to absent leak) is confirmed using radiopaque contrast injection into the LA cavity.

C. Complications. The complications of the procedure include pericardial effusion, cardiac tamponade, residual leakage, or major vascular complications requiring transfusion.

D. Outcomes. The two major randomized trials of LAAO versus anticoagulation therapy are the PROTECT-AF and PREVAIL studies. In totality, the trials demonstrate at least equivalence of the two strategies with respect to stroke outcomes. Long-term (4-year)

outcomes from PROTECT-AF demonstrated superiority in the primary efficacy outcome of stroke/death/systemic embolism in comparison with warfarin. There have been no major randomized trials of the novel oral anticoagulants compared with the WATCHMAN. In clinical practice, and based on the current trials, the WATCHMAN represents a good alternative to anticoagulation for patients who are intolerant of anticoagulation or at high bleeding risk.

X. ALCOHOL SEPTAL ABLATION. Septal myectomy (SM) is considered the historic gold standard for the treatment of symptomatic left ventricular outflow tract (LVOT) obstruction in patients with hypertrophic cardiomyopathy. Alcohol septal ablation (ASA) has emerged as an attractive, less invasive alternative to myectomy that is applicable to those patients with favorable anatomy for ASA who cannot or do not want surgery. Over the past 15 years, the number of ASA procedures done worldwide has surpassed the total number of myectomies performed in the past 50 years. ASA may be considered in patients who have clear evidence of septal hypertrophy (>18 mm) projecting into the LVOT, patients who have dynamic LVOT obstruction (gradient >50 mm Hg at rest or upon provocation), and patients who have been refractory to medical therapy. Patients with coexistent abnormalities of the mitral apparatus are best treated by surgery rather than ASA.

ASA entails creating a controlled myocardial necrosis by injecting alcohol into the septal perforator that perfuses the area of obstruction-inducing hypertrophy. Postablation, the LVOT gradient demonstrates a triphasic response. There is an immediate reduction in the LVOT gradient after a successful procedure, attributable to the loss of septal contractility and associated systolic anterior motion of the MV. Over the next few days, there may be an increase in the LVOT gradient because of recovery of the stunned myocardium and edema of the tissue. The more permanent decrease in LVOT gradient happens over the course of the next few months secondary to myocardial thinning and septal remodeling.

A. Procedure. ASA is performed via dual arterial access. Because transient heart block is common during the procedure, an active-fixation temporary pacemaker is inserted via the internal jugular vein

and left in place for 48 to 72 hours during inpatient observation for conduction deficits. A pigtail catheter is placed in the LV to allow LV, aorta gradient measurement during the procedure. A guiding catheter is introduced into the left main coronary artery and a guidewire advanced to the septal perforator of interest. Subsequently, a short "over-the-wire" (OTW) balloon is advanced to the septal perforator and inflated to obstruct backflow of alcohol from the septal to the left anterior descending artery. Angiographic contrast is injected through the balloon to ensure that there is absolutely no backflow into the LAD.

Echocardiographic contrast is then injected through the OTW balloon in order to map the myocardium that would infarct as a result of ASA. This is an important step, because it helps determine the appropriateness of the procedure and helps in selecting the optimal branch for alcohol injection. Subsequently, 1 to 2 mL of alcohol is injected slowly through the balloon based upon the degree of gradient reduction. The balloon is then deflated and removed.

B. Complications. Besides the routine vascular complications that may arise in any interventional procedure, new-onset right bundle branch block is a significant complication of this procedure and is reported in up to 50% of patients in some series. Complete heart block requiring a need for a permanent pacemaker may occur in about 10% of patients undergoing ASA. The other potential long-term complication includes ventricular arrhythmias, hypothesized to arise as a result of creation of arrhythmogenic myocardial scar. Recent meta-analyses have failed to demonstrate significant differences in ventricular arrhythmias between myectomy and ASA.

C. Outcome. Although there are no randomized comparisons between SM and ASA, large meta-analyses of observational data indicate no significant differences between the two modalities in terms of mortality and improvement in functional status postprocedure. The caveat of ASA is an increased incidence of conduction abnormalities requiring permanent pacemaker implantation, which is necessary in approximately 10% to 15% (a 2- to 3-fold higher rate than patients undergoing SM). Whereas residual gradients are slightly higher with

ASA, functional benefit remains similar. Ultimately, patient selection for ASA requires confirmation of appropriate LVOT and coronary anatomy and a conversation among interventionalists, cardiac surgeons, and patients regarding the relative risks and benefit of ASA versus SM for a given patient.

XI. PERCUTANEOUS PARAVALVULAR LEAK CLOSURE

A. Background. PVL is a rare but serious complication that may arise after surgical MVR or more rarely after SAVR. Although most PVLs are small and remain relatively asymptomatic, more than 10% of patients undergoing MVR or SAVR may develop large symptomatic PVLs with serious clinical consequences, such as heart failure, endocarditis, or hemolytic anemia. Many PVLs become clinically apparent within 1 year after valve surgery, but a significant proportion may either present later or not require any definitive treatment till later. Several risk factors, including reoperation (on the same valve), extensive annular calcification, evidence of endocarditis, large atria, renal failure, and older age, have been identified that may predispose a valve to develop PVL postsurgery. Unfortunately, reoperation for PVL is associated with increased morbidity and mortality. Transcatheter closure of symptomatic PVL in a relatively small number of high-risk patients has been attempted in several centers over the past two decades. The devices approved for closure of other intracardiac defects have been utilized in an off-label manner for transcatheter PVL closure.

B. Procedure. In order to deploy an occlusion device across a PVL, it is first necessary to cross the defect with a delivery catheter. Aortic PVLs are generally crossed in a retrograde manner from the femoral artery. The mitral PVL is most commonly crossed in the antegrade manner by advancing a catheter from the right atrium into the LA via transseptal puncture, sometimes via direct transapical access, and rarely in a retrograde manner via the femoral artery. Similar to percutaneous VSD/VSR closure, creation of an AV loop is helpful to form a supportive rail for the passage of equipment but may not be necessary if the delivery sheath passes easily with the aid of a stiff

wire either in the LV or advanced to the descending aorta. Once the delivery sheath is advanced across the defect, the plugging device is unsheathed into place. Multiple plugs may be placed until adequate closure is demonstrated by adjunctive ICE and/or TEE imaging.

C. Complications. Immediate and delayed device-related complications have been described as a result of technical failure. The early technical failure happens because of device impingement on nearby critical structures, and the delayed technical failure happens as a result of device embolization. Persistent PVL and/or its associated sequelae (ie, congestive heart failure [CHF] and hemolytic anemia) may be encountered after PVL closure. Although no procedure-related deaths have been described in any series, rare instances of strokes, dysrhythmias, and cardiac perforation have been described.

D. Outcomes. Transcatheter PVL closure is one of the most challenging structural heart disease interventions. The long-term outcomes after transcatheter PVL closure largely depend upon surmounting the limitations imposed by the current nonspecific devices for PVL closure, as well as challenges in imaging the area of interest. Over the long-term follow-up described in a few relatively large case series, resolution of hemolysis was reported in 60% to 83% of patients, improvement in CHF symptoms was reported in 50% to 100% of the patients, and repeat surgery was required in only 4% to 18% of the individuals. The incidence of long-term mortality has ranged from 25% to 30% over 3 to 36 months of follow-up across various studies.

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CHAPTER 66

Transthoracic Echocardiography

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I. INTRODUCTION. Transthoracic echocardiography (TTE) is a reliable and versatile tool for the assessment of cardiac structure, function, and hemodynamics. Compared with other cardiovascular imaging modalities, it is relatively inexpensive, does not expose the patient to radiation, is noninvasive, displays live real-time images, and is widely available.

II. BASIC PRINCIPLES OF ECHOCARDIOGRAPHY. Sound waves consist of mechanical vibrations that produce alternating compression and rarefaction of the medium through which they travel. **Ultrasound** consists of sound waves in the frequency range that is higher than what is audible to humans (>20,000 Hz). All waves can be described by their frequency (f), wavelength (λ), velocity of propagation (v), and amplitude. The velocity of ultrasound in soft tissue (eg, myocardium and blood) is 1,540 m/s. Frequency is defined by the number of cycles occurring per second (cycles/second or Hz), and wavelength is measured in meters. Velocity, frequency, and wavelength are described by the following relationship:

$$\textbf{Velocity} = \textbf{frequency} \times \textbf{wavelength or } v = f \times \lambda$$

The typical adult echocardiographic examination uses a transducer with ultrasound frequency between 2.5 and 3.5 MHz. Using the equation above a 3-MHz transducer will have an ultrasound wavelength of approximately 0.50 mm. This has important implications because image resolution cannot be >1 to 2 wavelengths (eg, 1 mm with a 3-MHz transducer). In addition, the depth of penetration of the ultrasound wave is directly related to the wavelength, with shorter wavelengths

penetrating a shorter distance. Therefore, higher frequency transducers result in the use of shorter wavelengths that improve image resolution but at the cost of reduced depth penetration.

Transducers use a piezoelectric crystal to generate and receive ultrasound waves. A piezoelectric substance has the property of changing its size and shape when an electric current is applied to it. An alternating electrical current will result in rapid expansion and compression of the material and thus produce an ultrasound wave. The piezoelectric crystal also deforms in shape when an ultrasound wave strikes the material, resulting in the production of an electric current. The transducer, and the piezoelectric crystal, thus oscillates between a short burst of transmitting ultrasound waves, with a brief period of no ultrasound transmission when it awaits reception of the reflected signals.

Tissue harmonic imaging has become the standard imaging technique in many laboratories. It utilizes the principle that as ultrasound waves propagate through tissue, the waveform becomes altered by the tissue, with the generation of new waveforms of higher frequency but that are **multiples of the baseline fundamental frequency**. Setting the transducer to receive only harmonic sound waves that are multiples of the fundamental frequency improves image quality significantly. This image quality improvement is based on the fact that weak signals, which tend to be artifacts, create almost no harmonics. In addition, shallow structures, such as the chest wall, generate weak harmonic signals, whereas at depths of 4 to 8 cm, where the heart is located, maximal harmonic frequencies develop. These phenomena result in fewer near-field artifacts and better endocardial definition. One limitation of harmonic imaging is that valve leaflets appear thicker—an artifact generated during image processing that appears to be related to the rapid motion of the leaflets.

The steps involved in creating a final ultrasound image are transmission and reception of waves, conversion to electrical signals, filtering, and extensive computer processing. The details of image processing, formation of artifacts, advanced physics, and technical aspects of echocardiography are beyond the scope of this chapter but are briefly discussed in Section VII.

Patient and probe positioning, electrocardiographic lead placement, and transducer selection are the first steps to beginning the echocardiographic examination.

A. Patient and probe positioning. For the parasternal and apical positions, the patient should be in the left lateral decubitus position, with the left arm extended behind the head, because this brings the heart into contact with the chest wall. The subcostal and suprasternal views require the patient to be in the supine position.

B. Electrocardiographic lead placement. The electrocardiogram (ECG) allows the identification of arrhythmias and timing of cardiac events during the echocardiographic examination, and it is used as a timing marker for a digital recording of images. Typically, digital "clips" are set to record a predefined number of cardiac cycles (usually one but sometimes two), with timing based on the ECG. It is important that irregular beats be identified and excluded from the analysis. For example, a post-ectopic beat will falsely increase the two-dimensional (2D) assessment of ejection fraction (EF) and the Doppler assessment of transaortic gradient. In general, any Doppler index requires an average of at least three measurements. For patients with atrial fibrillation, 7 to 10 beats should be averaged. For patients with very high heart rates, or with a noisy electrocardiographic signal, the digital clips can be set to record for a predefined period of time (usually 2 seconds).

C. Transducer selection. The adult echocardiographic examination typically begins with a 2.5- to 3.5-MHz phased-array transducer. Transducer frequency is important, because at higher frequencies, spatial resolution improves but at the expense of reduced depth penetration. Higher frequency (3.0-5.0 MHz) transducers may be used in thin or pediatric patients or intraoperatively for epiaortic scanning. Therefore, for optimal 2D resolution, select the highest frequency transducer that will provide adequate far-field penetration.

With regard to transducer frequency for the Doppler examination, lower frequency transducers can record higher velocities (see Doppler equation in Section IIIC.1). The Pedoff probe is a continuous wave (CW), nonimaging probe (typical frequency being 1.8 MHz) used

mainly to detect higher velocity profiles and confirm velocities obtained by other imaging methods.

III. IMAGING MODALITIES IN STANDARD ECHOCARDIOGRAMS

A. M-mode. Prior to 2D imaging, the echocardiogram was obtained when the transducer sent an ultrasound wave along a **single line** and then displayed the amplitude of the reflected signal as well as the depth of that signal on an oscilloscope. This was called an A-mode echocardiography. When these line-of-sight ultrasound images were plotted with respect to time, "motion" mode, or M-mode, was produced. Despite the increasing emphasis on 2D imaging, the M-mode display remains a complementary element of the transthoracic examination. Its **high sampling rate** of up to 2,000 frames/s, compared with 30 frames/s for 2D echocardiography, provides **excellent temporal resolution**, and thus it is very **useful in the timing of subtle cardiac events** that can be missed by the naked eye in 2D imaging. Rapidly moving structures such as the aortic valve, mitral valve, and endocardium have characteristic movements in M-mode. Deviations from these, such as diastolic fluttering of the mitral valve in aortic regurgitation (AR) and systolic aortic valve notching in dynamic left ventricular outflow tract (LVOT) obstruction, may be the only way to detect the underlying dysfunction not appreciated in other imaging modalities. M-mode also has excellent spatial resolution along the single line and can be used for precise size measurements, such as ventricular dimensions in systole and diastole. The M-mode image is displayed like a graph, with **time on the *x*-axis and distance from the transducer on the *y*-axis**, with the structures closest to the transducer at the top of the image. In order to align the line of sight accurately, **2D imaging should be used to position the M-mode cursor** through the structures of interest.

B. 2D imaging. 2D imaging provides **tomographic views** of various 2D planes of cardiac structures and acts as a guide for the M-mode and Doppler portions of the examination. A 2D echocardiographic image is essentially the scan line from M-mode that, instead of having a fixed line of sight, is swept back and forth across an arc. After complex manipulation of the **data received by the transducer from**

the multiple scan lines, a 2D tomographic image is generated for display.

Depending on the depth of the image, a finite amount of time is needed for each scan line to be sent and received by the transducer. As opposed to M-mode that has only one scan line and can provide up to 2,000 frames/s, 2D echocardiographic imaging can utilize 128 scan lines but at the expense of a lower rate of 30 frames/s. Faster frame rates can be obtained by electronic manipulation using parallel processing on current ultrasound machines. Doppler overlay of the 2D image tends to slow down the frame rate. This **reduction in temporal resolution** reinforces the need for M-mode to complement 2D imaging in echocardiography, especially for rapidly moving structures and in precise timing of events.

C. Doppler echocardiography. The introduction of Doppler techniques to echocardiography not only added new imaging capabilities but also transformed echocardiography into a modality that could provide **hemodynamic assessment** of the heart. Echocardiography has now become the preferred method, and in some cases, the gold standard, over cardiac catheterization for certain hemodynamic assessments.

1. Doppler principles. The Doppler principle states that sound frequency increases as the source moves toward the observer and decreases as the source moves away. The change in frequency between the transmitted sound and the reflected sound is termed the **Doppler shift**. This phenomenon is appreciated daily when an ambulance's siren becomes higher pitched, because of the increase in wave frequency, as it approaches the observer and then lower pitched once it has passed. This Doppler frequency shift directly relates to the velocity of the red blood cell by the following **Doppler equation**:

$$v = \frac{c\left(f_R - f_T\right)}{2f_T\left(\cos\theta\right)}$$

where v = velocity, f_R = frequency received, f_T = frequency transmitted, c = speed of sound in blood (1,540 m/s), and θ = angle

between moving object and ultrasound beam.

The cos θ in the Doppler equation makes the calculation of velocity depend on the angle between the beam and the moving structure (red blood cell). Echocardiography machines do not typically incorporate the angle for calculating the resultant velocity, and thus the goal is to have the angle between the ultrasound beam and the blood flow jet of interest to be as close to zero as possible (cos 0 = 1). When this is not possible, the angle should be <20° so that the true flow velocity is underestimated by <6% (cos 20 = 0.94). Adhering to this requirement sometimes mandates off-axis or unusual 2D images to align the Doppler ultrasound signal with the desired target.

2. **Spectral analysis** is the term used to describe the way in which pulsed-wave (PW) Doppler and CW Doppler are displayed. By convention, the horizontal axis reflects the time and is placed in the middle of the screen, with upward deflections representing frequency shifts toward the transducer and downward deflections for frequency shifts away from the transducer. The vertical axis represents the blood flow velocity (or frequency shifts), with the density of pixels on a grayscale reflecting the amplitude of the signal. The final result is that at each time point, the spectral analysis shows blood flow direction, velocity/frequency shift, and signal amplitude.

   a. **PW Doppler.** The purpose of PW Doppler mode is to measure the Doppler shift, and thus velocity, at a **specific location of interest within a small sample volume** (eg, mitral inflow velocity at the mitral valve leaflet tips, systolic velocity at the LVOT, and blood flow within the pulmonary veins). In this mode, a **single crystal** sends short bursts of ultrasound waves at a specific pulse repetition frequency (PRF) to a specific location, which are reflected from moving blood cells at this location and received by the same crystal. The maximal velocity that can be measured is limited by the time required to transmit and receive the ultrasound wave. This is called the **Nyquist limit** (one-half of the PRF). If a velocity greater than

the Nyquist limit is measured, the signal appears as a wrap around the baseline, known as **signal aliasing**. Hence, the peak velocity is limited by the depth of the area of interest and also by the transducer frequency (inverse relationship according to the Doppler equation; see previous text). **PW Doppler has excellent spatial/depth resolution, but it has limited capacity to measure high velocities because of the Nyquist limit**. It is, therefore, used primarily to measure low-velocity flow (<2 m/s) at specific sites in the heart.

b. **CW Doppler.** CW Doppler employs **two crystals, one continuously sending ultrasound waves and the other continuously receiving the waves**. It measures Doppler shift **along the entire beam**, rather than at a specific location. Unlike PW Doppler, CW Doppler measures the **maximal velocity along the entire ultrasound beam**, but it does not localize the precise position of that peak velocity. However, this is often apparent anatomically or can be deduced using PW Doppler or color-flow Doppler. **In general, CW Doppler is used to assess high-velocity flow and PW Doppler is used to measure low-velocity flow in specific areas**. Clinical applications of PW versus CW Doppler are listed in **Table 66.1**.

TABLE 66.1 Differences and Uses of PW Doppler and CW Doppler

Factor	PW	CW
Transducer crystal	Same transmitting and receiving	Different transmitting and receiving
Spatial resolution	Excellent—localizes to precise point	Poor—may be anywhere along the entire beam
Ability to measure high velocity (>2 m/s)	No (limited by Nyquist)	Excellent
Uses	Mitral inflow	Gradients in aortic stenosis
	Pulmonary venous flow and LVOT flow	Gradient and pressure half-time in mitral stenosis

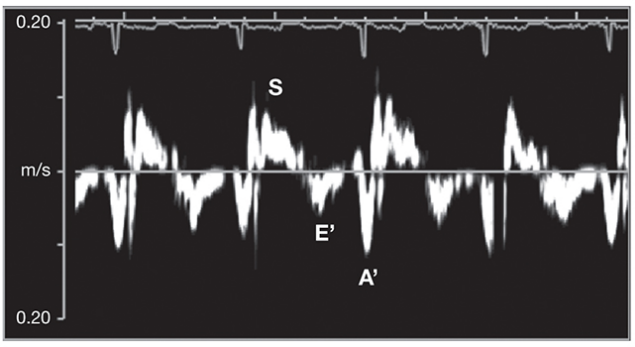
Factor	PW	CW
	Hepatic vein flow	Peak velocity in mitral regurgitation and measurement of d*p*/d*t*
	Tricuspid inflow	TR velocity—estimate RV systolic pressure

CW, continuous wave; LVOT, left ventricular outflow tract; PW, pulsed wave; RV, right ventricular; TR, tricuspid regurgitation.

c. **Color-flow imaging.** Although spectral (PW and CW) Doppler imaging is superior for accurate measurement of specific intracardiac blood flow velocities, the best way to visualize the overall pattern of intracardiac blood flow is with color-flow imaging. Color-flow Doppler is based on the principle of PW Doppler, with multiple sampling volumes at varying depths along a single scan line. A full color-flow map is generated by combining multiple scan lines along the areas of interest. To accurately estimate the velocity along a given scan line, the instrument compares the Doppler shift changes from several successive pulses (typically eight), and this is known as the **burst length**. Where Doppler shifts are detected, color pixels are displayed at that location, with the different colors representing the different degrees of Doppler shift based on a predetermined color spectrum. Tradition has set **blood velocity toward the transducer as shades of red and blood flow away as shades of blue (Blue Away)**.

Because this modality uses properties based on PW Doppler technology, color-flow Doppler has limitations similar to those of PW Doppler for velocity determination. When the flow velocity is higher than the Nyquist limit (indicated on the color map), color aliasing occurs (depicted as color reversal, red-to-blue or blue-to-red transition). The fact that color aliasing occurs can actually provide important hemodynamic information, such as the identification of flow acceleration or calculation of the proximal isovelocity surface area (PISA), which is discussed in Section VI.C.6.

d. Tissue Doppler imaging (TDI). TDI is based on adjusting standard Doppler to focus primarily on the low-velocity, high-amplitude **motion of the myocardium** (usually <20 cm/s) instead of the high-velocity, low-amplitude motion of red blood cells. Decreasing the filters (which normally eliminates low-velocity signals) and the Doppler transmit gain (which excludes the low-amplitude blood signals) results in the Doppler focusing primarily on myocardial motion. TDI can be displayed as either PW Doppler, typically at one aspect of the mitral annulus (usually septal or lateral), or color-flow TDI mapping of the entire myocardial area of interest (**Figure 66.1**). TDI has primarily been used as an adjunct for the evaluation of LV diastolic function, where the mitral annular TDI pattern shows a systolic (S) wave toward the transducer and two diastolic waves away from the transducer (corresponding to early relaxation and late atrial diastolic myocardial motion, labeled as *E′* and *A′*) (**Figure 66.2** and **Table 66.2**). With worsening diastolic function, *É* velocity decreases and is directly proportional to the rate of relaxation. TDI annular velocities decrease with age and may be affected by a myocardial infarction (MI) in the region adjacent to the annulus or surgery of the mitral valve. Therefore, TDI can be used to help differentiate a normal mitral inflow pattern (normal *É*) from a pseudonormal filling pattern (reduced *É*) (**Figure 66.2** and **Table 66.3**). TDI can also be used to assess LV filling pressures, myocardial deformation, and ventricular dyssynchrony.



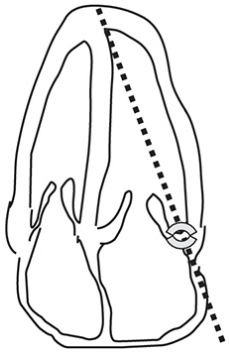


FIGURE 66.1 Tissue Doppler imaging (TDI) for diastolic function recorded from the apical four-chamber window using a 2-mm sample volume positioned in the lateral wall 1 cm from the mitral annulus. The TDI signal is toward the transducer in systole (S) as the myocardium moves toward the apex. In diastole, the myocardial velocity is directed away from the transducer first with early diastolic filling (*É*) and then with atrial contraction (*A′*).

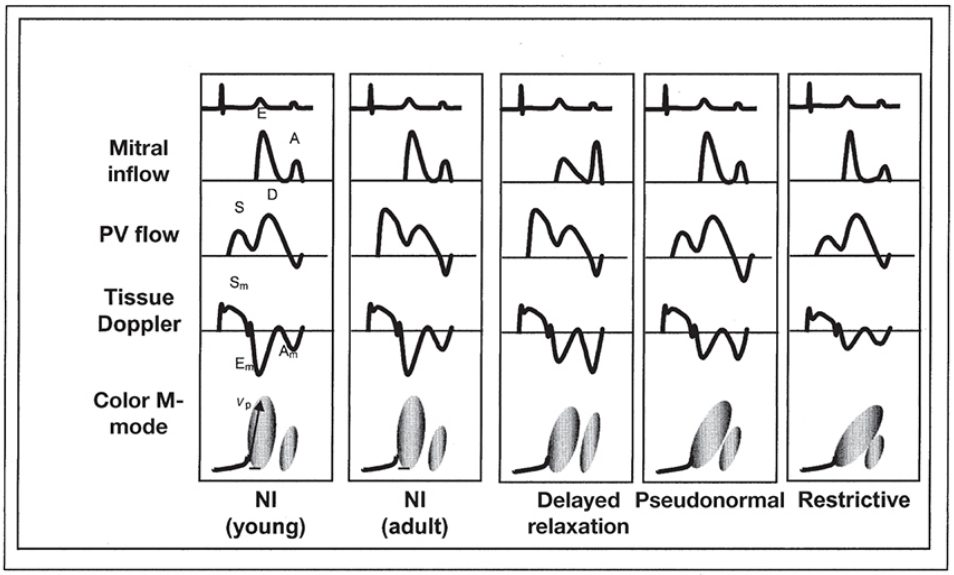


FIGURE 66.2 Diastolic function/dysfunction staging. *A*, atrial kick mitral inflow velocity; A_m, atrial annular velocity (*A′*); *D*, diastolic; *E*, early mitral inflow velocity; E_m, early diastolic annular velocity (*E′*); NI, normal; PV, pulmonary vein; *S*, systolic; S_m, systolic annular velocity; Tissue Doppler, mitral annular velocity by Tissue Doppler; V_p, velocity of propagation.

TABLE 66.2 Diastolic Function/Dysfunction Staging

	Normal Young	Normal Adult	Normal Elderly	Delayed Relaxation	Pseudonormal Filling	Restrictive Filling
Stage	Normal	Normal	Normal	I	II	III
E/*A* ratio	>1 (often >2)	>1	<1	<1	1-2	>2
DT (ms)	<220	<220	>220	>220	150-200	<150
S/*D* ratio	<1	≥1	>1	>1	<1	<1

	Normal Young	Normal Adult	Normal Elderly	Delayed Relaxation	Pseudonormal Filling	Restrictive Filling
Ar (cm/s)	<35	<35	<35	<35	>35	>25
V_p (cm/s)	>55	>55	<55	<55	<45	<45
E' (cm/s) (*E* annulus)	>10	>8	<8	<8	<8	<8

A, peak mitral inflow atrial contraction velocity; Ar, atrial reversal; DT, deceleration time; *E*, peak mitral inflow early diastolic flow velocity; *E´*, mitral annular early diastolic velocity; *S*/*D* ratio, systolic flow/diastolic flow from pulmonary vein tracing; V_p, propagation velocity from color M-mode.

TABLE 66.3 Standard Transthoracic Examination

PLAX

- Position transducer in the third or fourth left intercostal space parasternally (ridge toward right shoulder)
- Color Doppler—mitral and aortic valve flow and interventricular septum (in cases of ventricular septal defect)
- M-mode—three levels (below mitral leaflets, mid-mitral leaflets, and aortic valve)
- Move up an intercostal space to get better view of ascending aorta.
- Tilt transducer inferomedially to assess RV inflow. Color Doppler to assess tricuspid regurgitation and CW Doppler to estimate RVSP.

PSAX

- Rotate transducer 90° clockwise from PLAX and tilt the transducer from superior to inferior (LV apex view, mid-LV view, mitral valve view, and aortic valve level)
- Color Doppler at mitral valve level (localize mitral regurgitation if present)
- Color Doppler at aortic valve level (localize aortic regurgitation and assess flow in RVOT/pulmonic valve and tricuspid valve)
- PW Doppler—RVOT (level of pulmonic valve annulus)
- CW Doppler—RVOT/pulmonic valve and tricuspid valve (estimate RVSP)

A4C

- Transducer at apex—ridge toward left (move laterally and inferiorly if necessary to get true apex)
- Color Doppler—mitral flow and tricuspid flow
- Measure PISA if mitral regurgitation (zoom, decrease Nyquist, and measure radius).

- PW Doppler—mitral inflow—position at the level of mitral leaflet tips (gate 1-2 mm)
- PW Doppler—PV (usually right upper PV)—1-2 cm into vein (gate 3-4 mm)
- CW Doppler—across mitral valve (stenosis and/or regurgitation and to calculate PISA)
- CW Doppler—tricuspid flow (estimate RV systolic pressure)
- Tilt transducer anteriorly to obtain “five-chamber view,” that is, open up aortic valve/LVOT.
- Color Doppler—LVOT/aortic valve
- PW Doppler—LVOT—at the level of the aortic annulus
- CW Doppler—LVOT/aortic valve
- Tilting transducer posteriorly will bring the coronary sinus in view (along AV junction, emptying into right atrium).

A2C

- Rotate transducer approximately 60°-90° anticlockwise.
- Tilt posteriorly and rotate clockwise to open out descending aorta.

Apical long axis (apical three chamber)

- Rotate transducer further 30°-45° anticlockwise.
- Color Doppler—LVOT/aortic valve
- Recheck CW Doppler across aortic valve if evaluating for aortic stenosis.

Subcostal view—patient supine and legs bent at knees

- Subxiphoid, midline, tilt anteriorly under sternum with groove toward patients left for four-chamber view
- Color Doppler across interatrial septum to check for a PFO or ASD
- Rotate transducer 90° from four-chamber view until groove is pointing anterosuperiorly
- Same views as PSAX except rotated 90° clockwise
- Sweep from left to right to get apical, midventricular, and aortic valve levels
- IVC should be visualized when scan plane is directed toward the right midclavicular region with some counterclockwise rotation to open out long axis of IVC.
- Color Doppler—IVC flow
- PW of hepatic veins (may need to angle posteriorly)

Suprasternal view—patient supine and head tilted backward

- Transducer in suprasternal notch, with groove toward left (rotate to about 1 o’clock), parallel to trachea
- Color Doppler in arch and upper descending aortas (especially if suspected coarctation)

- PW Doppler in upper descending aorta (if assessing AR severity)

Pedoff probe

- Especially for checking maximal aortic valve gradient in aortic stenosis
- Apical position
- Right upper sternal border (aortic stenosis)

A2C, apical two chamber; A4C, apical four chamber; AR, aortic regurgitation; ASD, atrial septal defect; AV, atrioventricular; CW, continuous wave; IVC, inferior vena cava; LV, left ventricular; LVOT, left ventricular outflow tract; PFO, patent foramen ovale; PISA, proximal isovelocity surface area; PLAX, parasternal long axis; PSAX, parasternal short axis; PV, pulmonary vein; PW, pulsed wave; RV, right ventricular; RVOT, right ventricular outflow tract; RVSP, right ventricular systolic pressure.

D. Color M-mode (CMM). This technique, whereby color-flow Doppler is imposed on an M-mode image, permits excellent spatiotemporal distribution of velocity (color) data, although it is limited to the defined scan line. It is a valuable adjunct in the timing of cardiac events, which may not be readily appreciated by 2D and color-flow imaging alone. Its primary use has been in evaluating diastolic filling pattern where the LV inflow CMM pattern typically has two appreciable waves, the first demonstrating the early passive filling wave and the second later wave resulting from atrial contraction (**Figure 66.2**). The slope of the early filling wave (velocity of propagation, V_p) is primarily dependent on the rate of relaxation and is reduced with delayed relaxation. It is useful for differentiating a normal mitral inflow pattern (normal V_p) from a pseudonormal filling pattern (where impaired relaxation results in delayed flow propagation into the LV, slower V_p) (**Figure 66.2** and **Table 66.2**).

Other uses of CMM are the accurate measurement of AR jet diameter in the LVOT in the parasternal views and, with its superior temporal resolution, detection of diastolic mitral regurgitation (MR), which may be seen in certain conditions (severe acute AR, advanced diastolic dysfunction, and complete heart block).

IV. TOMOGRAPHIC VIEWS AND CARDIAC ANATOMY. Most echocardiography laboratories have similar protocols for acquisition of a complete echocardiogram. Each echocardiographic view is labeled first by the

transducer position (parasternal, apical, subcostal, and suprasternal) followed by the tomographic view of the heart (long axis, short axis, four chamber, and two chamber). To acquire these different views, the transducer is placed on different parts of the body and adjusted with rotation and angulation to optimize the final image. Standard imaging planes are illustrated in **Figures 66.3** to **66.8**; see **Table 66.3** for standard examination protocol, **Table 66.4** for normal echo dimensions, and **Table 66.5** for useful 2D examination tips.

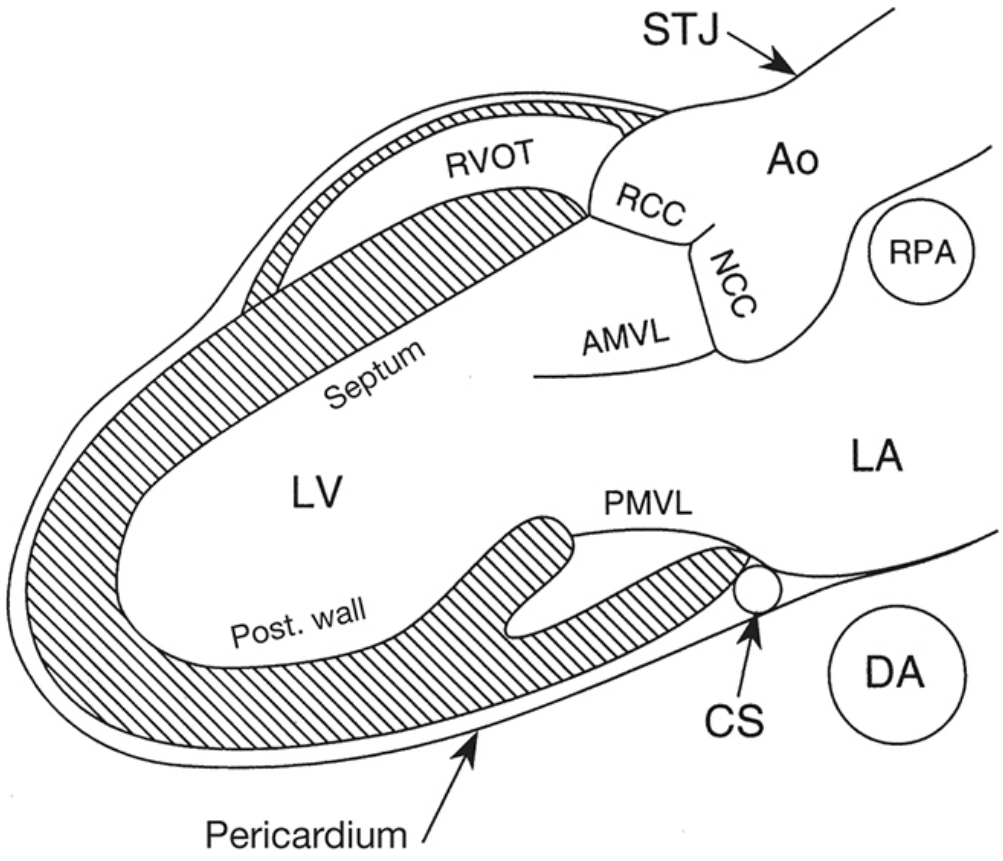


FIGURE 66.3 Schematic diagram of the parasternal long-axis view in diastole. AMVL, anterior mitral valve leaflet; Ao, aorta; CS, coronary sinus; DA, descending aorta; LA, left atrium; LV, left ventricle; NCC, noncoronary cusp; PMVL, posterior mitral valve leaflet; post. wall, posterior wall; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; STJ, sinotubular junction. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier. With permission.)

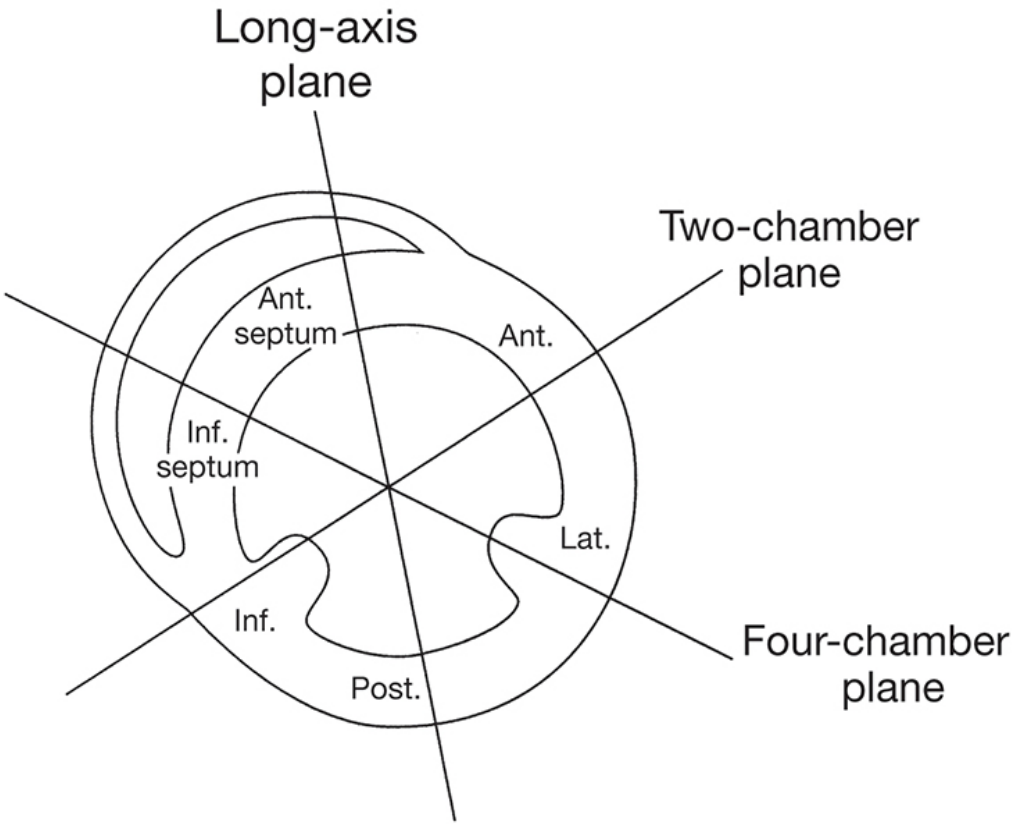


FIGURE 66.4 Schematic diagram of the parasternal short-axis view at the level of papillary muscles. Ant., anterior wall; Ant. septum, anterior septum; Inf., inferior wall; Inf. septum, inferior septum; Lat., lateral wall; Post., posterior wall. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier. With permission.)

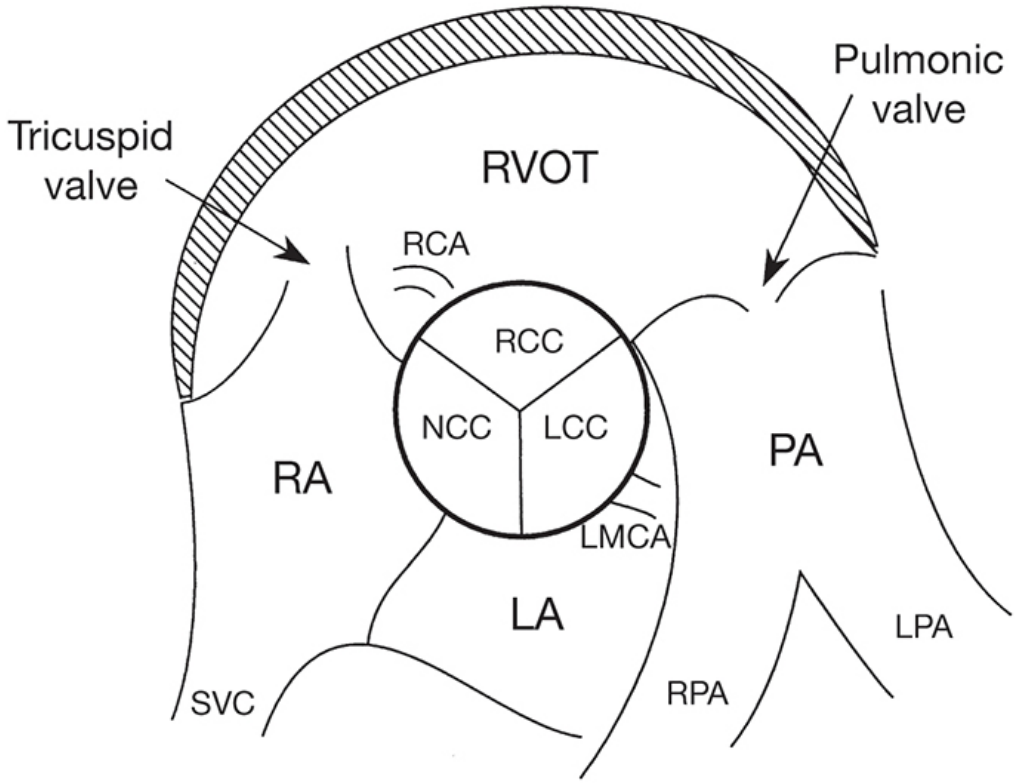


FIGURE 66.5 Schematic diagram of the parasternal short-axis view at the aortic valve level. LA, left atrium; LCC, left coronary cusp; LMCA, left main coronary artery; LPA, left pulmonary artery; NCC, noncoronary cusp; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; SVC, superior vena cava. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier. With permission.)

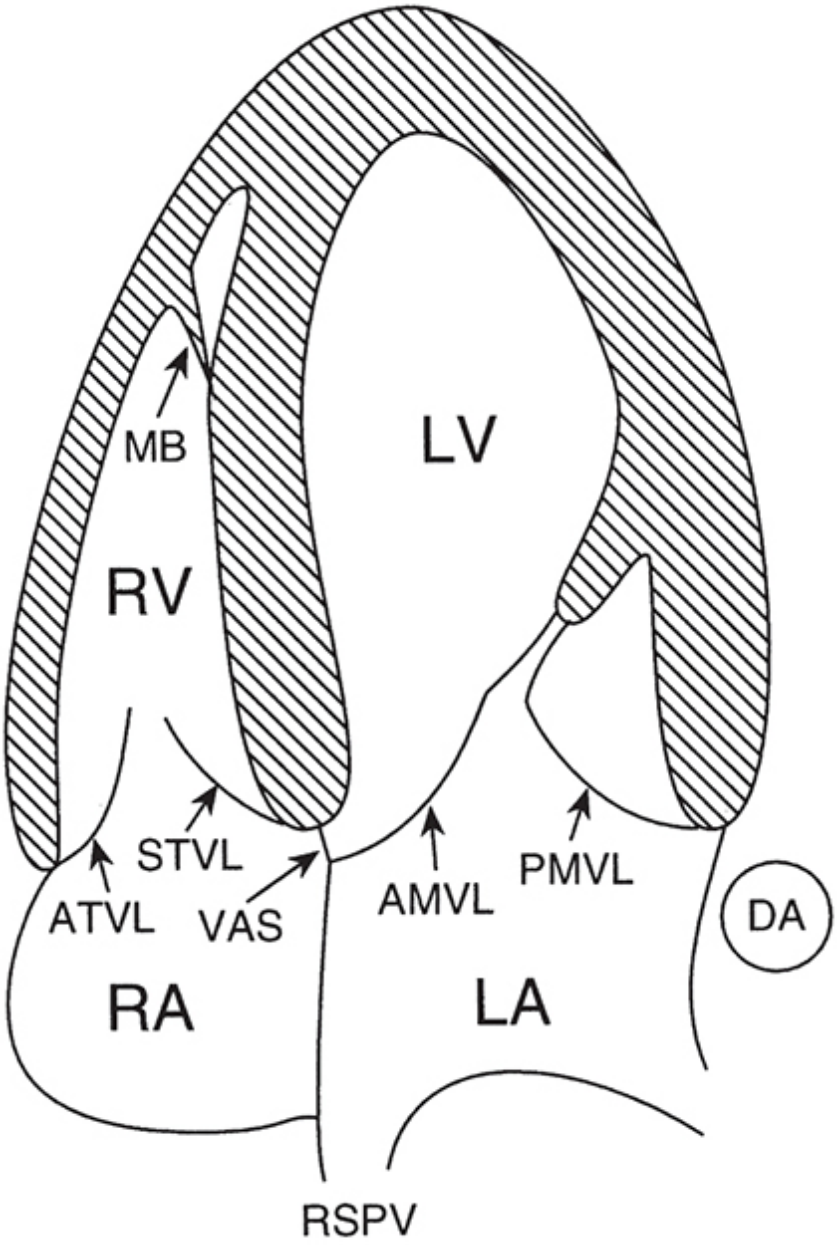


FIGURE 66.6 Schematic diagram of the apical four-chamber view. AMVL, anterior mitral valve leaflet; ATVL, anterior tricuspid valve leaflet; DA, descending aorta; LA, left atrium; LV, left ventricle; MB, moderator band; PMVL, posterior mitral valve leaflet; RA, right atrium; RSPV, right superior pulmonary vein; RV, right ventricle; STVL, septal tricuspid valve leaflet; VAS, ventriculoatrial septum (where communication from LV to RA may occur). (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier. With permission.)

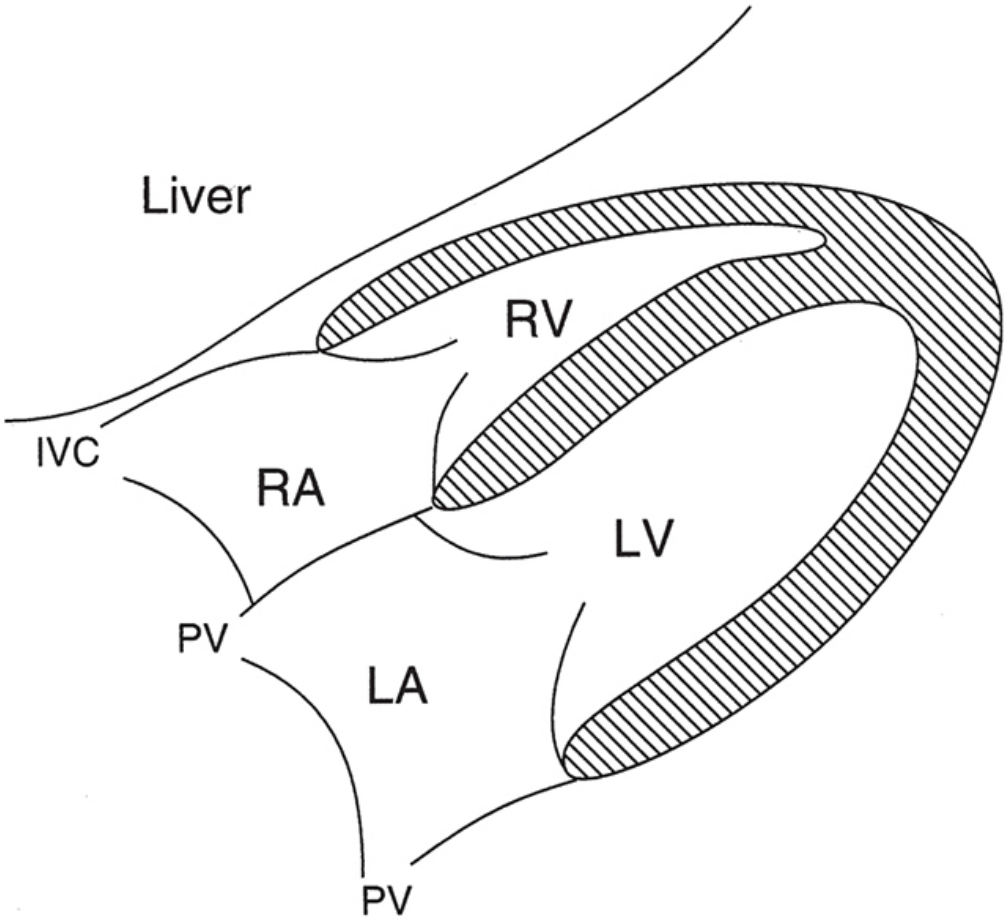


FIGURE 66.7 Schematic diagram of the four-chamber view from the subcostal approach. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; PV, pulmonary vein; RA, right atrium; RV, right ventricle. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier.)

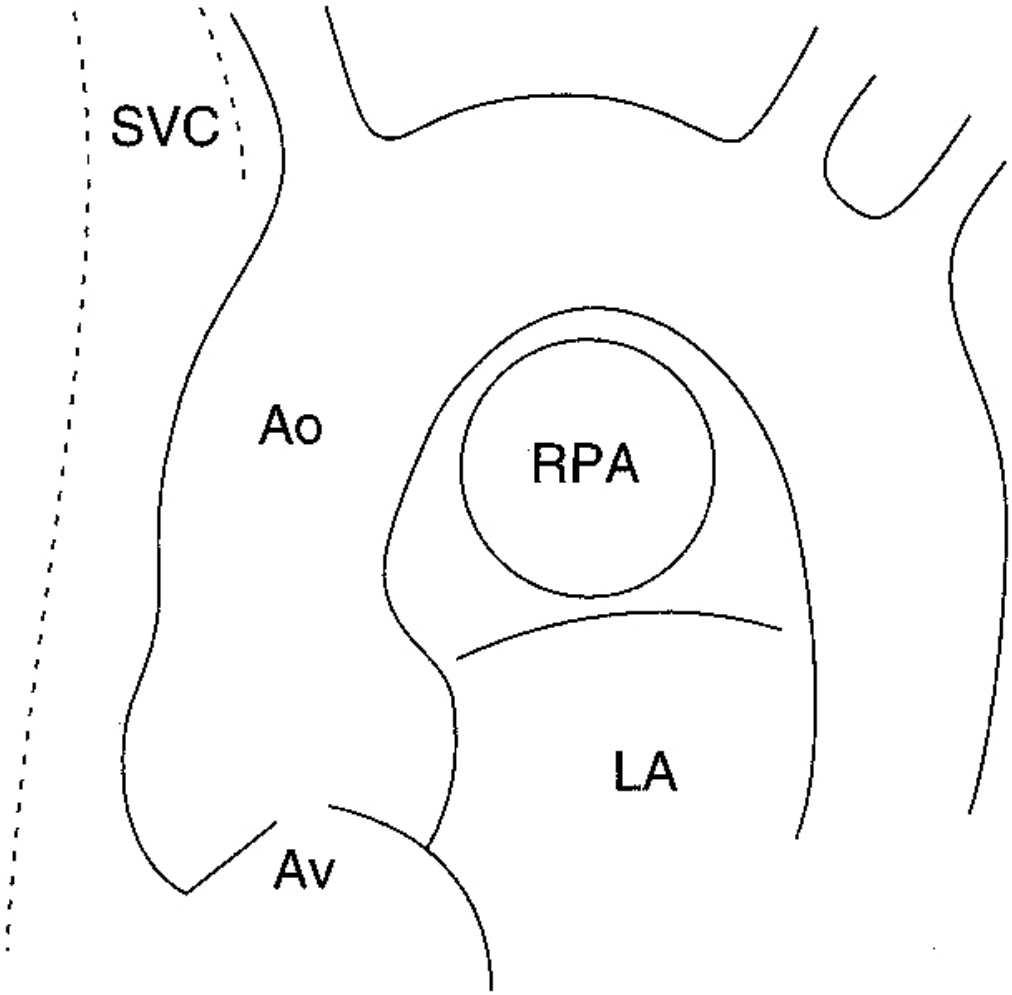


FIGURE 66.8 Schematic diagram of the aorta (Ao) and right pulmonary artery (RPA) from the suprasternal notch window. AV, aortic valve; LA, left atrium; SVC, superior vena cava. (Reprinted from Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. WB Saunders; 1995:21-64. Copyright © 1995 Elsevier. With permission.)

TABLE 66.4 Normal Echo Dimensions in Adults

	Reference Range	
Factor	**Male**	**Female**
Left Ventricle		
LV end-diastolic diameter (cm)	4.2-5.8	3.8-5.2
LV end-systolic diameter (cm)	2.5-4.0	2.2-3.5

Factor	Reference Range	
	Male	Female
Septal thickness (ED) (cm)	0.6-1.0	0.6-0.9
Posterior wall thickness (ED) (cm)	0.6-1.0	0.6-0.9
LV end-diastolic volume (biplane) (cm^3)	62-150	46-106
LV end-systolic volume (biplane) (cm^3)	21-61	14-42
Ejection fraction (%)	52-72	54-74
Left Atrium		
Left atrium (ES) (cm)	3.0-4.0	2.7-3.8
LA volume index (biplane-AL) (cm^3/m^2)	16-34	16-34
Aorta		
Aortic annulus (cm)	2.3-2.9	2.1-2.5
Sinuses of Valsalva (cm)	3.1-3.7	2.7-3.3
Sinotubular junction (cm)	2.6-3.2	2.3-2.9
Proximal ascending aorta (cm)	2.6-3.4	2.3-3.1

AL, area length; ED, end diastole; ES, end systole; LA, left atrial; LV, left ventricular.

TABLE 66.5 Tips for Transthoracic 2D Examination

- **Optimize patient position** (left lateral with left hand above head) and **environment** (darkened room).
- Ensure imaging in **harmonics** mode.
- Consider **contrast** to improve endocardial delineation for technically difficult studies.
- When parasternal and apical images are limited (body habitus, surgical drains, dressings, etc), the **subcostal window** may be the only accessible window.
- Consider **off-axis views** to enhance visualization of specific structures.
- Obtain images at **end expiration,** as the heart is closer to the transducer.
- **Avoid foreshortening LV apex** (especially in A2C)—true apex may be more inferior and lateral than expected.

- If there is a **concern of LV thrombus,** zoom and check with low-velocity color Doppler to ensure flow throughout. Consider the use of endocardial contrast if unclear.
- If an object is suspicious for an artifact, reassess in other imaging planes.
- **M-mode** can be useful, especially for the accurate timing of cardiac events (especially RV or RA collapse in the setting of possible tamponade or assessment of possible systolic anterior motion of the mitral valve).
- Adjust transducer **frequency** to maximum that permits adequate far-field penetration/depth.
- Set **time gain compensation** in the midrange with lower gain in the near field and higher settings in the far field to compensate for attenuation of the beam with increasing distance from transducer.
- Use the least amount of **depth** that adequately shows the entire area of interest.
- Adjust the **transmit gain/output** to optimize image brightness/quality—too low, everything appears black; too high results in a "whiteout." Initially set it to high and then adjust downward.
- Adjust the **"compress"/dynamic range**. Decrease if image quality is poor to produce high-quality contrast images. Increasing it will "soften" images. Typically, as compress is increased, the transmit gain should be decreased to maximize the spectrum of the grayscale.
- Adjust the **focus** (focal zone) to include the area of interest, because the beam is narrowest (improves image resolution) within this area, especially when imaging near-field structures (eg, looking for an apical LV thrombus from the apical windows).
- Set the **persistence** to low.

A2C, apical two chamber; LV, left ventricular; RA, right atrial; RV, right ventricular.

A. Parasternal. The parasternal position is typically obtained by placing the transducer at the left of the sternal border in the third or fourth intercostal space. The optimal position for the patient is usually the left lateral decubitus position, but a hybrid between the steep left lateral and supine position may be required to optimize the view. This position allows imaging of the long axis as well as the short axis of the heart.

1. **Parasternal long axis (PLAX).** The PLAX tomographic view is traditionally the first view of a standard transthoracic echocardiogram. The ultrasound beam is lined up between the patient's right shoulder and the left flank. The right ventricular outflow tract (RVOT) is located at the top of the image, the aorta to the right, the inferolateral (or posterior) wall on the bottom, and the cardiac apex on the left. The anteroseptum is visualized between the RVOT and the LV cavity. Tilting the transducer's tail toward the left shoulder with slight clockwise rotation aims the ultrasound beam inferomedially and brings the RV inflow into view. This is good for obtaining the tricuspid regurgitation (TR) velocity as well as viewing the tricuspid valve, RV apex, and the right atrium (RA).
2. **Parasternal short axis (PSAX).** While the transducer is in the parasternal position, rotating the transducer clockwise by approximately 90° displays the heart in the short axis. The ultrasound beam in this case is roughly from the left shoulder to the right flank. Using different degrees of transducer tilting, and occasionally moving up or down an intercostal space, results in four traditional views of the heart. On tilting from superior to inferior, the views obtained are aortic valve-RV outflow, mitral valve level, mid-ventricle at the papillary muscles, and the LV apex. The images appear as if viewing the heart from the apex and looking through to the base; therefore, the septum is on the left, lateral wall on the right, the anterior and anteroseptal walls at the top, and the posterior-inferior walls on the bottom of the screen.

B. **Apical.** The apical position is obtained with the patient in the left lateral position and the probe placed at the apical impulse. This position obtains images of the long axis of the heart.

1. **Apical four chamber (A4C).** The A4C view is obtained with the ultrasound beam transecting the thorax in a superior-inferior manner. Most institutions orient the transducer to place the LV on the right side of the screen and the RV on the left side. The apex is at the top of the image and the atria at the bottom, regardless of the

orientation. The inferoseptal and anterolateral walls as well as the apex of the LV can be assessed in this view.

2. **Apical five chamber (A5C).** A slight rotation of the transducer introduces a fifth "chamber," the proximal aorta, along with the aortic valve and LVOT. This view allows for qualitative assessment of aortic valve pathology and hemodynamic assessment of the LVOT and aortic valve.
3. **Apical two chamber (A2C).** Further rotation, 90° counterclockwise from the A4C view, obtains the A2C view. In addition to the left atrium (LA), the LV anterior wall, inferior wall, apex, and mitral valve are also well visualized.
4. **Apical three chamber (A3C).** A slightly more counterclockwise rotation (approximately 30°) brings the aorta back into view, resulting in the A3C, or apical long-axis, view. This essentially has the same anatomic structures as those in the PLAX view with a different orientation. The apex is better visualized, and the RVOT usually drops out of the image. Additional information on mitral and aortic valve hemodynamics can be obtained in this view, which is not ideally obtained in the PLAX view.

C. Subcostal. The subcostal view provides additional views of the ventricles, atria, and atrial septum to those acquired in earlier portions of the examination. In some patients, the subcostal view may be the only way to obtain images of the heart because the parasternal and apical locations may have poor windows (eg, hyperinflated lungs).

The subcostal position is obtained with the patient in the supine position and the probe located caudal to the xiphoid process. The transducer is placed in the midline nearly parallel to the long axis of the patient's body so that the ultrasound beam slices toward the spine. This shows the RV at the top right, the LV at the bottom right, and their respective atria on the left. Clockwise rotation along with inferior tilting brings the inferior vena cava (IVC) and hepatic veins into view for right-sided hemodynamic assessments.

D. Suprasternal. Placing the transducer in the suprasternal notch and pointing inferiorly can assess the ascending aorta, aortic arch, and

descending aorta. Hemodynamics from this position can better characterize AR as well as the presence of coarctation.

V. ADVANCED ECHOCARDIOGRAPHIC TECHNIQUES

A. Contrast echocardiography. Contrast echocardiography is performed by injecting either **agitated saline** or one of the **commercially available contrast agents** into an arm vein. Both are microbubbles that reflect ultrasound waves and opacify intracardiac chambers. The size of the microbubbles relative to the pulmonary capillary diameter determines whether they cross to the left side of the heart or get trapped in the pulmonary circulation. The choice of agitated saline versus commercial contrast agents depends on whether the goal is to visualize the RA and RV versus the LV and myocardium.

Agitated saline is sterile saline (preferably mixed with some blood), combined with a small quantity of air, which has been exchanged rapidly using a three-way stopcock between two syringes to create small bubbles. These relatively large (and unstable) bubbles are caught in the lung and do not routinely appear in the left side of the heart unless a shunt is present. The appearance of bubbles in the **LA within three beats** of the cardiac cycle after they are seen within the RA suggests a right-to-left **intracardiac shunt**—typically from a small patent foramen ovale. If bubbles appear in the **LA more than four beats** after they are seen in the RA, this more likely signifies an **intrapulmonary shunt**. There is a small risk of embolic complications in the use of agitated saline. Care should be taken to avoid injecting larger air bubbles by inspecting the syringe closely prior to injection and ensuring that the bubbles are very small.

Modern commercial contrast agents consist of either an albumin-based shell containing perfluorocarbon gas (Optison) or a synthetic phospholipid shell containing perfluoropropane gas (Definity). These microbubbles are much smaller (the size of a red blood cell) and more stable; therefore, they can cross the pulmonary capillaries and appear on the left side of the heart, where they opacify the LV cavity for improved endocardial definition and clarify the presence/absence of a suspected LV thrombus/mass. For optimal contrast imaging, it is

important to reduce the mechanical index (the output of the machine), typically to 0.4 to 0.6, because higher power ultrasound waves destroy microbubbles.

Contrast enhances Doppler signals. Agitated saline can be used to augment the signal from TR to better estimate peak right ventricular systolic function (RVSP), and commercial microbubble products (Optison and Definity) can be used to enhance the Doppler envelope in patients with aortic stenosis.

Contrast echocardiography was the subject of a black box warning from the Food and Drug Administration (FDA) because of concerns of significant adverse events. More recent data suggest that adverse events following contrast injection are no more common than in those in whom it is not used when appropriate adjustment for severity of illness is made. The FDA has recommended patients with pulmonary hypertension or unstable cardiac conditions such as recent MI, unstable angina, decompensated heart failure, ventricular arrhythmia, or respiratory failure should be monitored closely for at least 30 minutes after use. It is contraindicated when a fixed or even transient right-to-left shunt is present or with documented allergy to its components.

B. 3D echocardiography is obtained using a transducer that transmits and receives data simultaneously in a 3D volume, in the form of either real-time 3D images or simultaneous biplane (orthogonal) 2D images. The 3D data set can then be manipulated using different software packages to assess function and anatomy. It is of particular benefit for the localization of valvular abnormalities (especially for the complex 3D mitral valve structure), accurate LV volume calculation, improved assessment of the RV, guiding surgical interventions (eg, mitral valve repair), and complex congenital heart disease. 3D color-flow imaging allows for a comprehensive assessment of vena contracta and areas of flow convergence (PISA), which can improve the quantification of valvular regurgitation. It has been documented to allow for a more rapid evaluation of mitral valve area (MVA) in mitral stenosis as compared with conventional 2D planimetry.

C. **Myocardial mechanics—tissue strain, strain rate imaging, and speckle tracking.** Strain rate imaging allows for the estimation of regional myocardial deformation. Tissue strain, a dimensionless entity, is a measure of the relative deformation of tissue. Myocardial deformation in a segment of interest is assessed with reference to the adjacent segment, avoiding errors introduced by translational motion and tethering. **Strain rate is the rate of the deformation between two adjacent points of interest along a scan line and is expressed in seconds**. A strain rate curve can be derived by analyzing many adjacent segments along a scan line. Doppler techniques for assessing strain are not always ideal because of angle dependence, signal noise, and the need for a high frame rate. Doppler-independent techniques such as **speckle tracking** use ultrasonic reflectors (speckles) within tissues that can be followed from frame to frame through the cardiac cycle. This method can be used to assess the radial deformation and torsion of the ventricle. Strain rate is a relatively preload-independent measure of regional myocardial function. Clinical applications include assessment of myocardial ischemia, viability, diastolic function, subclinical LV dysfunction in valve disease and in particular in assessing the early effects of cardiotoxic chemotherapeutic agents on LV function, and cardiac involvement in systemic diseases, such as diabetes or amyloidosis. For instance, in amyloidosis, strain is often preserved at the apex, but it is diminished in other areas of the heart.

D. **Dyssynchrony.** Dyssynchrony occurs when different areas of the ventricles contract in an irregular pattern spatially and temporally. It is primarily seen in patients with impaired systolic function and electrophysiologic conduction delays. M-mode, 2D imaging, color Doppler, and tissue Doppler have all been employed to assess the amount of dyssynchrony, but no consensus exists on the optimal approach to evaluate ventricular dyssynchrony. After the implantation of a resynchronization device, Doppler echocardiography is used for the optimization of programmed timing. Some useful measures include the following:

1. A difference in the time to peak velocity of >65 ms between opposing walls (basal segments in four-chamber, two-chamber,

and three-chamber views yielding a total of six segments) using pulsed tissue Doppler

2. A difference of 40 ms in the interval from the QRS complex to the onset of flow in the RVOT versus the LVOT using pulsed tissue Doppler
3. Using M-mode or speckle tracking, a difference of 130 ms in the septal to posterior wall delay

VI. SPECIAL TOPICS

A. Systolic function. 2D imaging is currently the primary echocardiographic means of determining the systolic function of the heart. The most utilized measurement is the EF. In the past, EF was based on estimation by visual inspection; however, echocardiographic societies now recommend using standardized objective methods to minimize interobserver differences. LV volume is best measured using the modified Simpson method (disk summation method). This involves tracing the LV area in two orthogonal views (typically A4C and A2C) and dividing the LV into a number of cylinders of equal height. Total ventricular volume is calculated by adding up all the volumetric cylinders. All modern machines and digital echo reading systems have integrated software to create and combine the volume data after tracing the LV areas in both apical views. Based on the volumes measured in diastole and systole, stroke volume (SV) and EF can be estimated using **Simpson method**:

$$\text{Stroke volume (SV)} = \text{end - diastolic volume (EDV) - end - systolic volume (ESV)}$$

$$EF = SV / EDV \times 100\%$$

$$EF = EDV - ESV/EDV \times 100\%$$

Newer semiautomated methods in 3D echocardiography using full matrix-array transducers give accurate, reproducible assessments of LV volume and EF that are superior to 2D methods when magnetic resonance imaging is used as the gold standard. LV torsion uses

speckle tracking to assess LV systolic function by assessing the difference between the clockwise rotation of the base of the heart and the counterclockwise rotation of the apex of the heart (approximately 12°). Global strain also appears to be a robust parameter for the assessment of LV function.

B. Diastolic function. Doppler echocardiography remains the primary modality for assessing LV diastolic function and estimating filling pressures. In the **most recent** iteration of the guidelines, information obtained from **PW Doppler of mitral inflow, LA volume index, TDI of the mitral annulus, and TR velocity obtained from CW Doppler** are used for staging.

Patients with normal LVEF and diastolic dysfunction can be identified if they have >50% of the following:

1. Average $E/é > 14$,
2. Septal *é* velocity < 7 cm/s or lateral *é* velocity < 10 cm/s,
3. TR velocity > 2.8 m/s, or
4. LA volume index > 34 mL/mm².

Those with <50% have normal diastolic function, and those with 50% have indeterminate diastolic function.

For patients with abnormal LVEF or normal LVEF and abnormal diastolic function, grading of diastolic dysfunction relies on examination of the E/A ratio and E velocity in addition to the other variables.

Patients with an $E/A \leq 0.8$ and $E \leq 50$ cm/s have grade I diastolic dysfunction with normal left atrial pressure (LAP).

Those with $E/A \geq 2$ have grade III diastolic dysfunction and increased LAP. For those with an intermediate E/A ratio (>0.8 but <2) or $E/A \leq 0.8$ with $E > 50$ cm/s, the following criteria are taken into account:

5. Average $E/é > 14$,
6. TR velocity > 2.8 m/s, and
7. LA volume index > 34 mL/mm².

If two or all of the above criteria are negative, the patient has **grade I** diastolic dysfunction with normal LAP. If two or all of the

above criteria are positive, the patient has **grade II** diastolic dysfunction with increased LAP.

In the circumstance that data regarding only two of these variables are available, if both are negative, the patient has grade I diastolic dysfunction with normal LAP; if both are positive, the patient has grade II diastolic dysfunction with increased LAP; and if only one is positive, the grade of diastolic dysfunction and LAP cannot be determined.

Accurate assessment of diastolic dysfunction can be limited by many factors, including inadequate views, rhythm (atrial fibrillation or ventricular pacing), and mitral valvular dysfunction (severe annular calcification, severe regurgitation, prior valve replacement or repair).

C. Hemodynamics

1. Transvalvular pressure gradient. The **Bernoulli equation** allows measurement of relative pressure differences across valves, shunts, or the LVOT. In its complete form, the Bernoulli equation is too complex for routine clinical use, because it incorporates three main components, namely, convective acceleration, inertial term (flow acceleration), and viscous friction. In many clinical situations, the latter two components can be ignored, leaving the flow gradient across an orifice to be derived from the convective acceleration term alone:

$$\Delta P = 4 \times (V^2_2 - V^2_1$$

where V_2 is the velocity distal to an obstruction and V_1 is the velocity proximal to an obstruction.

The flow proximal to a narrowed orifice (V_1) is much lower than the peak flow velocity (V_2) and can be frequently ignored, leaving a **simplified Bernoulli equation**:

$$\Delta P = 4V^2$$

The simplified Bernoulli equation is unreliable when:

a. V_1 is > 1 m/s, which occurs in serial lesions (subvalvular and valvular stenoses) and mixed stenosis with regurgitation.

b. Viscous resistance becomes significant such as in the evaluation of long stenoses (eg, coarctation or a tunnel-like ventricular septal defect).

c. The inertial term (flow acceleration) is not negligible (flow through normal valves).

d. Absence of significant restriction of flow such as when there is such severe TR that the RA and RV effectively function as a single chamber.

It is important to realize that in aortic stenosis, the Bernoulli equation represents the **maximal instantaneous gradient** across the valve, which is always higher than the customary peak-to-peak gradient measured in the catheterization laboratory because the LV systolic peak and aortic peak pressures do not occur at the same time and, therefore, are not instantaneous.

The flow within the heart is pulsatile; hence, mean gradients are an important measure and are obtained by integrating the velocity profile over the ejection time. This can be readily obtained with the software available on all modern echocardiography machines by simply tracing the area of the velocity profile. The mean pressure gradient is then derived from the mean velocity data using the Bernoulli equation.

2. Intracardiac pressure measurement

a. **Estimated RA pressure** can be derived from the size of the IVC and its response to changes in respiration or a sniff (**Table 66.6**). Using a dilated IVC to assess elevated RA pressures is not accurate in mechanically ventilated patients; however, a small IVC of size <1.2 cm in a mechanically ventilated patient is 100% specific for an RA pressure <10 mm Hg.

TABLE 66.6 Estimation of RA Pressure

IVC Diameter	Change With Respiration/Sniff	Estimated RA Pressure (mm Hg)
Normal (<2.1 cm)	Decrease >50%	0-5
Dilated (>2.1 cm)	Decrease >50%	6-10
Dilated (>2.1 cm)	Decrease <50%	10-15
Dilated (>2.1 cm)	No change	>15

IVC, inferior vena cava; RA, right atrial.

b. Pulmonary artery systolic pressure (PASP) is estimated from the TR peak velocity. Provided that there is no tricuspid valve obstruction, peak TR velocity will depend on the pressure gradient between the RV and the RA. Estimated RVSP is equal to this pressure difference, determined from the peak TR velocity, plus the estimated RA pressure. In the absence of pulmonic stenosis, the RVSP is similar to the **PASP**:

$$\text{PASP} = 4 \times (\text{peak TR velocity})^2 + \text{estimated RA pressure}$$

c. Pulmonary artery diastolic pressure (PADP). Pulmonary regurgitation represents the pressure difference between the pulmonary artery (PA) and the RV at end systole. Hence, the end pulmonary regurgitation velocity can be utilized to measure the end-diastolic pressure difference between the PA and the RV. The RV end-diastolic pressure should be similar to the RA pressure; therefore, addition of estimated RA pressure to the end-diastolic pressure difference between the PA and the RV will estimate the PADP:

$$\text{PASP} = 4 \times (\text{end pulmonary regurgitant velocity})^2 + \text{estimated RA pressure}$$

d. Estimated LAP or left ventricular end-diastolic pressure (LVEDP). Provided that there is no mitral stenosis, LVEDP and

LAP should be the same. This important measure of LV diastolic function can be estimated by several methods.

(1) **Deceleration time (DT) of mitral inflow.** A DT of <150 ms is strongly suggestive of an elevated LVEDP/LAP. In very young patients, a DT <150 ms may be normal because of rapid equalization of pressures secondary to vigorous early diastolic relaxation.

(2) **Difference between pulmonary venous atrial duration and mitral atrial duration (Ar-A).** Normally, mitral A-wave duration is greater than pulmonary venous atrial reversal (Ar) duration. When LVEDP is increased, the velocity and duration of the mitral A-wave decrease, whereas pulmonary vein Ar velocity and duration increase. The difference between the duration of the Ar wave and the mitral A wave correlates with LVEDP. An Ar-A duration of >50 ms is specific for an elevated LVEDP >20 mm Hg. This is reliable in patients with reduced EF, but not in patients with normal EF. The primary limitation with this method is the difficulty in accurately measuring the duration of Ar.

(3) **Combined mitral inflow/CMM index (E/V_p ratio).** This index has been demonstrated to correlate with LAP/LVEDP, especially when these filling pressures are elevated. A ratio of >2 is suggestive of elevated filling pressures. In patients with normal EFs, especially with small ventricles and hyperdynamic function, the flow propagation velocities are not accurate.

(4) **Combined mitral inflow/TDI index (E/E' ratio).** This index has been shown to be a semiquantitative measure of LVEDP. A ratio of >10 (using the lateral annulus) or >15 (using the septal annulus) correlates with a wedge pressure of >20 mm Hg. A ratio of <8 (using the lateral annulus) correlates well with normal filling pressures. For intermediate values, other information such as LA size

should be incorporated to assess whether filling pressures are elevated.

3. **d*P*/d*t***. This index of LV contractility is the rate of pressure increase during isovolumic contraction and is traditionally obtained using invasive pressure transducers. It can be estimated from the CW Doppler of the MR jet. During isovolumic contraction, there is no change in LAP; therefore, MR velocity changes reflect d*P*/d*t*, with more rapid increases in MR velocity being associated with increased contractility. The pressure change between 1 and 3 m/s = 4 ($V_2^2 - V_1^2$) = 32 mm Hg. The time it takes the ventricle to accelerate an MR jet velocity from 1 to 3 m/s is measured and then the d*P*/d*t* is calculated as follows:

$$dP / dt = 32 \text{ mm Hg/time (in seconds)}$$

This has been demonstrated to correlate well with invasively measured d*P*/d*t*. It is considered normal when the calculated value is >1,200 mm Hg/s.

4. **Continuity equation** is an application of the principle of conservation of mass, which states that flow across a conduit of varying diameter is equal at all points. This equation is useful in quantifying a stenotic aortic valve area (AVA) that cannot be accurately measured using planimetry from the transthoracic window. Flow at any point in the heart is the product of the cross-sectional area (CSA) and the flow velocity. As flow velocity varies during ejection in a pulsatile system, individual velocities must be integrated to measure the total volume of flow (velocity time integral [VTI]). This is determined by tracing the spectral Doppler profile, using standard measurement software built into all echocardiography machines.

$$\text{Flow at any point} = \text{CSA} \times \text{VTI}$$

Based on the continuity equation, flow through the LVOT must be equal to the flow through the aortic valve; therefore, AVA can be calculated following below steps:

$$\text{Flow across the LVOT} = \text{flow across the aortic valve}$$

$$\text{Area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}} = \text{area}_{\text{aortic valve}} \times \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = (\text{area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}}) / \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = [(\text{diameter}_{\text{LVOT}}/2)^2 \times \pi \times \text{VTI}_{\text{LVOT}}] / \text{VTI}_{\text{aortic valve}}$$

$$\mathbf{Area_{aortic\ valve} = [(diameter_{LVOT})^2 \times 0.785 \times VTI_{LVOT}] / VTI_{aortic\ valve}}$$

The assumption is that the LVOT cross section is a circle. The greatest source of error in this equation is in the measurement of the LVOT diameter because the value is squared, resulting in magnification of any initial measurement error. The appropriate place to measure the LVOT can be difficult to define accurately in some calcified valves. The **dimensionless index** (DI) is the ratio of the VTI of the LVOT to the VTI of the aortic valve. It is preferable to use this to assess aortic stenosis when accurate measurement of the LVOT diameter is not possible or in those patients with a history of previous aortic valve replacement. A DI <0.25 suggests severe aortic stenosis.

$$\mathbf{DI = VTI_{LVOT} / VTI_{aortic\ valve}}$$

Of note, the flow across the LVOT per beat is the SV, which can thus be calculated from the product of the LVOT diameter and flow velocity (VTI_{LVOT}):

$$\mathbf{SV = (diameter_{LVOT})^2 \times 0.785 \times VTI_{LVOT}}$$

5. **Volumetric method to assess regurgitant volume/regurgitant fraction.** This is based on the conservation of flow, with total flow across a regurgitant valve being equal to the sum of the forward flow and the regurgitant flow. For example, for MR:

$$\mathbf{Regurgitant\ volume = (diameter_{mitral}^2 \times 0.785 \times VTI_{mitral}) - (diameter_{LVOT}^2 \times 0.785 \times VTI_{LVOT})}$$

$$\mathbf{Regurgitant\ fraction = regurgitant\ volume / total\ mitral\ flow}$$

Because of the multiple assumptions and calculations performed, this method is prone to error and is rarely used clinically.

6. The **PISA** method is another application of the principle of conservation of mass. It is based on the phenomenon that flow accelerates proximal to a narrowed orifice. Using color Doppler, as flow accelerates, its velocity may exceed the Nyquist limit, which results in color reversal because of aliasing. This is seen as a series of colored ("isovelocity") hemispheres with color-flow imaging, with the velocity of flow at the surface of this hemisphere being the aliasing velocity (Nyquist limit) of color flow in that direction. Decreasing the aliasing velocity will increase the size of the hemisphere, because the velocity at which color changes is reduced. In keeping with conservation of mass, blood flow at the surface of this hemisphere is the same as flow through the regurgitant orifice, and this is the basis of using the PISA method to estimate the regurgitant orifice area (ROA) of a valve. PISA has been most extensively used to estimate the mitral ROA to quantify MR.

$$\text{Flow at surface of hemisphere} = \text{flow through regurgitant orifice}$$

$$\text{Surface area of hemisphere} \times \text{velocity at hemisphere} = \text{ROA} \times \text{peak velocity of regurgitation [using CW Doppler through the mitral valve]}$$

$$2 \times \pi (\text{radius})^2 \times \text{aliasing velocity} = \text{ROA} \times \text{peak MR velocity}$$

$$\mathbf{ROA = 2 \times \pi (radius)^2 \times aliasing\ velocity / MR_{CW}\ peak\ velocity}$$

The greatest source of error is in defining the precise location of the ROA, so as to accurately calculate the radius.

This method can also be used to measure MVA in mitral stenosis (where forward flow convergence is seen and measured) and the aortic ROA in AR, although it may be difficult to obtain satisfactory visualization of the aortic PISA for quantification from the apical long-axis view (best view to appropriately line up AR jet with the Doppler). When the jet is eccentric, and a full hemisphere

is not visible, an angle correction should be considered. The PISA equation for MR can be simplified if the aliasing velocity is set to 40 cm/s, and it is assumed that peak MR velocity will be 5 m/s (equates to a normal LV-to-LA pressure gradient of 100 mm Hg). Using these two constants, the PISA equation is simplified to:

$$\mathbf{ROA} = (\mathbf{radius})^2/2$$

Peak MR velocity will increase or decrease depending on the changes in LV systolic pressure and LAP, and it cannot always be assumed to be 5 m/s. However, this method is useful for semiquantification and rapid assessment. Regurgitant volume can be calculated as follows:

$$\mathbf{Regurgitant\ volume} = \mathbf{ROA} \times \mathbf{VTI}_{\mathbf{MRjet}}$$

7. **Pressure half-time (*P*½)** is used to estimate the MVA, because the time for the pressure to fall by half across a stenotic valve is proportional to the degree of stenosis. It is the time interval for the peak pressure gradient to fall by half. Using the Bernoulli equation to convert pressure to velocity, there is a constant relationship between peak velocity and the velocity at *P*½.

$$\text{Pressure at half the peak pressure} = 1/2 \text{ peak pressure}$$

$$4 \times \left(V\,\tfrac{1}{2}\right)^2 = 0.5 \times \left(4 \times V_{max}\right)^2$$

$$V\,\tfrac{1}{2} = V_{max}/\sqrt{(2)}$$

In addition, the *P*½ has a constant relationship with the DT of the early mitral filling wave, and it is usually estimated from the following:

$$P\,\tfrac{1}{2} = 0.29 \times \mathrm{DT}$$

Hence, *P*½ can be easily measured by using the DT or by simply measuring the time interval from peak to ½ peak pressure (which

is determined from the V_{max}). Most echocardiographic measurement software packages automatically calculate $P½$ when the slope of the CW Doppler of the mitral inflow jet is measured. For mitral stenosis, an empirical constant has been validated to correlate $P½$ and MVA:

This has only been validated for native valves and will overestimate valve areas for prosthetic valves.

$$\text{MVA} = 220 / \left(\text{P}\,{}^{1}\!/_{2}\right)$$

The other primary use of $P½$ is to help quantify AR. The $P½$ of the AR Doppler velocity jet becomes shorter when the pressures in the aorta and the LV equilibrate more quickly. This can occur with increasing severity, especially in acute AR. A $P½$ <250 ms suggests severe AR. There are many limitations to this because of the fact that aortic and LV compliance and systemic vascular resistance affect $P½$.

VII. TECHNICAL ASPECTS AND ADVANCED IMAGE ACQUISITION

A. Machine settings. To obtain the best images and accurate Doppler information, it is important to optimize the machine settings during different parts of the examination (**Tables 66.3** and **66.5**).

1. **Time gain compensation.** These controls differentially amplify the echo signals returning from different depths to compensate for attenuation of the ultrasound beam with increasing distance from the transducer. This function is useful with higher frequency transducers, because they are associated with more attenuation at greater depths.
2. **Depth.** Start with the greatest depth to get an overview and then decrease the depth to include all of the target structure. A depth of 16 cm is usually adequate for the apical window and 12 cm for parasternal imaging. Increasing the depth decreases the frame rate, reducing temporal resolution.
3. **Transmit gain.** This adjusts the displayed amplitude (power) of all received signals and, therefore, affects the brightness of the echoes

displayed. Setting the power too low results in inadequate returning signals and poor image quality, whereas setting it too high results in image whiteout.

4. **Compress.** The compress setting is also known as a **dynamic range**. It converts the range of returning echo intensities, which may vary a billion-fold in intensity, into 100 to 200 visual shades of brightness or the "grayscale." Increasing the compress will "soften" the image and allow identification of lower level signals. Decreasing the compress results in the production of high-quality contrast images such that weaker signals are eliminated, noise is reduced, and the strongest echo signals are enhanced. Therefore, the compress/dynamic range is decreased when image quality is poor.
5. **Focus (or position).** The focal zone of the transducer indicates the region of the image at which the ultrasound beam is narrowest, and hence where spatial resolution is maximal. Therefore, it is important to reposition the focus to the area of greatest attention/importance, especially those in the near field. When adjusted proximally, however, distal structures may appear blurred as the ultrasound beams scatter.
6. **Persistence.** Persistence is the temporal averaging of the latest frame with the previous frames to produce a smooth or less noisy display. Fast-moving cardiac structures (eg, valve leaflets) may appear blurred if the persistence is set above low.

B. Imaging artifacts

1. **Acoustic shadowing.** Highly reflective structures block transmission of ultrasound to distal structures, causing poor imaging of these far-field structures. For instance, a mechanical mitral prosthesis prevents good visualization of the LA from the apical window.
2. **Reverberation.** This occurs when multiple linear echo signals are generated from a back-and-forth reflection between two strong reflectors of the ultrasound signal, before the signal returns to the transducer. These appear as multiple parallel irregular dense lines extending from the structure into the far field (eg, linear echo

density in the ascending aorta in the PLAX view simulating a dissection flap, which is a reverberation from a more anteriorly lying structure, such as a rib). Reverberation artifacts will be present at a multiple of the distance between the two strong reflectors—usually at twice the distance between the strong reflectors. Careful analysis of the artifact in multiple views and with color Doppler should be performed. Color-flow signals will be seen to pass through the artifact.

3. **Refraction.** Refraction of the ultrasound beam as it passes through a tissue layer can result in a side-by-side double image. This artifact is often seen in PSAX views of the aortic valve where the image appears to show two aortic valves overlapping.
4. **Beam width artifact.** Ultrasound beams are 3D and are reflected from 3D structures, but they are displayed in a 2D tomographic plane. Strong reflectors at the edge of a central beam, especially outside the narrow proximal focal zone, can be superimposed on a structure in the central zone, with the resulting appearance of a structure within the image, that is, outside the 2D tomographic plane (eg, an aortic valve in the LA in the A4C view).
5. **Range ambiguity.** Echo signals from earlier pulse cycles reach the transducer on the next receiving cycle because of re-reflection, resulting in deep structures that appear closer to the transducer than their actual location, and are manifested as the appearance of an anatomically unexpected echo. This can be confirmed by the disappearance of the artifact when the depth setting is changed.
6. **Side lobe artifacts.** In addition to the central beam, transducers produce side lobes 10° to 30° off axis. All echoes returning from structures in these peripheral beams are displayed, as if they arose from targets within the main beam. Therefore, strong reflectors may be imaged by these low-intensity side lobes and displayed in an erroneous position on the screen. This is a major source of "clutter" in cardiac cavities. Harmonic echoes have much lower intensity side lobes, with a resulting reduction in side lobe artifacts in the image.

C. Factors affecting color Doppler image. Many factors affect spectral Doppler and color-flow Doppler, and it is important to consider these. They can be broadly divided into three groups: machine settings, imaging factors, and hemodynamic factors (see **Table 66.7** for tips to optimize Doppler settings).

TABLE 66.7 Tips for the Transthoracic Doppler Examination

- Doppler (all modalities) is very **angle dependent**—angle between the ultrasound beam and the blood flow jet of interest should be <20°. To achieve this, off-axis views are often required.

PW and CW Doppler

- Shifting the **Doppler baseline** up or down can double the maximal velocity detected (still <2 m/s) for PW.
- Increasing the **depth** decreases the Nyquist limit and reduces the maximal velocity that can be measured with PW.
- Recheck high-velocity jets with the **Pedoff (CW)** probe to confirm peak velocity (include right upper sternal border positions when trying to obtain peak aortic stenosis velocity).
- Start with **high-gain setting** and reduce until noise and clutter are adequately suppressed.
- Set **wall filter** to low to avoid overestimation of low velocities.
- Decreasing the **compress** enhances the edges of the spectral envelope; increasing it enhances the various velocities displayed within the Doppler envelope.
- Initially set **"reject"** at low (20%-40%) to allow the display of a wide range of signals, then increase to remove signals that obscure the image (ie, to reduce noise).
- Adjust **gate width**—1-2 mm for mitral inflow and LVOT, 3-4 mm for pulmonary venous flow, and 5-10 for Doppler tissue imaging.

Color-Flow Doppler

- **Narrow** the sector and minimize the **depth** to maximize color resolution (increase frame rate).

- Spatial resolution is higher **axial** to the beam than lateral.
- Higher **transducer frequencies** result in an increased area of flow disturbance (reduces the Nyquist and increases ability to visualize lower velocities).
- Adjust **color gain** until just before noise appears in the color.
- Minimize **wall filters** during analysis of PISA/flow convergence, to avoid overestimating low velocities.
- Decreasing the **Nyquist limit** increases the size of any regurgitant jet as lower velocities are detected (normally not color coded at higher Nyquist velocities); therefore, set at 50-60 cm/s initially.
- Be careful not to miss or underestimate very **eccentric jets** of mitral regurgitation or aortic regurgitation.
- Remember that **chamber constraint** reduces the size of a jet—wall jets tend to underestimate the severity of regurgitation compared to a jet that is not constrained by a wall.

CW, continuous wave; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; PW, pulsed wave.

1. Machine settings

a. Nyquist limit. At any given depth, in color Doppler imaging, the Nyquist or aliasing velocity (which is related to the PRF) can be adjusted. Typically, it is set to 50 to 60 cm/s. The lowest velocity that is displayed on the color map is related to the Nyquist (minimal displayed velocity = Nyquist × 2/32). Therefore, decreasing the Nyquist increases the lowest velocity displayed, which has the effect of increasing the size of the jet area.

b. Transducer frequency. In color-flow imaging, higher transducer frequency reduces the peak velocity (Nyquist limit) that can be measured (see Doppler equation above). Lower Nyquist results in an increased color-flow jet area. Therefore, higher frequency transesophageal echocardiography generally produces larger areas of flow disturbance than TTE. In spectral

Doppler imaging, lower frequency transducers can measure higher velocities.

c. **Depth setting.** Minimizing the depth setting to encompass only the region of interest maximizes the PRF and frame rate.

d. **Gain.** Adjust the color gain until just before random noise appears in the color. Increased color gain increases the size of color-flow disturbance. 2D gain should be decreased during the color Doppler examination to maximize color-flow disturbance because each pixel is assigned to either 2D or color. In PW and CW Doppler, start with a high-gain setting until the desired signal is appreciated. The gain is decreased until noise and clutter are adequately suppressed.

e. **Baseline.** Used primarily for unwrapping aliased signals. Generally leave it in the middle of the color bar, but it can be adjusted to maximize the velocity that can be displayed with PW or color Doppler. This is also useful for highlighting a specific velocity as in proximal convergence analysis.

f. **Wall filter.** Excludes low-velocity, high-amplitude signals from myocardial motion. If set too high, it tends to decrease the color-flow disturbance. A typical initial setting is 400 Hz. The setting of the wall filter should be minimized during analysis of the proximal flow convergence region to avoid overestimation of low velocities (ie, set low for PW Doppler and high for CW Doppler).

g. **Beam width.** Beam width is especially important with PW and CW Doppler. As the ultrasound beam propagates, it spreads out. For example, when sampling pulmonary venous flow with pulse Doppler from the apical view, the sample volume may be at 16 cm depth and the ultrasound beam may be >1 cm in width. This can lead to the detection of aortic flow, which is displayed as if it arose along the beam axis (from the pulmonary vein) leading to beam width artifact.

h. **Gate length or sample size.** This is the size of the PW Doppler sampling region. It is usually set at 3 to 5 mm. Narrowing the gate focuses the velocity data to a smaller spatial area and can

help improve image quality, but it requires very accurate positioning to prevent missing of the appropriate sample area during cardiac motion.

i. **Scale.** Controls the range of Doppler velocities displayed. As the velocity scale increases, the velocity limits increase and the displayed waveform size decreases.

j. **Compress.** In spectral (PW and CW) Doppler, the compress setting adjusts the grayscale, which controls image softness. Decrease the compress to enhance the edges of the spectral envelope. Increase the compress to enhance the various velocities displayed within the Doppler spectrum. Set at 30 dB or higher initially.

k. **Reject.** In spectral Doppler, the reject control removes low-amplitude signals ("noise") from the spectral display. The reject control is initially set at a low level (20%-40% maximum) to allow the display of a wide range of signals. The reject is then increased to remove signals that obscure the image.

2. Imaging factors

a. **Interrogation angle.** Color-flow imaging measures only the component of flow that is parallel to the ultrasound beam. This is related to the true flow velocity by the cosine of the angle between the blood flow and the interrogating ultrasound beam. Satisfactory alignment (as parallel to the flow as possible) is vital to record the full and maximal velocity jet with spectral (both PW and CW) Doppler.

b. **Attenuation.** Loss of signal strength caused by too high a transducer frequency for the required depth results in a reduced area of color-flow disturbance.

c. **Acoustic shadowing.** Loss of signal strength caused by a proximal reflector of ultrasound (eg, a mechanical prosthetic valve preventing apical imaging of MR jet in the LA)

3. Hemodynamic factors

a. **Flow volume.** Increasing regurgitant volume results in an increased area of color-flow disturbance, and this is the basis

for the common practice of judging the severity of valvular regurgitation by the size of the color jet. However, as outlined in this chapter, many factors affect the size of the color-flow jet area. Therefore, it is important to include other factors in the assessment of regurgitation, such as ventricular and atrial sizes, the morphologic appearance of the valve, the width of the color jet at its narrowest point (vena contracta), and, in particular, more quantitative analysis using the proximal flow convergence region (PISA). Several cardiac cycles should be inspected with minor adjustments in the angle of interrogation to ensure that the largest jet is visualized.

b. **Driving pressure.** Increased pressure gradient across a regurgitant orifice results in an increased color-flow disturbance in the receiving chamber. Color jet size is closely related to jet momentum, given by flow rate multiplied by jet velocity.

c. **Chamber constraint in eccentric jets.** Impingement of a regurgitant jet against the walls of the receiving chamber will decrease the size of the color disturbance. For example, severe but eccentric MR may have a very small area of color-flow disturbance because the jet loses momentum to the constraining LA wall and appears narrower in a 2D view as it is splayed out over a larger surface area of the wall.

4. **Doppler artifact.** Mirror image artifact can be seen occasionally when the Doppler signal is duplicated on the other side of the baseline.

III. POINT-OF-CARE ULTRASOUND. Point-of-care ultrasound (POCUS) typically refers to ultrasonography performed and interpreted at the patient's bedside. POCUS is being increasingly used in settings such as the emergency department (ED), obstetrics/gynecology, and for bedside procedures since the advent of portable ultrasound. With the advent of handheld ultrasound devices, conducting a focused cardiac examination has become more feasible. Currently, there are four main portable or handheld ultrasound devices available (Butterfly iQ+ by Butterfly

Network Inc, Kosmos by EchoNous, Vscan Air by General Electric, and Lumify by Philips Healthcare).

As discussed at the beginning of this chapter, traditional ultrasound devices use piezoelectric crystals to convert electrical signals into ultrasound waves. With portable or handheld ultrasound devices, electric signals are instead converted to ultrasound waves using microchips made of "complementary metal oxide semiconductors." Given that no piezoelectric crystals are needed, the handheld ultrasounds are considerably cheaper than traditional devices. In addition, this technology enables the frequency to be modulated, allowing for both low- and high-frequency ultrasonography with a single probe. In contrast to typical ultrasound machines, the ultrasound probe in handheld devices itself performs its image processing, with the tablet or phone serving to display the image. Although the resolution and image quality are improving in the newer handheld ultrasounds, the gold standard is still a traditional, dedicated echocardiogram. Furthermore, although the convenience of having one probe is ideal with handheld devices, it does limit the ability to image with different frequencies. Another limitation of the handheld ultrasound itself is the lack of spectral Doppler. However, as the capability of these devices has increased, cardiac POCUS has progressively gained a larger role in the day-to-day management of patients.

A. Role of POCUS in the ED. Chest pain is one of the most common reasons patients present to the ED. Accurate and timely evaluation of these patients is critical in providing appropriate patient care. Crowding in the ED not only can lead to delayed patient care but also potential delayed diagnosis of life-threatening cardiac conditions. The use of POCUS to evaluate and triage patients can positively impact patient care and aid in more accurate and efficient patient triage.

The benefits of POCUS can be seen in the diagnosis of a wide variety of conditions, but it is particularly useful in cardiac care. In correlation with the patient's symptoms, cardiac POCUS can quickly evaluate for processes such as pericardial effusion or tamponade, acute decompensated heart failure, valvular disease, or regional wall motion abnormalities, to name a few. In the following sections, we discuss these conditions, focusing on key findings.

1. **Pericardial effusion.** Pericardial effusion, particularly if there is concern for pericardial tamponade, is a "must-not-miss" diagnosis while evaluating patients in the ED. Although tamponade is a clinical diagnosis, echocardiographic evaluation is crucial. Using POCUS, evaluation of patients presenting with chest pain and potential hypotension and dyspnea can be streamlined. When evaluating for a pericardial effusion, it is important to evaluate in multiple views to find the best "window" to assess the largest dimension of the effusion and determine accessibility for drainage. Typically, effusions less than 1 cm are considered small, between 1 and 2 cm are considered moderate, and greater than 2 cm are considered large. In addition to size, rate of fluid accumulation is important. Even with a small effusion, tamponade may be present as with acute effusions the pericardium has not had time to stretch and become more compliant. Thus, even 50 mL of fluid in the pericardium can lead to tamponade and the diagnosis of tamponade is not necessarily correlated with the size of the effusion. Many handheld POCUS probes have M-mode functionality, which can often aid in evaluating the RV. Using the PLAX and subcostal views, it is feasible to evaluate for RV collapse during early diastole. In addition, seeing systolic RA or RV collapse along with a dilated IVC that collapses less than 50% with respiration, typically seen on subcostal view, can be a specific sign for diagnosing tamponade. Full echocardiographic evaluation of pericardial effusion and tamponade is discussed in the section on pericardial effusion and tamponade.
2. **Acute decompensated heart failure.** POCUS can also be very useful in the evaluation of nonspecific dyspnea in the ED. Patients with a history of heart failure typically present with signs of volume overload. However, physical examination and/or history-taking may be challenging, especially in cases where patients also have altered mental status or are unable to provide history. In such cases, it can be useful to evaluate intracardiac pressures and function noninvasively with POCUS.

While evaluating patients in the ED, cardiologists and noncardiologists alike can obtain some simple views on bedside

ultrasonography to evaluate for acute exacerbation of systolic heart failure. Integration of key findings from PLAX, PSAX, and apical views can help determine biventricular function. In particular, by performing the PLAX view, one can quickly determine overall LV function and size, as well as RVOT size and function. From there, by turning the handheld ultrasound probe 90° superiorly, the LV function and RV free wall inward motion can be assessed. The A4C view can also be useful in evaluating both LV and RV longitudinal wall motion. In addition, the mitral and tricuspid valves can be interrogated for any overt dysfunction in this view.

With the subcostal view, it is feasible to better assess RA volume and the IVC. The IVC is typically seen flowing into the RA. IVC size and variation with respiration can provide important noninvasive hemodynamic measurements when evaluating for clinical heart failure. The IVC should be measured at end expiration directly proximal to the hepatic veins. It is important to note that the normal IVC has a natural narrowing at the IVC and RA junction and should not be measured there. Normal IVC diameter is less than or equal to 2.1 cm, and typically, the IVC collapses >50% with inspiration or sniffing. Refer to the echo hemodynamics section for further details.

3. **Acute valvular/aortic pathology.** Aortic and valvular pathologies are also differential in the assessment of patients, particularly those who are hemodynamically unstable or in acute care situations (ie, ED, critical care). Of course, a dedicated echocardiogram is the gold standard, but in cases where time is of the essence, POCUS can be critical in obtaining a cursory evaluation of acute aortic/valvular pathology.

   With aortic and aortic valve pathologies, certain conditions are "must-not-miss" diagnoses, especially when working in an acute setting (ie, ED or critical care environment) where patients may be hemodynamically unstable. Such conditions include, but are not limited to, acute aortic dissection and aortic aneurysms. Depending on the extent of an aortic dissection, particularly type A dissection, a dissection flap can sometimes be seen in the PLAX view as a mobile linear density in the aortic root/ascending aorta. With the

suprasternal view, the ascending aorta and the aortic arch can be interrogated to suggest the presence of a type A dissection. Color flow can be helpful in determining flow into a dissection flap. In addition to dissection, PLAX and suprasternal notch views can help identify aortic dilation/aneurysm or suggest the presence of coarctation.

With the PLAX and SAX views, it is possible to evaluate the structure of the aortic valve, as well as any associated severe AR or aortic stenosis. Particularly if there is a concern for aortic dissection, it is important to understand the presence and degree of AR. Although quantifying with spectral Doppler may not necessarily be possible with a handheld ultrasound probe, the degree of regurgitation or stenosis of a valve, as well as the level of obstruction if stenosis is present, may be estimated by looking at the direction of the jet, and visually estimating the vena contracta, and/or the PISA. Other findings such as diastolic MR can be supportive of acute severe AR. With the subcostal view, the abdominal aorta can be evaluated for any diastolic flow reversal, again providing information about the degree of regurgitation.

Acute mitral valvular pathology, such as acute mitral valve regurgitation, can also be assessed with POCUS. Integration of anatomic information from various views can help identify structural abnormalities of the mitral valve apparatus. In patients presenting with acute pulmonary edema, it is crucial to evaluate the mitral valve apparatus, especially if there is any concern for papillary muscle rupture. Because of the single blood supply of the posteromedial papillary muscle from the posterior descending artery (PDA), an MI involving the PDA (classically a posterior MI), can lead to acute MR. In addition, myxomatous disease and mitral pathology secondary to infective endocarditis can lead to acute mitral valve pathology. Again, valvular pathology can be further interrogated with color Doppler and visual estimation of the degree of regurgitation as stated above, as long as image quality permits.

4. **Regional wall motion abnormalities.** In patients presenting with chest pain, one of the most common complaints in the ED, POCUS

to assess for regional wall motion abnormalities in conjunction with physical examination, ECG, and labs can more accurately triage patients. Given the utility of the handheld ultrasound, a global assessment of wall motion can be made, understanding that full TTE is the gold standard. Typically, the PLAX and PSAX views, along with the A4C and A2C views, are most helpful in this assessment. Specific regional wall motion abnormalities are discussed in the section on stress echocardiography.

5. **Patients infected with COVID-19. During** the COVID-19 pandemic, handheld POCUS become more important in evaluating patients. Since COVID-19 infection can lead to a spectrum of cardiac manifestations, including acute LV heart failure, myocarditis, pericardial effusions, and RV dysfunction due to pulmonary embolism (PE)., POCUS can more accurately triage these patients, both in the ED and in the hospital. Furthermore, given the need to decrease COVID exposure, handheld probes and machines, by virtue of their small size, are much easier to appropriately disinfect and clean compared with the more bulky echocardiographic machines. Of course, it is important to note that the gold standard for echocardiography is still a full echocardiogram with a trained echocardiographer. However, handheld POCUS can not only aid in evaluation but also has the advantage of real-time bedside interpretation. Thus, POCUS has become an inexpensive and useful tool in evaluation of patients with COVID.

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CHAPTER 67

Transesophageal Echocardiography

Diarmaid Hughes and Maran Thamilarasan

I. INDICATIONS. In general, transesophageal echocardiography (TEE) is performed when there is a clinical question for which the information obtained using transthoracic echocardiography (TTE) or other imaging modalities is insufficient. This may be to better define pathology that has been identified by TTE, computed tomography (CT), or magnetic resonance imaging (MRI) or to obtain better images when transthoracic images are inadequate. The proximity of the esophagus to the heart allows for improved visualization of many cardiac structures, particularly those that are posteriorly located. In addition, higher frequency probes can be used, given the shorter distance between the probe and the heart, further enhancing the resolution. However, imaging planes are somewhat constrained by the relative position of the esophagus and heart, which, in turn, makes transthoracic imaging superior in the assessment of certain, particularly anterior, structures (ie, pulmonic valve) and Doppler measurements.

Indications for TEE in various conditions and clinical situations are listed in **Table 67.1**. Very common indications include examination to rule out a cardiac source of embolus and assessment of native valves, prosthesis, and intracardiac devices for endocarditis or its accompanying complications, such as abscess. The assessment of native and prosthetic valvular function, in terms of the degree and mechanism of regurgitation or stenosis, is a frequent indication for TEE. Acoustic shadowing by prosthetic valves, particularly in the mitral position, poses less of a problem for TEE than it does for TTE. Given the increasing prevalence of atrial fibrillation, another frequent indication for TEE is to assess left atrial and left atrial appendage pathology and function, particularly prior

to cardioversion. Congenital cardiovascular abnormalities, intracardiac shunts, as well as intracardiac tumors and masses can also be well delineated by TEE. Because of its ability to assess the ascending aorta, arch, and descending aorta, TEE also has an important role in the diagnosis of aortic dissection, aneurysms, and atheroma. In extremely technically difficult/limited transthoracic study, such as in postoperative and mechanically ventilated patients, TEE may be used for usual TTE indications, such as the assessment of left ventricular function. More recently, there has been an expanding role of TEE assessment prior to structural interventions to assess for suitability. While the role of the structural imager is becoming a subspecialty in its own right, it is standard practice that the diagnostic evaluation should be performed by any level II trained echocardiographer.

TABLE 67.1 Indications for TEE in Various Conditions and Clinical Situations

Condition	Indication
Infective endocarditis	Patients with at least moderate pretest probability such as *Staphylococcus* bacteremia, fungemia, prosthetic valves, or intracardiac device
	Detection of complications of endocarditis: abscesses and fistula
Cardioembolic source	Identification of left atrial and left atrial appendage thrombus or spontaneous echo contrast
	Identification of PFO, ASD, or atrial septal aneurysm
	Identification of aortic atheroma
	Evaluation of mitral and aortic valves for vegetation, tumors, and valve strands
Valvular heart disease	Evaluation of mechanism and severity of mitral regurgitation
	Characterization of valvular pathology such as aortic morphology
Prosthetic valves	Evaluation of suspected prosthetic dysfunction (stenosis, thrombosis, or regurgitation)
Atrial fibrillation/flutter	Assessment of left atrial and left atrial appendage thrombus prior to cardioversion (eg, if atrial fibrillation >48 h) or ablation

Condition	Indication
	Follow-up for resolution of thrombus after anticoagulation prior to cardioversion or ablation
Aortic disease	Evaluation for suspected acute aortic pathology: dissection, aortic trauma, and intramural hematoma
	Characterization of aortic aneurysm and atheroma
Interventional procedures	Guiding performance of interventional cardiac procedures (eg, percutaneous valve procedure, balloon valvuloplasty, closure of paraprosthetic leak, ASD, VSD, or PFO)
Intraoperative	Assessment of valve repair/replacement and evaluation of systolic function
Intracardiac masses	Detection of characterized masses such as tumors and thrombus
Critical care	Assessment of suspected papillary muscle rupture
	Assessment of mechanical complications of acute myocardial infarction or mural thrombus
	Evaluation of unexplained hypotension, especially in the ICU
	Assessment of early postoperative bleeding, which may result in localized accumulation of blood clots (especially posteriorly)
Congenital heart disease	Identification of site of origin and initial course of coronary arteries
	Detection of intracardiac shunts

ASD, atrial septal defect; ICU, intensive care unit; PFO, patent foramen ovale; TEE, transesophageal echocardiography; VSD, ventricular septal defect.

TEE is a useful imaging modality in both the operating room and the cardiac catheterization laboratory. In cardiothoracic surgery, TEE is used to assess the mechanism of valvular abnormalities and, subsequently, evaluate the efficacy of valve repair or replacement. TEE can be used to guide the location of the aortic cross-clamp so that segments with severe atheromatous involvement can be avoided, thereby reducing the risk of embolization. In addition, TEE can provide an assessment of left ventricular function and regional wall motion. As noted, newer transcatheter procedures have become widespread and so TEE has been

increasingly utilized to assist and help guide these cases. This includes guiding catheter position, transseptal puncture, implantation of percutaneous valves, guiding transcatheter valve repairs, placement of left atrial appendage occluding devices, as well as closure of paraprosthetic leaks, atrial septal defects, ventricular septal defects, and patent foramen ovale. Prevention and early recognition of complications achieved by TEE imaging are often crucial for periprocedural success.

II. CONTRAINDICATIONS

A. There are few **absolute** contraindications to the performance of TEE (**Table 67.2**). These include the **presence of pharyngeal or esophageal obstruction, esophageal tumor, active upper gastrointestinal bleeding, recent esophageal or gastric surgery, and suspected or known perforated viscus**. If there is instability of the cervical vertebrae, then the examination cannot be performed.

TABLE 67.2 TEE Contraindications

Absolute
Esophageal or pharyngeal obstruction
Suspected or known perforated viscus
Gastrointestinal bleeding that has not been evaluated
Instability of cervical vertebrae
Relative
Esophageal varices or diverticula
Cervical arthritis
Oropharyngeal distortion
Bleeding diathesis or overanticoagulation
Uncooperative patient

TEE, transesophageal echocardiography.

B. **Relative** contraindications include the **presence of esophageal varices** and **suspected esophageal diverticulum**. In these cases, it is

prudent to obtain gastrointestinal evaluation before proceeding, if the study must be performed. Severe cervical arthritis, in which patients may have difficulty with neck flexion, may make it difficult to pass the probe. Oropharyngeal pathology, anatomic distortion, or extreme muscle weakness can likewise make it difficult to proceed with the examination.

C. **Severe cardiopulmonary disease** is not a contraindication to evaluation by TEE (on the contrary, TEE can often provide critical information when used in these patients), but the operator must be particularly careful to minimize any stress on the patient. This is particularly true in **suspected aortic dissection**, where any sudden increase in blood pressure caused by patient discomfort could result in extension of the dissection. In cases where there is **respiratory instability**, endotracheal intubation with assisted ventilation should be considered prior to the procedure. Patients who are **hypotensive** may not be able to receive sedative agents, as these agents could lead to further hemodynamic compromise. In such patients, the examination may have to be performed with topical anesthesia alone. This is obviously much more difficult for the patient, and TEE should be done only if critical information is not obtainable by other methods.

D. Given the invasive nature of the procedure, prudence must be observed in patients who are prone to **bleeding**. The procedure is commonly performed on patients who are anticoagulated, such as in those with atrial arrhythmias prior to cardioversion. However, there is an increased risk in those who are over-anticoagulated. Although no set guidelines exist, it would seem advisable to **delay the examination if possible, in patients with an international normalized ratio >5 or a partial thromboplastin time >100 seconds**. **Thrombocytopenia** may also increase the risk, particularly with platelet counts <50,000 per cubic millimeter. TEE can still be performed if needed, as the absolute risk remains low, but meticulous attention must be given to nontraumatic esophageal intubation.

E. **Esophageal infections,** such as those that occur in the context of human immunodeficiency virus (HIV), do not necessarily represent

contraindications to the procedure. **Patient discomfort** caused by the presence of the probe in the esophagus may preclude the examination. Universal precautions should be followed (as they should for any patient). The standard disinfectants used to clean the probe will inactivate HIV.

F. A patient who is very uncooperative is at significant risk for complications from the procedure. In such a case, consideration should be given to aborting the TEE or to increase the level of sedation and prophylactic endotracheal intubation if required.

III. PERSONNEL

The American Society of Echocardiography has proposed the following guidelines for operators who wish to perform TEE: as background, attainment of at least level 2 experience in TTE; a minimum of 25 esophageal intubations under guidance; and a minimum of 50 supervised TEE examinations during training. Furthermore, operators should perform a minimum of 25 to 50 TEE examinations yearly to maintain competency.

The presence of a skilled assistant is invaluable during the procedure. The assistant should be either a sonographer or a registered nurse. The role of the assistant is to monitor vital signs during the procedure, ensure proper suctioning of oropharyngeal secretions, and administer medications.

IV. EQUIPMENT.

Necessary equipment is listed in **Table 67.3**.

TABLE 67.3 Equipment for TEE

- Echo machine and probe (calibrate prior to intubation)
- Sphygmomanometer
- ECG rhythm monitor
- Pulse oximeter
- Supplemental oxygen
- Wall suction with Yankauer

- Intravenous lines and tubing
- Topical anesthetic agents
- Sedative medications
- Bite block
- Gloves and goggles
- Emergency equipment
  - Drugs (eg, atropine, epinephrine, naloxone, flumazenil, and lidocaine)
  - Defibrillator
  - Intubation supplies

ECG, electrocardiogram; TEE, transesophageal echocardiography.

V. THE TRANSESOPHAGEAL PROBE. The probe is a modification of the standard gastroscope, with transducers in place of fiber optics. The conventional rotary controls with the inner and outer dials are present. The inner dial typically guides anteflexion and retroflexion, whereas the outer dial controls the medial and lateral movement of the tip. A locking mechanism is present, which must not be in effect when the probe is advanced or withdrawn, because esophageal trauma may result. The multiplane probe also has a lever control to guide rotation. Advancement and withdrawal of the probe, rotation of the probe about its long axis, and the manipulations available using the above rotary controls constitute the means by which specific images can be obtained (**Figure 67.1**). Most current generation probes are also equipped for three-dimensional (3D) imaging.

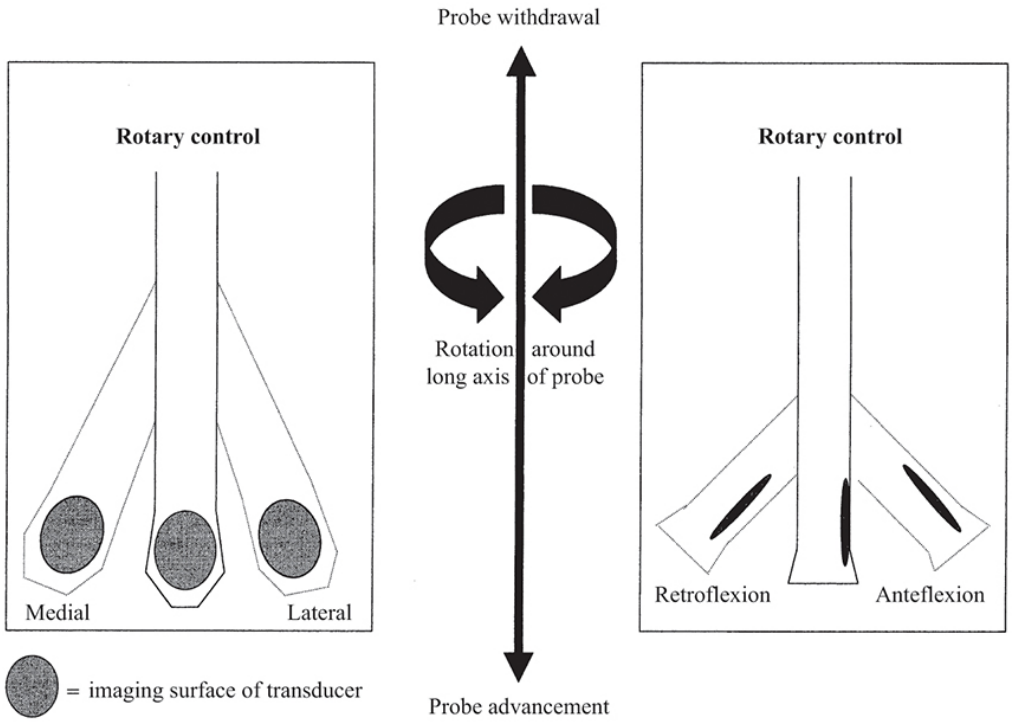

FIGURE 67.1 Specific images can be obtained by advancement and withdrawal of the probe, by rotation of the probe about its long axis, and by the manipulations that are possible using rotary controls.

VI. PATIENT PREPARATION (TABLE 67.4)

TABLE 67.4 Preparation for TEE

- Patient must have had nothing by mouth for at least 4 h prior to the procedure.
- Assess for possible contraindications:
  - History of odynophagia or dysphagia
  - History of mediastinal or cervical radiation that might have resulted in stricture formation
  - History of and workup for gastrointestinal bleeding
- Allergies to and previous tolerance of sedative medications
- Patient understanding of procedure and indications
- Informed consent of patient

TEE, transesophageal echocardiography.

A. The patient should have had nothing by mouth (NPO) for at least 4 to 6 hours before the procedure. Water is allowed up to 2 hours before the test. The clinician can rule out possible contraindications by asking for a history of odynophagia or dysphagia. It is important to be aware of any history of radiation therapy to the mediastinum or cervical region that may have resulted in stricture formation.

B. The extent of previous workup for any history of gastrointestinal bleeding must be reviewed. The clinician should review recent laboratory studies, paying particular attention to platelet count, hemoglobin level, and coagulation profile. Appropriate inquiries should be made with regard to allergies and former tolerance of sedative medications. The clinician should ensure that the patient understands the procedure, including risks and benefits, and that proper informed consent is obtained and documented before proceeding.

C. Step-by-step guide to the examination

1. The patient's **dentures** should be removed.
2. **An intravenous (IV) line** should be inserted to allow for administration of medications and saline contrast for study.
3. The American Heart Association does not recommend **antibiotic prophylaxis** for patients undergoing endoscopic procedures. The reported incidence of transient bacteremia with endoscopy is no higher than the contamination rates reported with blood cultures.
4. A **blood pressure cuff** should be placed on the patient's arm.
5. **Electrocardiographic leads** should be applied and connected to the telemetry monitor.
6. A **pulse oximeter** should be applied to the patient's finger or ear.
7. A **nasal cannula** should be used so that supplemental oxygen can be given as needed. Capnography is encouraged as well, to monitor respiratory effort.
8. While sitting up, the patient should be asked to gargle **viscous 2% lidocaine** for 1 minute and then swallow it for topical anesthesia.

Lidocaine (xylocaine) spray (4%) or Cetacaine spray (10%) is then sprayed on to the posterior tongue and upper pharynx. These procedures normally suppress the **gag reflex**, but, if necessary, this can be verified using a tongue depressor or gloved finger; additional **topical anesthesia** is then applied until the reflex is dulled. By visualizing the area being sprayed, inadvertent spraying of the vocal cord and resultant laryngospasm can be avoided. Methemoglobinemia has been reported with the use of benzocaine-containing product (eg, Cetacaine), which is usually manifested as central cyanosis and desaturation and can be treated with supplemental oxygen and methylene blue. Some operators advocate the use of drying agents to minimize oropharyngeal secretions (eg, glycopyrrolate). We generally have not found a need for the use of such agents, which can cause an increase in heart rate.

9. Have the patient lie down on the left side (left lateral decubitus position), facing the echo machine (alternatively, the patient can lie on the right side, with the machine on the right), with the neck flexed. TEE can be performed with the patient sitting but is easier in the lateral position.
10. **Midazolam,** a benzodiazepine, is the preferred agent for sedation, having the benefit of a short half-life. It also produces an antegrade amnesic effect and has anxiolytic properties. Typically, administer IV doses of 0.5 to 1 mg every 3 to 5 minutes until adequate sedation is achieved. The goal is to reduce anxiety without compromising respiratory drive and while maintaining the patient's ability to follow simple commands, such as swallowing when necessary. Check pulse oximetry and blood pressure before each dose. **Fentanyl**, a short-acting opioid analgesic, can be used for sedation (typically 25 mcg IV per dose) in conjunction with midazolam and may be better tolerated in patients with poor left ventricular function or renal impairment. An alternative sedative is **meperidine**, which is typically given in 12.5 to 25 mg IV doses. Meperidine and fentanyl possess an analgesic effect and help suppress the gag reflex as well. Again, **check vital signs before**

and after each dose. Additional doses of these sedatives and anxiolytics may be administered during the procedure if necessary. Sedation can lead to potential respiratory suppression; therefore, a benzodiazepine antagonist (eg, flumazenil 0.2-0.6 mg IV) and an opiate antagonist (eg, naloxone, increments of 0.1-0.2 mg IV doses) should be available if required.

11. With adequate sedation and topical anesthesia (diminution of gag reflex), **begin probe insertion**. There are two approaches that are generally used.
    a. The first is the **digital technique**, which is especially useful with larger profile probes. With this method, the bite guard is inserted into the shaft of the probe such that, after esophageal intubation, the bite guard can be moved into place. The distal end of the probe is lubricated. The imaging surface of the transducer is placed toward the tongue. The tip of the transducer is placed under the index finger, and it is slowly guided downward and posterior to the hypopharynx. At this point, the patient is asked to swallow, and gentle pressure is applied with the other hand to guide the probe down. Swallowing results in relaxation of the upper esophageal sphincter. If resistance is met, stop; let the patient relax, and reattempt or redirect as needed. Using the finger as a guide will help center the probe in the region of the hypopharynx over the esophagus and avoid the lateral recesses.
    b. An **alternative method is to use the rotary controls on the TEE probe** to guide the intubation. The bite guard is inserted first. The probe is inserted through the bite guard, and gentle anteflexion is applied as the probe is passed over the back of the tongue. The probe is then returned to the neutral position, or with slight retroflexion, as it is passed down into the esophagus. The patient is asked to swallow as the probe is advanced past the upper esophageal sphincter. The operator is still able to guide the probe if needed by insertion of a finger around the side of the bite guard.

Patients often gag as the probe enters the upper esophagus (even with adequate anesthesia); however, patients generally find it more comfortable once the probe has passed beyond this point (usually at 25 cm, past the level of the carina). The probe should be advanced to approximately 30 to 40 cm (mid-esophageal level).

In intubated patients, it is important to **secure the endotracheal tube firmly to one side of the mouth** to prevent dislodgment and inadvertent extubation. Direct visualization with a laryngoscope may be needed. **Sedation** is equally important in these patients, and given the tendency for partially sedated patients to bite on their tubes, a **paralyzing agent** is often required. Intubation in the supine position is not a problem because the airway is protected. Other catheters in the esophagus, such as feeding tubes or nasogastric tubes, often must be removed prior to the procedure; they may become interposed between the esophagus and the TEE probe, interfering with the images. If left in, these tubes may become dislodged by the TEE probe, and the tube position should be reconfirmed after the echocardiographic examination. For patients with tracheostomies, some operators will carefully and gently deflate the cuff to facilitate probe insertion.

VII. IMAGING. TEE technology has undergone much evolution, from the initial monoplane views to the current multiplane views and 3D views. Monoplane TEE provides images in the horizontal plane only, perpendicular to the shaft of the endoscope. Longitudinal relationships among cardiac structures are difficult to appreciate. With biplane TEE, the orthogonal longitudinal plane can also be obtained. Both monoplane and biplane systems required additional manipulation to obtain off-axis views, making the examination more difficult and more uncomfortable for the patient. With **multiplane TEE**, the transducer has a single array of crystals that can be rotated 180° around the long axis, producing a continuum of transverse and longitudinal images from a single probe position. This minimizes the probe manipulation necessary to obtain intermediate and off-axis images. Consequently, multiplane TEE has

increased sensitivity for the detection of sometimes-subtle abnormalities, including vegetations, periprosthetic leaks, left atrial appendage thrombi, and aortic dissection. The development of **real-time 3D TEE** (see Section VII.C) offers the possibility of assessing cardiac structures volumetrically. It has emerged as a clinically relevant modality by providing relatively high image quality, which may enhance clinical decision-making, especially in regard to structures with a complex anatomy such as the mitral valve. This technology is particularly used in the diagnostic assessment and guiding of structural interventions.

A. Basic views. The TEE examination tends to be more goal directed than the transthoracic examination, because there may be time constraints imposed by how long the patient can tolerate the esophageal probe. Initial views should focus on the question at hand, but it is still important to perform a comprehensive and thorough examination. Most operators prefer to begin with upper esophageal views before proceeding to transgastric views. The order of views obtained is not important, provided the operator develops a consistent and comprehensive approach.

B. The **probe may inadvertently rotate** during insertion and may require initial manipulation before starting the examination. The left atrium should be seen at the center of the screen. If the aorta is seen (which is posterior to the esophagus), then the probe must be rotated anteriorly. Slight retroflexion of the probe may be necessary to maintain adequate contact between the probe and the esophagus. Air in the esophagus, which is interposed between the probe and the heart, may affect image quality. This generally lessens as the examination progresses (from ongoing peristaltic activity in the esophagus). Similarly, the presence of a hiatal hernia may compromise image quality.

C. Multiplane TEE is now universal. Multiplane views are described in terms of the degrees of rotation required to obtain particular images. At each transducer location, start the array at 0° and rotate to 180° at 5° to 15° increments to obtain a complete sweep. The standard horizontal plane is designated as 0°. At approximately 45°, short-axis views are obtained. Ninety degrees is defined as the

longitudinal plane, whereas at around 135°, the true long-axis cardiac views are obtained. At 180°, a mirror image view of the standard horizontal plane is obtained. Given the variable anatomic relationships between structures, the degree of probe manipulation required to obtain the standard views will vary from patient to patient.

1. **Upper esophagus (30 cm)—base of the heart** (**Figure 67.2**). With the array at 0°, a five-chamber cross-sectional view of the left atrium, left ventricle, right atrium, right ventricle, and aortic valve is obtained. At 40° to 60°, the three leaflets of the aortic valve become visible (right coronary cusp at the bottom of the screen, noncoronary cusp on the top and to the left, and left coronary cusp on the right). Planimetry of the aortic valve orifice is often possible in this view. Subtle in-and-out movements allow for visualization of the proximal coronaries. The left atrial appendage is also seen in this view (zooming in on the atrial appendage, with subsequent rotation of the array, facilitates inspection for thrombus). At 60° to 100°, the tricuspid valve and right ventricular outflow tract/pulmonic valve become visible. At 120°, long-axis images of the left ventricular outflow tract (LVOT), aortic valve (noncoronary and right coronary cusps), and proximal ascending aorta are seen. Slight withdrawal of the probe at 110° to 120° permits visualization of the ascending aorta. With the probe withdrawn further into the upper esophagus (**Figure 67.3**), the pulmonary artery and its bifurcation can be visualized (from 0° to 45°).

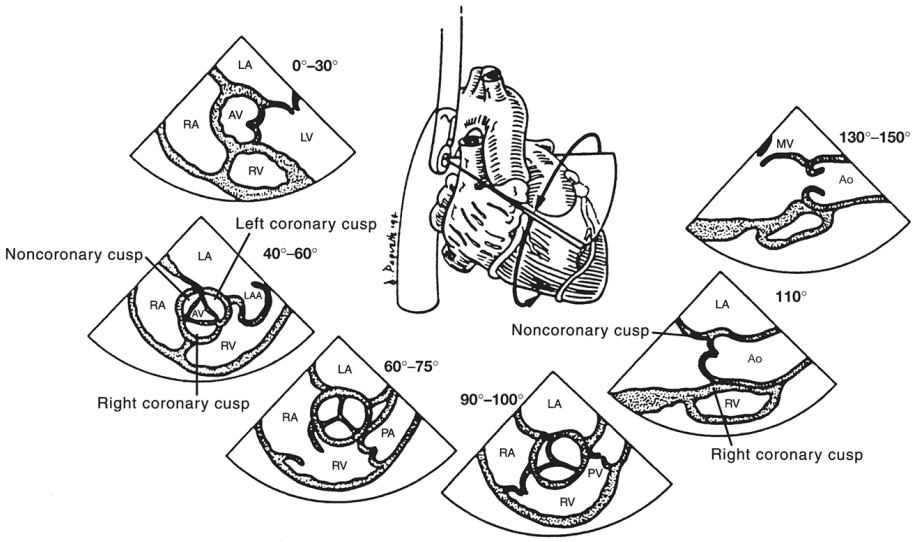

FIGURE 67.2 Schematic representation of selected multiplane transesophageal echocardiography views of the aorta (Ao) and aortic valve from the upper esophagus. AV, atrioventricular; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RV, right ventricle. (Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. Churchill Livingstone; 1996:15-68. Copyright © 1996 Elsevier. With permission.)

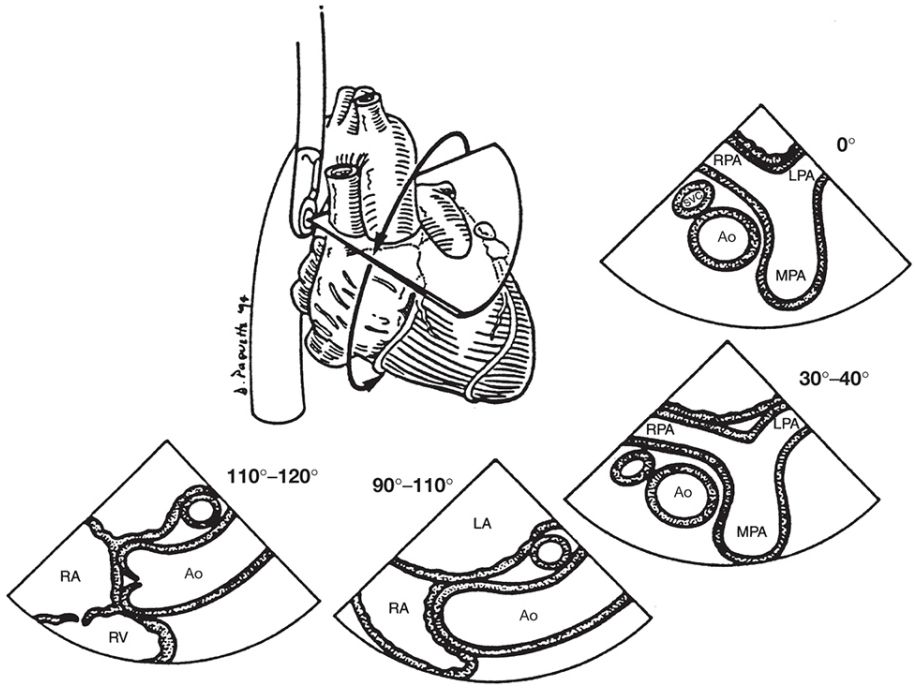

FIGURE 67.3 Schematic of some of the multiplane transesophageal echocardiography views of the aorta (Ao) and pulmonary artery that can be obtained from the upper esophagus. LA, left atrium; LPA, left pulmonary artery; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle. (Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. Churchill Livingstone; 1996:15-68. Copyright © 1996 Elsevier. With permission.)

2. **Lower and middle esophagus** (**Figure 67.4**). With the array at 0°, a four-chamber view is obtained (some retroflexion of the probe is needed for a true four-chamber view, because with anteflexion, one will see portions of the LVOT and aortic valve). This view is similar to an inverted transthoracic apical four-chamber view. With the left atrium and left ventricle kept in the center of the view field, rotation of the array allows for a thorough evaluation of the left-sided structures. Doppler interrogation of mitral inflow is generally performed with the array at 0° to 30°. Skillful maneuvers as the array is rotated to 90° allow for interrogation of both leaflets of the mitral valve, including the specific scallops of the leaflet. Rotation of the array to 90° to 110° reveals the two-chamber view (left atrium/left ventricle), with the anterior and inferior walls of the left ventricle visualized. The left atrial appendage and the left upper pulmonary vein are also seen. Long-axis views of the LVOT, aortic valve (right and noncoronary cusps), and proximal ascending aorta are obtained by rotation to 120° to 140°. The anterior mitral leaflet is particularly well visualized in these views. This complete sweep permits full delineation of the extent of mitral regurgitation.

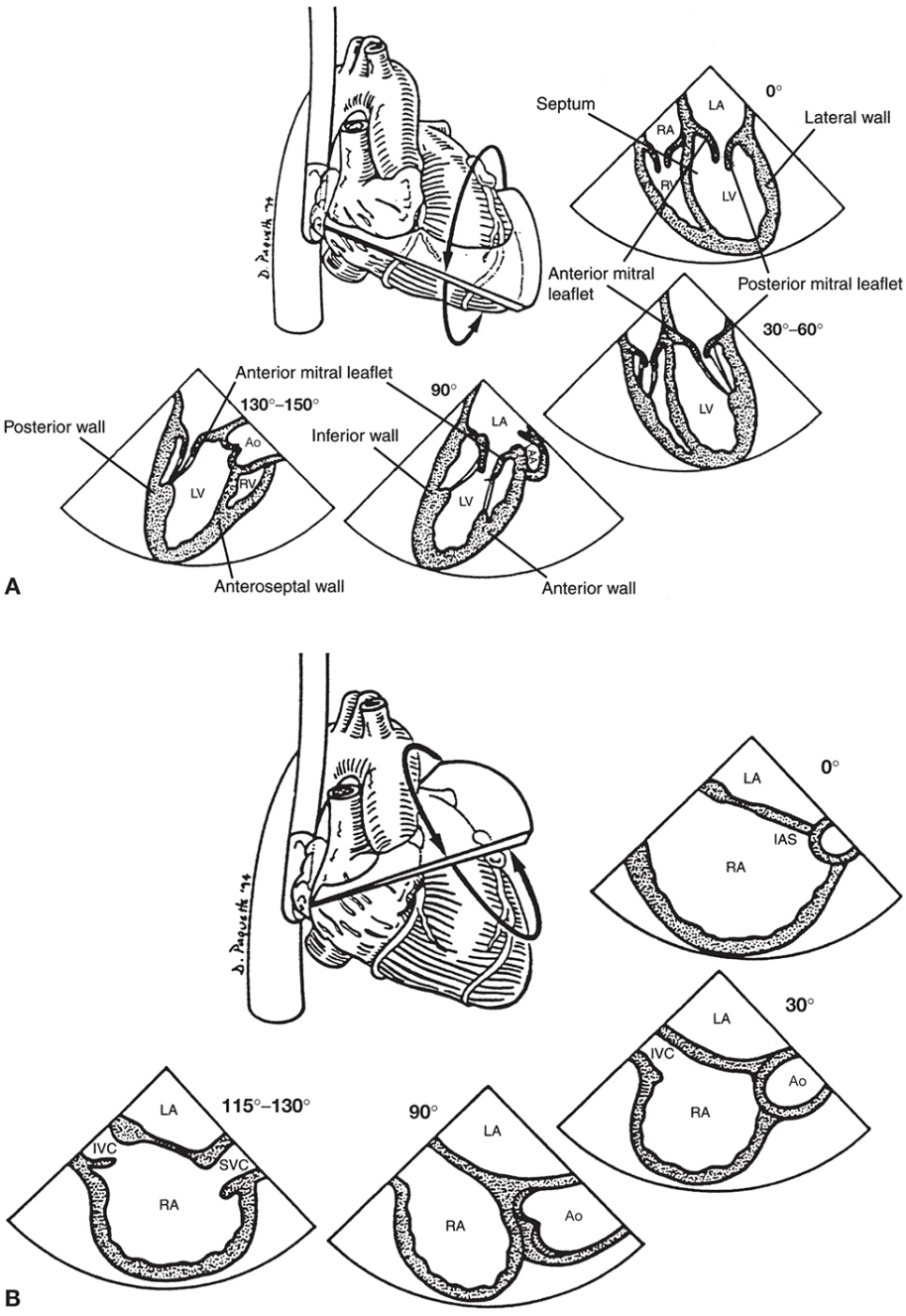

FIGURE 67.4 **A.** Schematic diagram showing some representative sections of the left heart that can be obtained with multiplane transesophageal echocardiography from the lower and middle esophagus. **B.** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the atria and interatrial septum that can be obtained from the lower middle esophagus. Ao, aorta; IAS, interatrial septum; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava. (**A** and **B**. Modified from

Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. Churchill Livingstone; 1996:15-68. Copyright © 1996 Elsevier. With permission.)

Similar views of right-sided structures and the interatrial septum can also be obtained from this position. At 0° (in the four-chamber view as described previously), the septal and anterior leaflets of the tricuspid valve can be seen. The endoscope is then rotated to bring the interatrial septum and the right atrium to the center of view (some withdrawal or advancement of the probe may be necessary to optimize visualization of the interatrial septum). By rotation of the multiplane array, the interatrial septum and fossa ovalis can be thoroughly examined for evidence of a patent foramen ovale or atrial septal defect. Agitated saline contrast can be given IV at this time to expose evidence of shunting; asking the patient to perform Valsalva maneuver or to cough can help identify right-to-left shunting. At approximately 100°, the superior vena cava (SVC) and inferior vena cava can be seen entering the right atrium, and the right atrial appendage can also be seen. This is a good view to identify anomalous pulmonary venous drainage into the right atrium or SVC or a sinus venosus atrial septal defect. Further rotation will allow for assessment of the right pulmonary veins.

3. Transgastric views

a. Proximal (**Figure 67.5A**). These are images obtained from the fundus of the stomach. A cross-sectional view of the left and right ventricles is obtained at 0°. By rotating the shaft of the endoscope to center with the left ventricle in the field of view, serial short-axis (“doughnut”) views of the left ventricle can be obtained. Anteflexion of the probe will give rise to basal views, with the mitral and tricuspid valves seen in cross section. With the transducer in a more neutral position, middle and apical short-axis views will be obtained.

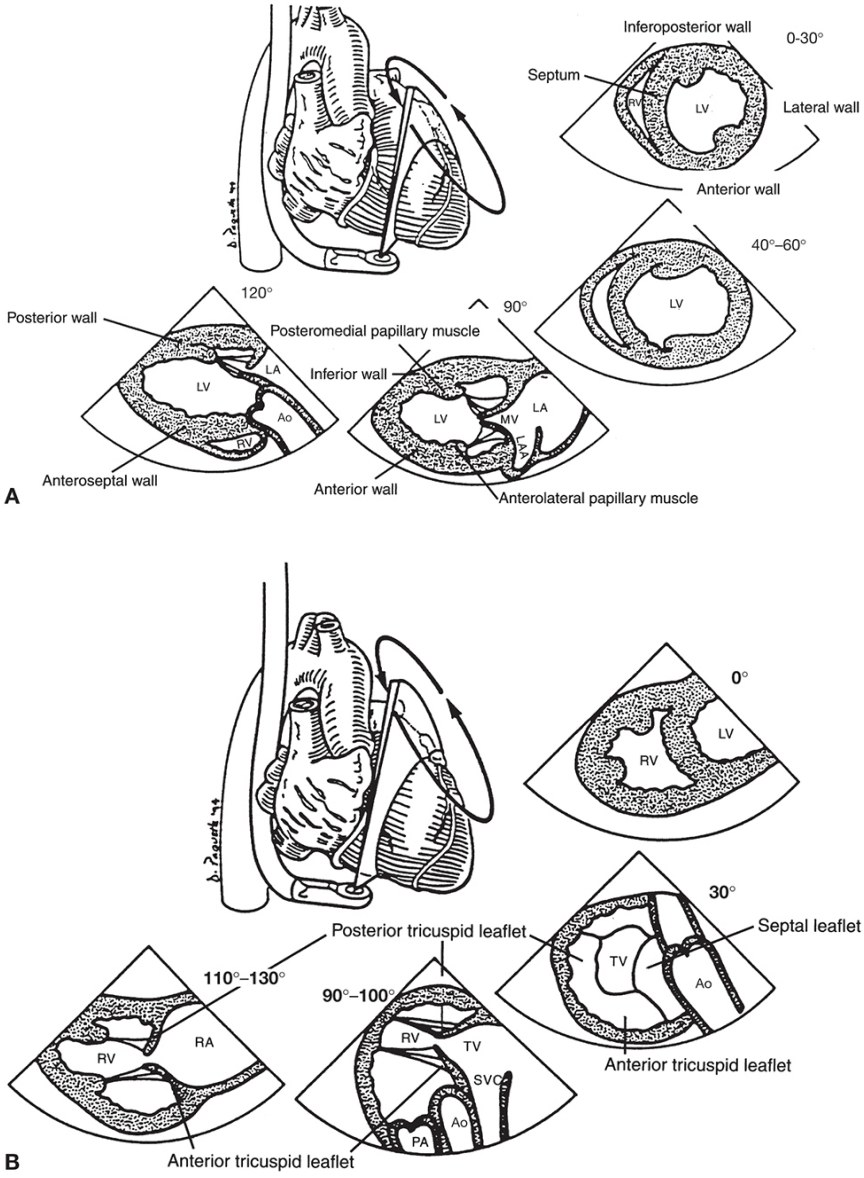

FIGURE 67.5 **A.** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the left heart from the proximal transgastric location. **B.** Schematic images from a transgastric, multiplane sweep through the right ventricle. Ao, aorta; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; RA, right atrium; RV, right ventricle; SVC, superior vena cava; TV, tricuspid valve. (Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. Churchill Livingstone; 1996:15-68. Copyright © 1996 Elsevier. With permission.)

At 80° to 100°, a two-chamber view of the left atrium (with appendage) and left ventricle (anterior and inferior walls of the left ventricle, mitral leaflets, and papillary muscles) will be obtained. At ≥120°, a long-axis outflow tract view with aortic valve and ascending aorta will be visualized. The anteroseptal and posterior walls of the left ventricle are seen. Depending on the alignment with the transducer, this view may be useful in obtaining velocities across the aortic valve.

Bringing the array back to 0° and rotating the shaft of the endoscope to center the right ventricle in view will allow for interrogation of the right-sided structures (**Figure 67.5B**). At 30° to 60°, the three leaflets of the tricuspid valve are visualized (anterior leaflet at the bottom, posterior leaflet on the top, and septal leaflet to the right). At around 70° to 80°, the right ventricular inflow tract view (SVC and tricuspid valve with anterior and posterior leaflets) is obtained. At 90° to 100°, the right ventricular outflow tract and pulmonary valve become visible as well. At 110° to 130°, the two-chamber view of the right ventricle and right atrium can be seen. By rotating to 130° to 150°, the papillary muscles and chordae supporting the tricuspid valve are further delineated.

b. Deep transgastric. The probe is advanced further into the stomach with the tip anteflexed. At 0°, a foreshortened five-chamber view is obtained. This view allows for Doppler interrogation of the aortic valve and LVOT. By rotating the multiplane array, different segments of the left ventricle apex can be visualized in the search for thrombus or aneurysm.

D. Aorta. Counterclockwise rotation of the endoscope brings the aorta into view. Typically, the probe is advanced beyond the diaphragm and then slowly pulled back, following the aorta back to the arch. Rotation of the probe is required to keep the aorta in view in the center of the screen. At the level of the diaphragm, the aorta is posterior to the esophagus. In the mid-esophagus, the aorta is medial, whereas the ascending aorta and arch lie anterior to the esophagus. At 0°, the aorta is seen as a circular structure. Long-axis images (at

100°-130°) provide additional information as needed at selected intervals. At the arch, the aorta is curved in front of the esophagus, presenting a sausage-shaped structure with the probe at 0°. Gentle clockwise rotation will follow the arch back to the ascending aorta. The ascending aorta is visualized in the longitudinal planes as discussed with the other views. The distal ascending aorta may be difficult to image fully, given the interposition of the trachea between the esophagus and the aorta in this region, and the greater the likelihood of encountering a gag reflex, the closer the probe to the pharyngoesophageal junction.

E. 3D probe. The current 3D TEE probes use fully sampled matrix array transducers, allowing a pyramidal volume of data to be acquired. Besides standard 2D imaging modalities, this transducer is able to perform 3D imaging in several modes: live X-plane imaging, live 3D echo, live 3D zoom, triggered full volume, triggered 3D color, and multiplanar reconstruction (MPR). Real-time X-plane imaging allows simultaneous biplane imaging from the same heartbeat. Live 3D mode displays real-time 3D images with a small pyramidal segment; 3D zoom mode displays the region of interest with a larger pyramidal segment in real time. Full-volume mode acquires a wider segment over several cardiac cycles, and color Doppler can also be added in this mode. MPR is a mode whereby simultaneous live X-plane imaging is shown along with a live 3D display. The 3D TEE is useful in the evaluation of native valves, prosthetic valves, interatrial septum, and left atrial appendage, as well as in the guidance of percutaneous interventional procedures, such as mitral valve repair, mitral or aortic valve implantation, closure of atrial septal defect, paraprosthetic leaks, and left atrial appendage. The assessment of specific cardiac structures in 3D does not follow an exact set of rules, but rather standard views are adapted to assess the individual structure or to demonstrate the specific pathology. The assessment of the mitral valve is ideally performed in live MPR, or 3D zoom (not full volume) from the mid-esophageal 90° (two-chamber view) and 120° (long-axis view). Once acquired, the image volume should first be rotated 90° counterclockwise around the *x*-axis, which results in en

face view of the mitral valve, followed by a 90° counterclockwise rotation in the *z*-plane, which results in the conventional display of the aortic valve superiorly on the screen, regardless of whether it is viewed from the left atrium (surgeon's view) or the left ventricle. From this view, detailed assessment of the mitral valve anatomy can be made as well as measurements such as the valve area, annular dimensions, and leaflet length. Color Doppler can be used in these 3D views, allowing for assessment of complex regurgitant jets and for 3D proximal isovelocity surface area (PISA) measurements. The tricuspid valve could be imaged from either the 0° mid-esophageal view, the 60° mid-esophageal view, or the 40° transgastric (with anteflexion) views. Off-axis four-chamber views would result in two adequately centered orthogonal images for live MPR or 3D zoom acquisition (not full volume). Occasionally, a distal esophageal view can give clear images of the tricuspid valve as the right heart border is near to the diaphragm. The tricuspid valve should be displayed in superior orientation to the interatrial septum or interventricular septum, regardless of whether the valve is viewed from the right atrium or the right ventricle. Thus, the image volume should first be rotated 90° counterclockwise around the *x*-axis to allow en face view of the tricuspid valve from the right atrium, followed by a 45° rotation in the *z*-plane to allow the septal leaflet to appear inferiorly at 6 o'clock. This allows for standardized assessment of the anatomy, given the large variability in the individual tricuspid valve leaflet anatomy. The aortic valve should be imaged from the mid-esophageal view, either in short axis (60°) or long axis (120°), using live MPR, 3D zoom, or full volume. The imaged aortic valve should be rotated (usually, 90° clockwise around the *y*-axis), in order to be displayed with the right coronary cusp oriented inferiorly (6 o'clock position), independent of whether it is viewed from the aorta or the LVOT. Live MPR allows for the correct alignment of imaging planes to calculate aortic annular and valve area measurements. Images of the pulmonic valve should be acquired either from the 90° high-esophageal view (3D zoom) or from the 120° mid-esophageal view (3D zoom also). The image volume should be rotated 90° counterclockwise around the *x*-axis, which results in en face view of the pulmonary valve. The

image should then be conventionally rotated 180° in the *z*-plane so that the anterior cusp is oriented superiorly (12 o'clock position), regardless of whether the valve is viewed from the pulmonary artery or the right ventricular outflow tract. Images of left and right ventricles should be performed individually by using full-volume acquisitions, from 0° to 120° mid-esophageal views with the index ventricle in the center of the screen. By convention, the left ventricular apex is oriented superiorly (12 o'clock), and right-sided structures are displayed on the left-hand side. The right ventricle is displayed with the left atrium oriented superiorly (12 o'clock position). The interatrial septum should be acquired at 0° while in 3D zoom or full volume. When viewed from the right atrium, the interatrial septum should be displayed with the SVC oriented superiorly (11 o'clock position), whereas if viewed from the left atrium, the right upper pulmonary vein should be oriented superiorly at the 1 o'clock position. The left atrial appendage should be imaged from the left atrium and displayed en face with the pulmonary veins oriented superiorly and longitudinally. 3D echo has the potential to acquire quantitative data on valve area (aortic and mitral valve stenosis) and on the size of the LVOT and aortic annulus, which may be important in aortic valve procedures such as transcatheter aortic valve replacement (TAVR) where accurate prosthesis size selection is vital.

III. PATIENT RECOVERY. The patient's NPO status should be maintained until the gag reflex has returned. The patient should be instructed to avoid oral intake for at least 1 to 2 hours after the test. When the patient commences oral intake, they should initially take a small sip of cold water. If the water does not feel cold in the back of the throat, then some topical anesthetic effect is still present. The patient should wait for another half an hour and test the throat again. Until this has dissipated, the patient should avoid any hot drinks to avoid scalding. Appropriate precautions should be followed if sedatives were used, because the effects persist for several hours. Patients may have dizziness and orthostatic symptoms for up to several hours and should be instructed to sit or lie down if this occurs. Patients should not drive or operate heavy

equipment until the next day. If the **esophageal intubation is traumatic** or there is evidence of significant blood staining of the saliva at the end of the TEE procedure, fluid should be withheld pending a full evaluation of the pharynx and neck seeking evidence of injury or of subcutaneous emphysema in the neck region, which may suggest esophageal perforation. A low threshold for referral for cervical neck x-ray to detect air in the mediastinum is indicated in this situation. Any concern about potential esophageal or pharyngeal perforation should lead to an immediate surgical consultation.

IX. PROBE CARE. Following use, the nonimmersible parts of the probe, such as the handle and rotary controls, should be cleaned with a bactericidal solution. The probe should be cleaned with soap, and water first, followed by the application of a proteolytic enzymatic detergent for at least 1 minute. It should then be rinsed for approximately 1 minute and then leak tested by connecting the probe to a vendor-dependent ultrasound transducer leakage tester. Afterward, the probe should be soaked for at least 12 minutes in a ready-to-use high-level disinfecting solution (glutaraldehyde free), with a fast onset of action, long-lasting efficacy, and minimal vapor pressure to avoid inhalation exposure risk (ie, *ortho*-phthalaldehyde). The probe should not be soaked in this solution overnight. Rinsing should then take place for at least 3 minutes to minimize the risk of allergic reaction, as well as mucosal, and skin or clothes staining. It should then be dried with a lint-free absorbent tray liner. Date of probe cleaning should be documented, and repeated weekly to avoid bacterial overgrowth.

X. COMPLICATIONS. In a reported series, the incidence of major and minor complications is 2% to 3%, with most being minor complications. Major complications (death, esophageal perforation, significant arrhythmias, congestive heart failure, and aspiration) occur with a frequency of 0.3%, with a reported mortality of <0.01%. Reported minor complications include transient hypotension, hypertension (particularly with agitation), transient hypoxia, transient bronchospasm, and arrhythmias (such as supraventricular tachycardia, nonsustained ventricular tachycardia, and transient atrioventricular block). Methemoglobinemia has been rarely

reported because of the anesthetic spray and should be considered if cyanosis occurs. Other complications of intubation include tracheal intubation, laryngospasm, and vocal cord paralysis. Sore throat is not uncommon after the procedure and may persist for a day. Anaphylaxis and other allergic reactions can occur because of the medications used.

XI. PITFALLS. The improved resolution and anatomic detail provided by TEE, as compared with TTE, is what makes it such a powerful diagnostic tool. However, this can also lead to misinterpretation of normal structures. Trabeculations in the atrial appendage can be mistaken for thrombi, and lipomatous hypertrophy of the interatrial septum can be incorrectly labeled as a mass, as can the eustachian valve. The transverse and oblique sinuses can be mistaken for abscess cavities. Off-axis images may create the appearance of a mass on the aortic valve when one of the cusps is cut obliquely. The lungs can give rise to reverberation artifacts, which can erroneously be diagnosed as dissection flaps (presence in nonanatomic planes, lack of disruption of color Doppler of blood flow, and crossing of normal anatomy all favor the diagnosis of artifact). Abnormal findings should be visualized and verified in several views to ensure that they do not represent imaging artifacts.

These pitfalls are best minimized by the experience of the operator, but variations in anatomy may provide diagnostic dilemmas for even the most skilled echocardiographer.

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CHAPTER 68

Pericardiocentesis

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I. INTRODUCTION. Pericardiocentesis is an important therapeutic and diagnostic procedure in cardiology. The most common indications are to relieve tamponade and to identify causes of pericardial effusions. When performed correctly by experienced operators, pericardiocentesis has proven to be an effective and safe procedure.

II. INDICATIONS. To date, the best formal guidance on pericardiocentesis comes from the 2015 European Society of Cardiology Guidelines. Most of these recommendations are level of evidence C, as they are based on case reports, retrospective series, and expert opinion. From a broad perspective, they recommend considering pericardiocentesis in patients with pericardial effusion who become symptomatic from the effusion, in patients with pericardial effusions measuring more than 20 mm, in patients with chronic (>3 months) pericardial effusions, or those in whom the effusion progresses despite empiric treatment with nonsteroidal anti-inflammatory drugs. This chapter aims to provide basic approaches to different clinical scenarios based on common indications for pericardiocentesis and review best practice techniques for performing the procedure safely and effectively.

A. Alleviation of cardiac tamponade. Cardiac tamponade is a clinical diagnosis characterized by hypotension, tachycardia, distended neck veins, pulsus paradoxus, and distant heart sounds. Functionally, it is a form of obstructive shock resulting from the accumulation of fluid in the pericardial cavity, causing increasing pericardial pressure and thus requiring increasing ventricular filling pressures (phase 1). This leads to ventricular interdependence due to the fixed space of the pericardium and can progress until pericardial pressure begins to

exceed ventricular pressure, decreasing cardiac output (phase 2), and, if left untreated, can cause further hemodynamic compromise until equilibration of left ventricular and pericardial pressures resulting in rapid clinical deterioration (phase 3).

1. Echocardiographic evaluation provides confirmatory evidence demonstrating the presence of pericardial effusion (regional or circumferential), inferior vena cava plethora, diastolic collapse of the right atrium and right ventricle, and increased respiratory variation of blood flow through the tricuspid and mitral valves. The normal pericardial cavity typically contains 15 to 50 mL of fluid. **The additional volume of fluid required to cause hemodynamic compromise is variable** and is dependent upon several factors, including the patient's volume status, the rapidity of fluid accumulation, and intrathoracic pressure (positive pressure ventilation increases intrathoracic pressure and may impair venous return to the left atrium, potentially further compromising left ventricular preload). Therefore, a relatively small but rapidly accumulating effusion can cause tamponade, particularly in the intravascularly depleted patient or in intubated subjects receiving positive pressure ventilation.

B. Evaluation of, and therapy for, pericardial effusion

1. **Idiopathic.** In patients presenting with large, idiopathic effusions, evaluation of pericardial fluid with cytology, culture, cell counts, and chemistries frequently assists in diagnosis. The cause of most effusions can be diagnosed with history, physical examination, laboratory evaluation, and pericardial fluid analysis. Fluid analysis has been shown to be more helpful than pericardial tissue biopsy for culture of viral and bacterial pathogens, and cytology is positive in 65% to 85% of cases of malignant effusion. It is recommended that large pericardial effusions (>20 mm) be drained if the effusion persists for more than 1 to 3 months because **up to one-third** of patients with large idiopathic pericardial effusions develop cardiac tamponade unexpectedly.
2. **Malignant.** Malignant pericardial effusions are a rare manifestation of metastatic disease; however, fluid cytology can

be of value if the primary tumor is unknown. The most common neoplasms associated with malignant pericardial effusion include those of lung, breast, and hematologic malignancy. Controversy exists regarding the most appropriate management of malignant effusions. There are no prospective, definitive studies comparing surgical management with pericardial window and pericardiocentesis, but surgery is commonly used because of the risk of reaccumulation. Large malignant effusions treated with simple pericardiocentesis without prolonged catheter drainage reaccumulate in as many as 60% of cases. However, several studies have indicated that when a pericardial drain is left in place for several days until drainage is <25 mL/d (average 4.8 days), the risk of reaccumulation decreases to about 12%. Sclerotherapy has a similar failure rate. Surgical treatment with pericardial window is usually effective in decreasing the risk of reaccumulation, but it carries a 30-day mortality of approximately 8%. Therefore, pericardiocentesis with drain placement is a very reasonable initial procedure for the diagnosis and management of malignant effusions; **moreover, if a patient has a large pericardial effusion, temporizing drainage may be performed to facilitate a safer induction of general anesthesia in prelude to a pericardial window**.

3. **After open-heart surgery.** Effusions after open-heart surgery are common, but they rarely lead to hemodynamic impairment. Data from the Mayo Clinic suggest that the incidence of significant effusion in patients aged 18 years or above up to 30 days after cardiac surgery with cardiopulmonary bypass is 1.5%. The risk of effusion is highest in patients after heart transplant and lowest in patients post–coronary artery bypass grafting. Renal failure, immunosuppression, pulmonary thromboembolism, prolonged cardiopulmonary bypass, and high body surface area are all independent risk factors for significant effusion. The role of anticoagulation in effusion formation is less clear, but it has been proposed to be an additional risk factor. Given these factors, a thoughtful discussion with surgical colleagues should occur prior

to proceeding with pericardiocentesis in the recent postoperative setting.

III. CONTRAINDICATIONS

A. Absolute. In emergent scenarios of cardiac tamponade, when circulatory collapse is imminent, there are no absolute contraindications. In these instances, pericardiocentesis is often a life-saving intervention.

B. Relative

1. **Anticoagulation.** The risk of bleeding is low with pericardiocentesis; however, if time permits, prothrombin time and partial thromboplastin time (PTT) should be obtained in all patients undergoing pericardiocentesis. An international normalized ratio >1.8 or PTT greater than twice the normal should be corrected with fresh frozen plasma before intervention. It should also be noted that **tamponade physiology, by leading to hepatic congestion, may produce or exacerbate coagulation abnormalities**. Of note, if the patient is coagulopathic, the subxiphoid approach may be less desirable as perforation of the hepatic vessels could lead to life-threatening bleeding.
2. **Thrombocytopenia.** Platelet counts should be >50,000 in nonemergency cases.
3. **Traumatic hemopericardium.** A patient with traumatic hemopericardium should be treated surgically.
4. **Type A aortic dissection.** Typically, hemorrhagic effusions secondary to type A dissections are treated emergently with surgery. However, in situations where tamponade and circulatory collapse are imminent, small-volume pericardiocentesis, with removal of the minimal amount of fluid necessary to maintain hemodynamic stability (typically 10-25 mL) is indicated to temporize patients before surgery. Data suggest that larger volume removal in these cases may be detrimental.
5. **Subacute free wall rupture.** As with dissections, free wall ruptures are best addressed surgically. However, as in pericardial effusions caused by type A dissection, draining a small volume of

fluid may be necessary to stabilize patients in preparation for operative repair of the free wall rupture.

6. **Small, loculated, or posteriorly located effusions** are technically more difficult to tap and have an increased risk of complication. Echocardiographic guidance is paramount if pericardiocentesis is attempted, and in some cases, echocardiography combined with fluoroscopy might be necessary. Another possibility is to use a computed tomography–guided approach with the help of interventional radiology.
7. **Purulent effusions.** Whereas suspected purulent or tuberculous effusions are considered an indication for pericardiocentesis, grossly infected pericardial fluid should be managed surgically. Again, in these cases, pericardiocentesis can be used to hemodynamically stabilize patients while awaiting definitive surgical management. If fluid is obtained, a way to differentiate purulent from tuberculous effusions is by measuring glucose and white cell count. In purulent effusions, there is a low glucose ratio (mean of ~0.3) and high white cell count (mean of 2.8/mL) with neutrophilic predominance (mean of 92%). On the contrary, a tuberculous effusion has a higher glucose ratio (mean of 0.7) and a lower white cell count (mean of 1.7/mL) with less neutrophilic shift (mean of 50%). In neoplastic effusions, the glucose ratio is even higher (~0.8), with an average white cell count of about 3.3/mL and 55% neutrophils.
8. **Recurrent malignant effusion.** As stated previously, the management of malignant effusions is controversial. Although pericardiocentesis is an effective and proven first-line therapy, recurrent effusions should be considered for pericardial window. The European Guidelines for pericardial disease recommend pericardiocentesis in the absence of tamponade in large effusions based on a recurrence rate of 40% to 70%. They also recommend considering intrapericardial instillation of cytostatic/sclerosing agents in addition to the treatment of the primary tumor, in order to prevent recurrences. However, this approach should be tailored

to each type of tumor and has not been validated in prospective trials.

IV. PERICARDIOCENTESIS VERSUS SURGICAL MANAGEMENT. The preferred procedural approach for pericardial drainage varies depending on the underlying etiology of the effusion, chronicity, size, hemodynamic impact, and suspected recurrence rate (**Table 68.1**).

TABLE 68.1 Approach to Pericardial Drainage

Pericardiocentesis
Most cases of cardiac tamponade
Large or symptomatic effusions refractory to medical treatment
High suspicion of tuberculous, purulent, or neoplastic pericarditis
Surgical Management
Cardiac tamponade because of aortic dissection or cardiac trauma; recurrent tamponade
Recurrence of large chronic effusions after failed pericardiocentesis
Purulent effusion
Loculated effusion
Need for pericardial biopsy
Coagulopathy

V. PATIENT PREPARATION. Ideally, pericardiocentesis is performed in a laboratory equipped for fluoroscopy and invasive hemodynamic monitoring. Ultrasound confirmation and guidance (either indirect to guide trajectory immediately before accessing the collection or real-time guidance) is now typically recommended, given the wide availability and ease of use at most institutions, and should be a routine part of patient preparation.

A. Informed consent. Patients should receive a clear explanation of the risks and benefits of pericardiocentesis, including the rationale for performing the procedure.

B. Monitoring. Patients should have heart rate, blood pressure, and oxygen saturations measured throughout the procedure. In addition, electrocardiographic monitoring is necessary. Worsening hemodynamics or falling oxygenation should alert the operator to the possibility of a procedural complication. Frequent ectopy (premature ventricular contractions, premature atrial contractions [PACs], or nonsustained ventricular tachycardia) may result from irritation of the myocardium, indicating impending perforation of a cardiac chamber.

C. Sedation. Pericardiocentesis is an anxiety-producing procedure for the patient. Appropriate pain relief and sedation should be administered prophylactically when this is clinically indicated, keeping in mind its potential impact on a patient with an already tenuous hemodynamic or respiratory state.

D. Intubation. The decision to intubate a patient with tamponade is challenging and controversial, and it is usually reserved for patients who develop severe respiratory insufficiency; if possible, it is best avoided as it may worsen and accelerate hemodynamic deterioration.

VI. TECHNIQUES

A. Echo guidance. Currently, ultrasound-guided pericardiocentesis is the standard approach at most institutions. It is feasible in over 95% of patients with pericardial effusions, especially when anterior or large. Patients are placed supine or in a slightly left lateral decubitus position. Echo guidance allows the selection of the most appropriate window to access the effusion and to ascertain the depth to which the needle should be inserted to obtain pericardial fluid.

1. Identifying the best window. The head is elevated approximately 30°, and a complete echocardiographic evaluation is performed with standard parasternal, apical, and subcostal views. In addition to these, it may also be necessary to obtain off-axis views with the purpose of identifying where the pericardial fluid is nearest and most accessible to the skin without any interposing structure. In general, there are three different approaches, apical, subcostal, and parasternal, with the first two being the most commonly used.

a. The subcostal approach has the lowest risk of causing pneumothorax, but the greatest risk of injuring the liver, or gastrointestinal tract, especially in patients who are obese. Moreover, the distance from the skin to the effusion is often the longest with the subcostal approach.

b. The apical approach has the lowest risk of injury to major vascular structures (coronary arteries or internal thoracic artery) but has the highest risk of injuring the left ventricle or triggering ventricular arrhythmias. It has an intermediate risk of pneumothorax.

c. The parasternal approach has the advantage of a small distance between the thoracic wall and the pericardium but has a higher risk of causing pneumothorax or puncture of an internal thoracic artery.

These three approaches are summarized in **Table 68.2**. The apical approach is most commonly used, followed by the subcostal, with the remaining performed in off-axis views. When planning an apical approach, it is useful to obtain extreme apical views, with displacement of the probe laterally and posteriorly, close to the midaxillary or posterior axillary line, and if needed with inferior displacement of the probe until the largest pocket of fluid with the greatest distance to the myocardium is identified. When planning a subcostal approach, the liver should be identified to avoid accidental laceration during the procedure. See Section VI.B for appropriate positioning for subxiphoid approach. Because it is air filled, lung tissue will block ultrasound waves and preclude imaging of the heart; consequently, the risk of pneumothorax is low if a good echocardiographic window is selected for the tap. While imaging, it is imperative to take note of the **distance to the fluid pocket** as well as **the probe trajectory**. Failure to maintain an appropriate trajectory is a common cause of failure in accessing a pericardial effusion percutaneously. Because real-time imaging of the needle tip accessing the pericardial fluid is not always possible, it is of vital importance to maintain

the trajectory of the needle during the pericardiocentesis identical to the trajectory of the echocardiographic probe when imaging.

TABLE 68.2 Advantages and Disadvantage of Different Access Sites in Performing Pericardiocentesis

Approach	Technical Details	Advantages	Disadvantages
Apical	• Find the largest fluid pocket closest to the skin. • Trajectory of the needle should be same as that of echo probe. • Use with echo guidance.	• Less possibility of injuring adjacent organs or vascular structures • Easiest to perform	• Higher risk of injuring the left ventricle wall with higher risk of ventricular fibrillation • Inappropriate for emergency situations where blind approach is the only option
Subcostal	• Place the needle in the subcostal space at a 45° angle relative to the transverse plane and direct it toward left shoulder. • Blind, echo-guided, or fluoroscopic approach	• Less risk of pleural puncture or pneumothorax • It is the safest approach in emergent situation, when ultrasound is not available.	• Higher risk of injuring the right coronary artery • If the right ventricle wall is injured, it is less likely to seal off leading to surgical intervention. • Higher risk of liver or colon injury
Parasternal	• The needle is inserted proximal to the sternum, close to the fifth left intercostal space. • Preferred approach is	• Less likelihood of puncturing the pleura or the lung than apical approach	• Higher risk of injury of the internal thoracic artery • Higher risk of pneumothorax than subcostal approach

Approach	Technical Details	Advantages	Disadvantages
	echo guided.		

d. **Prepping the patient.** Once the best window is selected, the probe's location is marked with a permanent marker and scrubbed with sterile chlorhexidine-alcohol or povidone-iodine solution. The entire torso is draped with sterile towels or a full-body sterile field if available. The patient should not move between the echocardiographic examination and the procedure.

e. **Echo probe.** We use a sterile sleeve over the echo probe so that the operator hold it on hand when performing the pericardiocentesis.

f. **Needle selection.** In previous descriptions of this technique, an 18-gauge Cook needle or sheathed catheter was typically used. In contemporary settings, our institution now routinely utilizes micropuncture needles (most commonly a 21-gauge needle with a 0.018-in wire), which are then used to deliver a 4-F micropuncture catheter prior to further upsizing. See further description below.

g. **Anesthetic.** Local anesthetic (eg, 1% lidocaine) is applied to the skin over the mark. Then deeper anesthetic is given over the superior aspect of the rib (if a chest wall approach is used). Occasionally, in a relatively superficial pericardial effusion, the pericardial space will be entered with the anesthetic needle, and pericardial fluid may be aspirated. Care should be taken when using an apical or intercostal approach to avoid damaging the neurovascular bundle at the lower rim of the rib at the superior aspect of the rib space.

h. **Entering the pericardium.** As above, outside emergent situations (and even sometimes in emergencies), a micropuncture kit with a 21-gauge needle on a syringe is advanced through the anesthetized tract while maintaining negative pressure in the syringe. We most commonly utilize asynchronous guidance with a clear demonstration of a safe trajectory via the phased-array sonographic probe and then

recapitulate that same trajectory without real-time guidance. In select circumstances (particularly when the fluid collection is relatively thin anteriorly without much clearance from underlying cardiac structures), we utilize live guidance with a linear sonographic probe to visualize the delivery of the 21-gauge needle into the pericardial space. Lastly, while during emergent situations an 18-gauge Cook needle can be utilized as an alternative, this comes with an increased risk of injury to the heart and surrounding structures and should be reserved for select circumstances with an experienced operator.

i. **Confirmation of position and catheter insertion.** When using a micropuncture kit, upon aspiration of the fluid, the micropuncture wire (typically a 0.018-in guidewire) is threaded through the needle while monitoring for atrial or ventricular arrhythmia. Although ideally wire would be demonstrated in the pericardium on imaging, ultrasonographic visualization of this thin wire may be challenging. If no arrhythmia is noted, the needle is exchanged for the 4-F micropuncture catheter; of note, although many kits are available, it is important to select a sheath with relative rigidity as a preclusively soft catheter may be difficult to deliver through the chest wall. Of note, return of serous or serosanguinous fluid during aspiration does not necessarily confirm access to the pericardial space, because pleural and peritoneal collections may be traversed during pericardiocentesis. Visualization of a more echogenic guidewire (most often the 0.035-in J-tipped wire, which will be used to deliver the larger drainage catheter) in the pericardial space is typically possible. If the position is not clear, the micropuncture catheter may be readvanced over this guidewire to facilitate injection of agitated saline contrast while performing simultaneous echocardiography. **The appearance of bubbles in the pericardial space confirms an appropriate location**. Bubbles appearing within a cardiac chamber suggest that the heart has been perforated and that the needle or catheter should be withdrawn. If agitated saline cannot be

visualized, one should reconsider the needle/catheter position. If the effusion is large, the contrast may not be visible from all echocardiographic windows; occasionally, it may be necessary to reinject saline and image from an alternative location. Once the location is confirmed, the pericardial drain catheter can be placed as below.

j. **Placing the pericardial catheter.** Once the intrapericardial position is confirmed and the 4-F microcatheter is placed, a floppy-tipped, 0.035-in guidewire is inserted into the pericardial space. The 4-F catheter is removed and a scalpel blade is then used to nick the skin, a 6F dilator is used to broaden the tract into the pericardium, and, finally, the dilator is removed and a 6F to 8F pericardial drainage catheter is threaded over the wire well into the pericardial space, ensuring at all times that the end of the wire is controlled. The wire is removed, and catheter placement can again be confirmed with agitated saline injection if needed. With a three-way stopcock, fluid for laboratory analysis should be collected with a large syringe upon initial drainage; the catheter is then attached to a 30-cm length of plastic tubing, which, in turn, may be connected to a vacuum bottle or drainage bag. If the catheter is being left to drain for some time, it should be sutured in place.

k. **Bloody pericardial fluid or frank blood aspirated?** Occasionally, very bloody fluid may be aspirated during pericardiocentesis, and confirmation of the needle placement may be difficult. Therefore, differentiating between blood (chamber perforation) and bloody effusion can be challenging. If needle position based on the above techniques is still in doubt, a few milliliters of the aspirate can be placed on a gauze pad; classic teaching suggests that if the fluid coagulates, it is blood from chamber perforation. Conversely, fluid that spreads out on the gauze forming a pinkish halo suggests an intrapericardial origin. In reality, effusions caused by cardiac rupture, dissection, or ongoing bleeding into the pericardial space may clot upon aspiration; this fluid should be sent for

hematocrit (to confirm that it is blood), and cardiothoracic surgery consultation should take place emergently.

2. **Electrocardiographic guidance via subxiphoid approach.** Electrocardiography (ECG)-guided pericardiocentesis is an alternative approach in which ECG monitoring is performed as the needle is advanced, while carefully watching for the presence of current of injury that would suggest the myocardium has been reached. This approach may be used if echocardiography is unavailable, or it may be used in conjunction with echocardiography. However, most experts agree that electrocardiographic guidance adds little to the safety of a carefully performed echocardiographically guided procedure. If ECG guidance is used instead of echocardiography, a subxiphoid approach is typically preferred.
    1. The patient is positioned at a 45° incline. Electrocardiographic limb leads are attached to the patient in the usual manner.
    2. The xiphoid process is identified, and a point just inferior and to one side of the process is marked. The region is prepared and draped sterilely, and local anesthetic is given around the mark with a 25-gauge needle. A 21-gauge steel spinal needle is attached to a syringe filled with local anesthetic. The needle should be approximately 10 cm long. With a sterile alligator clip, the V lead of the ECG monitor is attached to the metal hub of the spinal needle.
    3. The needle should be directed posteriorly at approximately 90° to the patient until the tip is below the costal margin. Then the hub of the needle should be depressed toward the patient's skin and advanced toward the left shoulder at an angle of 15° to 30° to the patient. Local anesthetic is injected as needed, and gentle suction should be applied to the syringe when advancing.
    4. ST elevations or premature ventricular contractions on the ECG monitor indicate that the needle is encountering the right ventricle. PR-segment elevation or frequent PACs indicate that the needle is penetrating the right atrium. In the average adult,

the distance from skin to pericardium is approximately 6 to 8 cm.

5. Once in the pericardial space, a catheter may be placed as described previously.

3. **Fluoroscopic guidance.** Fluoroscopy was previously the most common method used as to guide pericardiocentesis, but this approach has largely been supplanted by echocardiography. With fluoroscopy, a subxiphoid approach is also used. Patient positioning and anatomic approach is the same as described above for ECG guidance. For this approach, either a polytef-sheathed needle with an attached saline-filled syringe or a Tuohy-17, blunt-tip introducer needle can be used. The needle is directed to the left shoulder and toward the anterior diaphragmatic border of the right ventricle, at about 30° angle to the skin. The purpose is to avoid the coronary, pericardial, and internal mammary arteries with this direction and angulation. Upon penetration into the pericardial space, needle position may be confirmed with injection of radiopaque contrast media. The left lateral with a slight left anterior angiographic view, or an anteroposterior view, provides the best visualization of the puncturing needle in relation to the diaphragm and the pericardium. As the needle is advanced, the operator should perform moderate suction, and once fluid is obtained, it is advised to inject very small amounts of contrast until the pericardial silhouette is demarcated on the fluoroscope, a phenomenon known as the “halo sign.” Once the wire is advanced over the needle, it should be imaged to verify that it is in the intrapericardial space and not in a cardiac chamber. The soft J-tipped wire may be confirmed to be in the pericardium by identifying how it crosses from the right to the left chambers, because a wire in the right ventricle would not cross to the left side unless a ventricular septal defect is present. A drainage catheter may then be placed as described earlier.

4. **Blind approach.** In emergent conditions, blind pericardiocentesis may be necessary. A subxiphoid approach is used as described above, aiming the needle toward the left shoulder. However,

because of the significantly higher rates of complications and because of the increased availability of bedside ultrasound, blind taps should be avoided unless absolutely necessary.

B. DIAGNOSTIC STUDIES. If the cause of the pericardial effusion is not clear, the fluid should be sent for analysis. The primary causes of idiopathic effusions depend somewhat on the patient population but include tuberculosis (TB), viral infection, uremia, collagen vascular disease, neoplasia, surgery, and myocardial infarction. Therefore, all fluid from idiopathic effusions should be sent for bacterial and mycobacterial cultures, viral analysis, and cytologic examination; acid-fast bacillus smear; cell count; protein; glucose; and lactate dehydrogenase. If TB is suspected, evaluate for adenosine deaminase, interferon-gamma, pericardial lysozyme, and polymerase chain reaction. If malignancy is suspected, tumor markers including carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 72-4, and CA 19-9 may be sent for evaluation. Blood samples should be sent for chemistry, complete blood count, blood cultures (if bacterial infection is likely), thyroid-stimulating hormone, erythrocyte sedimentation rate/C-reactive protein, antinuclear antibody, and rheumatoid factor (if connective tissue disease is suspected). Consideration should also be given to conducting a tuberculin-purified protein derivative skin test.

C. COMPLICATIONS. Using echocardiographic guidance, the rate of complications is low. The largest series of echo-guided pericardiocenteses comes from the Mayo Clinic. Among the 1,127 procedures studied, major complications occurred in 1.2% of cases, and these included one death from right ventricular perforation, five nonfatal perforations that required surgery, one intercostal artery laceration, five pneumothoraces that required intervention, one episode of sustained ventricular tachycardia, and one episode of bacteremia. Minor complications occurred 3.5% of the time and included 11 chamber perforations that sealed spontaneously, 8 self-limited pneumothoraces, 9 pleuropericardial fistulas, and 2 episodes of nonsustained ventricular tachycardia.

Fluoroscopy appears to be associated with higher rates of complications. In one series of 352 procedures, complications included 2 (0.6%) deaths, 23 (5.6%) chamber perforations (3 requiring surgery), 5 (1.4%) arterial bleeds (3 diaphragmatic, 1 posterior descending artery, and 1 left internal mammary artery), and 2 pneumothoraces.

Blind pericardiocentesis has been associated with morbidity rates as high as 20% and mortality rates as high as 6%.

It is important to note that the above studies on safety largely do not routinely utilize micropuncture kit use, and thus, actual rates may be different with increasing adoption.

In general, complications are relatively rare in experienced centers, although one must be mindful of the following:

A. Pneumothorax. This is usually effectively avoided with echocardiographic imaging. If the parasternal approach is used, remaining close to the sternum decreases the risk of pneumothorax.

B. Myocardial perforation and chamber entry. This is usually asymptomatic and self-sealing, particularly if the left ventricle is entered. Right ventricular perforations have a somewhat higher likelihood of bleeding when perforated, but right atrial lacerations carry the highest risk. If laceration is suspected, the needle or catheter should be withdrawn, and the patient should be observed overnight in an intensive care setting. Serial echocardiograms are indicated to assess for changes in effusion size.

C. Arterial laceration. The left internal thoracic/mammary artery runs down the chest wall about 1 to 2 cm lateral to the sternum, with the vein running slightly more medial. Left chest wall and subxiphoid approaches must take this anatomy into consideration. The posterior descending artery may be lacerated on subxiphoid approaches if the needle is aimed too medially. On a chest wall approach, the intercostal arteries and nerves are avoided by passing the catheter just superior to the rib.

D. Infection. Sterile technique during the procedure and meticulous catheter care afterward if a drain is left in place minimize this risk.

As the Mayo series suggests, the risk of catheter-related infection is very low, even among immunosuppressed patients.

E. Death. This is exceptionally rare when procedures are performed by experienced operators with echocardiographic guidance.

VII. POSTPROCEDURE CARE

A. Chest radiography. A postprocedural chest film should be obtained in all patients to exclude pneumothorax.

B. Monitoring. Patients should be observed for 1 to 2 hours following the pericardiocentesis. Patients without significant comorbidities who have uncomplicated diagnostic taps may not require inpatient care following the procedure.

C. Drain care. Care of an indwelling pericardial catheter is similar to that for a central line. After the catheter is sutured in place, the site is treated with an antibacterial ointment and then dressed sterilely. The dressing should be changed every 2 or 3 days.

1. The drain should be aspirated every 6 hours. Continuous drainage can also be used, but the risk of catheter obstruction is higher. Following aspiration, the catheter is flushed with sterile or heparinized saline.
2. If the fluid becomes purulent or the patient becomes septic, the catheter must be removed.
3. Strict record of the volume of fluid draining from the catheter must be kept. The catheter is typically left in place for 1 to 2 days, but extended drainage has been associated with lower rates of effusion recurrence. When the drainage is <25 to 50 mL/d, the catheter can be removed.

D. Follow-up echocardiography. Before pulling the drain, an echocardiogram should be obtained to ensure resolution of the effusion. Sometimes, when the drainage volume is minimal, it may be useful to clamp the catheter for few hours and observe the patient for clinical signs of tamponade. Alternatively, an echocardiogram can also be performed in order to assess for reaccumulation once the drain is clamped.

E. Patient care. Patients may be ambulatory with the drain securely in place. Pericardial pain is best managed with nonsteroidal anti-inflammatory medications.

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KEY REVIEWS

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USEFUL VIDEO

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CHAPTER 69

Commonly Used Cardiovascular Formulae

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GENERAL HEMODYNAMICS

Mean arterial pressure (mm Hg) = Diastolic blood pressure (BP) + 1/3 (Systolic BP − Diastolic BP)

Stroke volume (mL) = End-diastolic volume − End-systolic volume

Cardiac output (L/min) = Heart rate × Stroke volume

Ohm's law $V = IR$

V = Pressure difference across the system

I = Cardiac output or flow

R = Resistance across the system

Systemic vascular resistance (Wood unit) =

$$\frac{\text{Mean arterial pressure} - \text{Central venous pressure}}{\text{Cardiac output}}$$

Pulmonary vascular resistance (Wood unit) =

$$\frac{\text{Mean PA pressure} - \text{Mean PCWP}}{\text{Cardiac output}}$$

PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure;

1 Wood unit = 80 dynes/s/cm^5

Pulmonary vascular resistance (echo) (Wood unit) =

$$\left(\frac{\text{Tricuspid regurgitation velocity}}{\text{RVOT VTI}}\right) \times 10 + 0.16$$

RVOT, right ventricular outflow tract; VTI, velocity time integral

Transpulmonary gradient (mm Hg) = Mean PAP − PCWP

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure

Fick equation

Cardiac output (L/min) =

$$\frac{VO_2\ (\text{mL/min})}{1.36\ (\text{mL}\ O_2/\text{g Hgb}) \times \text{Hgb}\ (\text{g/dL}) \times 10\ (\text{dL/L}\ [SaO_2 - SVO_2])}$$

Vo_2 (oxygen consumption); Sao_2, systemic arterial oxygen saturation; Svo_2, systemic venous oxygen saturation; Hgb, hemoglobin

Cardiac index (L/min/m^2) = $\frac{\text{Cardiac output (L/min)}}{\text{Body surface area } (m^2)}$

Body surface area (m^2) = [Height (cm) + Weight (kg) − 60]/100

Dubois formula for body surface area (m^2) =

$$\sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3{,}600}}$$

Stroke work (g m/beat) = Stroke volume × Mean arterial pressure × 0.0144

Stroke work index (g-m/m^2/beat) = $\frac{\text{Stroke work}}{\text{Body surface area}}$

Coronary flow reserve =

$$\frac{\text{Peak coronary velocity at maximal hyperemia}}{\text{Peak coronary velocity at baseline}}$$

Fractional flow reserve =

$$\frac{\text{Mean distal coronary pressure beyond stenosis}}{\text{Mean aortic pressure}}$$

VALVULAR DISEASE AND LEFT VENTRICULAR FUNCTION

Gorlin equation

Aortic valve area (cm^2) =

$$\frac{\text{Cardiac output (mL/min)}}{44.3 \times \text{Systolic ejection period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$$

Mitral valve area (cm^2) =

$$\frac{\text{Cardiac output (mL/min)}}{38 \times \text{Diastolic filling period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$$

Hakki equation

Aortic valve area (cm^2) =

$$\frac{\text{Cardiac output}}{\sqrt{\text{Peak to peak gradient}}} \text{ or } \frac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$$

Mitral valve area (cm^2) = $\dfrac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$

Simplified Bernoulli equation

Pressure difference = $4v^2$

If proximal velocity >1 m/s, then pressure difference = 4 [(distal jet velocity)^2 − (proximal velocity)^2]

Continuity aortic valve area (cm^2) =

$$\text{Diameter}_{\text{LVOT}^2} \times 0.785 \times \frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{Aortic value}}}$$

LVOT, left ventricular outflow tract; VTI, velocity time integral

Dimensionless index = $$\frac{VTI_{LVOT}}{VTI_{Aortic\ value}}$$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Stroke volume (mL) =

$$Diameter_{LVOT^2} \times 0.785 \times VTI_{LVOT}$$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Aortic regurgitant fraction (%) =

$$\frac{Aortic\ regurgitant\ volume}{LVOT\ stroke\ volume} \times 100$$

LVOT, left ventricular outflow tract

Mitral valve area (mitral stenosis) (cm_2) =

$$\frac{220}{Pressure\ half\ time}$$

Tricuspid valve area (tricuspid stenosis) (cm^2) =

$$\frac{190}{Pressure\ half\ time}$$

Pressure half time (ms) = 0.29 × Deceleration time

Proximal isovelocity surface area (PISA) method in mitral regurgitation

Regurgitant orifice area (cm_2) =

$$\frac{6.28\ r^2 \times \text{Aliasing velocity}}{\text{Mitral regurgitation velocity}}$$

r, radius of PISA

Simplified PISA when aliasing velocity ~40 cm/s and peak continuous wave mitral regurgitation velocity ~5 m/s

Regurgitant orifice area (cm_2) (cm_2) = $\frac{r^2}{2}$

r, radius of PISA

Mitral regurgitant fraction (%) =

$$\frac{\text{Mitral regurgitant volume}}{\text{Mitral value flow}} \times 100$$

Fractional shortening (%) =

$$\frac{\text{LVED dimension} - \text{LVES dimension}}{\text{LVED dimension}} \times 100$$

LVED, left ventricular end diastole; LVES, left ventricular end systole

Ejection fraction (%) =

$$\frac{\text{End diastolic volume} - \text{End systolic volume}}{\text{End diastolic volume}} \times 100$$

Estimated pulmonary artery systolic pressure (mm Hg) = RA pressure + 4 × (Peak tricuspid regurgitation velocity)$_2$

RA, right atrium

Estimated pulmonary artery end-diastolic pressure (mm Hg) = RA pressure + 4 × (Pulmonary regurgitation end-diastolic velocity)$_2$

RA, right atrium

Assessment of right atrial pressure (by echo)

IVC Diameter (cm)	IVC Collapse (%)	Estimated RA Pressure (mm Hg)
≤2.1	>50	3 (range 0-5)
≤2.1	<50	8 (range 5-10)
>2.1	>50	8 (range 5-10)
>2.1	<50	15 (range 10-20)

IVC, inferior vena cava; RA, right atrial.

Left atrial (LA) pressure (mm Hg) = Systolic blood pressure − 4 × (Mitral regurgitation velocity)^2

$$\textbf{Dp/dt}\ (\%) = \frac{32{,}000\ \text{mm Hg}}{dt\ (\text{in seconds})}$$

d*t*, time it takes velocity to go from 1 to 3 m/s

Tei index (myocardial performance index) =

$$\frac{\text{Isovolumic contraction time} + \text{Isovolumic relaxation time}}{\text{Ejection time}}$$

SHUNTS

$$\textbf{Shunt fraction } (Q_p/Q_s) = \frac{(SaO_2 - SVO_2)}{(PVO_2 - PaO_2)}$$

Sao_2, systemic arterial oxygen saturation

SVo_2, systemic venous oxygen saturation

PVo_2, pulmonary venous oxygen saturation

Pao_2, pulmonary arterial oxygen saturation

$$\textbf{MVO}_2\textbf{(\%)} = \frac{3 \times (SVC_{sat} + (IVC_{sat})}{4}$$

MVO_2, mixed venous saturation

SVC, superior vena cava

IVC, inferior vena cava

Q_p/Q_s (echo) =

$$\frac{\text{RVOT Cross-sectional area} \times \text{RVOT TVI}}{\text{LVOT Cross-sectional area} \times \text{LVOT VTI}}$$

TVI, time velocity integral

LVOT, left ventricular outflow tract

RVOT, right ventricular outflow tract

VTI, velocity time integral

ELECTROPHYSIOLOGY/ELECTROCARDIOGRAM

QT_c (ms) = $$\frac{QT}{\sqrt{\text{RR interval (seconds)}}}$$

Heart rate (beats/min) = $$\frac{60,000}{\text{Cycle length (ms)}}$$

Left ventricular hypertrophy

Limb lead criteria

1. R wave in lead I + S wave in lead III >2.5 mV

2. R wave in aVL >1.1 mV

3. R wave in aVF >2.0 mV

4. S wave in aVR >1.4 mV

Precordial lead criteria

1. R wave in V_5 or V_6 >2.6 mV

2. R wave in V_6 + S wave in V1 >3.5 mV

3. Largest R wave + largest S wave in precordial leads >4.5 mV

Cornell criteria

R wave in aVL + S wave in V_3 >2.0 mV for females and 2.8 mV for males

Duke treadmill score (DTS)

DTS = Exercise time (minutes) − (5 × Maximal ST deviation) − (4 × Angina score)

0 = No angina

1 = Nonlimiting angina

2 = Angina limiting further testing

DTS ≤−11 = High risk

DTS −10 to 4 = Moderate risk

DTS ≥5 = Low risk

Age-predicted maximal heart rate (beats/min) = 220 − Age

PHARMACODYNAMICS

Volume of distribution (L) =

$$\frac{\text{Amount of drug in body}}{\text{Plasma drug concentration}}$$

Loading dose (mg) =

$$\frac{(\text{Volume of distribution}) \times (\text{Plasma drug concentration})}{(\text{Fraction of dose that is active}) \times (\text{Bioavailability of drug})}$$

Clearance (L/h) =

$$\frac{\text{Rate of drug administration}}{\text{Steady-state plasma drug concentration}}$$

Half-life (h) = $\dfrac{0.693 \times \text{Volume of distribution}}{\text{Clearance (L/h)}}$

MISCELLANEOUS

Cockcroft-Gault

Glomerular filtration rate (mL/min) =

$$\text{Glomerular filtration rate (mL/min)} = \frac{[(140 - \text{Age}) \times \text{Weight (kg)}]}{72 \times \text{Creatinine}}$$

If female, multiply by 0.85

Ankle–brachial index =

$$\frac{\text{Pedal pressure}}{\text{Brachial pressure (higher of two sides)}}$$

Law of Laplace

$$\text{Wall tension} = \frac{\text{Pressure} \times \text{Radius}}{\text{Wall thickness}}$$

Central perfusion pressure = Mean arterial pressure − Intracranial pressure

Assessment of appropriateness of ascending aorta size to height

Aortic index =

$$\frac{\text{Maximal cross-sectional area of ascending aorta } (\text{cm}^2)}{\text{Height (m)}}$$

If ratio >10, consider repair of aorta.

Cholesterol mg/dL to mmol/L

1 mg/dL = 0.02586 mmol/L; 1 mmol/L = 38.7 mg/dL

Thus, 130 mg/dL = 3.45 mmol/L

Total cholesterol = LDL cholesterol + HDL cholesterol + 0.20 (Triglyceride level)

HDL, high-density lipoprotein; LDL, low-density lipoprotein

STATISTICS

	Disease Present	Disease Absent
Test result positive	a (True positive)	b (False positive)
Tests result negative	c (False negative)	d (True negative)

Sensitivity = $\frac{a}{a+c}$

Specificity = $\frac{d}{b+d}$

Positive predictive value = $\frac{a}{a+b}$

Negative predictive value = $\frac{d}{c+d}$

Likelihood ratio for a positive test =

$$\frac{\text{Sensitivity}}{1-\text{Specificity}} = \frac{a/a+c}{b/b+d}$$

Likelihood ratio for a negative test =

$$\frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{c/a + c}{d/b + d}$$

	Outcome Positive	Outcome Negative
Treated group	a	b
Control group	c	d

Relative risk =

$$\frac{\text{Risk of outcome in treated group}}{\text{Risk of outcome in control group}} = \frac{a/a + b}{c/c + d}$$

Relative risk reduction = (1 − Relative risk) × 100%

Absolute risk reduction = Difference in risk of outcome between control group and treated group

Absolute risk reduction = $c/c + d - a/a + b$

Number needed to treat = $\frac{1}{\text{Absolute risk reduction}}$

Odds ratio =

$$\frac{\text{Number of outcome events/Number of subjects}}{1 - (\text{Number of outcome events/Number of subjects})}$$

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