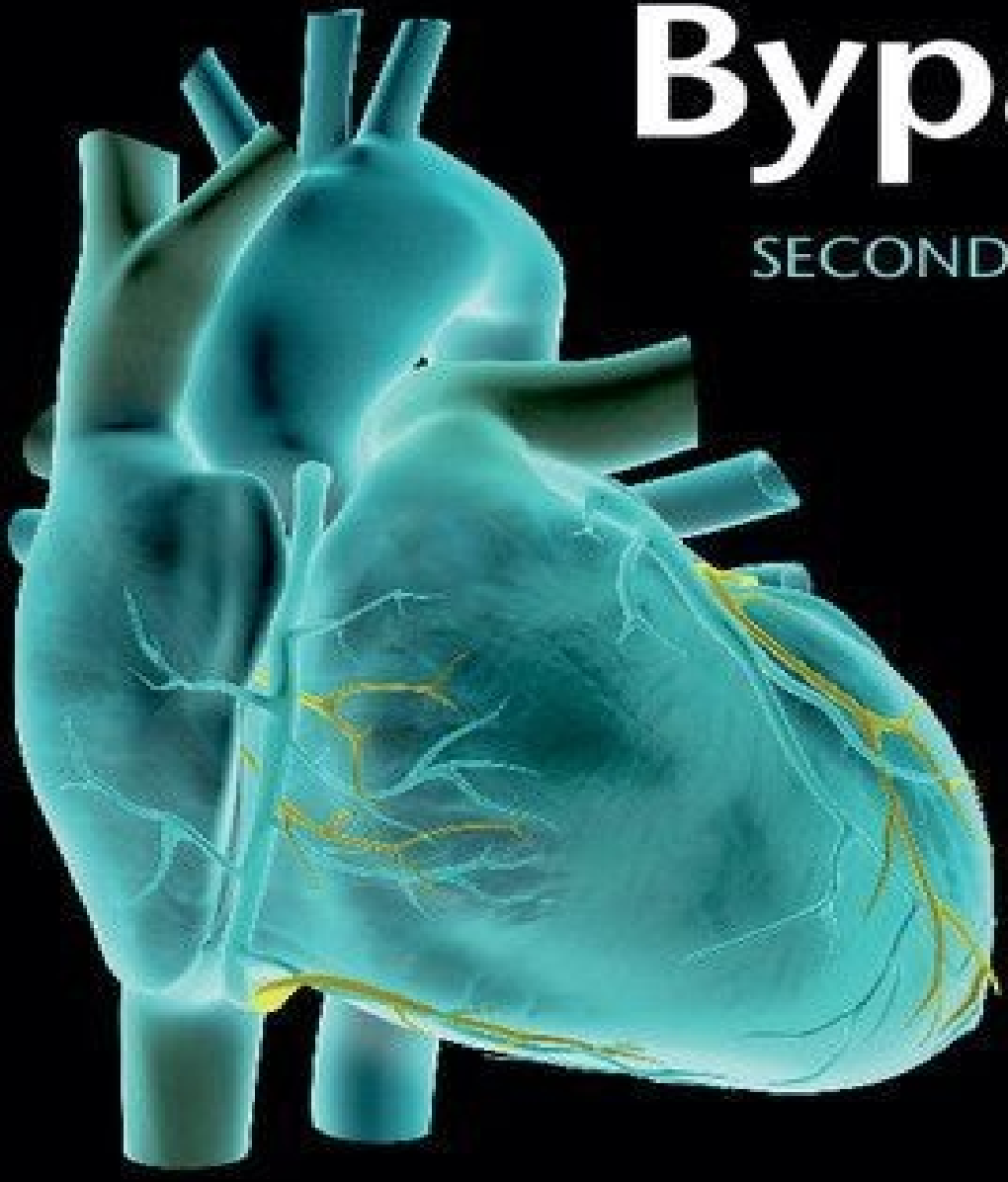
Edited by:
Sunit Ghosh
Florian Falter
Albert C. Perrino, Jr.

Cardiopulmonary Bypass

SECOND EDITION



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CARDIOPULMONARY BYPASS

Second Edition

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Preface

This book has been written to provide an easily readable source of material for the everyday practice of clinical perfusion. The first edition of this book provided an alternative to the large reference tomes relating to cardiopulmonary bypass. This second edition builds on the success of the first edition as an educational resource by including self-assessment questions at the end of each chapter and by including updated information in each of the chapters. We hope that newcomers to the subject will find this book useful, both in the clinical setting and in preparation for examinations, and that more experienced perfusionists and medical staff will find it useful for preparing teaching material or for guidance.

We would like to thank everyone who helped in the preparation of the manuscript, particularly those who contributed their expertise by writing chapters for this book.

Sunit Ghosh, Florian Falter, and Albert C. Perrino, Jr.

Chapter 1

Equipment and monitoring for cardiopulmonary bypass

Victoria Molyneux and **Andrew A. Klein**

The optimum conditions for cardiothoracic surgery have traditionally been regarded as a “still and bloodless” surgical field. Cardiopulmonary bypass (CPB) provides this by incorporating a pump to substitute for the function of the heart and a gas exchange device, the “oxygenator,” to act as an artificial lung. CPB thus allows the patient’s heart and lungs to be temporarily devoid of circulation, and respiratory and cardiac activity suspended, so that intricate cardiac, vascular or thoracic surgery can be performed in a safe and controlled environment.

History

In its most basic form, the CPB machine and circuit comprises plastic tubing, a reservoir, an oxygenator, and a pump. Venous blood is drained by gravity into the reservoir via a cannula placed in the right atrium or a large vein, pumped through the oxygenator and returned into the patient’s arterial system via a cannula in the aorta or other large artery. Transit through the oxygenator reduces the partial pressure of carbon dioxide in the blood and raises oxygen content. A typical CPB circuit is shown in Figure 1.1.

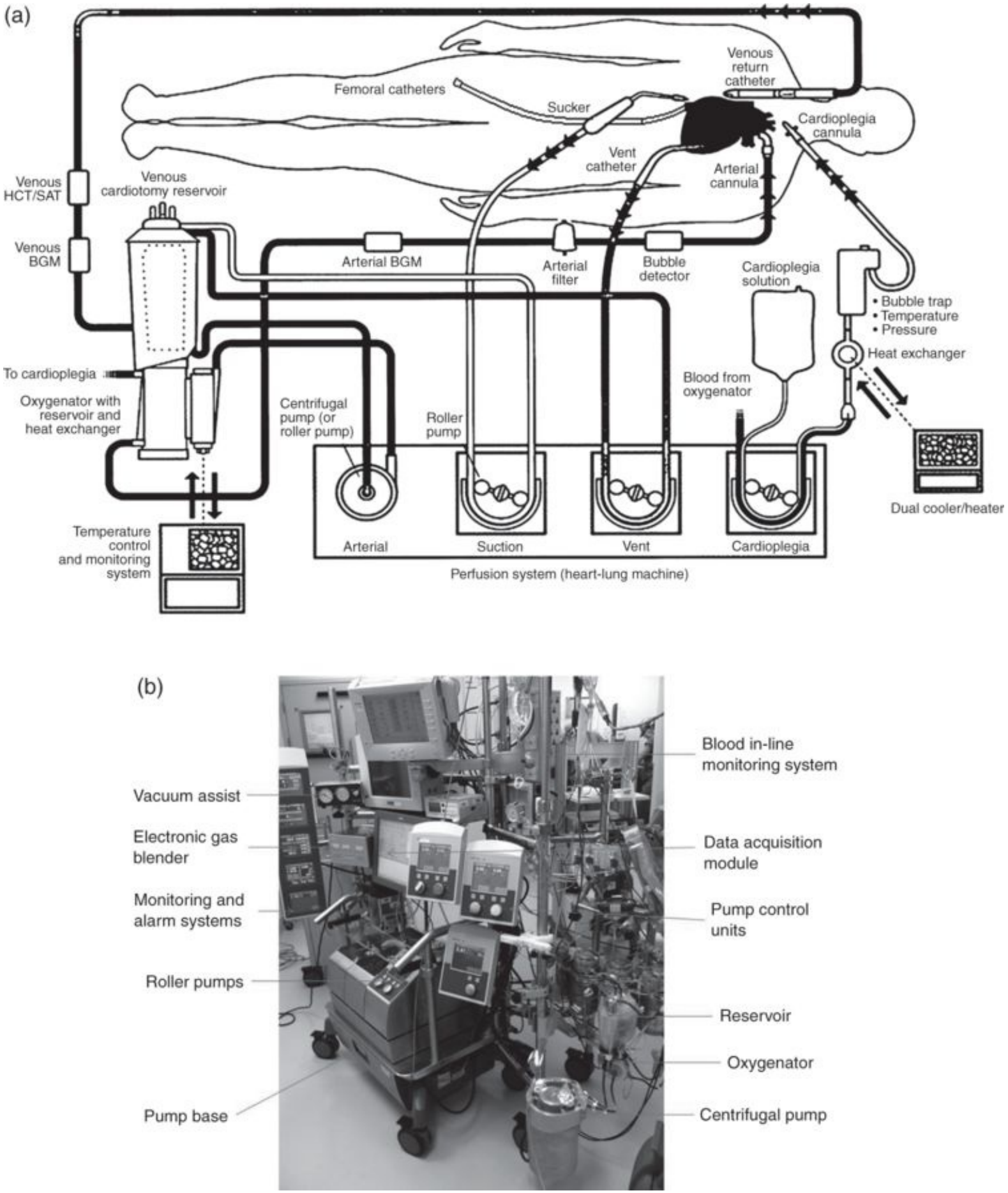


Figure 1.1 (a) Typical configuration of a basic cardiopulmonary bypass circuit. BGM = blood gas monitor; HCT = hematocrit; SAT = oxygen saturation. (b) Stockert cardiopulmonary bypass circuit in use.

Cardiac surgery has widely been regarded as one of the most important medical advances of the twentieth century. The concept of a CPB machine arose from the technique of “cross circulation” in which the arterial and venous circulations of mother and child were connected in series by tubing. The mother’s heart and lungs maintained the circulatory and respiratory functions of both, while surgeons operated on the child’s heart (Dr Walton Lillehei, Minnesota, 1953, see Figure 1.2). Modern CPB machines (see Figure 1.1b) have evolved to incorporate monitoring and safety features in their design.

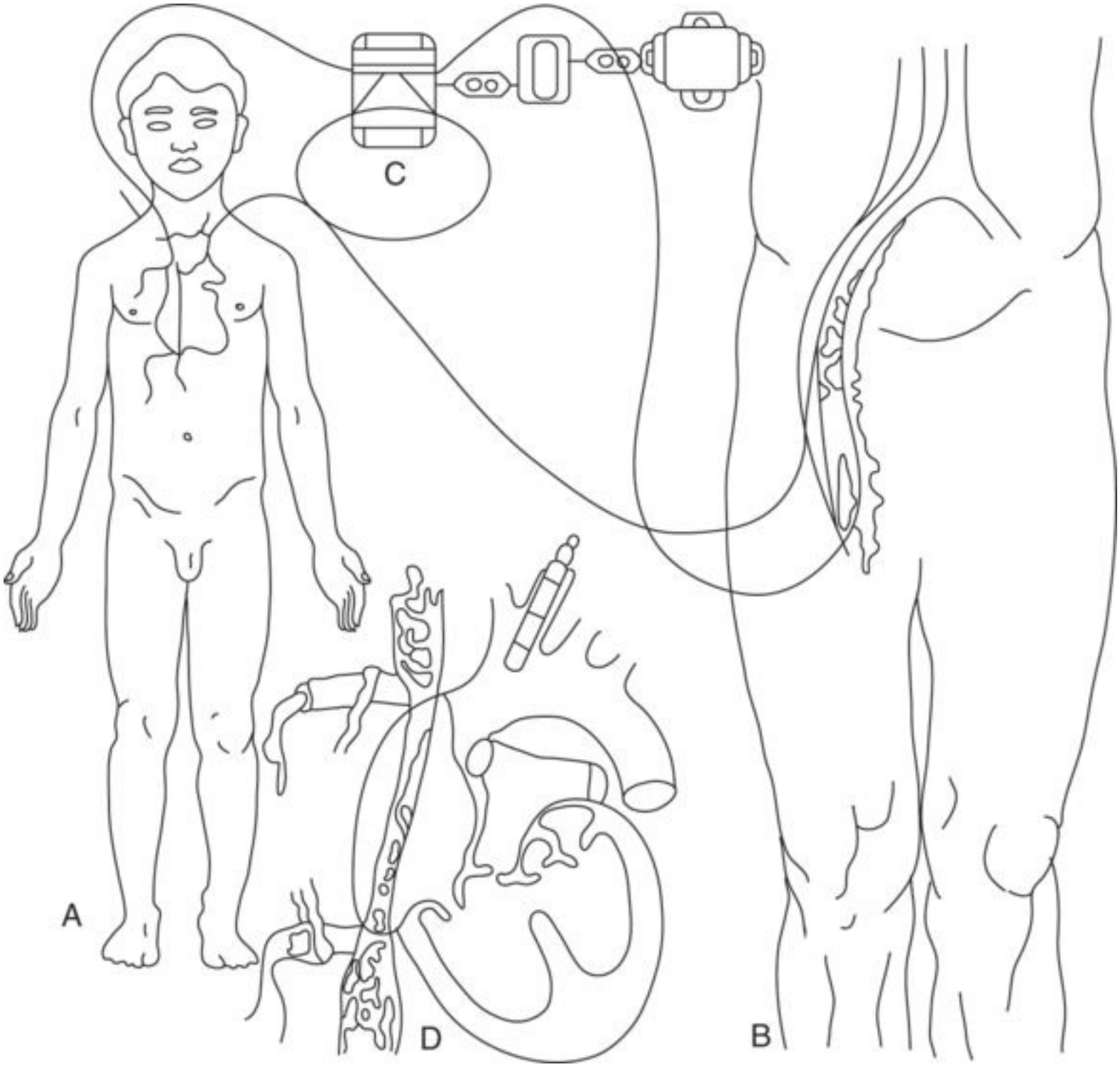


Figure 1.2 Depiction of the method of direct vision intracardiac surgery utilizing extracorporeal circulation by means of controlled cross circulation. The patient (A), showing sites of arterial and

venous cannulations. The donor (B), showing sites of arterial and venous (superficial femoral and great saphenous) cannulations. The Sigma motor pump (C) controlling precisely the reciprocal exchange of blood between the patient and donor. Close-up of the patient's heart (D), showing the vena caval catheter positioned to draw venous blood from both the superior and inferior venae cavae during the cardiac bypass interval. The arterial blood from the donor circulated to the patient's body through the catheter that was inserted into the left subclavian artery.

(Reproduced with kind permission from Lillehei CW, Cohen M, Warden HE, et al. The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg Gynecol Obstet 1955; 101: 446. Copyright American College of Surgeons.)

John Gibbon (Philadelphia, 1953) is credited with developing the first mechanical CPB system, which he used when repairing an atrial secundum defect (ASD). Initially, the technology was complex and unreliable and was therefore slow to develop. The equipment used in a typical extracorporeal circuit has advanced rapidly since this time and although circuits vary considerably among surgeons and hospitals, the basic concepts are essentially common to all CPB circuits.

This chapter describes the standard equipment and monitoring components of the CPB machine and extracorporeal circuit as well as additional equipment such as the suckers used to scavenge blood from the operative field, cardioplegia delivery systems, and hemofilters (see Tables 1.1 and 1.2).

Table 1.1 Components of the CPB machine and the extracorporeal circuit

Equipment	Function
Oxygenator system, venous reservoir, oxygenator, heat exchanger	Oxygenate, remove carbon dioxide, and cool/re-warm blood
Gas line and FiO_2 blender	Delivers fresh gas to the oxygenator in a controlled mixture
Arterial pump	Pumps blood at a set flow rate to the patient
Cardiotomy suckers and vents	Scavenges blood from the operative field and vents the heart
Arterial line filter	Removes microaggregates and particulate matter > 40 μm
Cardioplegia systems	Deliver high-dose potassium solutions to arrest the heart and preserve the myocardium

Cannulae	Connect the patient to the extracorporeal circuit

Table 1.2 Monitoring components of the CPB machine and the extracorporeal circuit

Monitoring device	**Function**
Low-level alarm	Alarms when level in the reservoir reaches minimum running volume
Pressure monitoring (line pressure, blood cardioplegia pressure, and vent pressure)	Alarms when line pressure exceeds set limits
Bubble detector (arterial line and blood cardioplegia)	Alarms when bubbles are sensed
Oxygen sensor	Alarms when oxygen supply to the oxygenator fails
S_aO_2, S_vO_2, and hemoglobin monitor	Continuously measures these levels from the extracorporeal circuit
In-line blood gas monitoring	Continuously measures arterial and venous gases from the extracorporeal circuit
Perfusionist	Constantly monitors the CPB machine and the extracorporeal circuit

Tubing

The tubing in the CPB circuit interconnects all of the main components of the circuit. A variety of materials may be used for the manufacture of the tubing; these include polyvinyl chloride (PVC, by far the most commonly used), silicone (reserved for the arterial pump boot), and latex rubber. The size of tubing used at different points in the circuit is determined by the pressure and rate of blood flow that will be required through that region of the circuit, or through a particular component of the circuit (see).

Table 1.3 Tubing sizes commonly used in different parts of the extracorporeal circuit (adults only)

Tubing size	**Function**
3/16” (4.5 mm)	Cardioplegia section of the blood cardioplegia delivery system
1/4” (6.0 mm)	Suction tubing, blood section of the blood cardioplegia delivery system

3/8” (9.0 mm)	Arterial pump line for flow rates < 6.7 l/minute, majority of the arterial tubing in the extracorporeal circuit
1/2” (12.0 mm)	Venous line, larger tubing is required to gravity drain blood from the patient

PVC is made up of polymer chains with polar carbon–chloride (C–Cl) bonds. These bonds result in considerable intermolecular attraction between the polymer chains, making PVC a fairly strong material. The feature of PVC that accounts for its widespread use is its versatility. On its own, PVC is a fairly rigid plastic, but plasticizers can be added to make it highly flexible. Plasticizers are molecules that incorporate between the polymer chains allowing them to slide over one another more easily, thus increasing the flexibility of the PVC. However, one disadvantage is that PVC tubing stiffens during hypothermic CPB and tends to induce spallation; that is, the release of plastic microparticles from the inner wall of tubing as a result of pump compressions.

Other materials used to manufacture perfusion tubing include latex rubber and silicone rubber. Latex rubber generates more hemolysis than PVC, whereas silicone rubber is known to produce less hemolysis when the pump is completely occluded, but can release more particles than PVC. As a result of this, and because of PVC’s durability and accepted hemolysis rates, PVC is the most widely used tubing material. The arterial roller pump boot is the main exception to this, as the rollers constantly compress the tubing at this site, so silicone tubing is used for this purpose.

Arterial cannulae

The arterial cannula is used to connect the “arterial limb” of the CPB circuit to the patient and so deliver oxygenated blood from the heart–lung machine directly into the patient’s arterial system. The required size is determined by the size of the vessel that is being cannulated, as well as the blood flow required. The ascending aorta is the most common site of arterial cannulation for routine cardiovascular surgery. This is because the ascending aorta is readily accessible for cannulation when a median sternotomy approach is used and has the lowest associated incidence of aortic dissection (0.01–0.09%). After sternotomy and exposure, the surgeon is able to assess the size of the aorta before choosing the most appropriately sized cannula (see).

Table 1.4 Arterial cannulae flow rates in relation to type/size

Cannulae	Size	Flow rate (l/minute)

	French gauge	mm	
DLP angled tip	20	6.7	6.5
	22	7.3	8.0
	24	8.0	9.0
DLD straight tip	21	7.0	5.0
	24	8.0	6.0
Sarns high flow angled tip	15.6	5.2	3.5
	19.5	6.5	5.25
	24	8.0	8.0
Sarns straight tip	20	6.7	5.9
	22	7.3	6.0
	24	8.0	6.0

Thin-walled cannulae are preferred, as they present lower resistance to flow because of their larger effective internal diameter. This leads to a reduction in arterial line pressure within the extracorporeal circuit and increased blood flow to the patient.

Arterial cannulae with an angled tip are available. These direct blood flow towards the aortic arch rather than towards the wall of the aorta; this may minimize damage to the vessel wall. In addition, cannulae with a flange near the tip aid secure fixation to the vessel wall. Cannulae that incorporate a spirally wound wire within their wall to prevent “kinking” and obstruction are commonly used (see Figure 1.3).

Straight tip

Rings

Curved tip

Bump

Suture

Flange

Figure 1.3 Commonly used arterial cannulae.

(Reproduced with kind permission from Edwards Lifesciences.)

Venous cannulae

Venous cannulation for CPB allows deoxygenated blood to be drained from the patient into the extracorporeal circuit. The type of venous cannulation used is dependent upon the operation being undertaken. For cardiac surgery that does not involve opening the chambers of the heart, for example, coronary artery bypass grafts (CABGs), a two-stage venous cannula is often used. The distal portion, i.e., the tip of the cannula, sits in the inferior vena cava (IVC) and drains blood from the IVC through holes around the tip. A second series of holes in the cannula, a few centimeters above the tip, is sited in the right atrium, to drain venous blood entering the atrium via the superior vena cava (SVC).

An alternative method of venous cannulation for CPB is bicaval cannulation – this uses two single-stage cannulae that sit in the inferior and superior vena cavae, respectively. The two single-stage cannulae are connected using a Y-connector to the venous line of the CPB circuit. Bicaval cannulation is generally used for procedures that require the cardiac chambers to be opened, as the two separate pipes in the IVC and SVC permit unobstructed venous drainage during surgical manipulation of the dissected heart and keep the heart completely empty of blood (see Figure 1.4).

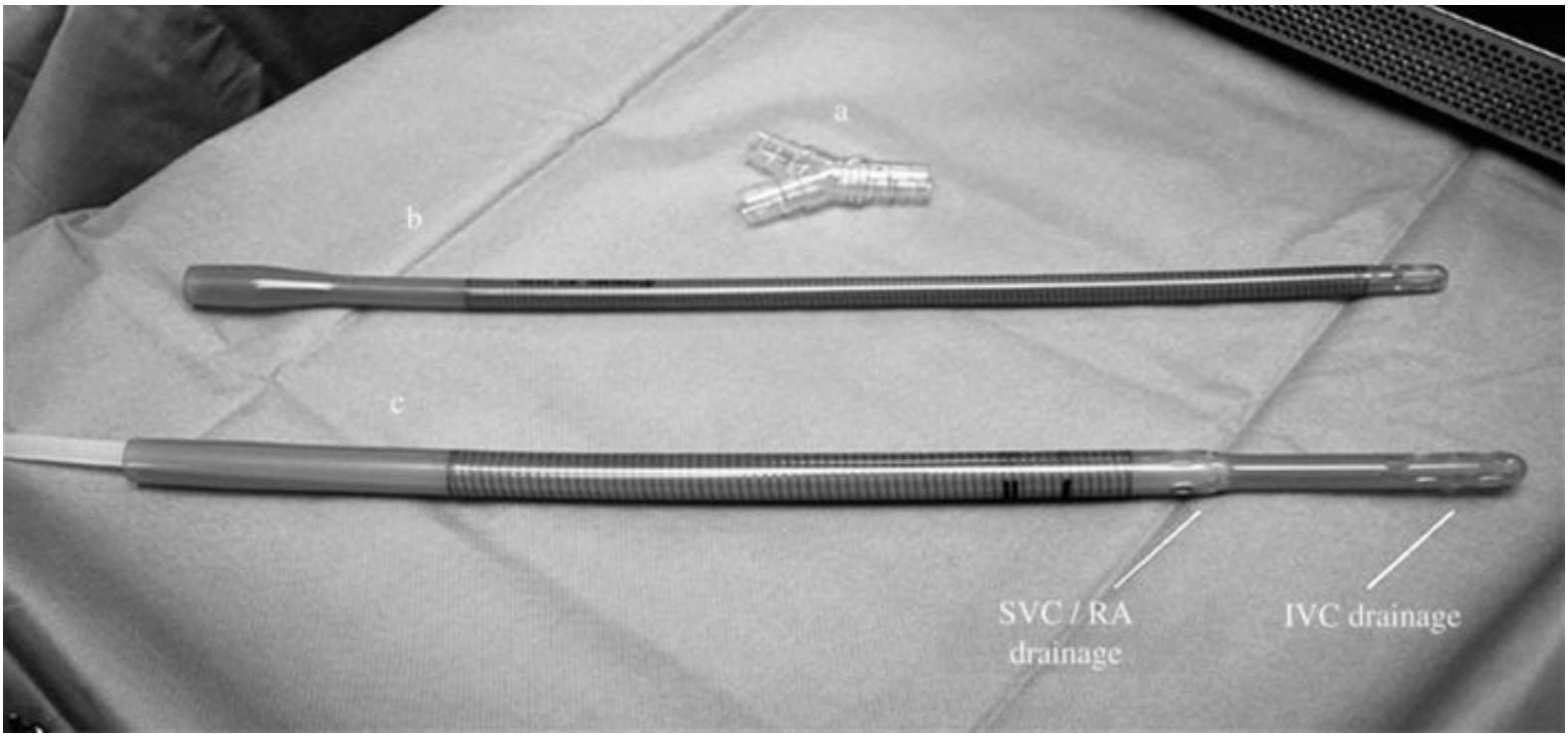


Figure 1.4 Commonly used venous cannulae: Y-connector to connect single-stage cannulae (a); single-stage cannula (b); two-stage cannula (c). RA, right atrial; SVC, superior vena cava; IVC, inferior vena cava.

The femoral veins may also be used as a cannulation site for more complex surgery. In this instance, a long cannula, which is in essence an elongated single-stage cannula, may be passed up the femoral vein into the vena cava in order to achieve venous drainage.

As with arterial cannulation, the size of the cannulae will depend on the vessels being cannulated as well as the desired blood flow. It is important to use appropriately sized cannulae in order to obtain maximum venous drainage from the patient so that full flow can be achieved when CPB is commenced.

Pump heads

There are two types of pumps used in extracorporeal circuits:

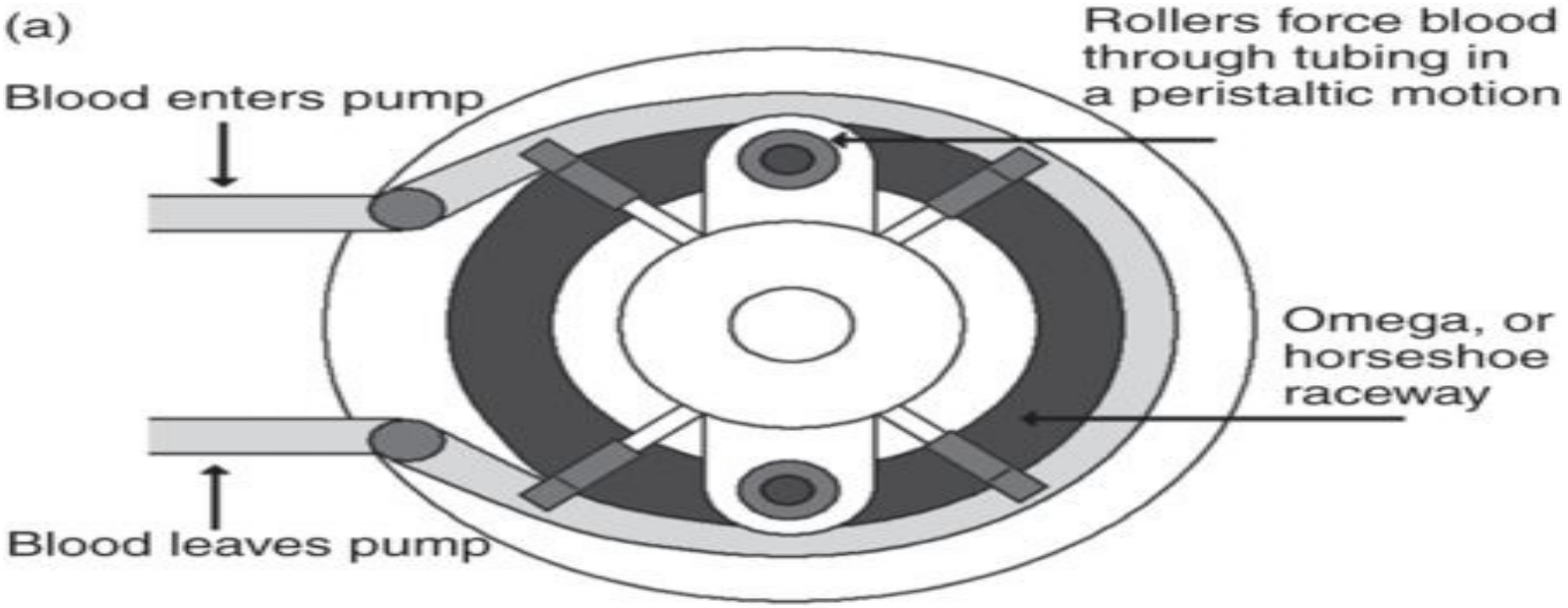
1. Those that directly generate flow – roller pumps.
2. Those that generate pressure – centrifugal pumps.

Roller pumps

Initial technology developed in the mid-twentieth century used non-pulsatile roller pumps in CPB machines. This technology has not changed greatly over the past 50 years.

Roller pumps positively displace blood through the tubing using a peristaltic motion. Two rollers, opposite each other, “roll” the blood through the tubing. When the tubing is intermittently occluded, positive and negative pressures are generated on either side of the point of occlusion. Forward or retrograde flow of blood can be achieved by altering the direction of pump head rotation; thus roller pumps are commonly used as the primary arterial flow pump as well as for suction of blood from the heart and mediastinal cavity during CPB to salvage blood. Roller pumps are relatively independent of circuit resistance and hydrostatic pressure; output depends on the number of rotations of the pump head and the internal diameter of the tubing used (see Figure 1.5).

(a)


Rollers force blood through tubing in a peristaltic motion
Blood enters pump
Omega, or horseshoe raceway
Blood leaves pump

(b)


STÖCKERT S3
Pump 1
0.00
0

Figure 1.5 (a) Line drawing of a roller pump; (b) a roller pump.

(Reproduced with kind permission from Sorin Group.)

This type of positive displacement pump can be set to provide pulsatile or non-pulsatile (laminar) flow. Debate over the advantages and disadvantages of non-pulsatile or pulsatile perfusion during CPB still continues. Non-pulsatile perfusion is known to have a detrimental effect on cell metabolism and organ function. The main argument in favor of pulsatile perfusion is that it more closely resembles the pattern of blood flow generated by the cardiac cycle and should therefore more closely emulate the flow characteristics of the physiological circulation, particularly enhancing flow through smaller capillary networks in comparison to non-pulsatile perfusion. The increased shear stress from the changing positive and negative pressures generated to aid pulsatile perfusion may, however, lead to increased hemolysis. Roller pumps have one further disadvantage: sudden occlusion of the inflow to the pump, as a result of low circulating volume or venous cannula obstruction, can result in "cavitation," the formation and collapse of gas bubbles due to the creation of pockets of low pressure by precipitous change in mechanical forces.

Centrifugal pumps

In 1973, the Biomedicus model 600 became the first disposable centrifugal pump head for clinical use. The Biomedicus head contains a cone with a metal bearing encased in an outer housing, forming a sealed unit through which blood can flow. When in use the head is seated on a pump drive unit. The cone spins as a result of the magnetic force that is generated when the pump is activated. The spinning cone creates a negative pressure that sucks blood into the inlet, creating a vortex. Centrifugal force imparts kinetic energy on the blood as the pump spins at 2000–4000 rpm (this speed is set by the user). The energy produced in the cone creates pressure and blood is then forced out of the outlet. The resulting blood flow will depend on the pressure gradient and the resistance at the outlet of the pump (a combination of the CPB circuit and the systemic vascular resistance of the patient). Flow meters are included in all centrifugal pumps and rely on ultrasonic or electromagnetic principles to determine blood flow velocity accurately (see Figure 1.6).

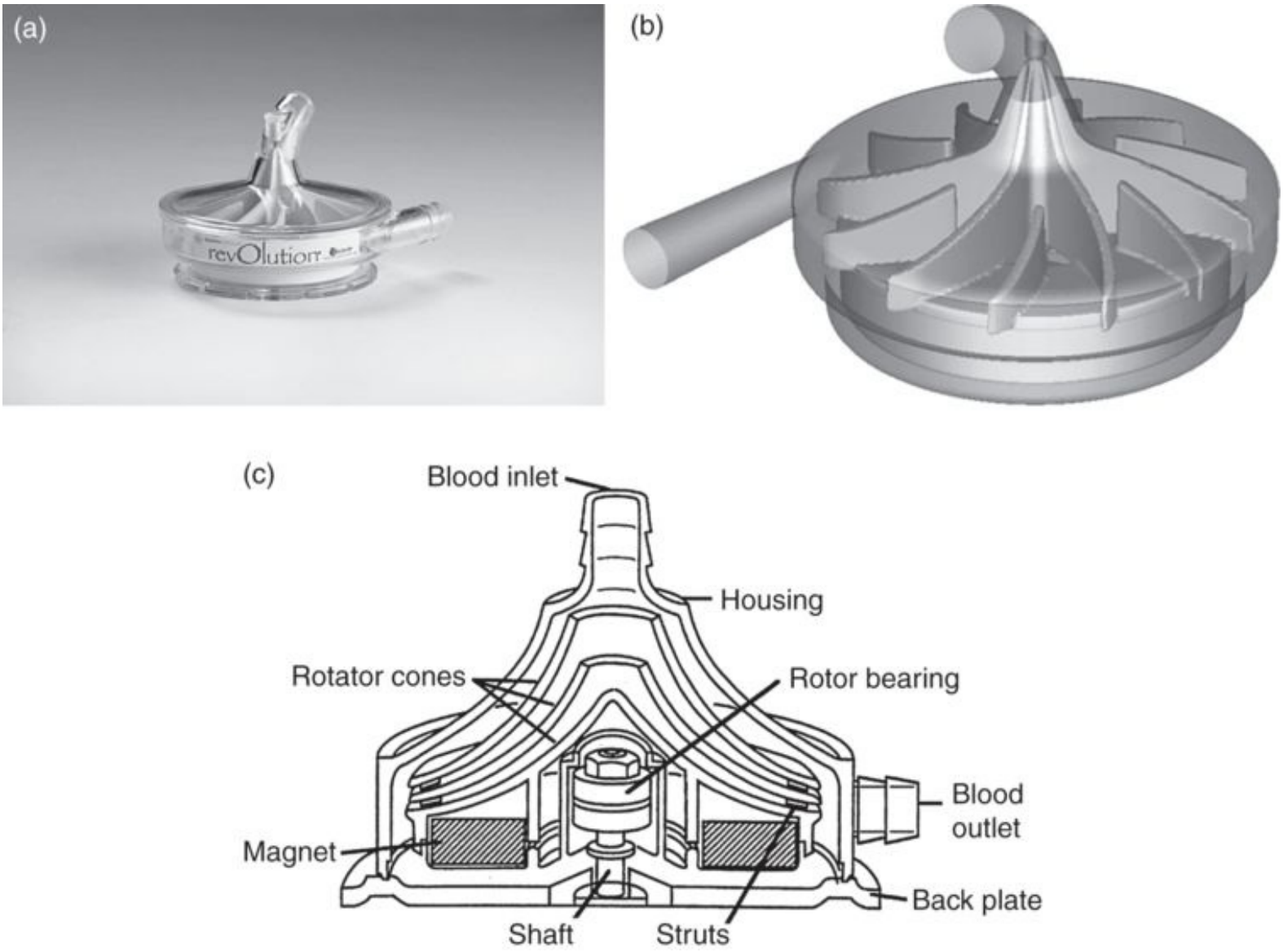


Figure 1.6 (a) Centrifugal pump. (b) Schematic diagram of centrifugal pump. (c) Schematic cut through centrifugal pump.

(a, b Reproduced with kind permission from Sorin Group.)

Despite extensive research, there is little evidence to show any benefit of one type of pump over another in clinical practice. Centrifugal pumps may produce less hemolysis and platelet activation than roller pumps, but this does not correlate with any difference in clinical outcome, including neurological function. They are certainly more expensive (as the pump head is single use) and may be prone to heat generation and clot formation on the rotating surfaces in contact with blood. In general, they are reserved for more complex surgery of prolonged duration, during which the damage to blood components associated with roller pumps may be theoretically disadvantageous.

Reservoirs

Cardiotomy reservoirs may be hardshell or collapsible. Hardshell reservoirs are most commonly used in adult cardiac surgery; collapsible reservoirs are still used by some institutions for pediatric and adult cases. Hardshell reservoirs usually are comprised of a polycarbonate housing, a polyester depth filter, and a polyurethane de-foamer. The reservoir component of the CPB circuit therefore provides high-efficiency filtration, de-foaming, and the removal of foreign particles (see Figure 1.7).

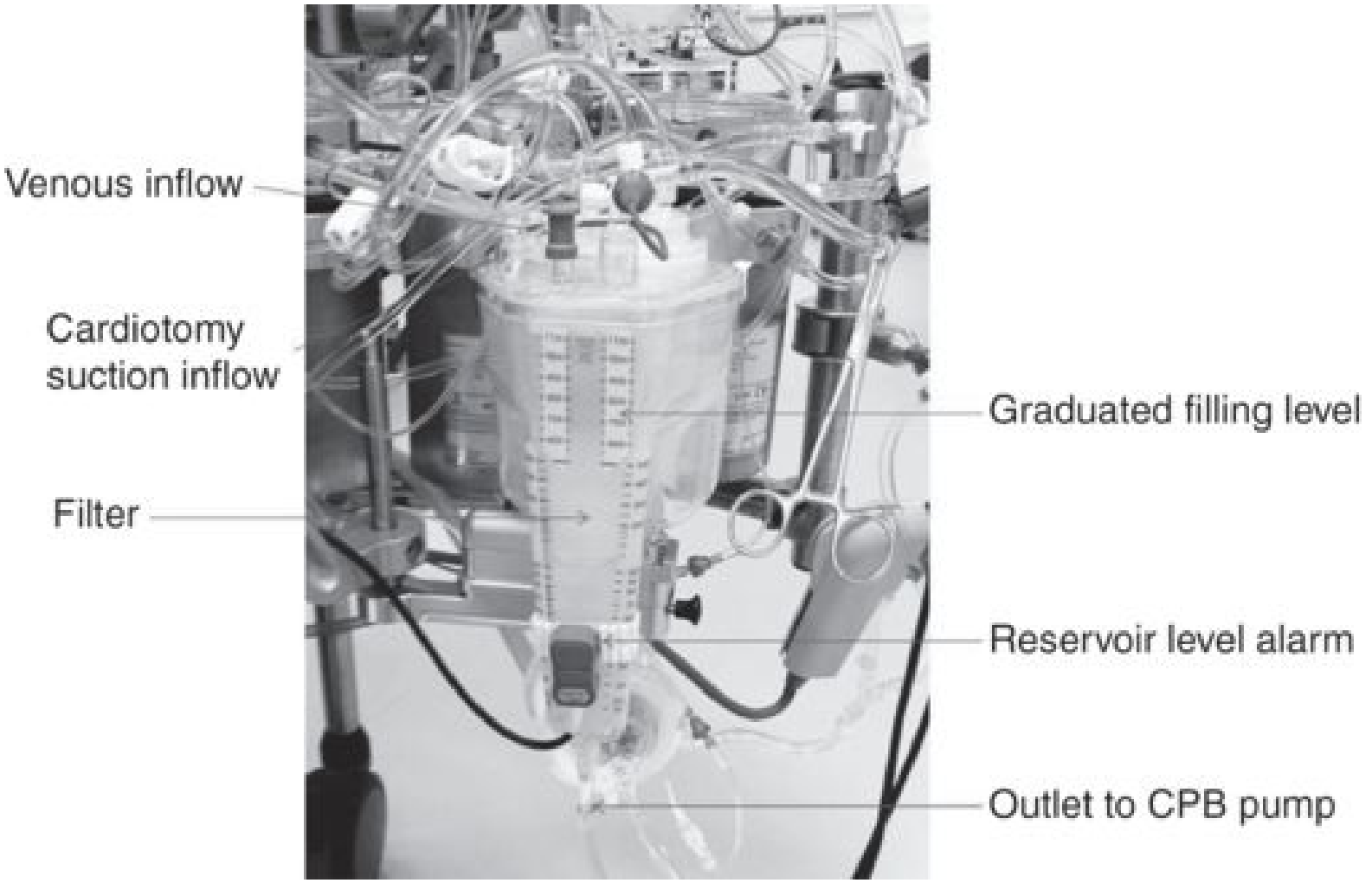


Figure 1.7 Reservoir in CPB circuit.

The reservoir acts as a chamber for the venous blood to drain into before it is pumped through the oxygenator and permits ready access for the addition of fluids and drugs. A level of fluid is maintained in the reservoir for the duration of CPB. This reduces the risks of perfusion accidents, such as inadvertently pumping large volumes of air into the arterial circulation if the venous return to the CPB machine from the patient is occluded for any reason.

Vacuum-assisted venous drainage may be used to optimize venous drainage during CPB. The use of vacuum assistance can reduce hemodilution and subsequent transfusion requirements because circuit tubing length is reduced and, as in most cases, venous drainage is improved there is lesser need to ‘top up’ the venous reservoir level with fluid. The top level of the cardiotomy reservoir is positioned at the patient atrial level, making it possible to downsize the length and diameter of venous and arterial lines. A

negative pressure of approximately −30 mmHg is applied as soon as the maximal gravity drainage is reached. During bypass, when the blood level in the reservoir decreases to the safety limit level, a small increase in negative pressure is used to improve venous drainage. For weaning from bypass, the negative pressure is gradually decreased to zero, then the reservoir is opened and the venous line progressively closed. The main drawbacks described have been retrograde flow in the venous line with cerebral air embolus and an increased incidence of gaseous microemboli.

Blood that is scavenged from the operative field via the suckers is returned to the reservoir. Suction relies on the "Venturi" effect, which is the change in pressure and fluid flow velocity through a narrowing in a tube, in this setting the narrowing being the sucker tip. Suctioning blood from the operative field thus inevitably leads to damage to blood cells and also results in concomitant entrainment of high volumes of air. The salvaged blood may contain tissue debris; it is therefore vital for this blood to be filtered through the reservoir before being pumped to the patient. The reservoir is constantly vented to prevent the entrained air causing a pressure build-up in the reservoir, which can occur if the suckers are left running at a high level for the duration of the procedure. The salvaged blood from the "vent" suckers that the surgeon uses to drain blood from the cardiac chambers and prevent the heart from distending during CPB is also returned to the reservoir.

Oxygenators

The present success of cardiac surgery relies on extracorporeal perfusion techniques employing an efficient gas exchange mechanism: the oxygenator. The requirements of the oxygenator include efficient oxygenation of desaturated hemoglobin and simultaneous removal of carbon dioxide from the blood. The oxygenator therefore acts as an artificial alveolar–pulmonary capillary system.

$$\text{Volume of gas diffused} = \frac{\text{Diffusion coefficient} \times \text{Partial pressure difference}}{\text{Distance to travel}}$$

The oxygenator provides an interface of high surface area between blood on one side and gas on the other (Figure 1.8). The distance gas has to travel across the interface is minimized by constructing the membrane from very thin material.

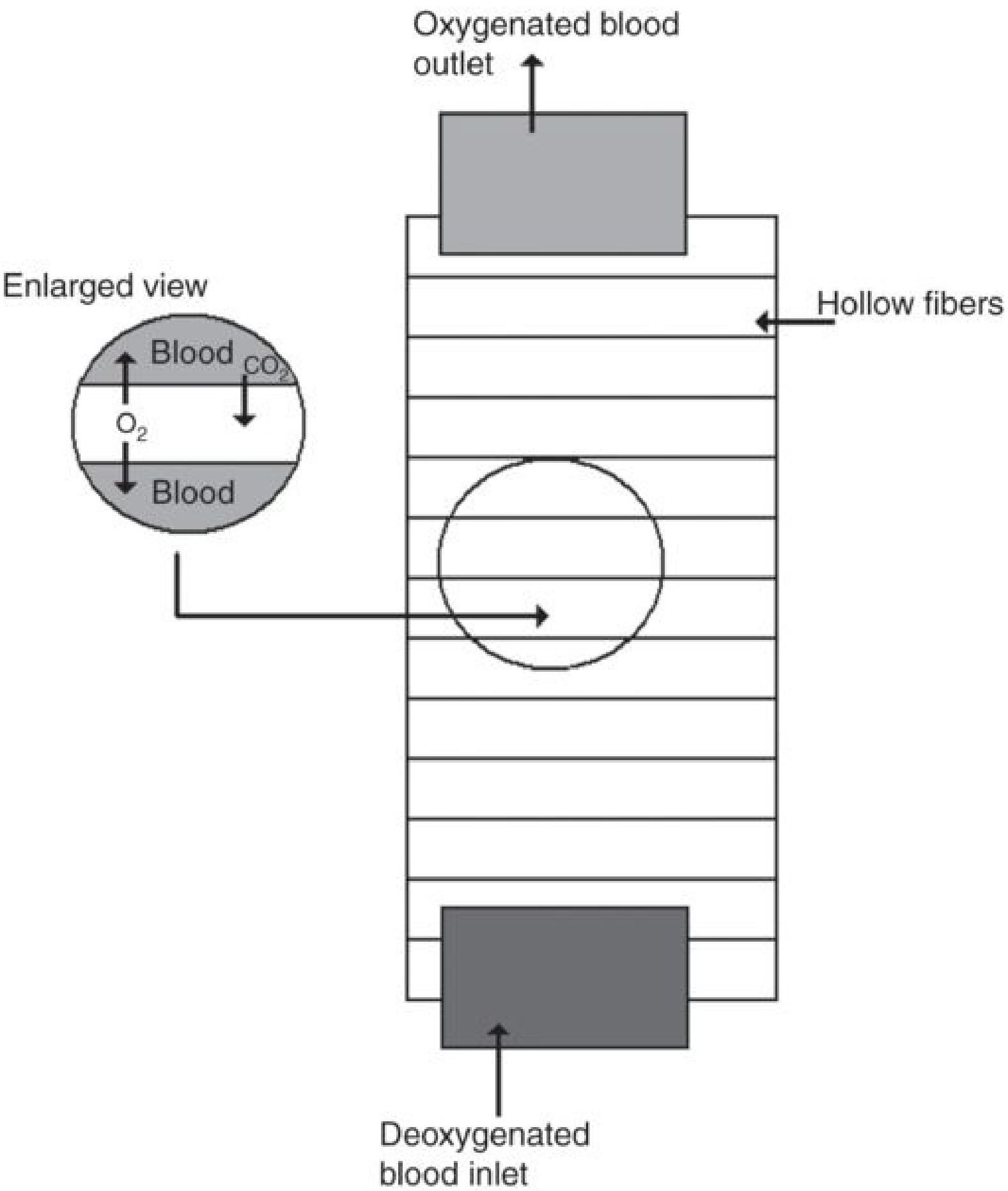


Figure 1.8 Schematic cut through an oxygenator.

In the early 1950s, attempts were made to oxygenate the blood using techniques such as cross circulation between related humans, or circuits incorporating animal lungs to provide gas exchange for patients undergoing open heart surgery. In 1955, DeWall and Lillehei devised the first helical reservoir to be used; this was an early form of the bubble oxygenator. One year later, in 1956, the rotating disc oxygenator was developed. In 1966, DeWall introduced the hardshell bubble oxygenator with integral heat exchanger. Subsequently, Lillehei and Lande developed a commercially manufactured, disposable, compact membrane oxygenator.

Currently, most commonly used oxygenators are membrane oxygenators with a microporous polypropylene hollow fiber structure. The membrane is initially porous, but proteins in blood rapidly coat it, preventing direct blood/gas contact. The surface tension of the blood also prevents plasma water from entering the gas phase of the micropores during CPB and prevents gas leakage into the blood phase, thus reducing microemboli. However, after several hours of use, evaporation and condensation of serum leaking through micropores leads to reduced efficiency and therefore the majority of these types of oxygenators must be changed after about 6 hours.

The majority of oxygenators consist of a module for gas exchange with an integrated heat exchanger (see Figure 1.9). An external heater–cooler unit pumps temperature-controlled water into the heat exchanger, which is separated from the blood by a highly thermally conductive material. This is biologically inert, to reduce activation of inflammatory mediators and components of the clotting cascade on contact with blood. The external heater–cooler has digital regulating modules to allow precise control of temperature through thermostat-controlled heating and cooling elements within the console. Controlled cooling and re-warming of the patient are crucial to ensure an even distribution of temperature throughout the body and to prevent damage to blood components, proteins, and tissues.

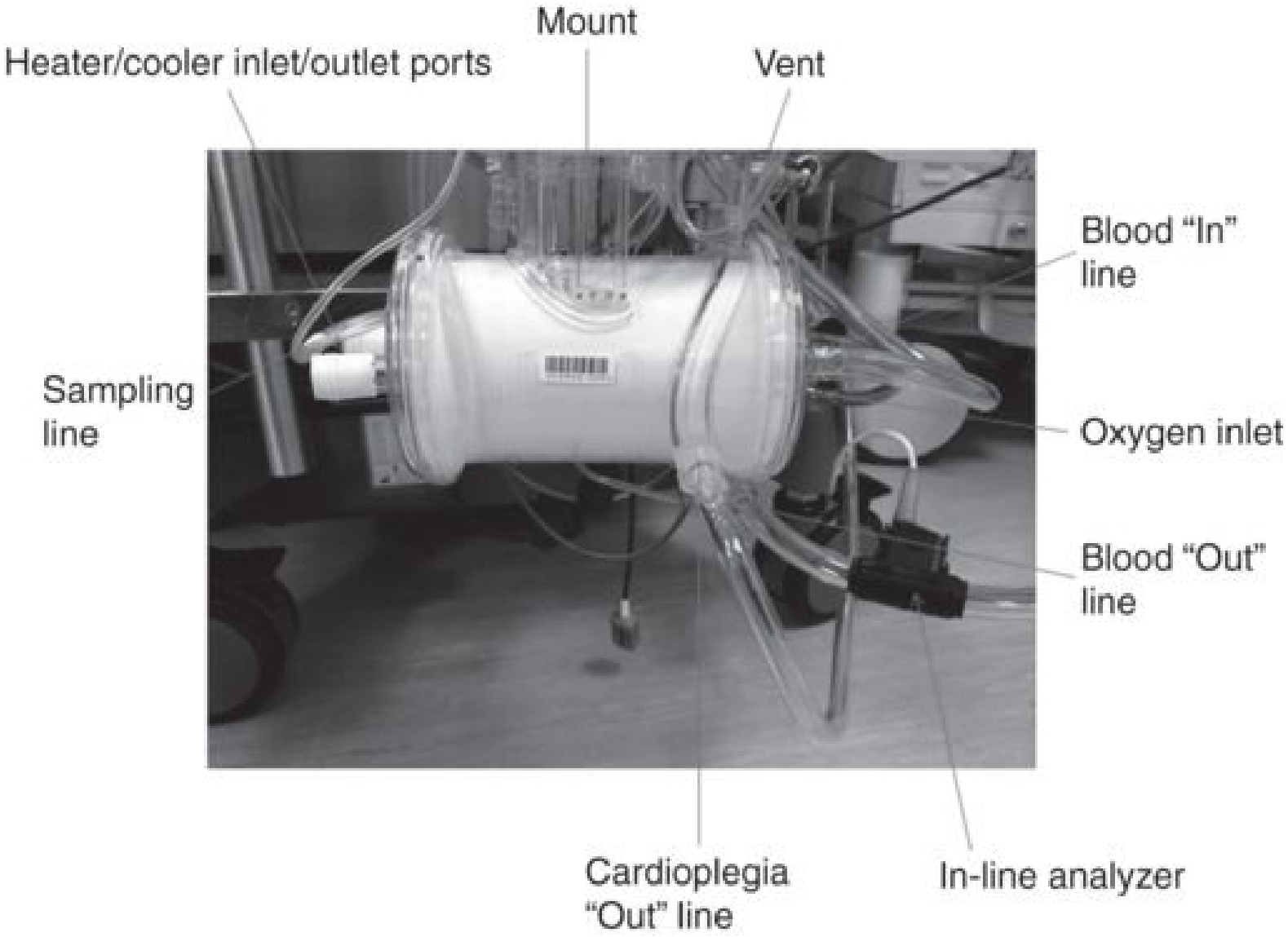


Figure 1.9 Oxygenator combined with a reservoir and a heat exchanger in a single unit.

The Cobe Duo (Cobe Cardiovascular CML-Duo) adult cardiovascular membrane oxygenator is comprised of a microporous polypropylene pleated sheet that has a prime volume of approximately 250 ml and works on the principle of diffusion. Blood first passes over an integral heat exchanger and then moves into the oxygenator compartment. Gas supplies of oxygen, air, and carbon dioxide are delivered to the membrane in controlled quantities. This "sweep" gas flows inside the fibers and has a higher concentration of oxygen than venous blood on the outside of the fibers, enabling oxygen to move along a concentration gradient across the membrane into the blood to create equilibrium. Carbon dioxide, which is present in a high concentration in the venous blood, moves in the opposite direction, across the membrane into the gas phase (see Figures 1.8 and 1.9). The exhaust gases are scavenged from outlet ports on the back of the oxygenator.

Gas supply system

The gas supply system provides a source of oxygen, air, and carbon dioxide to the oxygenator. A blender mixes piped oxygen and air to the concentration set by the user, and the gas is delivered at a rate set on a flow meter (see Figure 1.10). Flow meters may be digital controllers or mechanical rotameters. An oxygen analyzer is included in the gas circuit to continuously display the concentration of oxygen delivered in order to prevent the inadvertent administration of a hypoxic mixture. An anesthetic vaporizer may be incorporated, along with a means of scavenging waste gases.

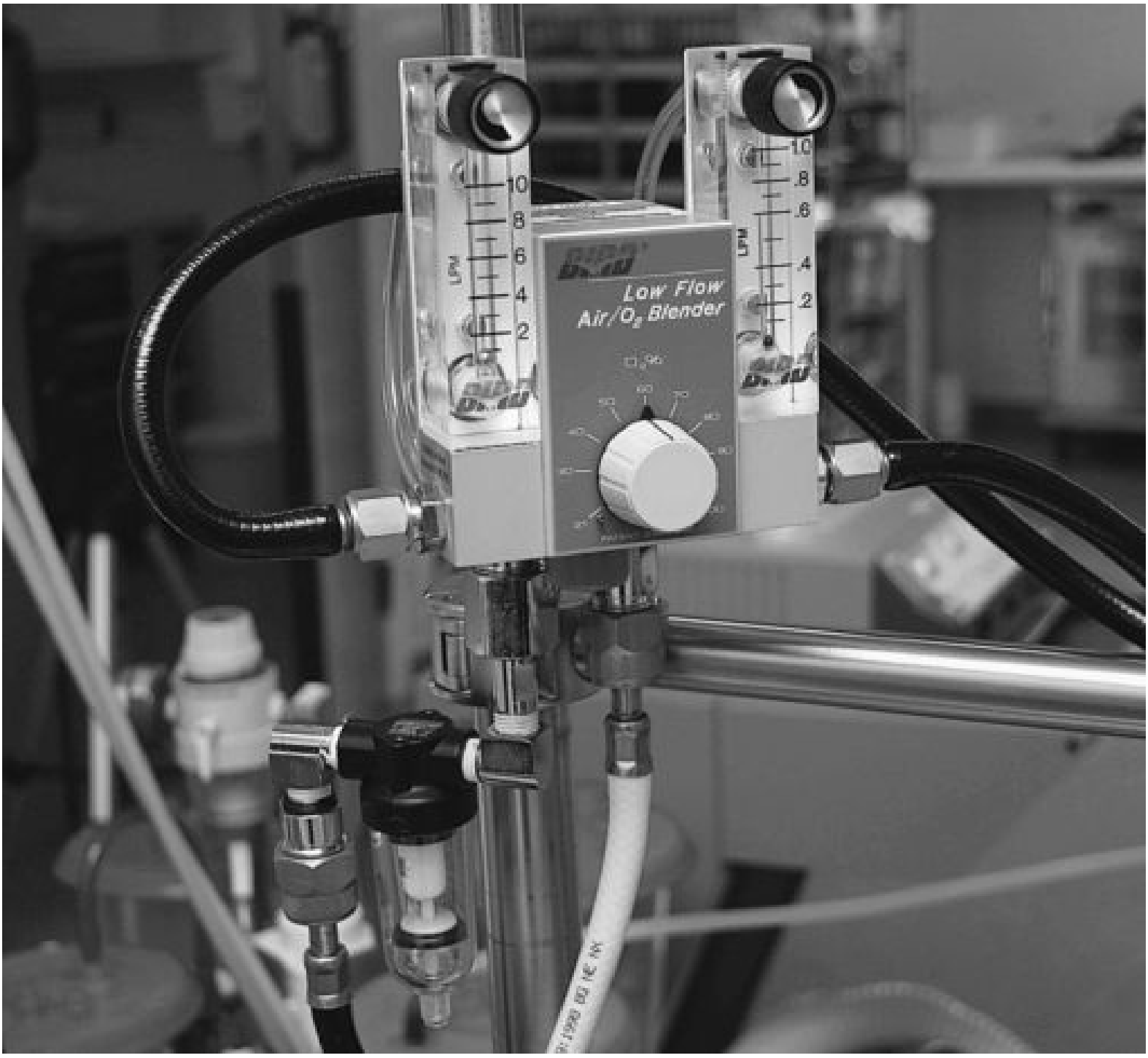


Figure 1.10 Rotameters on a CPB machine to regulate sweep gas flow.

Filters and bubble traps

There are numerous filters that can be used within the extracorporeal circuit. These range from 0.2 μm gas line filters to 40 μm arterial line filters (see Table 1.5).

Table 1.5 Filtration devices used within the CPB circuit

Filter type	Application and specification
Gas line	Removes 99.999% of bacteria found in the gas stream minimizing cross-contamination between the patient and the equipment
Pre-CPB	0.2 μm filter is used during the priming and recirculation phase. It is designed for the removal of inadvertent particulate debris and microbial contaminants and their associated endotoxins
Arterial line	Designed to remove microemboli > 40 μm in size from the perfusate during extracorporeal circulation. This includes gas emboli, fat emboli and aggregates composed of platelets, red blood cells and other debris
Leukodepletion	Reduces the levels of leukocytes, either from the arterial line or cardioplegia system, and excludes microemboli > 40 μm
Cardioplegia	Blood cardioplegia: > 40 μm filter. Crystalloid cardioplegia: > 0.2 μm filter. Low priming volume filter for cell-free solutions. Removes inadvertent particulate debris and microbial contaminants and their associated endotoxins
Blood transfusion	Designed to reduce the levels of leukocytes and microaggregates from 1 unit of packed red blood cells or whole blood
Cell salvage	Designed for the filtration of salvaged blood to remove potentially harmful microaggregates, leukocytes, and lipid particles

Adapted from Pall product specifications 2007.

Arterial line filters are the most commonly used additional filtration devices. They are indicated for use in all CPB procedures and there are a number of filters available with slightly different characteristics (see Table 1.6).

Table 1.6 Different commercially available arterial line filters

Manufacturer	Filter type	Fiber material	Filter size

			(µm)
Lifeline-Delhi	Screen	Unspecified	40
Medtronic	Screen	Carmeda coated or I coated filter material	38
Sorin-Dideco micro physio	Screen	Phosphorylcholine-coated	40
Pall	Screen	Heparin-coated polyester	40
Terumo Capiox®	Screen	Polyester	40
Membrane solutions	Screen	Polyester	40

Screen filters remove particles by mechanical retention and impaction. They have a specific pore size and remove air by velocity separation and venting. Swank is the only manufacturer of depth filters at present. This type of filter creates a tortuous path between fibers and retains particles mechanically. There is not normally a specific pore size. Air is removed by entrapment during transit of blood through the pathway between fibers. There is some experimental evidence that more modern screen filters, such as the Terumo Capiox FX-25, may reduce gaseous microemboli.

The US Food and Drug Administration (FDA) have outlined key areas of importance pertaining to arterial line filters (FDA, 2000). These are summarized as follows:

- amount of damage to formed blood elements, clotting, and hemolysis
- degree of pressure drop resulting in inadequate blood flow, damage to the device or structural integrity, and damage to the arterial line
- structural integrity of the product
- excessive pressure gradients, for example, blood damage and inadequate blood flow
- filtration efficiency and gas emboli-handling capacities
- user error
- blood incompatibility and the requirements of ISO 10993: Biological Evaluation of Medical Devices
- compatibility of the product when exposed to circulating blood and infections
- shelf life

These stringent criteria aim to ensure the production of high-quality arterial line filters that will not have any deleterious effects on the CPB circuit or patient.

Suckers and vents

The suckers attached to the CPB circuit allow blood to be salvaged from the operative field and to be returned to the circuit via the reservoir.

"Vent" suckers are specifically used to drain blood that has not been directly removed from the heart by the venous pipes. The most common sites for placing dedicated vents are:

- the aortic root
- the left ventricle
- the right superior pulmonary vein
- the left ventricular apex
- the left atrium or pulmonary artery

The main reasons for venting the heart during CPB are:

- to prevent distension of the heart
- to reduce myocardial re-warming
- to evacuate air from the cardiac chambers during the de-airing phase of the procedure
- to improve surgical exposure
- to create a dry surgical field, especially during the distal coronary anastamosis phase of CABG surgery

There are complications associated with all sites used for venting, most commonly relating to injury to tissues at the site. Venting via the left ventricular (LV) apex, however, is associated with particularly serious consequences including:

- damage to the LV wall due to excessive suction
- LV wall rupture if inadequately closed at the end of the bypass period
- embolization through air entrained into the LV

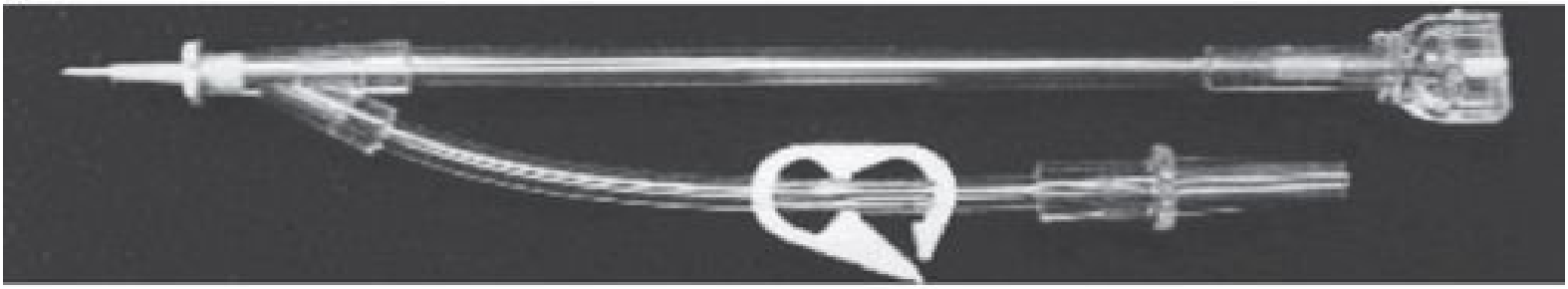
Active venting with high levels of suction can lead to air being introduced into the arterial side of the CPB circuit due to a small percentage of air being sucked into the venous side of the reservoir and oxygenator, passing through the circuit into the arterial side. Therefore, suction pressure and duration should be kept to a minimum.

Cardioplegia delivery systems

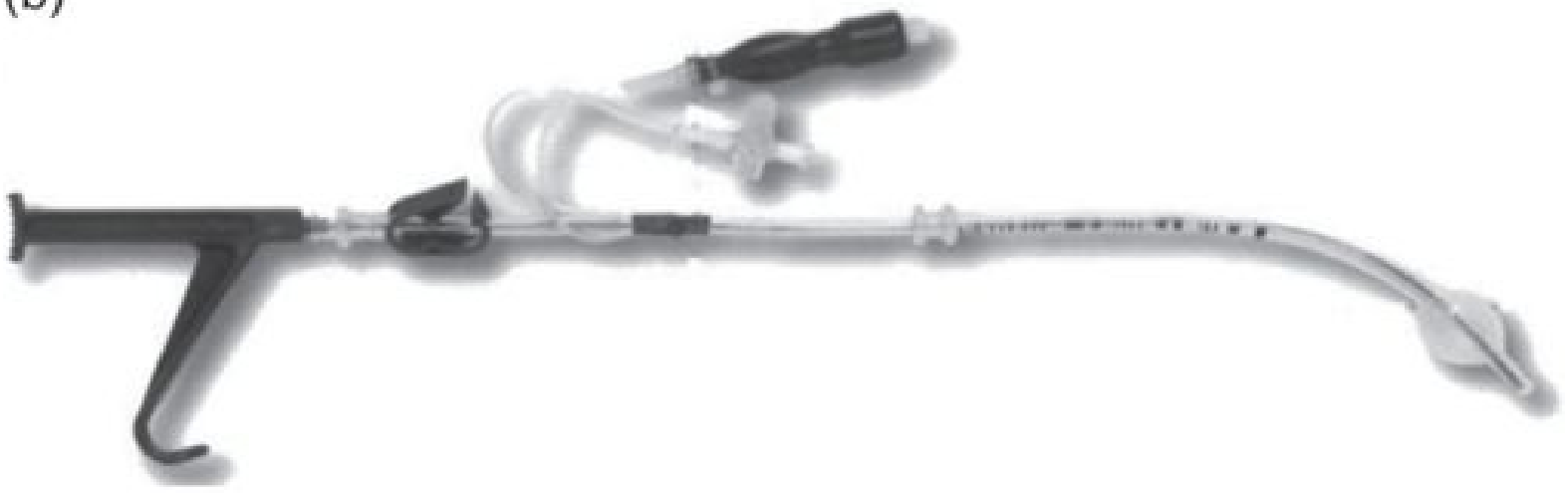
One of the major concerns during cardiac surgery is protection of the heart during the operation. Myocardial protection is discussed more fully in Chapter 7. During the period in which the heart is devoid of blood supply, the myocardial cells continue to utilize high-energy phosphates (adenosine triphosphate, ATP) to fuel metabolic reactions anaerobically. This results in depletion of energy reserves and the build-up of products of anaerobic metabolism, such as lactic acid. These processes decrease myocardial contractility in the period immediately following restoration of blood flow and myocardial function remains compromised until ATP reserves are restored and the products of anaerobic metabolism decline in concentration. Preservation of myocardial function during the ischemic period, that is, during the period in which the aorta is cross-clamped, is best achieved by putting the heart into a state of hibernation using a solution generically termed “cardioplegia.” The purpose of cardioplegia is to cause rapid diastolic cardiac arrest. This produces a still, flaccid heart, which facilitates surgery and also is the state in which myocardial metabolism is almost at its lowest levels. Further reduction in the metabolic state of the heart is achieved by cooling using cold cardioplegia and also by core cooling of the body.

The common constituent of all cardioplegia solutions is a high concentration of potassium, as this produces diastolic cardiac arrest. The other constituents of cardioplegia vary widely from normal saline solution to blood mixed with complex antioxidants. The delivery of cardioplegia may be as a single bolus, intermittent boluses or continuous infusion, or combinations of all three. The administration techniques have progressed from un-monitored pressurized delivery into the root of the aorta; current practice is discussed more fully in Chapter 7. The delivery sites for the cardioplegia vary according to surgical preference and the operation being performed and include: directly into the aortic root, the coronary ostia, the saphenous vein graft or retrograde via the coronary sinus. The flow rates and pressures that the cardioplegia solution is delivered at will vary depending on the mode of delivery. Different types of cannulae are available for delivery of cardioplegia via the various sites (see Figure 1.11).

(a)



(b)



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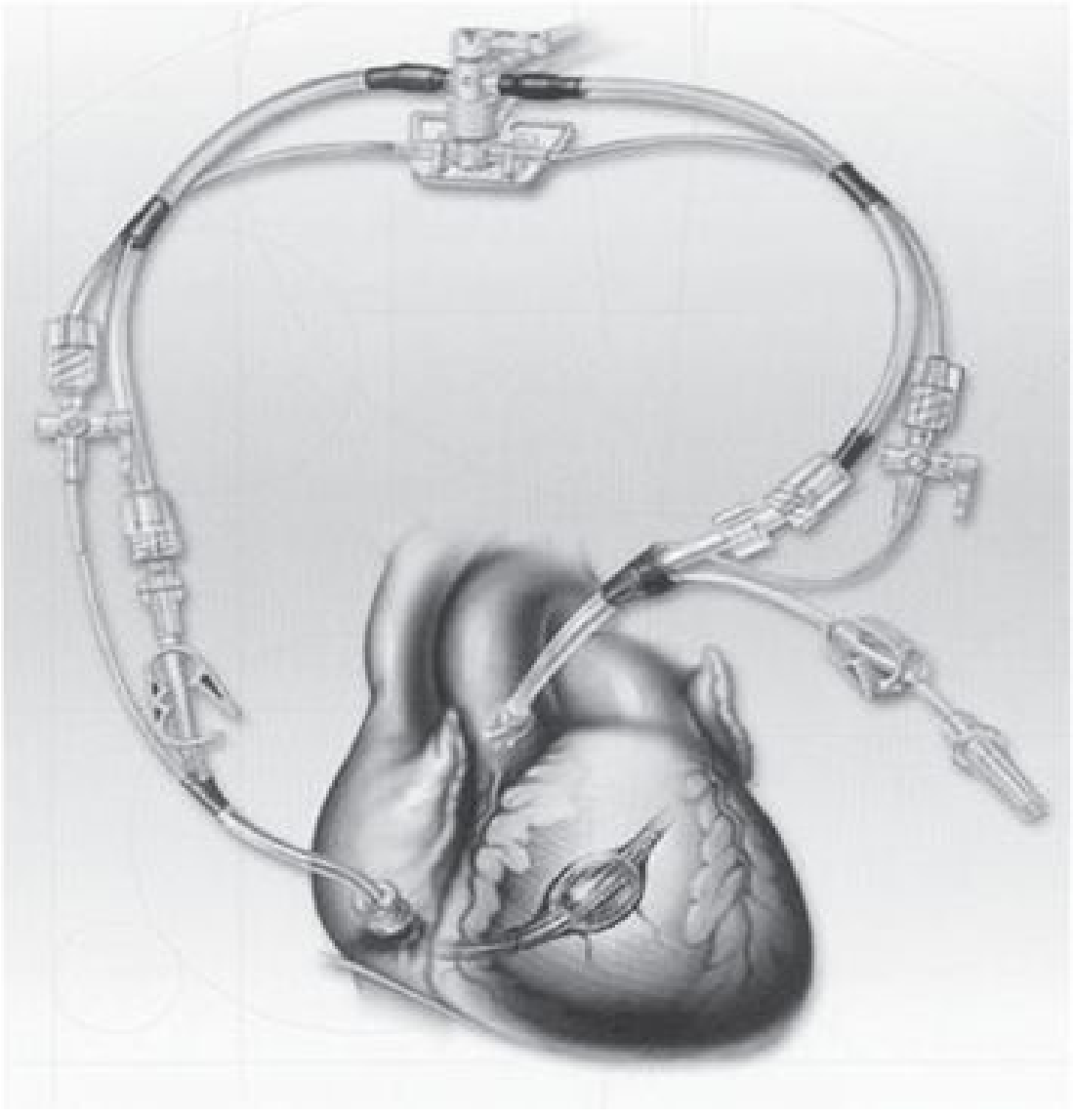

Figure 1.11 (a) Double-lumen aortic root cannula, which can be used to deliver cardioplegia and as an aortic root vent. (b) Retrograde cardioplegia delivery cannula. (c) Schematic drawing of antegrade and retrograde cardioplegia delivery.

(Reproduced with kind permission from Edwards Lifesciences.)

Many different designs of cardioplegia delivery systems are available (see Figure 1.12). Almost all of the systems allow delivery of warm and cold solutions and allow the mixing of crystalloid solutions with blood (see Table 1.7).

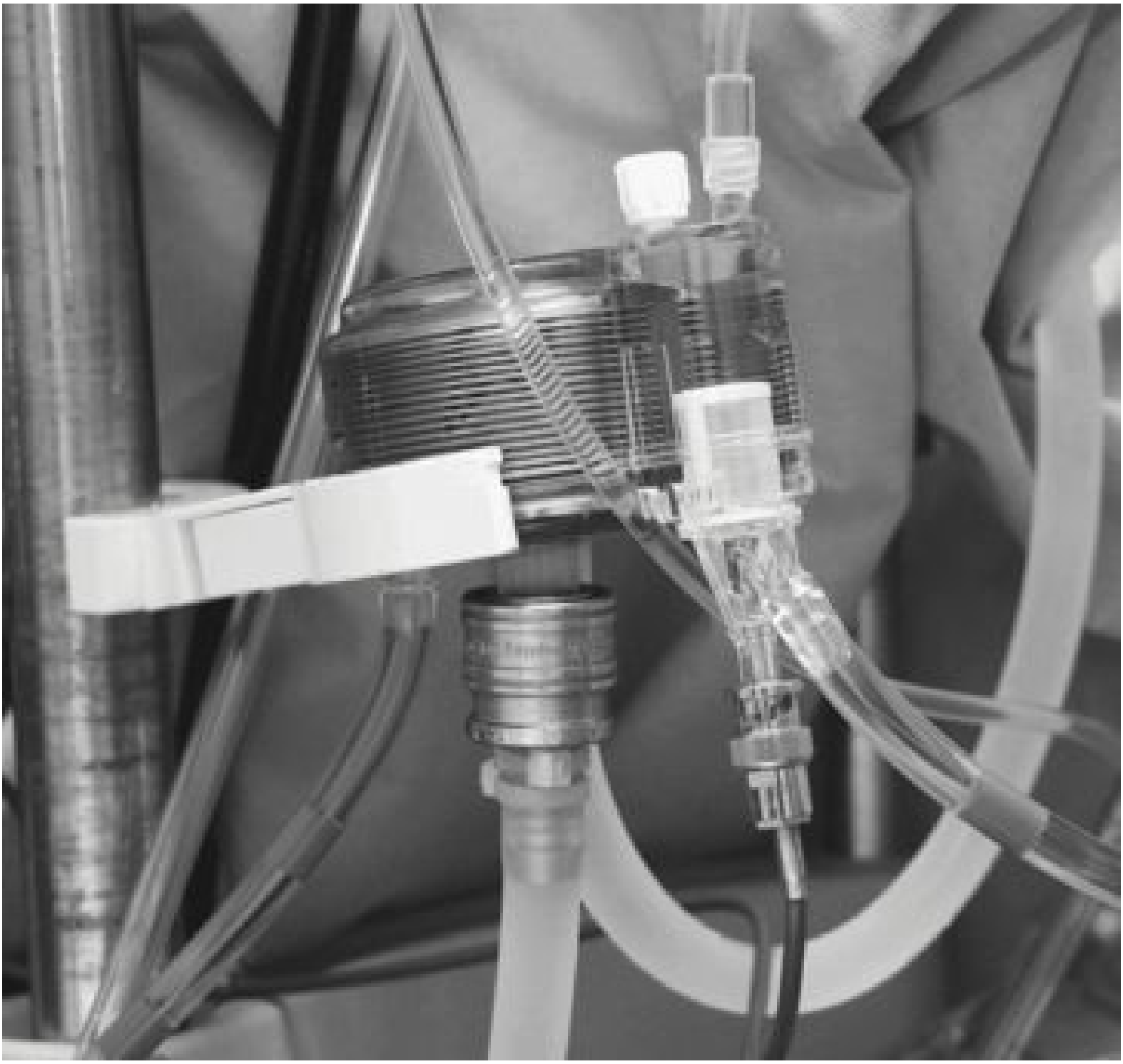

Figure 1.12 Cardioplegia delivery system: allows mixing of blood and cardioplegia solution and warming or cooling of solution before application.

Table 1.7 Cardioplegia delivery systems

Manufacturer	Integrated heat exchanger	Air trap removal	Delivery system
Sorin	Yes	Yes	Blood cardioplegia 4:1 ratio via roller pump
Medtronic	Yes	Yes	Blood cardioplegia 4:1

			ratio via roller pump (can also be used with a syringe driver for the potassium solutions)
Lifeline-Delhi	Yes	Yes	Blood cardioplegia 4:1 ratio via a roller pump
Aeon Medical	Yes	Yes	Blood cardioplegia 4:1 ratio via a roller pump

The systems also allow the monitoring of the cardioplegia infusion line pressure. This is essential when delivering cardioplegia into small vessels and the coronary sinus to prevent damage.

Hemofilters

Also known as ultrafilters or hemoconcentrators, these contain semipermeable membranes (hollow fibers) that permit passage of water and electrolytes out of blood. They are normally connected to the CPB circuit at a high pressure port or line, such as the systemic flow line, to provide a driving force for blood through the device. This allows blood to be filtered before being returned to the patient. Fluid removal is usually 30 to 50 ml/minute, and depending on the membrane used, molecules of up to 20,000 daltons are removed. Hemofiltration may be used during or after CPB, mainly to manage hyperkalemia or acidosis, but also to concentrate the blood if the hematocrit (HCT) is low and circulating volume is adequate (see Figure 1.13).

Figure 1.13 Hemofilters.

(Reproduced with kind permission from Sorin Group.)

Monitoring

Extracorporeal perfusion techniques require a large amount of vigilance from the entire team involved in the patient's care. Set-up and safety features during CPB are discussed in more detail in Chapter 2.

In-line blood gas analysis and venous saturation/hematocrit monitors

The theoretical advantages of using continuous in-line blood gas and electrolyte monitoring during CPB are well established; however, the clinical impact remains controversial. These devices may be divided into those using electrochemical electrodes and cuvettes, which are placed in the circuit, and those that use light absorbance or reflectance, which require sensors placed external to the circuit tubing.

The Terumo CDI500 in-line blood gas analyzer is an optical fluorescence and reflectance based in-line system that continuously monitors 11 critical blood gas parameters with laboratory quality accuracy (see Figure 1.14). This level of sophistication and accuracy is, not surprisingly, expensive, and is reserved in many centers for particularly complex or prolonged cases – such as when gas analysis is changed from alpha-stat to pH-stat during the cooling or re-warming periods of procedures involving deep hypothermic circulatory arrest (DHCA).

Figure 1.14 Terumo CDI 500 in-line monitoring system, providing real-time blood gas, acid/base, Hb/HCT, and electrolyte analysis.

There are more basic and commonly used forms of in-line monitoring available for use during CPB. Venous and arterial blood oxygen saturations can be continuously monitored during CPB using devices that rely on the absorbance or reflectance of infrared light signals. Although not always completely accurate, these devices are a valuable tool for observing and recording trends.

Non-invasive simultaneous arterial and venous saturation monitors are also available for use during CPB (see Figure 1.15). These have sensors that clip onto the outside of the venous and arterial tubing and continuously display venous and arterial saturations simultaneously on a screen mounted on the frame of the CPB circuit. These tools all aid safe perfusion practice and are used in conjunction with laboratory blood gas analysis.

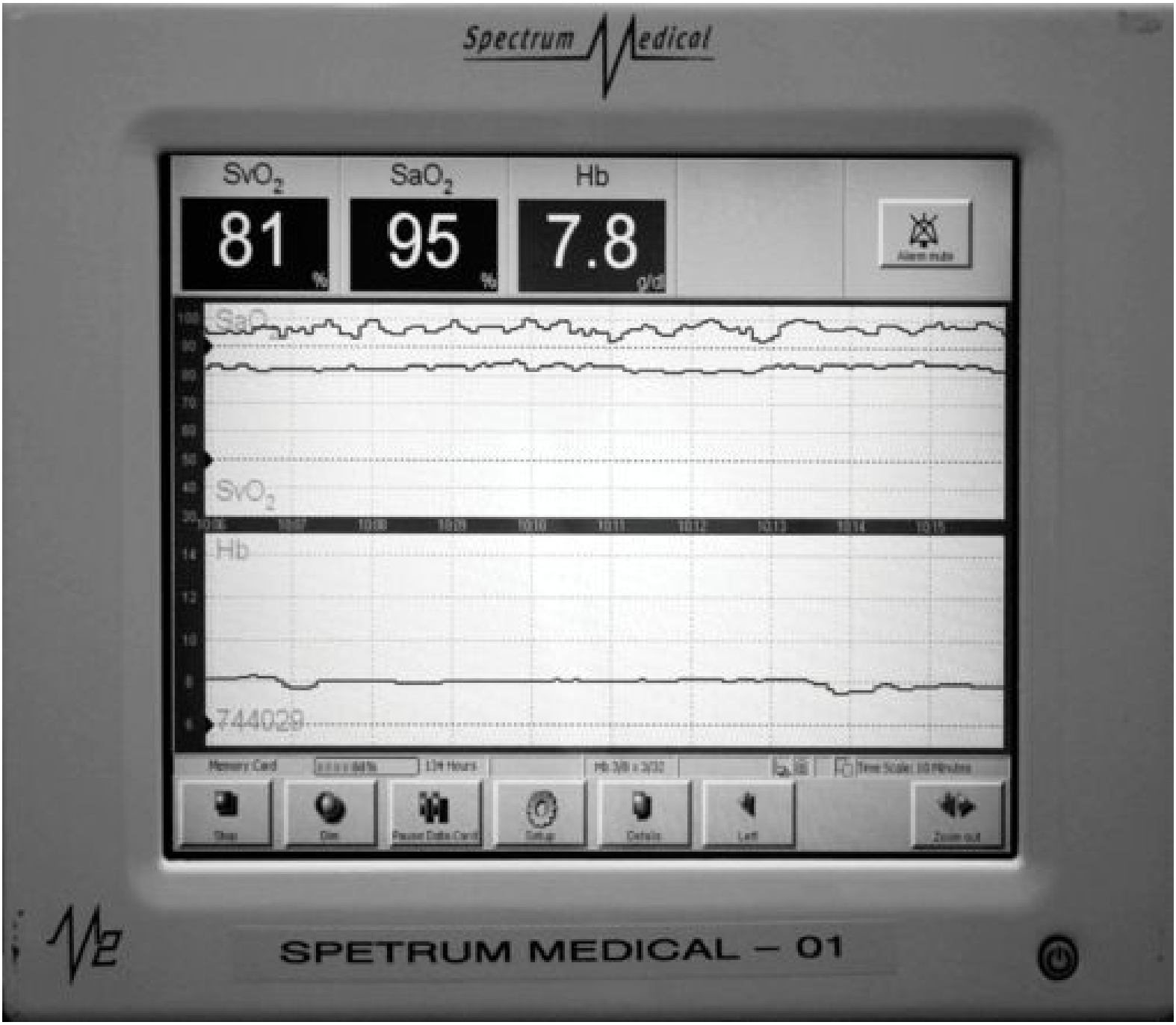

Figure 1.15 Spectrum Medical in-line real-time saturation and Hb monitoring system.

Many modern CPB machines now have integrated data acquisition modules to allow all data during CPB to be collected, printed, and stored.

Alarms

Ideally all alarm systems are linked into the computer system of the CPB circuit and directly regulate or stop the pump flow when appropriate. The alarm systems used within the circuit aid the perfusionist in running a safe pump and are all vital components of the circuit. The alarms are engaged prior to initiating CPB and are not turned off, or overridden, until the patient has been separated from CPB. The

perfusionist, in an analogous fashion to a pilot, is the main safety device for the CPB circuit and constantly monitors all of the parameters associated with running the pump.

Mini-bypass system

There has been some recent interest in the development of miniature extracorporeal circulation (see Figure 1.16a). These are designed to reduce foreign surface area, priming volume (as little as 500 ml) and blood–air contact. This leads to decreased hemodilution, and thus reduced blood transfusion requirements, and may reduce the inflammatory response to CPB.

(a)


IDEAL

(b)

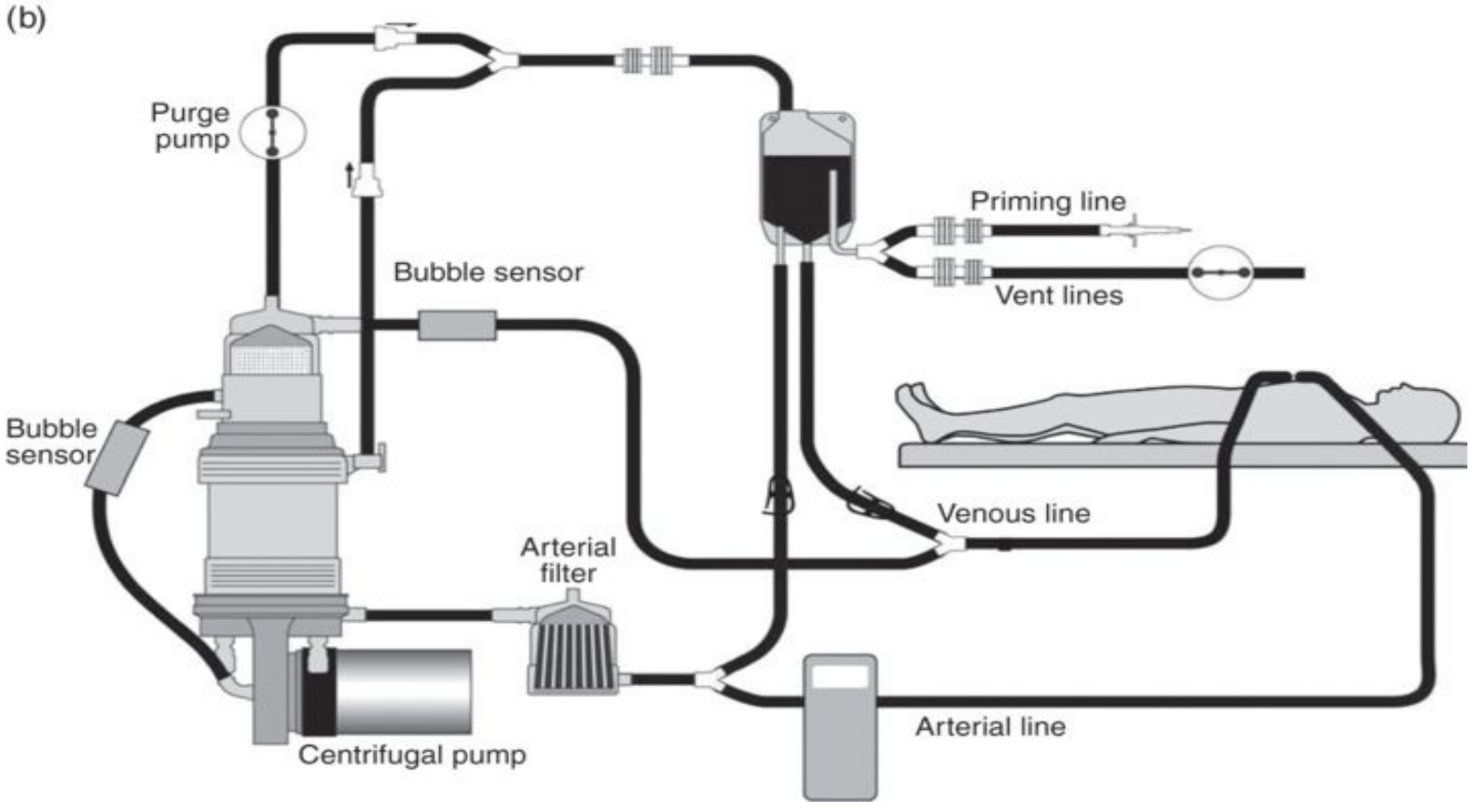
Purge pump
Priming line
Bubble sensor
Vent lines
Bubble sensor
Venous line
Arterial filter
Arterial line
Centrifugal pump

Figure 1.16 (a) Mini-bypass system. (b) Schematic drawing of mini-bypass circuit.

(Reproduced with kind permission from Sorin Group.)

Such circuits usually do not include a reservoir, heat exchanger and cardiotomy suction but increasingly incorporate arterial filters (see Figure 1.16b).

Self assessment

1. A typical CPB circuit contains:

A Oxygenator

B Centrifugal or roller pump

C Reservoir

D Carbon dioxide cylinder

E Filter

Answers: A: True; B True; C True; D False; E True

2. With regards to arterial cannulae:

A Thick-walled are preferred

B May incorporate a flange to prevent accidental dislodgement

C Should be connected to the arterial limb of the CPB circuit

D Should be > 22 G size

E Usually placed in the proximal aortic arch

Answers: A False; B False; C True; D False; E False

3. Centrifugal pumps:

A Spin at > 5000 revs/minute

B Do not directly contact blood

C Blood flow depends on systemic vascular resistance of the patient

D Reduce gaseous embolization

E Are more expensive than roller pumps

Answers: A False; B True; C True; D False; E True

4. In a standard CPB circuit, the cardiotomy reservoir:

A Should be level with the patient's heart

B Contain a filter

C Should always contain at least 800 ml blood or an alarm will sound

D Drainage may be vacuum-assisted

E Are effective at defoaming blood

Answers: A False; B True; C False; D True; E True

5. A standard oxygenator:

A Has lots of solid fibers

B Is most commonly a membrane-type design

C Is re-usable (not single use)

D Fibers are made of polypropylene

E Can be used for > 24 hours

Answers: A False; B True; C False; D True; E False

6. Reasons for placing a surgical vent in the heart during CPB include:

A To stop the heart emptying

B To reduce myocardial re-warming

C To help with de-airing

D To help keep a bloodless surgical field

E Surgical vents are not required in modern cardiac surgery

Answers A False; B True; C True; D True; E False

7. With regards to mini-bypass (miniature extracorporeal circulation):

A No cardiotomy reservoir included

B No cardiotomy suction included

C No cardioplegia included

D Heater-cooler included

E Reduces inflammatory response to CPB

Answers: A True; B True; C False; D False; E True

Suggested Further Reading

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Chapter 2

Cardiopulmonary bypass circuit set-up and safety checks

Hannah Kiziltug and **Simon Colah**

Assembling the cardiopulmonary bypass (CPB) circuit and checking the CPB machine for faults prior to clinical use is an essential part of the provision of extracorporeal perfusion. This chapter describes the procedure for 'setting up' the CPB system and the safety checks which should be undertaken before embarking on a case.

Philip Kay and Christopher Munsch in *Techniques in Extracorporeal Circulation* state: "Cardiopulmonary bypass is a dynamic artificial environment conferring a shock state on the body with its own potential for severe morbidity and mortality". Vigilance is thus paramount to the conduct of CPB. Modern perfusion systems are designed to optimize safety. Technological advances have seen the incorporation of automatic alarms and fail-safe devices; however, the perfusionist's attention to detail and observance of pre-bypass checklists and protocols still underpins safe practice. Human error is a far greater cause of accidents than mechanical mishap.

Preparing the CPB circuit and machine, attention to the patient's clinical details, and the surgical requirements for the procedure all form part of the process of safe provision of CPB. By necessity the preparation of the CPB machine and assembly of the disposable circuit components should "ritualistically" follow a routine dictated by institutional protocols.

CPB machine preparation and circuit set-up

CPB circuits are made up of a number of disposable items. Principally these are:

- the integrated membrane oxygenator/hardshell (or softshell) venous reservoir,

- cardioplegia set,
- arterial line filter, and
- custom tubing pack.

All components are rigorously checked. In particular, the disposable items are closely examined with regard to expiry date and integrity of the packaging.

There are many ways to set up a CPB circuit. Departmental preferences and specific patient requirements dictate the approach. A commonly used sequence for setting up and priming a standard CPB system is outlined in Appendix 2.1, together with a synopsis of electronic safety devices in Appendix 2.2, at the end of this chapter.

Securing the gas hoses to the gas source, checking that gas supplies of air and oxygen are functional, and attaching the scavenging line initiates the process. The CPB machine console is then powered and temporarily disconnected ascertaining that the power failure alarm and back-up battery unit are fully functional. Most operating rooms have an uninterruptible power supply (UPS), essentially a series of batteries linked to the hospital generator that powers the CPB machine, anesthetic machine, intravenous infusion pumps, and other vital equipment should there be a mains power failure. It is essential that the CPB machine is connected to a UPS.

The integrated oxygenator/venous reservoir is placed on its secure holder and orientated to allow full view of the reservoir. The oxygen/air delivery line and scavenging hose are attached to the appropriate ports on the base of the oxygenator. The sampling port manifold is positioned with taps secured. Tubing to the dedicated systemic, arterial flow pump is put into place and connected to the venous reservoir outlet and oxygenator inlet. The cardioplegia tubing is positioned, but not aligned at this stage, in the designated pump backplate. This expedites the priming of the cardioplegia circuit. The cardioplegia delivery system differs from the systemic flow pump or sucker pumps in that a pump which accommodates two segments of tubing with varying diameters within it may be used, so that blood and cardioplegia solution mixed in the desired ratio (usually 4 parts blood to 1 part cardioplegia) can be dispensed. Alternatively two separate pumps may be used to independently deliver the blood and cardioplegia in a 4:1 ratio.

Roller pump heads are checked to ensure that they only rotate in one direction.

The arteriovenous loop (A-V loop), which when divided will be connected to the venous and arterial cannulae by the surgeon, is connected to the venous reservoir inlet and oxygenator outlet. The arterial line filter (with bypass link), pressure transducer, and bubble detector are attached to the systemic flow tubing (see also Figure 1.1). The bubble detector is coupled to the CPB machine console so that if air is sensed in the arterial line an alarmed automatic pump cut out facility is activated. Likewise, the

transduced pressure in the arterial line links to the CPB machine console, so that if the line pressure exceeds a set limit (usually 350 mmHg), through unintentional clamping or kinking, the pump will stop. This is preceded by slowing of the pump at a slightly lower pressure threshold (usually 300 mmHg). Suction and venting tubing (color coded for safety and ease of use) are then fixed into the various roller head assemblies. Two sets of water lines from the heater/cooler unit are attached to the oxygenator and blood cardioplegia heat exchange device. Water is circulated to ensure that there is no dangerous water leak.

The cardioplegia pressure transducer and purge lines are connected to the cardioplegia delivery device.

Just prior to priming, the arterial line filter is flushed with CO_2. Once flushed and the CO_2 is turned off and disconnected, the arterial line filter inlet and outlet and the cardioplegia delivery line are clamped off. The arterial line should also be clamped if there is a recirculation shunt line distal to the arterial line filter. Some centers flush the whole circuit with CO_2 to displace air. This reduces the risk of gaseous emboli as carbon dioxide is nearly 30 times more soluble in blood than nitrogen.

One to two liters of prime fluid is added to the venous reservoir. The arterial pump is turned on at approximately 4–5 l/minute while the perfusionist observes prime filling the pump tubing, the oxygenator, and any ancilliary lines. These must be closed or clamped after priming while fluid recirculates via the arterial recirculation line back into the venous reservoir. The arterial pressure dome is primed and secured to the transducer, the arterial line filter is retrogradely primed, and its bypass line clamped. Flow through the A-V loop is established, left-recirculating and inspected for air bubbles, before clamping the recirculation line. It is necessary to ensure that the cardioplegia circuit is primed and air free and that the pump occlusions have been adjusted, so that they are just “under-occlusive.” The arterial and venous lines are then clamped and the prime allowed to recirculate through the filter and purge lines.

There are two ways to check the roller heads for occlusion: either check each roller at the “6 o’clock” position or together at the “9.15” position, with the circuit pressurized at 250 mmHg and the arterial line clamped. Any rapid drop in pressure may indicate that connections are not secure or that an “occlusion” has been incorrectly set. Centrifugal pumps are non-occlusive and should be gravity filled to ensure good de-airing. Centrifugal consoles have integrated flow probes that are unidirectional. As they are afterload sensitive, pump speed must be set to produce forward flow before initiating bypass.

The inflow to the sucker pumps is clamped and the rollers are adjusted to avoid collapse of the tubing. The vent line should have a one-way, pressure relief valve in-line to prevent inadvertent air entry into the heart and to prevent cavitation inside cardiac chambers.

Temperature probes are placed into the arterial, venous, and cardiolegia ports and visualized on the LED display. The level sensor is placed at, or above, 400 ml and the bubble detector placed on the

arterial line distal to the filter. All alarms, pressure ranges, timers, and cardioplegia parameters can now be set in preparation for bypass.

Mini-bypass circuit safety features

Mini-bypass techniques have been developed in an attempt to reduce priming volume and hence the degree of hemodilution and requirement for blood transfusion. In addition mini-bypass circuits may lessen the inflammatory response and microembolic load associated with CPB. The system is designed as a completely closed circuit eliminating blood to air contact. Mini-bypass uses a centrifugal pump without a reservoir, a computer chip driven bubble trap and an air protection system (APS) that operates an external pump to remove any trapped air. An additional bubble trap can be used in the aortic vent line, and is connected to the main venous line. These bubble traps prevent any unwanted air entering the centrifugal pump, which can cause air locking of the pump and halt the flow of blood. The pressure measured in the venous line ranges from −25 to −75 mmHg and is dependent on preload, pump speed, blood viscosity, cannula size, and placement. A closed venous bag is connected to the arterial and venous sides of the circuit and the air protection circuit. It enables ease of priming, adding volume and air handling as well as the ability to perform retrograde autologous priming.

The functions of the safety devices used along the circuit are as follows:

- Air emboli protection pre-venous bubble trap – becomes activated on detection of air in the venous line, sending a signal to a computer chip in the roller pump which turns on and removes air from the top of the bubble trap to the soft shell bag where it can be expelled. The pump is set to operate for 5 seconds and stop in the event of air recognition. Occlusion setting on the pump is essential. In addition to the APS there is a ramp down chip in the centrifugal console that is programmed to reduce pump speed to 1000 rpm allowing more time for air removal.
- Level sensor on the vent bubble trap – if there is a reduction in the volume of blood in the bubble trap due to displacement by entrained air, the level sensor is activated and operates the automatic arterial clamp. This temporarily stops flow, allowing air to be removed.
- Negative pressure control – If preload falls such that the RA or IVC become adherent to the cannula tip, cavitation and loss of venous return can occur. The negative pressure control, set at −90 mmHg, triggers the pump speed to ramp down; this reduces the negative pressure, allowing extra fluid to be added, thus restoring equilibrium of blood supply and delivery.

- Bubble detector post bubble trap – If the venous bubble trap fails to eliminate sufficient air the pump may de-prime. If air begins to pass towards the pump the autoclamp is triggered to stop flow. Air anywhere in the system can be displaced up into the soft shell bag.
- Ultrasonic blood flow meter provides accurate flow measurement.
- Automated arterial clamp – placed after the oxygenator, protects the patient during adverse events, such as retrograde flow and is activated much faster than the perfusionist could react manually.
- Line pressure autoclamp control – similar to that used in a conventional circuit, is triggered when the circuit pressure exceeds 300 mmHg.

Each one of the safety devices must be tested and checked before connecting the circuit to the patient. The APS module is set up to control the number of revolutions of the roller pump, controlling air removal. This system must never be turned on if there is no flow or pressure in the circuit as it will pull air across the membrane into the circuit.

An emergency back-up plan, with all equipment and supplies available in the event of mechanical failure or uncontrollable venous air, should be in place to be instituted if needed.

A cell saver can be used to process cardiotomy blood, although some centers attach a cardiotomy reservoir to the mini-bypass circuit to collect shed blood. Blood cardioplegia is connected and used in the same way as in the conventional system.

Mini-bypass circuit assembly

The circuit, developed at Castle Hill Hospital, Hull contains:

- Sorin ECCO oxygenator® with integrated Revolution pump and APS
- AV sash with pre-bypass filter and arterial filter
- Vent bubble trap (VBT)
- soft shell venous reservoir(SHVR)
- Air removal line with one-way valve used with APS
- Three-way taps, monitoring lines with pressure isolators, connectors, and manifold
- Vent sucker line, table tubing harness, and quick prime line

Mini-bypass assembly and checks

- Mount the SHVR, ECCO, and pump, connect the oxygen line and external oxygen saturation lines
- Connect the arterial and venous lines to the ECCO
- Place the VBT between the SHVR and venous line
- Place drug manifold from the arterial filter to venous line
- Connect negative pressure and APS purge line to the top of the VBT
- Connect the end of the APS line to the SHVR via the dedicated computer-controlled pump
- Connect the oxygenator recirculation line to the SHVR

Priming mini-bypass

- Flush the circuit with carbon dioxide
- Connect water lines, recirculate and check for leaks after 5 minutes
- Clamp the oxygenator and venous recirculation lines
- Clamp out the VBT
- Clamp out the arterial filter, place a clamp on the venous line close to the VBT
- Add priming volume 1000 ml Hartmann's solution and 300 ml 10% mannitol via the quick prime line to the venous bag
- Remove the recirculation clamps allowing prime to displace air up into the bag. Remove air from the top of the bag and turn on the air purge controller (APC) pump. Gently tap the oxygenator to ensure total air removal
- Remove the proximal arterial filter clamp and allow the filter to prime
- Remove the distal arterial clamp and gently remove all air from the arterial filter
- With the APS on, control the AV line air removal by removing the venous clamp slowly, never allowing the VBT to empty
- Prime and clamp out the VBT and place the appropriate tube and connector to link the vent line when handed down from the table
- Prime the pressure isolators and connect to their respective transducers
- Add 5000 units of heparin and recirculate

- Complete set-up checklist

Design and use of a pre-bypass checklist

Experience from other high-risk industries, such as aviation or maritime, demonstrate that disasters are often associated with poor checking procedures. The format of the CPB checklist is either written or automated and best signed off by two perfusionists. Ideally, the primary perfusionist does the checking while the second perfusionist works through the list. The American Society of Extra-Corporeal Technology and the European Board of Cardiovascular Perfusion publish an excellent array of perfusion guidelines and checklists (see Figure 2.1). The list covers all aspects from sterility to back-up components.

Pre-bypass checklist

☐ **Patient:** _____

☐ ID correct

☐ Chart reviewed

☐ **Sterility**

☐ Components: integrity and expiry date

☐ **Heart-lung machine**

☐ Power connected

☐ Start-up normal

☐ Back-up power

☐ **Heater-cooler**

☐ Start-up normal

☐ Water connections: flow verified

☐ Water temperature: _____°C/F

☐ **Gas supply**

☐ Gas lines connected

☐ Flow meter/blender in order

☐ Vaporizer shut off

☐ CO_2 flush

☐ **Pump**

☐ Roller heads not obstructed

☐ Flow meter: calibration & direction

☐ Tubing holders secure

☐ Occlusion set: _____ mmHg

_____cmH_20/min

☐ **Tubing**

☐ Pump tubing condition inspected

☐ Suckers functional and sucking

☐ One-way valves: direction correct

☐ Circuit shunts closed

☐ **ID:** _____

☐ **Monitoring**

☐ Temperature probes positioned

☐ Pressure transducers calibrated

☐ In/on-line sensors calibrated

☐ **Safety & alarms**

☐ Low-level alarm engaged

☐ Air detector engaged

☐ Pressure alarm limits set

☐ Temperature alarm limits set

☐ Cardiotomy reservoir vented

☐ **Oxygenator**

☐ Gas line attached

☐ Heat exchanger integrity inspected

☐ Scavenger attached

☐ **Debubbling**

☐ Tubing

☐ Oxygenator

☐ Cardioplegia

☐ Arterial filter/bubble trap

☐ **Accessories**

☐ Tubing clamps

☐ Hand cranks

☐ Backup circuit components

☐ **Anticoagulation**

☐ Heparin in: _____time

☐ Patient properly anticoagulated

☐ **Ready to start bypass**

☐ Signature: .....

Figure 2.1 Pre-CPB checklist (reproduced by kind permission of The European Board of Cardiovascular Perfusion). The EBCP (www.ebcp.org) promotes the use of pre-bypass checklists in the practice of clinical perfusion. The suggestions in this checklist are designed as the minimum requirements for CPB procedures and each institution should adapt this to suit its own requirements. The EBCP can accept no liability whatsoever for the adoption and practice of this suggested checklist.

Safety concerns prior, during and after CPB

Before embarking on a case the perfusionist should review the patient's notes. The most important details are:

- planned procedure and likelihood of additional procedures,
- allergies,
- significant co-morbid conditions, such as diabetes or renal dysfunction, and
- metabolic or hematological abnormalities, such as anemia, thrombocytopenia or hyperkalemia.

The patient's blood group should be confirmed and the availability of bank blood checked.

Details of the patient's height and weight are essential to calculate:

- dose of heparin (usually 300 mg/kg) required for CPB,
- body surface area (BSA) in meters^2, which is required to determine the "ideal" flow rate at normothermia (BSA × cardiac index) and so to select appropriately sized venous and arterial cannulae, and
- predicted HCT on initiation of CPB

Safety issues relating to the pre-, intra-, and post-CPB periods are summarized in Tables 2.1, 2.2, and 2.3.

Table 2.1 Pre-CPB safety concerns

Heparin given, activated clotting time (ACT) > 400 seconds
Arterial cannula correctly placed, pulsatile swing on an anaeroid pressure gauge connected to a side arm of the arterial line
Venous reservoir has a safe level of prime, additional fluid available to add, low-level alarm activated

Oxygen analyzer monitoring gas supply to oxygenator on, alarm activated

Sweep rate appropriate for patient (usually 2–3 l, $FiO_2 = 0.6$)

Venous cannula relatively free of air

Shunt lines are clamped, apart from arterial filter purge line and drug administration manifold line

No clamps on the arterial or venous lines placed by surgical team

Alarm overrides deactivated

Vasopressors prescribed and available

Table 2.2 Safety concerns during CPB

Concern	Common causes
Low-level alarm on venous reservoir	Impaired venous return Tubing kinked Air lock Hemorrhage Misplaced venous cannula Clotting within circuit
High-pressure alarm on arterial line	Clamping or kinking of line Manipulation of the aorta Clotting within circuit Aortic dissection
Bubble alarm	Air in line Sensor malfunction
Low mixed venous oxygen saturation	Erratic flow Considerable time spent with suboptimal flows Hemorrhage Depth of anesthesia lightening Shunt clamp inadvertently removed

	Excessive transfusion with non-blood products
Clotting	Inadequate heparinization
Poor blood gases despite adequate sweep gas delivery and pump flow	Oxygenator failure
Electrical activity of the heart	Intervals between cardioplegia too long Too little cardioplegia delivered Aortic regurgitation
Hyperthermia	Overaggressive re-warming strategy Failure to maintain temperature gradient between heat exchanger and venous blood < 10°C

Table 2.3 Safety concerns on separating from CPB

Ventilation not established
Intracardiac vent still in place
Shunt lines open on CPB with the potential to exsanguinate the patient into circuit
Suction still in use during protamine administration
Inattention to level in venous reservoir while transfusing
Draining the venous line while cannula still positioned in the right atrium
Dismantling the CPB circuit before hemodynamic stability has been achieved

Conclusion

Surveys by Jenkins *et al*. (1997) and Mejak *et al*. (2000) report the number of pump-related incidents to be 1:140 and the likelihood of permanent injury or death of the patient after such an incident to be 1:1350. A multitude of health care organizations, not least the Institute of Medicine (IOM), have called for a 90% reduction in preventable patient injuries.

Since the beginning of CPB in the early 1950s the focus on safety has evolved and improved. Today, the quality of components is excellent. CPB machines incorporate in-built alarms with autoregulatory feed back systems, together with real-time data acquisition. Yet surveys confirm the mishap rate is slow to fall. Accredited training, scrupulous attention to detail, and use of checklists and protocols will hopefully continue to improve safety. The key factors contributing to a safer perfusion service are summarized in Table 2.4.

Table 2.4 Key factors contributing to a safer perfusion service

Accreditation of training programs
Certification and re-certification of perfusionists
Conferences, yearly appraisals, departmental quality assurance meetings
Reporting of adverse occurrences
Quality in-house training
Electronic data acquisition with associated audit facilities
Departmental protocols, especially outlining procedures in abnormal and emergency situations
Manufacturer product alerts acted on
Equipment maintenance records and quality assurance logs kept

Self assessment

1. Regarding CPB circuits:

A The bubble detector ensures that an alarm sounds and the pump cuts out in the presence of air in the arterial line

B The CPB machine must be connected to a universal power supply (UPS)

C The cardioplegia delivery system pump may accommodate separate segments of tubing of differing diameter; one for blood and one for cardioplegia solution

D The circuit may be flushed with CO_2 before priming with heparinized solution

Answers: A True; B False; C True; D True

2. The non-disposable parts of the CPB circuit include:

A The venous reservoir

B The arterial line filter

C The heat exchangers

D Roller pumps

E The cardioplegia set

Answers: A False; B False; C True; D True; E False

3. Prior to initiating CPB it is essential to check the following patient parameters:

A Age

B Allergies

C Height and weight

D Blood group

E Sex

Answers: A False; B True; C True; D True; E False

4. While on CPB common causes for a high-pressure alarm on the CPB circuit arterial line include:

A Air lock

B Clotting within the circuit

C Hemorrhage

D Aortic dissection

E Depth of anesthesia lightening

Answers: A False; B True; C False; D True; E False

5. Safety features present on a CPB circuit include:

A Bubble detector with alarm and automatic pump cut-out facility

B Pressure transducer usually set to 350 mmHg

C Level sensor on the venous reservoir system set at or above 200 ml

D Temperature probes with out-of-range temperature alarm

E Color-coded tubing

Answers: A True; B True; C False; D True; E True

6. With regard to safety when using mini CPB:

A The air protection system can safely be turned on when there is no flow in the circuit

B A fall in blood volume in the VBT is detected by the level sensor which is activated to clamp the automatic venous clamp

C The negative pressure control is usually set to −90 kPa and if preload falls triggers the pump speed to decrease thus reducing the negative pressure

D A full emergency back-up plan including all equipment must be available in the event of mechanical failure

E Activation of the air protection system causes the roller pumps to turn, removing air from the top of the bubble trap

Answers: A False; B False; C False; D True; E True

7. When considering priming of a mini-bypass circuit:

A An initial CO_2 flush is not required

B The oxygenator is primed prior to the arterial filter

C A greater volume of prime is required for a mini than a conventional bypass system

D During the priming process the VBT must be allowed to completely empty

Answers: A False; B True; C False; D False

8. When setting up a CPB circuit, place the following events in the correct order

1 Prime the line

2 Check the power source and UPS

3 Connect the gas hoses to the gas source

4 Flush the line with CO_2

5 Connect the oxygenator/venous reservoir

A 3 2 5 1 4

B 2 3 5 4 1

C 5 2 3 4 1

D 3 2 5 4 1

E 5 3 2 1 4

Answer: D

Appendix 2.1

Procedure for setting up and priming a standard heart–lung bypass system

(adapted, with permission, from *London Perfusion Science* Protocols)

1.1 The heart–lung machine and accessories

1.1.1 Connection checks:

(a) All cables, plugs and sockets are checked

(b) All cables should be laid neatly, so that they are not likely to be damaged and where they are least likely to cause accidents

(c) All parts of the apparatus, including heater/chiller and pump light (if it is to be used) are checked for power

(d) Gas lines are fitted to the wall outlets and connections; hoses, mixers, and flow meters are checked for leaks

(e) Gas flow to the oxygenator is checked

1.1.2 Each pump head is checked:

(a) For power

(b) The rollers and guides are moving

(c) The pump heads are free from foreign bodies

(d) The pump heads are set to rotate in the correct direction

(e) The flow/rpm settings on the console are accurately calibrated

(f) For winding handles

(g) That the tubing inserts are of the correct size for the tubing to be used

1.1.3 That other electrical safety devices are in working order:

(a) Battery back-up (UPS) is charged

(b) Pressure transducers

(c) Level detectors

(d) Bubble detectors

1.2 The set-up of disposable heart–lung equipment

1.2.1 The oxygenator:

(a) Remove packaging and check its integrity and sterility

(b) The oxygenator is examined for obvious faults and debris

(c) The oxygenator is placed securely into its holder

(d) Any gas outflow cap is removed

(e) The gas connection is made

(f) Remove any venting cap on the reservoir

(g) The CO_2 flush is initiated until priming

(h) The water connections to the heater/chiller are now made, the heat exchanger and all connections are checked for leaks with the water running at 37°C

1.2.2 The circuitry

(a) Remove packaging and check its integrity and sterility

(b) The circuitry is checked for faults (cracked connectors, kinked tubing, etc.)

(c) Check the silicone pump boot and place so it is lying correctly in order to prevent wear or damage from the tube guides or rollers

(d) Check that the pump boot tube is securely held at both the outlet and the inlet. Rotate the pump to check the tubing is correctly seated

(e) Do the same with sucker tubing, checking direction of flow

(f) With attention to sterile technique, connect the pump lines to the oxygenator, ensure they have been connected in the correct direction and not crossed over

(g) The lines should be sufficiently long that they may be moved to the neighboring pump head if necessary

(h) Any cuts to tubing should be made cleanly and perpendicular to the length of the tubing, using a sterile blade

(i) The outflow line should now be connected to the outflow port of the oxygenator

(j) The recirculating lines should now be similarly connected as required by the manufacturer's specifications

(k) All pressure connections can be made secure using nylon ties

1.2.3 The cardiotomy reservoir if required:

(a) The cardiotomy reservoir can be used for any surgery where intracardiac clot is suspected, where it is anticipated that large quantities of blood will be used, or where the use of auto transfusion is anticipated

(b) The reservoir and its packaging is checked as above and inserted into the appropriate holder

(c) Remove any venting cap and using the ⅜" cardiotomy return, connect the cardiotomy to the oxygenator, ensuring that this return line cannot be kinked or obstructed

(d) Connect the sucker lines and recirculation lines to the cardiotomy reservoir

1.2.4 The cardioplegia system if required:

(a) Remove packaging and check its integrity and sterility

(b) The circuitry is checked for faults (cracked connections, kinked tubing, etc.)

(c) Assemble circuit according to the manufacturer's instructions

(d) Ensure all connections (oxygenator, recirculation lines, etc.) are secure and correct

(e) Water lines are connected to the cardioplegia administration set heat exchanger Water is circulated to ensure that it is free from leaks

1.2.5 The centrifugal pump if required:

(a) Remove packaging and check its integrity and sterility

(b) The relevant flow and drive connectors should be connected to the console

(c) The battery charger should be examined to determine whether or not there is sufficient battery back-up

(d) The perfusionist should check that the relevant hand-crank mechanism is available in case of power failure

(e) The drive motor heads must be examined for dirt, as this may impair the function of the device, including the possibility of disengagement

1.2.6 Arterial line filters if required:

(a) Check the filter for sterility, any damage or debris

(b) If the filter is to be cut into the arterial line this should be carried out using the appropriate sterile technique

(c) Ensure the filter holder is positioned to prevent the stretching or kinking of lines

(d) Position the filter securely in the holder

An air bubble trap would be primed in a similar fashion.

1.2.7 Cell saver if required:

(a) Remove outer packaging and check its integrity and sterility

(b) Open the collection reservoir portion of the set and secure firmly in holder

(c) Connect the vacuum source to the reservoir

(d) The washing portion of the set should only be opened when either enough blood has been collected to salvage or the perfusionist is confident that enough blood will be collected to salvage

(e) The washing portion of the set should be assembled neatly

(f) All ports and connections should be checked, closed, and tightened where necessary

1.2.8 Pre-bypass filters if used:

If the circuit contains a pre-bypass filter there are a number of points the perfusionist must remember:

- The pre-bypass filter should be removed before priming the circuit with blood
- The pre-bypass filter should be removed if the low pressure suction is required before the lines have been divided

A ½" × ⅜" connector should be readily available to replace the pre-bypass filter if necessary.

1.3 In-line blood chemistry/gas analyzer (e.g. CDI 500) set-up and calibration

1.3.1 Set-up of CDI 500 arterial sensor shunt:

(a) Turn off monitor and after the monitor has self-tested select the required configuration of the sensor shunt

(b) Select calibration

(c) Verify the K* calibration value on the sensor packaging

(d) Check that the calibrator's cable is connected to the monitor

(e) Remove the blue cap from the base of the sensor shunt and attach to one of the calibrator's ports

(f) Loosen the blue cap on the top of the sensor shunt

(g) Initiate calibration by pressing √ twice on the monitor

(h) Calibration lasts 10 minutes

(i) After calibration tighten large luer cap and remove gas filter

1.3.2 Set-up of CDI 500 venous line sensor:

(a) Remove venous sensor from packaging and cut into venous line

(b) After the monitor has been switched on and has self-tested the venous probe can be connected to the venous sensor

1.4 Priming the system

The perfusionist should ensure if possible that the following patient details are available from the anesthetic and surgical staff, to provide a basis on which to decide the priming strategy:

- Height and weight
- Renal status
- Hb/HCT
- Heart size
- Fluid status

1.4.1 Standard prime:

(a) 1 l Hartmann's solution is checked

(b) Preservative-free heparin should be injected into the liter bag of Hartmann's (dose per liter of prime as per institutional protocol) and labeled

(c) The Hartmann's is run into the system via a giving set or rapid prime line. It is important that this heparinized prime runs through the length of the circuit (i.e. all filters are exposed to this heparinized prime). The prime is delivered via a cardiotomy port (if a cardiotomy is in use)

(d) The reservoir should be inspected for obvious bubbles and tapped to remove them

(e) Sufficient prime should be added to the system to maintain a dynamic priming volume

(f) It is most important at this stage that the oxygenator manufacturer's instructions are carefully adhered to

(g) Turn off the CO_2 flush

(h) A gravity feed prime is undertaken, with de-bubbling taking place in a logical fashion, beginning with the oxygenator reservoir and progressing to the arterial line and so on

(i) The "sash" should be clamped off, the arterial pump switched on, and the prime recirculated

(j) The pressure line may now be connected, via an air-free isolator to the line pressure gauge and pressure transducer

(k) The recirculation lines are securely clamped, and the "sash" primed

(l) It is important to remember that air is easily dragged across the membrane of hollow fiber oxygenators, therefore the following precautions should be taken to avoid this:

- The venous line should be partially occluded so as to offer a resistance, and therefore maintain a positive pressure as the prime is recirculating
- The pump should be switched off slowly to avoid the momentum effect (see below)

(m) When the circuit appears clear of bubbles, the recirculation rate should now be increased to around 5 l/minute, to remove any bubbles from within the oxygenator membrane with the venous line partially clamped maintaining a post-membrane pressure of around 80 mmHg. Before the "sash" is divided, a final check must be made by both perfusionist and surgeon for the presence of bubbles. Before stopping the recirculation, the pump should be turned down slowly reducing the chances of the inertia effect of a sudden reduction in flow that would cause air to be dragged across the membrane

1.4.2 Priming cardioplegia if required:

(a) The type, temperature, and concentration of blood cardioplegia should be determined from the surgeon in advance. This information should be held in the hospital's database (e.g. proportion 4:1, 2:1, etc., the need for any "hot shots," etc.)

(b) Bags of Ringer's solution should be carefully prepared. The vials of cardioplegia should be carefully checked before injection. The bags must be labeled clearly as soon as this has been done.

(c) The cardioplegia circuit is primed with Hartmann's solution or Ringer's solution checking that all air has been purged

(d) During priming, care must be taken that the main prime does not become contaminated with cardioplegia

(e) The cardioplegia pump boots are placed in the raceway and appropriate-sized collets fitted (if applicable), or a check is made to ensure that the ratio is correctly programmed into the pump console

(f) The occlusion of the pump is then set as with the arterial pump (see later)

1.4.3 Priming the arterial line filter if required:

(a) Place clamps either side of the arterial filter before the oxygenator is gravity primed

(b) Once the circuit is primed, stop the pump, slowly release lower clamp and allow prime to flow retrogradely through the filter via the bypass line, expelling air through the purge line. The retrograde flow is provided by the prime in the "sash"

(c) Release the top clamp, start the pump

(d) Invert the filter and de-air as normal

(e) Clamp the arterial filter bypass loop

1.4.4 Priming centrifugal pump if required:

Centrifugal pumps differ from roller pumps in several important respects:

- They are non-occlusive devices
- They are constant energy devices

· A length of ⅜" PVC tubing is connected to the outlet of the venous reservoir and clamped. A length of ⅜" PVC tubing is also connected to the oxygenator inlet port

· The outlet of the membrane compartment is connected to the circuit as with a roller pump

· If a 'BioPump' bi-directional flow probe is required it should be inserted into the arterial line, at least 6" away from the nearest connector

· The oxygenator venous reservoir is primed with heparinized Hartmann's solution, as described in the routine procedure

· The centrifugal pump is cut in as required ensuring sterile technique using a sterile blade

· The clamp on the inlet tube is then slowly released, allowing the prime to slowly fill the head. The outlet port of the head (which is tangential to the body of the head) is held uppermost. The head is thus filled with the priming solution, as much air as possible is purged

· The oxygenator is gravity primed as above

· The head should again be examined for bubbles and if found should be manipulated out of the inlet port back into the venous reservoir

· When the outlet of the centrifugal head is clamped any air will collect at the center of the casing (low mass). If the pump is then switched off the collected air will travel vertically into the inlet tube. As before, this air can be manipulated back into the venous reservoir

1.4.5 Calibrating the flow probes

With the circuit fully primed:

(a) The motor drive is switched off

(b) Clamps are positioned some 6” on either side of the probe

(c) Calibrate the flow probe as directed by the manufacturer’s instructions

1.5 Setting occlusions

1.5.1 Occlusion of the arterial pump if a roller pump is used:

(a) Clamp the arterial line and any recirculating lines and close the sampling ports

(b) The pump is carefully turned until the pressure on the gauge is around 300 mmHg and the rate of fall of pressure can be observed

(c) Tighten the occlusion until there is no fall of pressure in this high pressure range (this ensures that there are no other leaks in the circuit and that all clamps are competent)

(d) Adjust the occlusion until the fall off of pressure over the lower 260–280 range takes approximately 10 seconds

(e) Both rollers must be treated individually. Should the occlusion between rollers be obviously unequal, the pump should be changed

1.5.2 Occlusion of the suction pumps:

(a) A clamp is placed on the negative side of the sucker boot and the pump is turned until the boot collapses with the vacuum created

(b) The occlusion should now be “backed off” until the vacuum is cleared

(c) The occlusion setting is then again increased until the vacuum is just drawn and held

(d) In order to check the direction of rotation of the sucker/vent roller pumps, a small quantity of heparinized saline or other appropriate fluid should be used by the scrub nurse to check the suction

Appendix 2.2

Electronic Safety Devices

(adapted, with permission, from *London Perfusion Science* Protocols)

2.1 Level sensors

- The level sensor should be positioned at around the 400 ml mark on the reservoir
- If the option is available, level sensors should be set to slow the pump down before stopping it
- Level sensors should not be overridden unless it is absolutely necessary

2.2 Bubble detectors

- Perfusionists must use a gas bubble detector placed in the circuit: it is usual practice to have the bubble detector on the arterial outlet of the circuit

2.3 Pressure alarms

- Most modern heart–lung machines have integrated electronic alarms for limits of pressure during a case
- These limits should be checked and correctly set to appropriate parameters before each case

2.4 Temperature alarms

- Most modern heart–lung machines have integrated electronic alarms for limits of temperature during a case
- Arterial blood, venous blood, and cardioplegia temperature alarms should be checked and correctly set to appropriate parameters before each case
- Where available the water temperature alarm limits should also be checked and set

2.5 Gas alarms

- Most modern gas blenders have alarms for gas failure

- These alarms can be checked when the gas lines are connected to the hospital gas supply
- Connecting the lines then disconnecting them individually should trigger the alarm

2.6 Electrical failure alarm

- Most modern heart–lung machines have an integrated alarm that sounds when the mains power supply fails and UPS is activated. If this occurs, all unnecessary equipment should be turned off to conserve the battery.

Suggested Further Reading

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Chapter 3

Priming solutions for cardiopulmonary bypass circuits

Christiana Georgiou and **Joanne Irons**

The cardiopulmonary bypass (CPB) circuit must be primed with fluids to allow perfusion to be rapidly established on initiation of CPB without the risk of air embolism. The composition of the ideal CPB priming solution has been studied and argued over for decades and is still a matter for debate.

Currently used primes have evolved from historical concepts. In general a solution with electrolyte content and osmolarity similar to the intravascular and interstitial compartments is used thus providing a fluid which, when mixed with blood, is capable of maintaining oxygen delivery, carbon dioxide removal, and physiological homeostasis.

Prime volume and hemodilution

The minimum "safe" volume of prime required is the minimum volume that fills both the venous and arterial limbs of the circuit and maintains an adequate volume in the venous reservoir to ensure that no air is entrained into the arterial side of the circuit during initiation of CPB. This volume is determined by both the caliber and length of tubing connecting the patient to the CPB machine and by the design, and therefore capacity, of the venous reservoir and oxygenator. Reduction of the prime volume may thus be achieved by modification of the circuit. In adults priming volumes are commonly in the range of 1400–1800 ml regardless of patient size or weight.

Acceptable hemodilution

John Gibbon performed the first successful CPB procedure in Philadelphia in 1953. At that time, donor blood was used as a priming solution. However, the cost and availability of blood, and side effects such as the risk of transmitting infectious diseases and immunosuppression, have led to the use of crystalloid or colloid-based primes.

Initiation of CPB inevitably leads to hemodilution by the priming fluid. The volume of the prime in relation to the patient's weight and hematocrit determines the degree of hemodilution. If this is likely to cause unacceptable hemodilution, then blood may be added to the prime. In children, especially infants and neonates, this often poses a problem as even the minimum priming volume (700–800 ml in pediatric circuits) can be far greater than the blood volume, making the use of non-blood-containing primes impossible.

Some degree of hemodilution is beneficial as blood viscosity is reduced, improving microcirculatory flow and reducing hypertension. However, hematocrit is the main determinant of the oxygen-carrying capacity of blood and severe hemodilution may compromise oxygen delivery, cause hypotension, and induce ischemic organ injury.

Theoretically, the minimum acceptable hematocrit should meet the oxygen delivery required to match systemic oxygen consumption. However, oxygen delivery is also influenced by pump flow rate and systemic temperature and oxygen consumption will alter proportionately with temperature.

The degree of acceptable hemodilution remains under debate and varies among institutions with a large number of studies showing that both severe hemodilution and the transfusion of blood increase the risk of postoperative adverse outcomes. Most centers aim for a hematocrit less than 30% during CPB; however values as low as 14% have been advocated by some, while others have suggested using venous oxygen saturation rather than a specific hematocrit value as a transfusion trigger. Experience with Jehovah's Witness patients who refuse blood transfusions show that cardiac surgery and CPB with low hematocrits is not only possible, but is also relatively safe.

Factors affecting the hematocrit during CPB include:

- patient size
- preoperative hemoglobin concentration/hematocrit
- pre-CPB blood loss
- pre-CPB fluid administration
- CPB prime volume
- urine output

Autologous blood priming

One method of reducing the degree of hemodilution without using donor blood is to use autologous blood to partially prime the CPB circuit. This method replaces part of the CPB prime volume with the patient's own blood thus reducing the degree of hemodilution. Autologous priming of the CPB circuit can be by either antegrade or retrograde routes:

Antegrade priming is achieved by partial filling of the venous reservoir with the patient's own blood from the venous limb of the CPB circuit on initiation of CPB, but before institution of CPB flow through the oxygenator and arterial limb of the circuit.

Retrograde priming is achieved by retrograde filling of the venous reservoir via the arterial limb of the CPB circuit just prior to the initiation of CPB. This displaces the fluid prime volume in the arterial line tubing, filter, and oxygenator and partially fills the reservoir with the patient's blood.

Both methods reduce the volume of crystalloid in the prime by replacing it with about 400 to 500 ml of the patient's blood and have been shown to reduce hemodilution and blood transfusion during cardiac surgery. However, they have not shown any other beneficial effects with regard to clinical outcomes.

Safe autologous priming relies on good teamwork between the perfusionist, anesthetist, and surgeon to select appropriate patients and to ensure hemodynamic stability, usually with the help of vasopressors, during the period of partial exsanguination of the patient.

In general, acceptance of a degree of hemodilution during CPB, the use of autologous priming, collection and processing of shed mediastinal blood, and the return of residual pump blood at the end of CPB can all lead to a decrease in allogenic blood transfusion and its associated risks.

Mini-bypass circuits

Changes in circuit design can allow for a smaller prime volume. The mini-extracorporeal circulation (MECC) system is a semi-closed circuit with no reservoir and shorter tubing length. Prime volumes are reduced to only 450 ml and this leads to less hemodilution and less blood transfusion, and possibly a reduced inflammatory response.

Priming solutions

There are many different recipes for priming solutions using crystalloid, colloids or blood as primary constituents.

Blood

Historically, blood was used to prime the CPB circuit in an attempt to preserve a high hematocrit as early in the evolution of CPB this was thought to be an important determinant for successful outcome. It later became clear, however, that use of allogenic blood in the prime may have worsened rather than improved outcomes.

In part, accumulation of knowledge about the deleterious effects of blood primes and acceptance that a lower hematocrit is compatible with good outcomes has led to acceptance of crystalloids as priming solutions. The introduction of hypothermic bypass in the 1960s, the inability of blood banks to support cardiac surgery with large amounts of whole blood, and the prevalence of blood-borne infections were also important in the shift to "clear," non-blood primes. The main issues prohibiting the routine use of blood as priming fluid are summarized in Table 3.1.

Table 3.1 Problems associated with using blood as priming solution

Cost	Very high compared to crystalloids or colloids
Availability of donors	Worldwide shortage of donor blood
Risks of transfusion	Blood-borne infection Transfusion reactions Immunosuppression

Crystalloids

In general, an ideal priming solution should have the same tonicity, electrolyte composition, and pH as plasma. Of these ideal properties the most important is that of "tonicity," in order to avoid red cell lysis and the fluid shifts from the extracellular to the intracellular compartment that occur with hypotonic solutions. Fluid shifts may occur in any organ or tissue, but the organs most vulnerable to fluid accumulation are the brain and lungs. Intracellular fluid gain can cause cerebral or pulmonary edema and impaired organ function.

Dextrose

In 1962, Cooley et al showed improved outcome by adding 5% dextrose to the prime instead of just blood. 5% Dextrose later fell out of favor for three reasons: firstly the realization that metabolism of glucose leads to a hypotonic solution; secondly the dilutional effect on bicarbonate causes systemic

acidosis; and thirdly concerns that hyperglycemia may worsen neurological outcome. For these reasons glucose-containing solutions should not be a major constituent of a prime and only those fluids with a near physiological sodium concentration should be used.

Balanced crystalloid solutions

Crystalloids used in CPB prime have generally a balanced salt composition and a similar oncotic pressure to plasma. Suitable solutions used today include Lactated Ringer's solution (Hartmann's), Ringer's solution, normal saline, Plasma-Lyte, and Normosol.

All of these solutions have similar sodium concentrations (130–150 mmol/l) and may contain physiological concentrations of potassium (Hartmann's, Plasma-Lyte). There are some differences in anion composition, but all have chloride as a major anionic constituent, the balance in Hartmann's or Plasma-Lyte being made up with lactate or acetate respectively. Both lactate and acetate are ultimately metabolized to bicarbonate in the liver, thus producing a near ideal physiological solution.

Hartmann's solution is the most commonly used crystalloid in priming fluids in the UK, although there is variation in practice among different units. Normosol-A and Plasma-Lyte are balanced solutions more commonly used in the USA.

Problems associated with the use of crystalloids as priming fluids are summarized in Table 3.2.

Table 3.2 Problems associated with using crystalloids as priming solutions

Metabolic acidosis	Crystalloid solutions have been implicated as one of the potential causes of the disturbance of pH associated with development of metabolic acidosis on initiation of CPB. This acidosis is probably caused by hyperchloremia and is more likely to occur with normal saline, which has a higher chloride load than the more "physiological" solutions Other possible reasons for this include an increase in unmeasured anions such as acetate and gluconate. This metabolic acidosis is a benign phenomenon and probably accounts for much of the base deficit observed while on bypass
Edema	Crystalloids have a similar osmotic pressure to plasma. This means only 25% will remain in the vasculature and 75% within the interstitium, increasing the risk of interstitial edema

Colloids

Colloid solutions have been advocated for use in the CPB prime on account of their potential to counteract the decrease in colloid oncotic pressure associated with hemodilution of albumin and other circulating plasma proteins during CPB. This reduction in colloid oncotic pressure causes movement of water out of the intravascular space and into the interstitial and intracellular spaces, contributing to postoperative edema and subsequent organ dysfunction. Thus using colloids, with their high molecular weight, to maintain oncotic pressure and reduce fluid shifts in theory seems an attractive strategy.

Commonly used colloids include albumin, dextrans, gelatins, and starches.

Albumin

Albumin is a natural colloid and accounts for 75–80% of the plasma oncotic pressure in the blood. It is most often used as priming fluid in combination with a crystalloid fluid. In addition to maintaining plasma oncotic pressure, it also coats the bypass circuit, increasing biocompatibility and decreasing the inflammatory response, coagulopathy, and bleeding. However, the use of albumin is limited by cost, supply issues, and the risk of anaphylactoid reactions or infection. It is rarely used in the UK, although is still used regularly in the USA.

Dextrans

Dextrans are also natural colloids, which maintain plasma oncotic pressure; however, problems with coagulopathy deter their use in CPB.

Gelatins

Gelofusine is a synthetic colloid and is the most commonly used colloid in the UK, often in combination with a crystalloid solution. Again, problems arise with impaired hemostasis and anaphylactoid reactions.

Hydroxyethyl starch (HES)

Starches are synthetic colloids with high molecular weights. They have an increased degradation time and some may remain in the body for years, with unknown long-term consequences. They are associated with a decreased diuresis, lower hematocrit, and coagulopathy.

There has been much interest in HES over the last few years and the European Medicines Agency has recently suspended their use following safety concerns over an increased risk of renal failure and

death in their use in sepsis, despite a number of studies showing no detrimental effect on renal function associated with their use for CPB priming.

In general, the use of colloid-based primes has not been shown to significantly influence clinical outcomes such as the duration of ventilatory support, length of intensive care unit stay or hospital stay. None of the types of colloids has been shown to have significant advantages over any of the others. The lack of measurable benefit, potential risks, and the significant cost penalty incurred in comparison to crystalloid fluids have resulted in colloids no longer being widely used as a priming fluid in adult CPB. The main issues arising from the use of colloids as priming fluids are listed in Table 3.3.

Table 3.3 Problems associated with using colloids as priming solutions

Cost	Higher than crystalloids
Availability	Albumin not readily available in all centers
Interstitial edema	Colloid solutions ought, theoretically, to remain in the intravascular space. However in practice the "tight junctions," which render the endothelial lining impermeable to large molecules, become more permeable on activation of the systemic inflammatory response associated with CPB. This may paradoxically increase the amount of extravasated fluid as the high-molecular-weight constituents of colloid solutions become trapped in the interstitial fluid, potentially adding to edema by drawing more free fluid into the interstitium
Coagulopathy and hemostasis post surgery	High volume infusion of colloids may impair hemostasis
Infection hazard	Particularly albumin solutions
Anaphylactoid reactions	Can occur with some colloids, e.g. gelofusine, albumin

Additives

A number of additives have been trialed as CPB technology evolved in order to enhance safety and improve outcomes. Presently, the two most commonly used additives are mannitol and sodium bicarbonate.

Mannitol

Mannitol is a hypertonic, low-molecular-weight crystalloid widely used as a common constituent of primes. The indication for its use during CPB is for its properties as a potent osmotic diuretic. Maintenance of urine output both during CPB and in the immediate postoperative period is desirable to enhance elimination from the body of the fluid load presented by pre-bypass intravenous fluids, the priming fluid volume, and cardioplegia solution. It has also been postulated that mannitol may help to preserve renal function and reduce the incidence of post-CPB renal dysfunction, although the evidence for this is extremely weak.

In addition, mannitol is a free radical scavenger and it is appealing to think that the free radicals produced during periods of hypoperfusion, ischemia, and reperfusion might be "mopped up" during bypass, thus reducing end-organ damage. However, this concept remains unproven.

Sodium bicarbonate

Sodium bicarbonate is often added as a buffer to "unbalanced" priming solutions. However, it is also being used as an additive in balanced solutions for its potential to reduce the incidence of acute renal dysfunction post cardiac surgery, although the evidence for this is tenuous.

Experimental oxygen-carrying solutions

The idea of using oxygen-carrying solutions as blood substitutes may be an attractive means of maintaining oxygen delivery. This would address the expense, limited supply and disease transmission associated with blood transfusion. Both hemoglobin-based substitutes and perfluorocarbons have been researched in the context of use in the CPB priming fluid, but none have yet proven to be both safe and efficacious as alternatives for oxygen carriage. Despite several decades of research no molecule seems close to being marketed as a viable alternative to red cells in the clinical arena and it remains to be seen whether there is any future for the use of these oxygen-carrying solutions during CPB.

Self assessment

1. Adult priming volumes:

A Depend on patient's weight.

B Depend on patient's sex.

C Usually 1400–1600 ml is required.

D Depend on the venous and arterial limb of the circuit only.

E Can be reduced by using MECC.

Answers: A False; B False; C True; D False; E True

2. Hemodilution:

A Initiation of CPB leads to hemodilution by the priming fluid.

B The degree of hemodilution is greater in patients with smaller blood volumes such as children.

C Hemodilution is always detrimental to the patient.

D The degree of hemodilution can be measured using the hematocrit.

E Autologus blood priming increases the degree of hemodilution.

Answers: A True; B True; C False; D True; E False

3. Blood as a priming solution:

A It is the ideal priming solution as it maintains a high hematocrit which is compatible with a good outcome.

B It is cheap and readily available from the blood banks.

C "Clear" primes are preferred and reduce the risk of blood-borne infections and immunosuppression.

D During the first bypass procedure in 1953 blood was used as the priming solution.

E Blood is the most common priming solution used in the UK.

Answers: A False; B False; C True; D True; E False

4. Glucose-containing solutions should not be a major constituent of a prime because:

A Metabolism of glucose leads to a hypertonic solution.

B The dilutional effect on bicarbonate causes systemic alkalosis.

C It can cause hypoglycemia.

D It can be associated with a worse neurological outcome.

E Patients can develop diabetes in the long term.

Answers: A False; B False; C False; D True; E False

5. One of the problems associated with crystalloids as a priming solution is systemic metabolic acidosis. This is thought to be due to:

A Hypernatremia.

B Hyperkalemia.

C Hypokalemia.

D Hyperchloremia.

E Hypochloremia.

Answers: A False; B False; C False; D True; E False

6. Albumin:

A It is a natural colloid and accounts for 50% of plasma oncotic pressure in the blood.

B It is commonly used in the UK and rarely used in the USA.

C It coats the bypass circuit, increasing the biocompatibility.

D There is a risk of anaphylaxis reactions and infection.

E It is most often used as a priming fluid alone.

Answers: A False; B False; C True; D True; E False

7. Colloids:

A Synthetic colloids include HES and gelatins.

B Natural colloids include albumin and dextrans.

C They can cause coagulopathy and bleeding post surgery.

D They do not cause interstitial edema.

E They can cause infections and anaphylactic reactions.

Answers: A True; B True; C True; D False; E True

8. Mannitol:

A It is a hypertonic, low-molecular-weight crystalloid.

B It is a potent osmotic diuretic.

C There is strong evidence that it helps to decrease the incidence of post-CPB renal dysfunction.

D It may reduce end-organ damage acting as a free radical scavenger.

E It is rarely used as a constituent of a prime.

Answers: A True; B True; C False; D True; E False

9. Additives:

A Sodium bicarbonate is only used in unbalanced priming solutions to act as a buffer.

B Heparin is rarely added to CPB prime.

C Sodium bicarbonate may lower the incidence of post-CPB renal failure.

D Sodium bicarbonate cannot be used together with mannitol.

E There is strong evidence that steroids reduce the inflammatory response during CPB.

Answers: A False; B False; C True; D False; E False

10. Oxygen-carrying substitutes:

A Perfluorocarbons are safe and efficacious alternatives for oxygen carriage.

B They have diminished the problems of cost and supply associated with donor blood.

C No alternative to red cells has been found despite decades of research.

D They are commonly used as a priming solution in CPB.

E They are associated with the transmission of infection.

Answers: A False; B False; C True; D False; E False

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Chapter 4

Anticoagulation, coagulopathies, blood transfusion, and conservation in cardiac surgery

Liza Enriquez and **Linda Shore-Lesserson**

Anticoagulation is required for any form of extracorporeal circulation to prevent activation of the coagulation system by contact between blood and artificial, non-biological surfaces.

Cardiopulmonary bypass circuits are comprised of a large surface area of plastic and synthetic material, which if left to come into contact with blood without appropriate anticoagulation, would result in formation of clots within the circuit in a matter of minutes. In order to safely conduct CPB for the duration required for surgical procedures, or to maintain patients on extracorporeal support, anticoagulation must be adequate to prevent the development of even “microvascular” clots. In its most serious form microvascular coagulation can lead to death, and in lesser forms can lead to impairment of organ function, manifesting as neurological dysfunction or renal dysfunction. Furthermore, any clots within the CPB system can trigger the development of disseminated intravascular coagulation (DIC), which results in the rapid consumption of clotting factors and failure of the body’s coagulation system.

Heparin is the most commonly used anticoagulant in the context of CPB. This chapter describes the coagulation pathway, the pharmacology of heparin, monitoring of anticoagulation status, problems associated with heparin usage, alternatives to heparin, the reversal of anticoagulation following termination of CPB, and the prevention and management of bleeding.

The coagulation cascade

Coagulation occurs by interaction of a series of proteins that are activated and propagated by a variety of stimuli. These stimuli include contact with foreign surfaces, contact with receptors on the surfaces of platelets, and by release of factors produced by the systemic inflammatory response, all of which are pertinent in the context of CPB.

Most of the proteins required for the cascade are produced by the liver as inactive precursors which are then modified into clotting factors. The implication of the term “cascade” is that a small stimulus results in a reaction which may be amplified to produce a significant clot.

There are two routes for activation of the coagulation system. The intrinsic pathway is activated by contact with collagen from damaged blood vessels or any negatively charged surface. Platelet activation is normally involved. The extrinsic pathway is activated by contact with tissue factor from the surface of extravascular cells. Both routes end in a final common pathway – the proteolytic activation of thrombin and the cleaving of fibrinogen to form a fibrin clot. The intrinsic pathway is the predominant route, with the extrinsic pathway acting synergistically (see Figure 4.1). Although the cell-mediated process for coagulation is a more physiological explanation for the in vivo reactions that lead to activation and propagation of clot formation, it is helpful to think of coagulation in terms of intrinsic/extrinsic pathways related to the insults incurred during extracorporeal circulation.

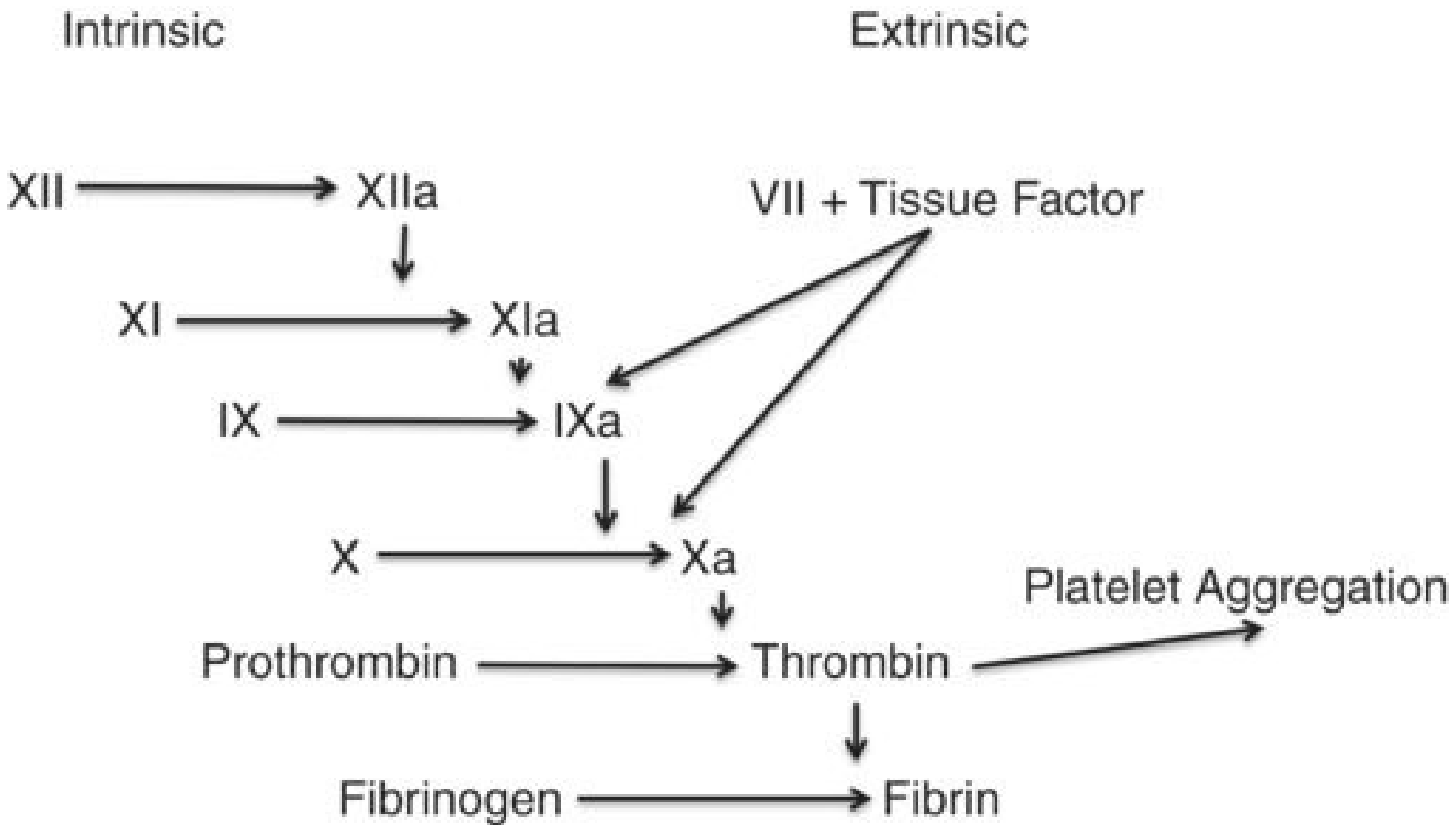

Figure 4.1 Overview of extrinsic and intrinsic clotting pathways.

Pharmacological strategies for anticoagulation during CPB

Heparin

Unfractionated heparin (UFH) remains the standard anticoagulant for CPB for several reasons. It is relatively safe, easy to use, has a fast onset of action and is measurable, titratable, and reversible. It is also cost effective.

Structure

Natural heparin is a polymer with a molecular weight ranging from 3 to 40 kDa; the average molecular weight of most commercial heparin preparations is in the range of 12–15 kDa. Heparin is a member of the glycosaminoglycan family of carbohydrates (which includes the closely related molecule heparan sulfate) and consists of a variably sulfated repeating disaccharide unit that is negatively charged at physiological pH. Heparin is normally released by mast cells and basophils in the body and is commercially derived from bovine lung or porcine intestinal mucosa.

Mechanism of anticoagulant action

Heparin contains a specific pentasaccharide sulfation sequence that binds to the enzyme inhibitor antithrombin III (AT-III) causing a conformational change that results in increasing AT-III's activity. The activated AT-III then inactivates thrombin and other proteases involved in blood clotting. These factors include IIa (thrombin), Xa, IXa, XIa, and XIIa. It is most active against thrombin and Xa. The rate of inactivation of these proteases by AT-III can increase by up to 1000-fold due to the binding of heparin to AT-III. In addition, heparin increases the activity of heparin cofactor II, which also inhibits thrombin.

Heparin's onset is immediate and has a half-life of approximately 2.5 hours at doses of 300–400 USP units (U)/kg. It is provided in units, with 1 U, according to the US Pharmacopoeia, maintaining fluidity of 1 ml of citrated sheep plasma for 1 hour after recalcification.

Dosing

Dosing of heparin can vary among institutions. The most common initial dose for CPB is 300–400 USP U/kg. Some centers base the initial dose on a bedside ex vivo heparin dose–response titration. Many institutions add heparin to the CPB priming solution at approximately the same concentration as that

of the patient's bloodstream or as a fixed dose. Supplemental heparin doses are guided by monitoring of anticoagulation using the activated clotting time (ACT) or heparin concentration monitoring.

Monitoring

The ACT is a functional assay of heparin anticoagulation and is the most widely employed test. Although the minimum ACT required for safe conduct of CPB remains unknown, most institutions use a level between 400 and 480 seconds. Hypothermia, hemodilution, platelet function abnormalities, and low fibrinogen are some of the factors that can prolong ACT, even in the context of incomplete heparinization. ACT monitoring will be discussed in further detail under the section "Point-of-care testing."

Heparin resistance

Heparin resistance is an important and well-recognized complication of heparin therapy that has an incidence of 4–26% in patients undergoing cardiac surgery. Heparin resistance is defined as failure to raise the ACT to expected levels despite an adequate dose and plasma concentration of heparin. Clinical conditions involving congenital or acquired AT deficiency are associated with heparin resistance. AT independent mechanisms of heparin resistance include elevated factor VIII levels and/or fibrinogen levels as well as the concomitant use of nitroglycerin. Hemodilution during CPB can decrease AT levels, though usually this does not result in heparin resistance because it is also associated with dilution of procoagulant factors. Prior treatment with heparin causes depletion or dysfunction of AT and this is the most likely reason that cardiac surgery patients will present with heparin resistance. Another cause of heparin resistance is the presence of large quantities of heparin-binding protein in the circulation, which bind to and inactivate heparin.

Administering additional heparin boluses of up to 600–800 USP U/kg may be necessary to obtain an ACT level sufficient for the conduct of CPB. Definitive treatment is aimed at increasing levels of AT. In the past, AT repletion was performed by administering fresh frozen plasma (FFP), which contains antithrombin; however, the risks associated with exposure to allogenic blood products and the availability of AT concentrates make this practice obsolete. The administration of AT concentrate is now recommended as a Class I indication for patients with heparin resistance and a Class IIb indication for patients with suspected AT depletion who are undergoing CPB. AT-III concentrate is available in both human purified form and recombinant form.

Heparin-induced thrombocytopenia (HIT)

A reduction in platelet count is commonly seen with heparin therapy. A mild decrease in platelet count that develops early in the course of heparin therapy is generally benign and thought to be a result of platelet activation. These patients can safely receive heparin for cardiac surgery. Heparin-induced-thrombocytopenia (HIT) is a clinicopathological syndrome that occurs later in heparin therapy (5–14 days after administration) and is a more severe decrease in the platelet count that is felt to be immune-mediated. Antibodies against the complex formed between platelet factor 4 (PF4) and heparin bind to platelets, activate the platelets, and cause the resultant platelet count to drop precipitously. In the setting of endothelial injury, this enhancement in platelet activation predisposes to the formation of platelet clots (white clots) and thrombosis. Figure 4.2 shows an extracorporeal membrane oxygenation (ECMO) cannula with clot from a patient with previously unknown HIT.

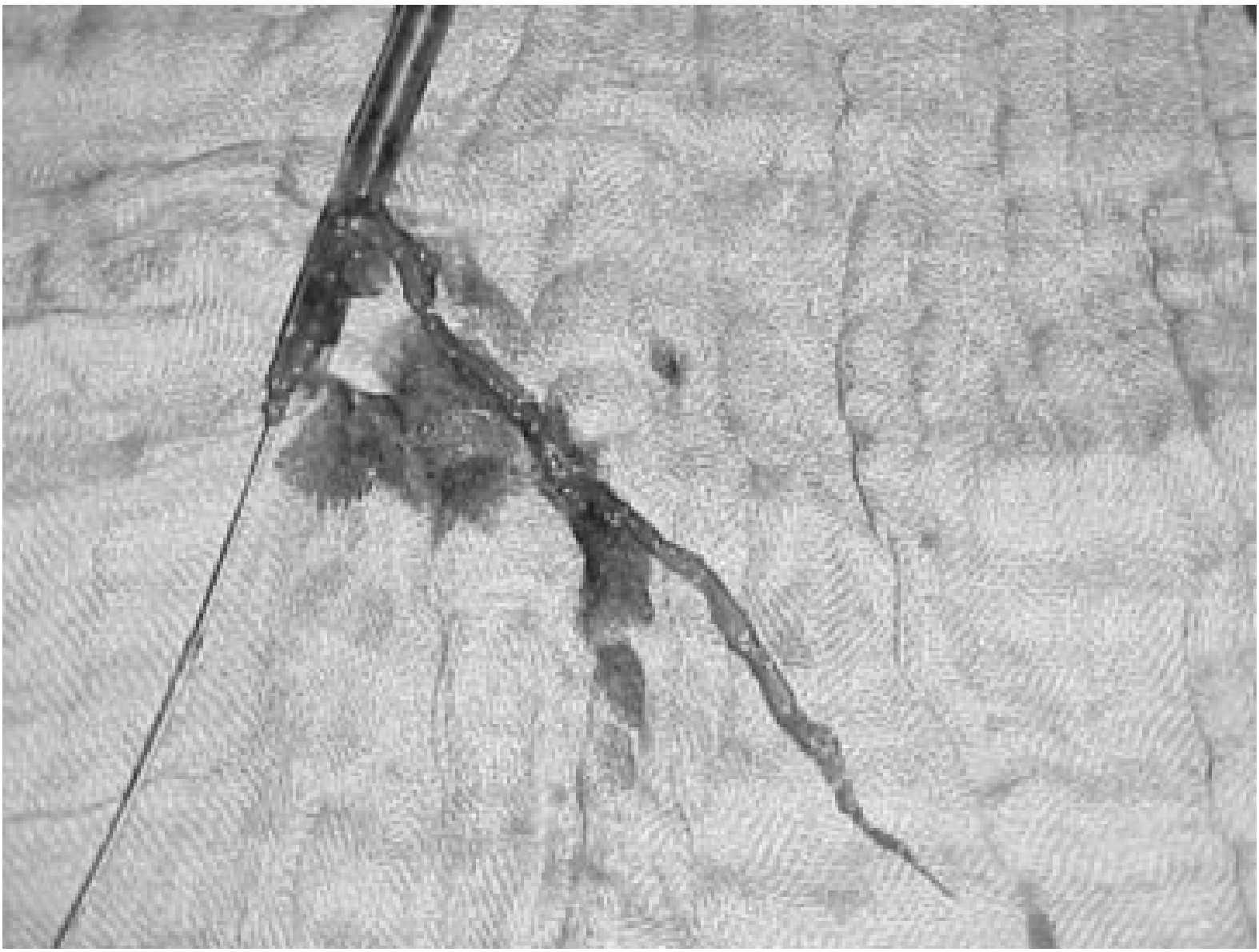

Figure 4.2 An ECMO cannula with clot from a patient with previously unknown HIT.

HIT requires both clinical evidence (thrombocytopenia or thrombosis) and laboratory findings to confirm the diagnosis. Laboratory diagnosis can be made in two ways: functional assay or antibody-based

assay. Functional tests include the serotonin-release assay (SRA) and the heparin-induced platelet activation (HIPA) assay. These assays detect heparin-dependent platelet activation in the presence of the patient's sera and UFH and are highly sensitive and specific. In the SRA, when an affected patient's serum is exposed to heparin, an exaggerated platelet release reaction occurs and serotonin is released from dense granules. Using C-14-labeled serotonin, the magnitude of the platelet release reaction, or reactivity, is measurable. The HIPA assay measures hyper-aggregability in response to heparin. The basis for the test is that normal platelets exposed to the plasma from HIT positive patients will be hyper-aggregable in the presence of heparin. Other more recently introduced functional tests of platelet hyperactivity include whole blood tests. Whole blood impedance aggregometry (WBIA) is a new method which measures platelet activation using a HIT reactive donor. It provides a rapid turnaround time and is easy to perform. Morel-Kopp et al published a multi-center study showing the efficacy of WBIA in diagnosing HIT with a reported sensitivity of 90%.

The antigen assay most commonly used is the enzyme-linked immunosorbent assay (ELISA) which measures IgG, IgM or IgA antibodies that bind to the PF4/heparin or PF4/polyvinyl sulfonate complex. Because not all of the antibodies are capable of causing clinical HIT the specificity of these tests are only moderate. The Particle Gel Immunoassay is a gel centrifugation assay that uses PF4/heparin antigen-coated complexes bound to red high density polystyrene beads. When a patient's serum containing anti-PF4/heparin antibodies comes in contact with the antigen, agglutination occurs. This test provides results within 15 minutes and has higher specificity than a standard ELISA (although lower than the functional assays). Its disadvantage is in its sensitivity (higher rate of false-negatives). The Particle Gel Immunoassay is available in Canada and Europe.

A systematic method called the "4 Ts" described by Warkentin estimates the probability of HIT using a scoring system based on clinical presentation. It involves the criteria of thrombocytopenia, timing of platelet count decline, thrombosis, and other causes of low platelets. Scores of 0–3 points suggest the clinical probability of HIT is low, 4–6 points intermediate, and 7–8 points high. Combining the clinical score with a laboratory test for HIT provides the highest predictivity for HIT (see Table 4.1).

Table 4.1 The 4 Ts scoring system

Category	2 Points	1 Point	0 Points
Thrombocytopenia	> 50% drop or nadir ≥ 20×10^9/l	30–50% drop or nadir 10–19 $\times 10^9$/l	< 30% drop or nadir < 10×10^9/l
Timing	Day 5–10, or Day 1 with heparin within the	> Day 10 or unclear timing, or < Day 1 if	< Day 4 with no recent heparin exposure

	last 30 days	heparin exposure within last 30–100 days	
Thrombosis	Proven thrombosis, skin necrosis or acute systemic reaction after heparin bolus	Progressive, recurrent or silent thrombosis, erythematous skin lesions	None
Other causes of thrombocytopenia	None evident	Possible	Definite

The American College of Chest Physicians (ACCP) has published evidence-based guidelines on the treatment and prevention of HIT for patients undergoing cardiac surgery with previous HIT, as well as for those with acute or subacute HIT. Management of these patients can be summarized as follows: Patients with a history of HIT who are antibody negative and require cardiac surgery can receive unfractionated heparin (Grade 2C). The ACCP grading system considers the strength of any recommendations to be dependent on two factors: (1) the benefits and risks, and level of confidence in estimates of those benefits and risks and (2) the quality of the evidence upon which the recommendations are based. Grade 1 is a strong recommendation where the benefits outweigh the risks and Grade 2 is a weaker recommendation when there is less certainty about the magnitude of the benefits versus the risks. The letter following the grade indicates whether the recommendation is based upon high- (A), moderate- (B), or low-quality (C) evidence. For patients with acute HIT who require cardiac surgery, the guideline developers recommend delaying surgery, if possible, until HIT antibodies are negative (Grade 2C). In patients with acute HIT or subacute HIT who require urgent cardiac surgery, bivalirudin is suggested rather than other non-heparin anticoagulants (Grade 2C). Another strategy involves combining the use of unfractionated heparin and antiplatelet agents such as a prostacyclin analog or a glycoprotein IIb/IIIa inhibitor.

Alternatives to unfractionated heparin

Low-molecular-weight heparin

Intravenously administered low-molecular-weight heparin (LMWH) has a half-life at least twice as long as that of UFH and possibly several times as long for some LMWH compounds. LMWH has not been used with much success during CPB and has resulted in frequent hemorrhagic problems. Part of the problem is that the anti-Xa activities of LMWH agents are not reversed by protamine. Protamine neutralization only reverses the factor IIa inhibition which is the predominant inhibition seen with UFH. Therefore, anti-Xa

inhibition remains intact and may predispose patients to bleeding. LMWH therapy also complicates heparin monitoring because activated partial thromboplastin time (APTT) (and presumably ACT) is much less sensitive to Xa inhibition and will not accurately measure the full anticoagulant effect. Factor Xa inhibition can be measured, but not with a simple bedside test. LMWHs are not recommended for use in HIT patients for the above reasons and because there can be some cross-reactivity of the HIT antibodies with LMWH.

Direct thrombin inhibitors

The direct thrombin inhibitors (DTIs) are felt to have advantages over UFH and actually serve as better anticoagulant agents. The DTIs directly inhibit the procoagulant and prothrombotic actions of thrombin, inhibit free and clot-bound thrombin, and do not require a cofactor. Another main advantage is that they do not interact with or produce heparin-dependent antibodies. However, they do not have a direct antidote, such as protamine. The main differences between the two types of thrombin inhibitors are listed in Table 4.2.

- **Argatroban –** A monovalent thrombin inhibitor. This is a synthetic molecule derived from L-arginine and is widely used in patients with HIT who require percutaneous coronary intervention. Its half-life is 45–55 minutes, it lacks cross-reactivity with heparin antibodies, and is monitored via the aPTT or ACT. There is no antidote. Argatroban is metabolized in the liver requiring dose adjustments in patients with moderate liver disease. Argatroban has not yet been approved for use in CPB but it is labeled by the FDA for the medical treatment of HIT patients.
- **Bivalirudin –** A bivalent thrombin inhibitor. This is a synthetic peptide based on the structure of hirudin. Its advantage is its short half-life of 25 minutes. It is monitored via the aPTT, ACT or ecarin clotting time, if available. The dose for CPB is a 1 mg/kg bolus followed by a 2.5 mg/kg/hour infusion. Bivalirudin is metabolized by proteolytic enzymes present in the blood and by the kidney. Dose adjustments are necessary for patients with renal insufficiency. The results of two prospective, open-label, multi-center trials assessing bivalirudin in on-pump and off-pump cardiac surgery (CHOOSE-ON and CHOOSE-OFF respectively) provided clinical evidence that bivalirudin is a safe and effective anticoagulant for patients with or at risk of HIT who are undergoing cardiac surgery. Currently, bivalirudin is widely used in cardiac catheterization laboratories as the anticoagulant for percutaneous coronary intervention, even in patients without HIT.

Table 4.2 Key differences between direct thrombin inhibitors (DTIs) and indirect thrombin inhibitors

	Heparin	DTIs
Mode of action	Indirect	Direct
Cofactor needed	Yes – AT-III	No
Inhibits clot-bound thrombin	No	Yes
Activates platelets	Yes	No
Antigenicity	Yes	No
Antidote drug	Yes – protamine	No

“Reversal” of anticoagulation

Heparin neutralization

Protamine is a naturally occurring polypeptide with multiple cationic sites, a “polycation” that binds and inactivates heparin.

Several protamine dosing techniques have been utilized. The recommended dose range of protamine for heparin reversal is 1–1.3 mg protamine per 100 U of heparin. Other approaches include calculating the protamine dose based on the heparin dose–response curve generated by heparin titration automated systems. Adequacy of heparin neutralization should be assessed by repeating the ACT test 3 to 5 minutes after reversal.

Protamine administration is commonly associated with hypotension, particularly following rapid injection; while true anaphylaxis to protamine is rare, systemic vasodilatation, raised pulmonary vascular resistance, and right ventricular dysfunction due to the non-immunological types of reactions outlined below occur more frequently. Protamine should therefore be administered at a judicious rate with concomitant titration of intravenous fluid and/or vasopressor to counteract the hemodynamic effects.

Protamine reactions have been classified into three types. A Type I reaction may result from rapid administration resulting in decreases in both systemic and pulmonary arterial pressures, decreased preload, and hypotension. The Type II reaction is immunological and is categorized as IIA anaphylaxis, IIB anaphylactoid and IIC non-cardiogenic pulmonary edema. Type III reactions are caused by heparin/protamine ionic complexes that can adhere in the pulmonary circulation and cause pulmonary vasoconstriction. This results in catastrophic pulmonary hypertension and resultant right heart failure.

Alternatives to protamine

Platelet factor 4 (PF4)

PF4 is a potent antiheparin compound and can be found on the surface of activated platelets. PF4 utilizes lysine residues at its C-termini to neutralize heparin, rather than electrostatic binding that occurs with protamine neutralization. It is hypothesized that the cause of heparin-induced thrombocytopenia is an immunological reaction to the PF4/heparin complex.

Methylene blue

This chemical dye binds electrostatically to heparin in a similar fashion to protamine. Large doses do not effectively restore the ACT to normal. An inhibitor of nitric oxide synthetase, methylene blue, increases pulmonary and systemic vascular resistance at higher doses, making its use quite hazardous.

Omit neutralization

Owing to drug metabolism and elimination, heparin activity will dissipate spontaneously with time with consequent decline in anticoagulation. This option may result in an increase in transfusion requirements, hemodynamic instability, and may result in consumptive coagulopathy as a result of hemorrhage and transfusions.

Heparinase

Heparinase, an enzyme produced by the gram-negative Flavobacterium, hydrolyzes the heparin molecule into smaller inactive fragments. Some of these small fragments do possess the potential for some anti-Xa activity, thus the utility of heparinase in reversing heparin after CPB is limited.

Monitoring anticoagulation status in the operating room

Point-of-care testing (POC)

Point-of-care testing devices allow the monitoring of hemostasis “at the bedside” rather than sending specimens to a central laboratory facility. These instruments rapidly assess coagulation and/or platelet function to aid in providing appropriate targeted therapy. As a result there is a reduction in blood loss and transfusion, fewer complications, and cost reduction.

The ACT is an automated variation of the Lee–White or whole blood clotting time and is the most commonly used test to measure heparin anticoagulation. It uses an activator such as celite or kaolin to activate clotting, then measures the clotting time in a test tube or cartridge. Normal baseline ACT levels, without any heparin in the blood, should be between 80 and 140 seconds. For CPB, prolongation of the ACT to greater than 400 or 480 seconds is considered adequate, though this is highly debated. For off-pump coronary artery bypass operations (OPCAB), "partial heparinization" may be used in some centers whereby an ACT greater than 300 seconds is targeted. There are many ACT devices used in the operating room to confirm adequate anticoagulation for CPB which utilize a variety of different testing platforms. Commercially available ACT machines include the Hemochron (International Technidyne Corp, Edison, NJ, USA) and the i-STAT System (Abbott Point of Care Inc, Princeton, NJ, USA). In addition the viscoelastic tests thromboelastography (TEG) and Sonoclot have assays that have been adapted to measure the clotting time in heparinized patients.

During CPB the sensitivity of the ACT to heparin is altered by hemodilution and hypothermia. As a result ACT measurements do not correlate with heparin concentration or with antifactor Xa activity. The HMS Plus Hemostasis Management System® (Medtronic, Minneapolis, MN, USA) uses protamine titration assays to determine the blood heparin level. This device can also provide a dose–response curve for an individual patient and indicate how much heparin to administer in order to reach a specific targeted ACT before going onto CPB. The protamine titration assay can be utilized to estimate the proper protamine dose after CPB.

Tests of platelet function

Thromboelastography (TEG)

Thromboelastography measures the viscoelastic properties of blood as it is induced to clot under a low shear environment. The patterns of change in shear elasticity enable the determination of the kinetics of clot formation and clot growth, and provide information about clot strength and stability. The strength and stability of the clot provides information about the ability of the clot to cause hemostasis effectively, while the kinetics determine the adequacy of quantitative factors available for clot formation.

There are four major parameters to the TEG tracing, which measure different stages of clot development: R, K, alpha angle, and MA (maximal amplitude). In addition, clot lysis indices are measured as the amplitude at 30 and 60 minutes after MA (LY30 and LY60) (see Figure 4.3). Normal values vary depending on the type of activator used.

- **R value –** This is a measure of clotting time from the start of the bioassay to the initial fibrin formation (2 mm amplitude). The R time can be prolonged by coagulation factor deficiencies, anticoagulation, severe thrombocytopenia, and hypofibrinogenemia; it can be shortened in hypercoagulability states.
- **K value –** This represents clot kinetics, measuring the speed to reach a specific level of clot strength. It is the time from beginning of clot formation (the end of R time [2 mm]) until the amplitude reaches 20 mm. K time can be prolonged by coagulation factor deficiencies, hypofibrinogenemia, thrombocytopenia, and thrombocytopathy; it is shortened in hypercoagulable states.
- **Alpha angle –** This is the angle between the horizontal line through the TEG tracing and the line tangential to the developing "body" of the TEG tracing at 20 mm. The alpha angle represents the acceleration (kinetics) of fibrin build-up and cross-linking (clot strengthening). It is increased in hypercoagulable states and decreased in thrombocytopenia and hypofibrinogenemia.
- **MA –** This is the maximum amplitude reflecting the ultimate strength of the clot, which depends on platelet number and function and platelet interactions with fibrin. It is increased in hypercoagulable states and decreased in thrombocytopenia, thrombocytopathy, and hypofibrinogenemia.
- **Lysis –** Indices measured by the TEG include LY30 and LY60. These are measured as a percent reduction in MA at 30 or 60 minutes after MA respectively. LY30 or LY60 are increased in states of fibrinolysis.

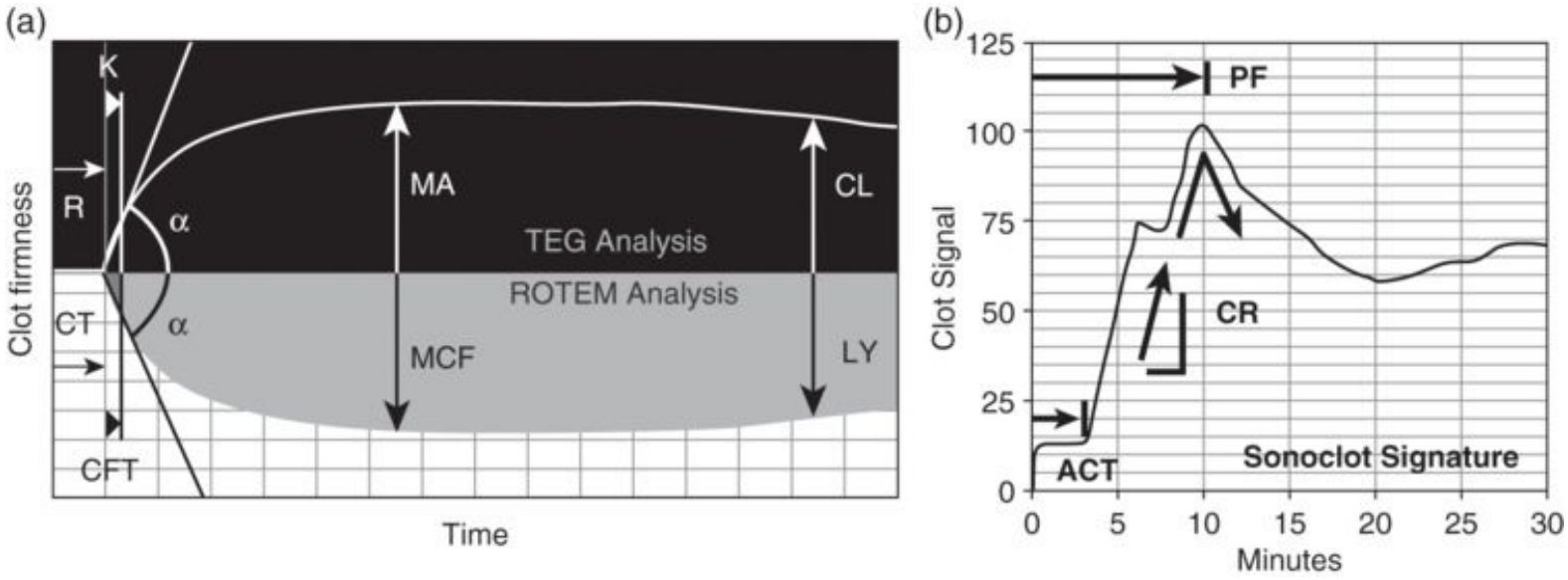

Figure 4.3 (a) TEG, ROTEM, and (b) Sonoclot tracings

(reproduced with permission from Ganter MT, Hofer CK. Coagulation monitoring: current techniques and clinical use of viscoelastic point-of-care coagulation devices. Anesth Analg. 2008;106(5): 1366–1375)

Rotational thromboelastometry (ROTEM) is similar to the TEG as it is a viscoelastic measure of clot formation, but it differs in the way the viscoelastic changes are measured during the hemostatic process. In the TEG the plastic cup is slowly oscillated and the pin attached to a torsion wire in the blood sample transmits the signal. In ROTEM, the cup remains stationary and the signal is transmitted by an optical detection system attached to the oscillating pin. The parameters measured in both systems are similar but have different nomenclature.

1. Initial fibrin formation: R on TEG and clotting time (CT) on ROTEM

2. Clot kinetics/formation time: K on TEG and clot formation time (CFT) on ROTEM

3. α/Angle-Rate of polymerization of clot: α on both instruments

4. Strength of the clot: MA on TEG and maximum clot formation (MCF) on ROTEM

5. Clot lysis at 30 minutes (fibrinolysis): CL or LY30 on TEG and clot lysis (CL) or A30 on ROTEM

Sonoclot is also a viscoelastic test of clot formation that uses an ultrasonic vibrational method to stimulate clot formation. The instrument provides information on the different phases of hemostasis in the form of a qualitative graph known as the clot signature. It also provides quantitative results: the ACT representing the clot formation time, the clot rate (CR) representing the rate of fibrin polymerization, and

platelet function (PF) representing the quality of the clot retraction. PF values range between 0 (no platelet function) and 5 (strong platelet function) (see Figure 4.3)

Agonist-induced POC tests of platelet function

The newest group of POC platelet function tests was specifically designed to measure agonist-induced platelet-mediated hemostasis. These monitoring systems include the VerifyNow® (Accumetrics, San Diego, CA, USA), the Platelet Function Analyzer, PFA-100® (Siemens Medical Solutions USA, Inc, Malvern, PA,USA), Multiplate® (DiaPharma Group, Inc, West Chester, OH, USA),and PlateletWorks® (Helena Laboratories, Beaumont, TX, USA) (see Table 4.3).

Table 4.3 POC devices to assess platelet function

Instrument	Mechanism/agonist	Clinical utility
Thromboelastograph®	Viscoelastic/thrombin, ADP, arachidonic acid (AA)	Post-CPB, trauma, liver transplant, pediatrics, obstetrics, drug efficacy
ROTEM®	Viscoelastic/thrombin, ADP, AA	Post-CPB, trauma, liver transplant, hypercoagulability, thrombosis
Sonoclot®	Viscoelastic/thrombin	Post-CPB, liver transplant
PlateletWorks®	Platelet count ratio/ADP, AA, collagen	Post-CPB, drug therapy
PFA-100®	In vitro bleeding time/ADP, epinephrine, collagen	von Willebrand's disease, congenital disorder, aspirin therapy, post-CPB
VerifyNow®	Agglutination/thrombin receptor agonist peptide (TRAP), AA, ADP	Drug therapy
Multiplate®	Electrical impedance/AA, ADP, TRAP, collagen	Post-CPB

Coagulation disorders after CPB

Persistent bleeding after CPB is multifactorial. It is usually associated with long bypass times (> 2 hours) as a result of which platelet dysfunction, hemodilution, protein activation/consumption, and fibrinolysis occur. Prompt diagnostic and therapeutic action is necessary to avoid impaired hemodynamics due to hemorrhage.

Platelet abnormalities

Thrombocytopenia can occur after CPB due to dilution of blood volume with the extracorporeal circuit volume and platelet consumption or sequestration. Platelet function impairment is considered to be the main hemostatic defect during CPB. Platelet dysfunction occurs from contact with the extracorporeal surfaces, hypothermia, down-regulation of receptors, and by exposure to heparin and protamine. In addition, patients on antithrombotic medications preoperatively can have platelet dysfunction that becomes significantly exaggerated after CPB. Many patients taking aspirin or other platelet-inhibiting drugs regularly cannot discontinue therapy within 7 days of surgery and unfortunately no antidote can correct the platelet defect. These patients have a very difficult bleeding diathesis that often requires multiple transfusions and/or procoagulant factor therapy.

Systemic inflammatory response syndrome

Contact of blood with the CPB circuit results in the systemic inflammatory response syndrome (SIRS), which is characterized by the activation of the kallikrein–bradykinin system, complement, coagulation pathways, and fibrinolysis. SIRS may cause disseminated intravascular coagulation (DIC) by aggravating consumption of coagulation factors. The use of heparin-bonded CPB circuits makes the extracorporeal circuit more biocompatible thus effectively reducing the proinflammatory aspects of CPB (see Chapter 11).

Heparin rebound

This phenomenon may be observed after apparent adequate reversal of heparinization and may be explained by a redistribution either of protamine to peripheral compartments or of peripherally bound heparin to the central compartment. Treatment is with small incremental doses of protamine.

Hypothermia

Hemostasis is impaired by hypothermia in many ways including: sequestration of platelets, transient platelet dysfunction, activation of a specific heparin-like factor Xa inhibitor, slowing of the enzymatic

reactions involved in the coagulation cascade, and accentuation of fibrinolysis.

Fibrinolysis

The CPB circuit contains a large surface of thrombogenic material and, despite clinically adequate doses and blood concentrations of heparin, activation of coagulation pathways is accompanied by persistent fibrinolytic activity causing consumption of coagulation factors.

Other causes

Hemodilution, liberal use of cardiotomy suction, and prolonged CPB all further aggravate coagulopathy.

Prevention of bleeding

Antifibrinolytic agents

- The synthetic antifibrinolytic agents ε-aminocaproic acid (EACA) and tranexamic acid (TA) bind to lysine binding sites in both plasminogen and plasmin and produce a structural change. This prevents the conversion of plasminogen to plasmin and also prevents the activation of plasmin. Minimization of plasmin activity inhibits fibrin degradation, decreases the formation of fibrin degradation products (FDPs), and decreases lysis of existing clots. It is these FDPs that inhibit platelet function, so the lysine analog antifibrinolytic agents also have an indirect effect in preserving platelet function. Dosing of these agents is highly variable and is dependent on institution and country. Typical regimens are given below:
- EACA 100–150 mg/kg bolus, followed by infusion at 10–15 mg/kg/hour, or 4–6 g bolus, followed by infusion at 1 g/hour
- TA: 10–50 mg/kg bolus, followed by infusion at 1–15 mg/kg/hour, or 5 g bolus, followed by repeat boluses to total of 15 g.

Heparin and protamine dosing

- Heparin and protamine dosing: ACT should return to baseline following administration of protamine, or the heparin/protamine titration should yield a heparin concentration of 0 U/ml. If this is not the case, additional doses of protamine (25–50 mg) may be necessary. Re-heparinization (heparin rebound) after apparent adequate reversal may be explained by a secondary rise in

plasma heparin concentration due to redistribution either of protamine to peripheral compartments or of peripherally bound heparin to the central compartment.

- Some clinicians advocate the use of a reduced heparin dose in conjunction with heparin-bonded circuits to decrease postoperative blood loss and transfusion requirements. This strategy is successful only when used as a part of a complex multi-interventional blood conservation program.

Management of the bleeding patient

Determining the cause of bleeding quickly is vital to expedite treatment of the bleeding patient. Surgical causes of bleeding generally present with high volume chest tube drainage early after operation. Non-surgical causes of bleeding usually manifest as a generalized ooze.

Hypothermia (< 35°C) accentuates hemostatic defects and should be corrected. The administration of platelets and coagulation factors should generally be guided by additional coagulation studies, but empirical therapy may be necessary when such tests are not readily available, or following massive transfusion.

If oozing continues despite adequate surgical hemostasis and the ACT is normal, or the heparin-protamine titration assay shows no residual heparin, thrombocytopenia or platelet dysfunction is most likely. Both defects are recognized complications of CPB. If point-of-care tests to delineate the hemostatic defect are not available, platelet transfusion may be necessary. Significant depletion of coagulation factors, particularly factors V and VIII, during CPB is less commonly responsible for bleeding but should be treated with fresh frozen plasma or prothrombin complex concentrates; both the prothrombin time and partial thromboplastin time are usually prolonged in such instances. Hypofibrinogenemia (fibrinogen level < 100 mg/dl or a prolonged thrombin time without residual heparin) should be treated with cryoprecipitate or fibrinogen concentrate.

Recent studies support the use of fibrinogen concentrates in acquired hypofibrinogenemia seen after CPB; however, more studies are needed in order to determine dose, efficacy, and safety.

The use of prothrombin complex concentrate (PCC) is now recommended for life-threatening bleeds. PCC is a human plasma-derived factor concentrate previously used for the management of hemophilia B and is now utilized in the urgent reversal of vitamin K antagonists. The inactivated concentrate contains factors II, IX, and X, with variable amounts of factor VII. The most recent guidelines published by the ACCP recommend the use of a four-factor PCC along with vitamin K to rapidly reverse warfarin-associated major bleeding rather than the use of FFP (Grade 2C). The advantages include a greater

increase in clotting factors, lower infusion volume, faster preparation time, lack of blood group specificity, and a better safety profile.

Desmopressin (DDAVP) is an analog of vasopressin that releases von Willebrand factor (VWF) from normal endothelial cells and is used in the treatment of hemophilia. Factor VIII coagulant activity increases 2- to 20-fold in addition to an increase in factor XII levels. Desmopressin has been beneficial in subgroups of patients, such as cirrhotic and uremic patients, undergoing cardiac surgery. It affords no hemostatic benefit to patients taking aspirin prior to cardiac surgery and is not recommended as a prophylactic hemostatic agent for patients undergoing elective cardiac surgery. It may also be used to augment the function of exogenous transfused platelets. Desmopressin 0.3 μg/kg (intravenously slowly over 20 minutes) can increase the activity of factors VIII and XII and the von Willebrand factor by releasing them from the vascular endothelium. DDAVP may be effective in reversing qualitative platelet defects in some patients, but is not recommended for routine or prophylactic use.

Accelerated fibrinolysis may occasionally be encountered following CPB and should be treated with ε-aminocaproic acid (5 g followed by 1 g/hour) or tranexamic acid (10 mg/kg), if not already given prophylactically; the diagnosis should be confirmed by clotting tests showing elevated fibrin degradation products (>32 mg/ml), or evidence of clot lysis on thromboelastography.

Recombinant factor VIIa (rFVIIa, NovoSeven) is a vitamin K-dependent glycoprotein that promotes hemostasis by activating the extrinsic pathway of the coagulation cascade. Tissue factor-bearing cells present tissue factor to rFVIIa. This complex can activate factor X to factor Xa, as well as factor IX to IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process can also occur on the surface of activated platelets. rFVIIa has been approved for use in hemophilia patients who are resistant to factor VIII concentrates (i.e. have antibodies). Numerous reports have been published in cardiac surgery of factor VIIa as an “off-label” treatment option in patients with probable or identifiable coagulation defects or as a rescue therapy in hemorrhagic patients refractory to other treatments.

Transfusion and the use of algorithms

Point-of-care testing in conjunction with transfusion algorithms can reduce both transfusion requirements and blood loss. Many transfusion algorithms have been published and demonstrate a successful reduction in bleeding and transfusion requirements in high-risk cardiac surgical patients. Most of these transfusion algorithms utilize thromboelastography or thromboelastometry; others use point-of-care prothrombin time

(PT) and international normalized ratio (INR) testing and/or tests of platelet function and number. Any combination of tests that examines the presumed defects incurred during CPB will accomplish the same goal – the reduction in the transfusion of blood products by more rational and specific guidance of that transfusion therapy.

Hemostasis and bleeding in conjunction with cardiac surgery is a multifactorial problem. The defects that occur are dynamic in origin and knowledge of physiological responses to CPB continues to evolve.

Self assessment

1. Which of the following are true?

A. Contact between the artificial surfaces of the CPB circuit and blood activates the coagulation cascade.

B. Heparin is a naturally occurring polymer with a range of molecular weights and is composed of repeating disaccharide units which carry a negative electrostatic charge.

C. Heparin acts by directly binding to factor Xa.

D. The usual dose of heparin given for CPB is 500 USP U/kg (5 mg /kg) to achieve an ACT of > 400 seconds.

E. Heparin resistance may occur due to antithrombin III deficiency.

Answers: A True; B True; C False; D False; E True

2. Select which of the following are true with regard to the reversal of heparin-induced anticoagulation (select one or more):

A. Heparin is rapidly metabolized and its anticoagulant effect wears off spontaneously within 30 minutes.

B. Protamine is a naturally occurring positively charged molecule that binds to and inactivates heparin.

C. The dose of protamine required to reverse heparin anticoagulation is 2 mg of protamine per 100 USP units of heparin administered.

D. Side effects of protamine and the protamine-heparin complex commonly include hypotension and right ventricular dysfunction.

Answers: A False; B True; C False; D True

3. Are the following statements true or false?

A. Cardiopulmonary bypass causes thrombocytopenia, platelet dysfunction, and fibrinolysis.

B. Cardiopulmonary bypass causes a systemic inflammatory response syndrome which may lead to disseminated intravascular coagulation.

C. Once reversed by protamine, administered heparin in the circulation is permanently inactivated.

D. Hypothermia aids blood clotting and is useful in preventing bleeding.

E. Antifibrinolytic agents should not be used during cardiac surgery.

Answers: A True; B True; C False; D False; E False

4. Answer Yes or No to the following questions:

A. Is ACT the most commonly used test of anticoagulation during CPB?

B. Does TEG measure the kinetics of clot formation and the strength and stability of the formed clot?

C. Does TEG provide any information about thrombocytopenia?

D. Are assays of heparin concentration in blood used to determine the adequacy of anticoagulation and dose of protamine required for reversal?

Answers: A Yes; B Yes; C Yes; D Yes

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Chapter 5

Conduct of cardiopulmonary bypass

◈

Christiana Burt, **Saran Hutton**, and **Betsy Evans**

The pump is your friend!

Caves, 1976

The safe conduct of cardiopulmonary bypass (CPB) requires excellent teamwork, clear communication, and collaboration between surgical, anesthetic and perfusion teams. A comprehensive understanding of both the mechanics and physiology of CPB is essential to achieve optimum benefit and reduce the risks. Before each case, a WHO briefing should take place, specifically to ensure that all members of the team are aware of the intended method for cannulation, the systemic and myocardial temperatures required during surgery, the technique of myocardial protection to be used, whether deep hypothermic circulatory arrest (DHCA) will be required, and the most appropriate sites for monitoring during CPB.

Prior to assembly of the CPB circuit, patient demographic data and information relating to physiological and pathological state are required to enable selection of equipment tailored to the patient's needs.

Arterial cannulation

The arterial cannula is usually the narrowest part of the CPB circuit with resultant high resistance, pressure gradients, high velocity jets, and turbulence. The effect of jets on the interior wall of the aorta can lead to arterial dissection, embolization, and flow disturbances in head and neck vessels.

The "performance index" of an arterial cannula is the pressure gradient versus the outer diameter at any given flow. The narrowest portion of the catheter that enters the aorta should be as short as safely possible and the diameter should then gradually increase in size to minimize the gradient. Pressure

gradients greater than 100 mmHg can cause excessive hemolysis and should be avoided. Many different types of cannulae are available and are discussed further in Chapter 1.

"Straight" arterial cannulae are the most commonly used, with some having a flange to allow secure fixation to the aorta with minimal tip within the vessel. The straight design allows non-turbulent blood flow through the cannula, but results in a single jet of blood, which can cause damage to the aortic wall. The straight nature of the cannula means that the flow direction is reliant on the surgical placement. In addition to direct placement in the aorta these cannulae can be used for peripheral (e.g. femoral or axillary) arterial cannulation or within a graft.

Right-angled cannulae have been designed to allow the blood flow jet to be directed around the aortic arch, assuming correct placement. Right-angled "diffusion" cannulae, with diffusion holes and a sealed end, may attenuate the damaging jet effect by changing the flow characteristics into the aorta. However, concern has been expressed regarding increased hemolysis due to the more turbulent flow effect through the cannula. These cannulae are not suitable for femoral placement.

Connection to patient

Usually arterial inflow is directed into the ascending aorta. The advantages of this site are:

- ease;
- safety;
- single incision;
- size of cannula not usually limited by vessel diameter; and
- no risk of limb ischemia.

The site for cannulation in the ascending aorta is traditionally determined by intraoperative palpation for calcific atherosclerotic plaques; however, newer techniques such as epivascular ultrasound scanning can be used to help determine plaque-free areas for cannulation. Transesophageal echocardiography (TEE) is not always useful due to the passage of the patient's airway between the esophagus and ascending aorta, which renders an echo "blind spot" preventing visualization of the whole ascending aorta. If significant atherosclerosis is present such that aortic cannulation and cross-clamping is deemed unsafe, because of the risk of stroke due to dislodgement and embolization of atherosclerotic material, femoral arterial cannulation should be considered. It must be noted that retrograde perfusion via femoral arterial cannulation is not without risk of embolization of atheroma and in such instances subclavian or innominate

arterial cannulation may be preferable. In the event of a totally calcified “porcelain aorta,” alternative strategies that minimize aortic handling such as OPCAB surgery or the use of DHCA may be appropriate.

Prior to insertion of the aortic cannula, the chosen site is prepared with placement of opposing purse-string sutures and clearance of the adventitial tissue within the boundaries of these sutures. With the mean arterial pressure controlled at between 60 and 70 mmHg, to avoid excessive bleeding or trauma to the aorta, particularly dissection, a full-thickness incision is made in the aortic wall through which the aortic cannula is passed. Only 1–2 cm of the cannula tip is advanced and directed towards the arch to avoid inadvertent cannulation of the head and neck vessels or dissection of the posterior wall of the aorta. The aortic cannula is immediately de-aired by allowing blood to fill the tubing, which is then clamped and secured with the purse-string sutures, prior to connecting to the arterial inflow circuitry of the CPB machine. During connection to the circuit it is essential to ensure that no air is present at the connection site. When the connection is complete the perfusionist will inform the surgeon of the “swing” on the arterial pressure line and the pressure within the system to confirm correct intraluminal placement of the cannula.

Complications of aortic root cannulation

If air is introduced into the aortic line during aortic cannulation, the line must be disconnected from the aortic cannula and the air aspirated prior to reconnection. If gross air embolism is noted in the aortic line during established CPB, it may be possible for the perfusionist to remove the air via recirculation lines in the CPB circuit with only a brief interruption to pump flow. If gross systemic air embolism occurs, de-airing of the cerebral circulation must be attempted. With the patient in the Trendelenberg position CPB is terminated followed by removal of the arterial cannula from the aorta, leaving the purse-string sutures loose. The arterial line is filled and then inserted into the superior vena cava (SVC). Retrograde perfusion to the cerebral circulation via the SVC using low flow rates (1–2 l/minute), at a blood temperature of 20°C, enables de-airing of the cerebral circulation back to the aorta. During this de-airing process the perfusionist should re-prime the circuit, followed by the surgeon re-cannulating the ascending aorta and recommencement of CPB at 28°C until surgery is completed. CPB should be discontinued at a core temperature of 35°C. The use of relative hypothermia increases the solubility of gaseous emboli and may reduce the extent of cerebral injury.

Further potential complications of aortic root cannulation are summarized in Table 5.1.

Table 5.1 Complications of aortic root cannulation

Inability to introduce the cannula	Adventitia occluding the incision site

	Inadequate incision size
	Atheromatous plaque within aortic wall
Intramural placement	
Embolization of atheromatous plaque	
Air embolization on connection to the circuit	
Persistent bleeding around cannula	
Malposition of tip towards aortic valve or into arch vessels	
Dissection of aorta	
Kink in circuit	
Inadequate size leading to high pressure and low flow generation	
Aneurysm formation at site of cannulation at later stage	

Peripheral arterial cannulation

Indications for the use of peripheral arterial cannulation not only include aortic aneurysm or an aorta that is not suitable for cannulation due to calcification, but also to establish CPB in anticipation of complications arising from redo-sternotomy. Increasingly, peripheral cannulation is also being used to enable “limited access,” minimally invasive surgery. Femoral cannulation renders it necessary to use smaller size cannulae, with consequent higher pressure gradients, jet effects, and possibly lower flow rates; this may be improved by cannulation of iliac arteries.

Axillary cannulation is usually employed in cases of ascending aortic dissection, to avoid the risk of inadvertent retrograde perfusion via the false lumen of the dissection, which can occur with femoral cannulation in these patients. The axillary artery is less likely than the femoral artery to have atherosclerotic disease or dissection and also has good collateral flow, with less risk of limb ischemia. In addition to these benefits it provides antegrade flow, with reduced risk of cerebral embolization. Direct arterial cannulation or indirect cannulation via a side graft can be used to access the axillary artery; side graft placement and cannulation is usually preferable to direct cannulation.

The potential complications of peripheral cannulation are summarized in Table 5.2.

Table 5.2 Complications of peripheral cannulation

Trauma to vessel
Retrograde arterial dissection with retroperitoneal hemorrhage or extension of dissection to aortic root
Thrombosis or embolism
Hemorrhage
Limb ischemia (can be reduced by using an end to side polytetrafluoroethane (PTFE) graft sutured to the vessel)
Malperfusion of cerebral and systemic circulation as a result of cannulation of the false lumen of an aortic dissection
Lymph fistula or lymphocele
Infection
Late vascular stenosis

Venous cannulation and drainage

Venous blood inflow to the CPB circuit is usually achieved by gravity drainage, using the “siphon” effect, but earlier CPB circuits used suction to aid venous drainage; in pediatric cases, drainage is still often aided by applying suction to the venous lines. Gravity siphoning as the means of obtaining adequate drainage relies on:

(1) no air being present in the tubing between the patient and the pump, otherwise an “airlock” develops and drainage stops; and

(2) the venous reservoir being kept below the level of the patient’s thorax.

The degree of venous drainage is determined by the patient’s central venous pressure (CVP), the difference in height between the patient and the top of the blood level in the venous reservoir, and resistance exerted by the circuit (cannulae, lines, and connectors). The CVP is influenced by intravascular volume and venous compliance; which is in turn influenced by sympathetic tone. This is largely dependent on the extent of inflammatory response to CPB and on drugs used perioperatively.

Excessive drainage may cause the veins to collapse around the cannulae with intermittent reduction in venous drainage and the potential for generation of gaseous emboli in the circuit; a phenomenon referred to as “cavitation.”

The new generation of optimized low prime circuits and those employing “mini-bypass” (see later) require a kinetic effect on the venous drainage. These units tend to be mounted higher on the CPB machine in order to decrease tubing length via closer proximity to the patient. However, by doing so, the siphon effect can no longer be employed for venous drainage so a vacuum is applied to the system. This vacuum is controlled via a vacuum assist device, which allows the perfusionist to control the degree of “suck” on the system. A vacuum of between −20 and −40 mmHg is typically required to adequately drain the patient.

The various available types and sizes of venous cannulae are discussed in Chapter 1. The cannula tip is the narrowest component in the venous circuit and therefore the limiting factor for venous drainage. The appropriate size is selected based on the flow characteristics of the cannula (detailed in the manufacturer’s guidelines) and the required flow for the patient based on cardiac index. One-third of total flow is derived from SVC drainage and two-thirds from IVC drainage.

Cannulae can be divided according to three main criteria:

- single versus two-stage (cavo-atrial);
- straight or angled; and
- metal or plastic.

Connection to the patient

This is usually achieved by right atrial (RA) cannulation. There are three basic approaches:

- **Single** – A cannula is passed through the RA appendage: this route is advantageous because it is quick and the least traumatic, but it is most sensitive to changes in position of the heart and venous drainage can be impaired with cardiac retraction. This technique cannot be used if the right heart is to be opened.
- **Cavo-atrial** – This uses a “two-stage” cannula with a wider proximal portion, with side holes, which lies in the RA and a narrow extension, with end and side holes, extending into the inferior vena cava (IVC). This cannula is typically inserted through the right atrial appendage and cannot be used if the right heart is to be opened.
- **Bicaval** – Purse-string sutures are placed on the posterior–inferior RA wall and the RA appendage to enable direct cannulation of the IVC and SVC, respectively. Tapes or snares are

passed around the vessels with the cannulae in place to ensure that the patient's entire venous return flows into the CPB circuit, preventing air from entering the venous lines when opening the RA, or blood leaking past the cannulae into the RA; this is referred to as caval occlusion or total CPB and is the technique of choice if the right heart is to be opened.

It should be noted that the right heart may need to be vented via the pulmonary artery to prevent right ventricular (RV) distension due to return of blood into the RA via the coronary sinus. Occasionally high SVC or even innominate vein cannulation may be required to facilitate the operation, for example, resection of an RA tumor mass or during operations needing access to the SVC such as some heart transplant or heart–lung transplant procedures (Domino heart).

In clinical practice most CABG and aortic valve replacement (AVR) surgery is performed with venous drainage via cavo-atrial cannulation. This usually provides adequate drainage as long as right heart decompression is constantly monitored and communication is maintained between the team regarding venous return, with the necessary adjustments of cannulae position during the operation to accommodate changes in heart position.

Air entry into the venous side of the circuit may lead to an "air lock," causing obstruction of venous drainage, or to systemic gaseous microemboli. The most common reason for air entry into the system is failure to seal the site around the cannulae adequately. Care must therefore be taken to ensure that purse-string sutures are air-tight, especially if vacuum-assisted venous drainage is being used.

Peripheral venous cannulation

This is usually performed via the femoral or iliac veins and is used in the following instances:

- unstable patients for emergency establishment of CPB prior to sternotomy or anesthetic induction;
- selected redo-surgery: to provide controlled conditions during sternotomy and exposure of the heart;
- aortic surgery;
- thoracic surgery;
- minimal access surgery; and
- extracorporeal membrane oxygenation (ECMO).

The essential requirement is for adequate venous drainage and subsequent flow rates for CPB. With peripheral cannulation this is achieved by using as large a cannula as possible, and passing the cannula into the RA (often using transesophageal echocardiography (TEE) guidance). Vacuum-assisted venous

drainage is advantageous under these circumstances, given the smaller cannula diameter and increased resistance from the cannula length.

Possible complications associated with venous cannulation are listed in Table 5.3.

Table 5.3 Complications of venous cannulation

Low cardiac output due to compression of the heart during IVC purse-string placement	
Damage to SVC/IVC/right pulmonary artery while passing tapes around cavae	
Reduction in cardiac output prior to commencement of CPB when cannulae are in place	
Atrial dysrhythmia	
Malpositioning of cannula tip	SVC cannula into the azygos vein IVC cannula into the hepatic vein RA cannula into LA in the presence of an atrial secundum defect
RA trauma and bleeding from cannulation sites	
SVC or IVC laceration on manipulation of cannulated RA	
Narrowing of cavae after decannulation and closure of purse-string suture	
Low venous return during CPB	Kinks in circuit with obstruction of line Reduced venous pressure – volume or pressure related (drugs, anesthetic agents) Air lock Inadequate height of patient above CPB venous reservoir Inadequate size of cannula

Cardiotomy suction

During cardiac surgery “shed” blood often needs to be suctioned from the operative field to maintain visibility for surgery and from cardiac chambers to prevent distension of the heart. After systemic heparinization and confirmation of an adequate ACT (usually > 350), shed blood is salvaged through

designated “cardiotomy” suckers and vents and collected in the reservoir for recirculation within the CPB circuit.

Cardiotomy suction is most commonly generated by use of a roller pump, requiring repeated adjustment of pump flow rate by the perfusionist and sucker position by the surgeon due to the degree of negative pressure that can develop at the sucker tip leading to hemolysis of red blood cells and occasional occlusion of the sucker.

It is essential that the direction of the cardiotomy suckers be confirmed prior to use, to ensure that they are indeed sucking and not blowing air towards the patient. This can be tested by submergence of the sucker tips in clear fluid and observation that the fluid is being sucked away from the field and air is not exiting the sucker creating bubbles (a “sucker test”). There exists the potential for fatal air embolism if a sucker attached to an aortic root vent was to blow air into the patient instead of remove blood.

In extreme cases of hemorrhage, after heparinization with the arterial cannula *in situ*, the patient can be placed on “sucker bypass”; the shed blood in the operative field provides venous return to the CPB circuit until formal venous cannulation can be secured.

Adverse effects of cardiotomy suction

Blood suctioned from the surgical field is highly “activated” with regard to coagulation factors, fibrinolytic mediators, leukocytes, and platelets. It is a major source of hemolysis, microparticles, fat, cellular aggregates, inflammatory mediators (tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), C3a) and endotoxins, and a cause of platelet injury and loss. A potential determinant of injury caused by cardiotomy suction is the amount of room air co-aspirated with the blood.

Commonly used strategies to reduce the side effects of cardiotomy suction are shown in Table 5.4.

Table 5.4 Strategies to reduce the side effects of cardiotomy suction

Hemostasis throughout operation to minimize shed blood	
Minimize aspiration of air through the cardiotomy suction by	avoidance of high negative pressures
	slow rates of suction
	not sucking the surgical field dry
	keeping the suction tip under level of blood
Filtration of cardiotomy suction blood (leukocyte depletion)	
Cell salvage blood instead of cardiotomy suction	

Venting the heart

The left side of the heart receives blood while on CPB from bronchial arteries and Thebesian veins and the right heart from the coronary sinus and “leakage” around venous cannulae. As the ventricles are unable to eject this blood during the period of arrest, a vent must be placed to protect the heart from distension. Ventricular distension is undesirable because excessive myocardial stretching increases myocardial oxygen demand and impairs subendocardial perfusion.

Most commonly, a roller pump is utilized to create the suction for the vent in the same manner as the cardiotomy suckers and as such, the direction of the pump must also be confirmed via a “sucker test.” A one-way valve may also be included to further reduce the risk of air being inadvertently introduced via the vent site.

On occasions, blood can return from abnormal sources. These include:

- left-sided SVC;
- patent ductus arteriosus (PDA);
- atrial septal defect/ventricular septal defect;
- anomalous venous drainage;
- aortic regurgitation; and
- systemic to pulmonary shunt.

Venting the left heart

The left ventricle (LV) needs to be vented if it is filling from any source but not ejecting. It will fill primarily because of aortic insufficiency, or during cardioplegia administration. Venting:

- prevents distension of the ventricle;
- reduces myocardial re-warming;
- prevents ejection of air; and
- provides a bloodless surgical field.

Surgical inspection and palpation of the LV to monitor the degree of distension is crucial on commencing CPB, during aortic cross-clamping, and during initial administration of cardioplegia. The use of a left atrial pressure monitoring line and pulmonary artery (PA) catheter can help detect moderate LV distension, which is sometimes a subtle finding. TEE can also be used to assess distension of the heart. If the heart is well decompressed and empty, then it will not be possible to obtain recognizable images; however, if there is blood present in the heart then TEE views will be obtainable and can be used to assess for active chamber enlargement.

Venting the right heart

The venous cannulae effectively vent the right side of the heart, keeping it empty of blood except for any "leakage" past the cannula, which can be minimized by using bicaval cannulation and caval snares. When antegrade cardioplegia is administered, releasing the caval snare will permit venting of cardioplegia solution returning via the coronary sinus to the right heart.

Placement of a pulmonary arterial vent will keep the right ventricle empty of fluid. The presence of a persistent left SVC requires additional drainage of the coronary sinus or RA in most cases.

Venting methods

Venting can be achieved via:

- the aortic root cardioplegia cannula – this method does not allow venting during cardioplegia administration;
- the right superior pulmonary vein – a vent is passed into the left atrium and through the mitral valve into the LV;
- the left ventricular apex; and
- the pulmonary artery – this may not be effective at venting the LV when there is aortic regurgitation with a competent mitral valve.

It must be remembered that venting the heart is not without complications. These can be immediate or delayed. "Steal" of systemic perfusion may occur if excessive venting of the heart is employed in the presence of aortic regurgitation. Systemic air embolism may occur when the vent is inserted or removed. Bleeding can occur from the vent site, particularly if an LV apical vent is used. Later complications of venting include stenosis of the pulmonary vein or pulmonary artery, or aneurysm of the LV apex, depending on the vent site used.

General management of CPB

Before commencing CPB the perfusionists must have completed a series of "checks" as detailed in Chapter 2.

Transitioning the patient onto CPB

The general sequence of events entailed in commencing CPB is described below and summarized at the end of this chapter in Appendix 5.1:

- The patient must be systemically heparinized (300–500 IU/kg) with confirmation of adequate anticoagulation (usually ACT > 400 s). ACT targets vary among institutions and are the subject of much practical and academic debate. Heparin resistance must be considered if a therapeutic ACT cannot be achieved despite additional systemic boluses of heparin. Antithrombin III (AT-III) deficiency can be treated by giving AT-III-rich blood products such as FFP or AT-III concentrate. Repeat ACT readings should result in an elevated reading without the need for further heparin.
- Recirculation of CPB prime through the circuit to ensure that perfusate is warm and lines are air free.
- Division of the arterial and venous lines after clamps are applied at the patient and pump ends.
- The arterial line is connected to the aortic cannula, enabling rapid transfusion, if required, directly from the pump. During connection to the arterial line, the arterial cannula is allowed to bleed out slowly from the patient and the CPB prime is simultaneously advanced up the arterial line to ensure an air-free connection.
- Release of the aortic line clamp, after which the pressure "swing" is confirmed to indicate correct positioning of the aortic cannula.
- Retrograde autologous priming may be used to reduce the effect of hemodilution due to large prime volumes in the CPB circuit. The cardiotomy reservoir is primed to a minimal level and the patient's arterial blood is used to fill the circuit to a "safe" level after placement of the arterial cannula (this is approximately 400 ml). Hemodynamic consequences of this technique need to be considered for each patient. This technique is discussed in more detail in Chapter 3.
- The venous cannula is connected to the venous line.
- CPB is initiated, after instructions from the surgeon, by the perfusionist releasing the arterial line clamp and slowly transfusing the patient with the CPB prime. Arterial flow should be

unobstructed and with an initial line pressure of less than 100 mmHg. The perfusionist must confirm that the oxygenator gases and CPB safety alarms are switched on prior to CPB.

- The venous clamp is gradually released after confirmation that the arterial line is unobstructed; the patient's venous blood is then diverted into the circuit. The right heart should decompress with a fall in CVP to less than 5 mmHg.
- A period of 1–2 minutes of transition occurs while the perfusionist gradually increases the rate of arterial flow and venous return to the heart is reduced. The arterial pressure changes to a non-pulsatile waveform. Pulsatility while on CPB indicates aortic valve insufficiency, inadequate venous drainage or excessive bronchial venous return into the heart.
- Most CPB systems generate non-pulsatile flow, but some do have computerized configurations to allow for pulsatile flow generation. Alternatively, pulsatile flow can be generated via an intra-aortic balloon pump, if in situ. There are many reported benefits of pulsatile flow such as increased renal, cerebral, and myocardial perfusion together with a reduction of the stress response to CPB. However, in clinical studies, the conclusions are equivocal.
- Cooling of the patient, if required by the surgeon, is commenced once the patient is on full flow and adequate decompression of the heart is confirmed.

Recommended flow rates for CPB

The primary requirement for CPB is to provide a systemic O_2 delivery (DO_2) that is sufficient to meet systemic O_2 demand (VO_2). In contrast to the intact native circulation, DO_2 is not controlled by reflex mechanisms, but by the perfusionist. During CPB whole body DO_2 is a function of pump flow and arterial oxygen content, the latter being primarily determined by the hematocrit (HCT). The major determinants of VO_2 are temperature and level of anesthesia.

Oxygen consumption (VO_2) can be calculated using the Fick equation:

$$VO_2 = Q(C_{(a-v)})O_2$$

VO_2 = minute oxygen consumption (ml/minute)

Q = cardiac output (l/minute)

$$(C_{(a-v)})O_2 = 1.34 \times Hb + P_{(a-v)}O_2$$

where 1.34 is the hemoglobin oxygen content at 100% saturation (ml/g), Hb is the hemoglobin concentration (g/l), and $P_{(a-v)}O_2$ is the arteriovenous oxygen partial pressure difference (mmHg).

Effective blood flow results in maintenance of near-physiological tissue perfusion. Effective perfusion is reduced by anatomical shunting of arterial blood around the capillary bed to the venous circulation, e.g. via bronchial or pulmonary collaterals, and by the physiological shunt created by blood suctioned from the surgical field.

Indices of adequate total perfusion include pH, lactate, and S_vO_2 (hemoglobin oxygen saturation in venous blood). A low S_vO_2 during CPB indicates an imbalance between DO_2 and VO_2 and requires a change in perfusion conditions. It can reflect insufficient pump flow, HCT, hemoglobin oxygen saturation, inadequate anesthesia or increasing temperature. All of these parameters should be optimized to ensure effective blood flow and consequent perfusion of organs.

In adults at normothermia, clinical and experimental data support a minimum flow index of 1.8 l/minute/m^2. Kirklin and Barratt-Boyes recommended a flow index of 2.2 l/minute/m^2 for adults at a temperature of 28°C or above. The patient's body surface area (m^2) is worked out from a normogram plotting height in meters and weight in kilograms. Patients with a body surface area greater than 2 m^2 should have the flow maintained at 1.8–2.2 l/minute/m^2 to avoid excessively high flows through the machine leading to hemolysis. This can be mitigated however with the use of different sized pump boot tubing. The pump boot is the portion of tubing that sits in the raceway of the pump and the roller displaces the blood within the tube with each rotation of the pump, thus creating forward flow. The size of the tubing in the pump boot can be altered depending on the size of the patient. Where a patient has a surface area in excess of 2.4 m^2, it is worth considering a 1/2 inch pump boot instead of a 3/8 inch boot. This decreases the number of rotations that the pump has to make to provide the same flow, thereby decreasing the risk of hemolysis.

Table 5.5 shows recommended flow rates for different surface areas.

Table 5.5 Recommended flow rates (l/minute) for different surface areas and flow index

Body surface area (m^2)	**Flow index 1.8 l/minute/m^2**	**Flow index 2.2 l/minute/m^2**	**Flow index 2.4 l/minute/m^2**
1.60	2.88	3.52	3.84
1.80	3.24	3.96	4.32
2.00	3.60	4.40	4.8
2.20	3.96	4.84	5.28

Flow rates are reduced at lower body temperatures as VO_2 also decreases (see Appendix 5.1).

Hemodilution

As the CPB circuit is primed with crystalloid or colloid, hemodilution of the patient inevitably results. The degree of hemodilution caused by CPB can be calculated before initiating bypass so that the prime solution can be adjusted to incorporate packed red blood cells if unacceptable levels of anemia are anticipated.

$$\text{CPB HCT} = \frac{\text{Preop HCT} \times \text{PBV}}{\text{PBV} + \text{CPB prime volume}}$$

where PBV = patient's blood volume (l) and CPB prime volume = extracorporal prime volume (l).

Benefits of hemodilution include reduced blood viscosity and an increase in microvascular blood flow, but these effects are partially counterbalanced by the reduction in oncotic pressure, which may promote tissue edema.

Mean arterial blood pressure (MAP)

An acceptable MAP on CPB is that which provides adequate tissue perfusion. Adequate tissue perfusion is, however, also influenced by the pump flow rate and the core body temperature. MAP is determined by flow rate and arteriolar resistance. In general, higher pressures should be maintained in the presence of known cerebrovascular disease, in particular carotid stenosis, renal dysfunction, coronary disease or left ventricular hypertrophy.

On commencement of CPB there is a transient drop in systemic pressure. This is due to vasodilatation associated with the sudden decrease in blood viscosity resulting from hemodilution by the CPB prime solution and, secondarily, from the systemic inflammatory response (SIRS) associated with CPB. However, as CPB continues there is a gradual increase in perfusion pressure due to increasing vascular resistance. This is a result of equilibration of fluid between the vascular and tissue "compartments," hemoconcentration from diuresis, the increase in blood viscosity seen with hypothermia, and the progressive increase in circulating levels of catecholamines and renin as part of the stress response to CPB.

It is important to emphasize that manipulation of MAP alone is not sufficient to guarantee adequate organ perfusion. Neither a low MAP with a high flow nor a high MAP with a low flow are sufficient in themselves. Whole body DO_2 must firstly be optimized and secondly, vascular resistance altered to bring the MAP into the autoregulatory range for critical organ beds, with due consideration to underlying pathophysiology.

Pulmonary artery (PA) and left atrial (LA) pressure

On CPB the PA and LA pressures should be close to zero. PA or LA pressure monitoring is useful during CPB to assess left ventricular distension, in particular in cases where increase in blood flow back to the left heart is expected (cyanotic heart disease, large bronchial flow in chronic lung disease or aortic regurgitation). Care must be taken with PA catheters to ensure that migration of the catheter tip does not occur, leading to “wedging” and subsequent PA rupture or infarction of the lung.

Central venous pressure (CVP)

On CPB, CVP is expected to be close to zero and no more than in single digits. An increase in CVP indicates impaired venous drainage to the reservoir. The causes of an increase in CVP are inadequate cannula size, obstruction to the line or cannula tip, and insufficient height difference between the patient and the reservoir to enable gravity siphon drainage. The consequence of an increase in CVP during bypass is to reduce effective perfusion of critical organs with resultant edema. The liver is particularly sensitive to reduced flow as nearly three-quarters of hepatic blood flow occurs at near venous pressure. If a persistently high CVP, uncorrected by attention to the factors mentioned above, is noted during CPB the patient’s head and eyes should be closely observed for signs of engorgement and consideration given to altering the venous cannulation to improve drainage.

Electrocardiogram

The ECG must be recorded throughout CPB to ensure that it remains isoelectric during cardioplegic arrest. Following removal of the aortic clamp and resumption of myocardial activity persistent ST segment changes may be related to ischemia resulting from inadequate re-vascularization, coronary ostial obstruction, e.g. by an incorrectly seated aortic valve prosthesis, or air/particulate embolization. Additionally, the ECG is useful in guiding the postoperative management of epicardial pacing.

Temperature

The principal reason for hypothermic CPB is to protect the heart and other organs by reducing metabolic rate and thus oxygen requirements. In the myocardium, hypothermia sustains intracellular reserves of high-energy phosphates and preserves higher intracellular pH and electrochemical neutrality. Myocardial cooling can be achieved with cold cardioplegia, pouring cold topical solution on the heart and cooling jackets, as well as by systemic hypothermia. Systemic hypothermia is not uniform due to different blood flow to different vascular beds. High blood flow rates and slow cooling ensures less variation in

systemic hypothermia. Temperature should be measured at multiple sites and the advantages and limitations of each site needs to be recognized. During cardiac surgery temperature can be measured in the following locations: nasopharynx, tympanic membrane, pulmonary artery, bladder or rectum, arterial inflow, water entering heat exchanger, and venous return.

Nasopharyngeal temperature probes underestimate, but approximate to brain temperature, with the mixed venous temperature on the CPB circuit being an approximation of average body temperature. Bladder and rectal temperatures give an indication of core body temperature, but these can be erroneous due to interference from varying urine production and fecal matter, respectively. These low blood flow sites tend to underestimate temperature so are particularly valuable following deeper levels of hypothermia. On re-warming the aim is to achieve uniform normothermia. To avoid rebound hypothermia after cessation of CPB, which occurs if too great a temperature gradient is allowed to develop between peripheral and core temperatures, vasodilators can be used to promote more uniform re-warming by distributing greater blood flow, and therefore heat, from the core to peripheries. The process of re-warming must be controlled to avoid rapid changes in temperature, or excessive blood temperatures, which can result in microbubble formation due to the reduced solubility of gases in blood as the temperature increases, denaturing of plasma proteins, hemolysis, and cerebral injury. As a general guide for every 1°C drop in temperature there is an associated 7% drop in oxygen demand, i.e. a 7°C reduction in temperature results in a 50% drop in oxygen demand (see Table 5.6).

Table 5.6 Hypothermia: temperature ranges and indications for use

Hypothermia	Temperature (°C)	Use
Tepid	33–35	Good for short operations, healthy patients with higher HCTs
Mild	31–32	Protection of beating heart and neurological systems
Moderate	25–30	Protection of non-beating heart and neurological systems
Deep	15–20	DHCA for typically 40–60 minutes

At < 15°C oxygen is too tightly bound to hemoglobin and is therefore unavailable to tissues. In addition, the viscosity of the blood can be too high for effective flow through the CPB circuit.

Urine volume

Urine volume on CPB is monitored as an indicator of renal perfusion. Indications for diuretic use during CPB include hyperkalemia, hemoglobinuria, and hemodilution. Furosemide is used for treatment of hyperkalemia and mannitol is used to generate alkaline urine to treat hemoglobinuria.

Transesophageal echocardiography (TEE)

TEE is applied increasingly as a routine part of surgery when intracardiac cavities are opened. It is a useful tool to assess adequacy of de-airing of the heart. In addition, TEE can be used to assess intracardiac structures (valves, prostheses, septal walls, left and right ventricular outflow tracts), the position of cannulae and regional wall motility.

Laboratory investigations

This is discussed in detail in Chapter 6. Minimal monitoring during CPB requires measurement of PO_2, PCO_2, base excess (BE), hemoglobin, HCT, pH, potassium, glucose, and coagulation status using ACT.

Termination of CPB

Table 5.7 provides a checklist of the basic conditions that need to be fulfilled before weaning can be attempted. Terminating CPB is a gradual process with constant communication between surgeon, anesthetist, and perfusionist. The first step is for the perfusionist to restore the blood volume to the heart by gradual occlusion of the venous return. The patient is partially supported by the CPB machine with blood passing through both the heart and the lungs. The heart begins to eject blood when a critical volume is reached. The perfusionist continues to return blood from the venous reservoir to the patient while continuing to occlude the venous line until the patient is weaned from CPB. Termination of CPB is achieved by complete occlusion of the arterial and venous lines.

Table 5.7 Checklist before weaning from CPB

Patient position on operating table is neutral
Operation completed and vent sites closed
Hemostasis secured
Heart de-aired (confirmed with TEE if available)

Ventilation of lungs recommenced and adequate

Acceptable Hb/HCT, potassium, glucose, and acid-base status on arterial blood gas analysis

Acceptable core temperature achieved

Heart rhythm and rate appropriate

Parameters for initial filling pressure when off CPB are determined

Inotropic support prepared if necessary

Transfusion of blood to the patient is still possible through the arterial cannula following cessation of CPB. The venous cannula is removed when the patient is stable and the process of reversing heparin with protamine is due to commence. Some surgeons leave the venous purse-string suture untied but snared to enable rapid re-insertion of a cannula for emergent return to CPB if required. Prior to protamine administration cardiotomy suction is stopped to avoid clotting within the bypass circuit. The protamine should be administered slowly due to its propensity for causing systemic vasodilatation and pulmonary vasoconstriction. Transfusion of residual blood from the pump is usually required to support cardiac filling during protamine administration; generally boluses of 100 ml are given, titrated against MAP and CVP, PA or LA pressures and direct observation of the heart. The aortic cannula is typically removed when protamine administration is completed, the patient is stable, and there is no further requirement for transfusion of residual blood via the CPB machine. The two purse-string sutures on the aorta are tied to secure the cannulation site.

The remainder of the blood in the bypass circuit can be retained for transfusion by the anesthetist directly or it can be processed through a cell-salvage device to maximize the red cell concentration of this “pump blood.” After transfusion a further dose of protamine may be administered to counteract the heparin in the pump blood.

Transition from CPB to physiological circulation is more often than not an uneventful process. In some circumstances, particularly when operating on patients with severely impaired ventricular function, or if there has been a long ischemic period during the procedure, weaning from CPB may require measures to be taken to support the circulation. Such measures are discussed in Chapter 8.

Miniature extracorporeal circulation

Miniature extracorporeal circulation or “mini-bypass” has been around for more than 10 years, but has recently been enjoying an increase in interest. The main differences between a mini-bypass circuit and a standard CPB circuit are:

- Shorter length of tubing
- Absence of a venous reservoir

In essence, mini-bypass is little different from an ECMO circuit. As a result of these changes, the priming volume for the circuit is almost a quarter of that of a standard circuit, around 500 ml compared to up to 2000 ml. The major advantage of this is reduced dilution of the patient’s circulating volume, with a resulting higher hemoglobin and hematocrit and corresponding reduced need for administration of red blood cells while on bypass. In addition, the absence of the venous reservoir decreases the amount of blood–air interface, thereby aiming to reduce the inflammatory effect of CPB.

Each feature however has its own potential disadvantages and some alterations to the management of the circuit are necessary compared to a standard circuit. The reduced length of tubing means that the bypass pump has to physically be closer to the operating table, with greater attention paid to sterility of the drapes and a reduced amount of space for movement of the surgical team and access to the tubing for the perfusionist. The absence of a venous reservoir removes a degree of flexibility and safety in terms of variations in venous drainage depending on surgical manipulation of the heart and venous cannulae. If venous drainage reduces, the mini-bypass pump will simply stop. As a result of this most perfusion teams will have a lower threshold for addition of crystalloid, colloid or blood products into the circuit, which may negate some of the advantages of the reduced prime volume.

Initial mini-bypass circuits were completely “closed” and did not allow any air–blood interface including the use of pump suction, which had to operate separately via a cell-saver system. Subsequent versions allowed the use of one pump sucker or vent in a ‘semi-closed’ set-up with a bubble trap. However it does not take much air to overwhelm a bubble trap and constant vigilance is required to optimize the use of any sucker or vent and to ensure that any air aspirated into the circuit is removed before it reaches the arterial side.

While the number of case reports and case series of the use of mini-bypass in various forms of cardiac surgery is increasing rapidly, the majority of outcome data so far is in the setting of elective, low-risk CABG surgery. In this setting mini-bypass has been shown to reduce the transfusion of red blood cells and has not been associated with an increase in major adverse events. As such its use is expanding.

Appendix 5.1

Protocol for the conduct of "routine" CPB

(Adapted, with permission, from *London Perfusion Science* Protocols.)

1. Connection of the circuitry to the patient

- The surgeon will ask for the CPB lines to be divided
- The pump flow is slowly reduced and the venous line clamped, followed by the arterial line, beyond the recirculating Y-connector
- The surgeon will cannulate the aorta or peripheral arterial vessel
- If required, the arterial pump is continuously turned to assist an air-free connection
- When the line is free of air the surgeon will connect the arterial line and confirm that the connection is satisfactory
- The clamp from the arterial line is removed and repositioned behind the recirculating Y-connector
- The swing on the "Tycos" gauge is checked
- If required, 50 ml blood is transfused to determine the adequacy of the swing
- Perfusionist should state there is a "good swing" if the gauge swings freely and reflects the patient's blood pressure
- If the perfusionist has any doubts about the cannulation, they must inform the surgeon immediately, continuing to voice their misgivings until they are confident that the cannula is satisfactorily placed
- Surgeon will cannulate the venous circulation (via RA, IVC, and SVC or peripherally)
- Be prepared to use the pump suckers to deal with any blood loss
- Be prepared to transfuse the patient to replace this lost blood volume

2. Initiating bypass

- If the gases have not yet been switched on, they are now correctly set according to the patient's rated flow

- The perfusionist must now clearly inform the medical staff that he/she is “going onto bypass”
- The clamp on the arterial line is removed and the pump is slowly turned at first, gradually increasing the rpm
- When going onto bypass with a centrifugal pump, forward pressure must be generated before the line clamp is removed. The drive motor is therefore turned on while the aortic line is still clamped, in order to generate sufficient forward pressure, to exceed the patient’s arterial pressure; above 2000 rpm is usual
- The perfusionist must monitor the pressure on the line pressure (electronic or Tycos) during this stage, looking for any sign of obstruction: at the same time monitoring the venous and arterial pressures and, of course, monitoring the blood level in the venous reservoir, as the pump speed is increased
- Having raised the pressure on the venous side, the venous clamp is removed – more quickly if air has been left in the venous line – until this air has been removed. Perfusionists should then control the venous pressure with their clamp until they have achieved full rated flow for the patient
- The anesthetist should be informed when full flow has been achieved, so that ventilation may be discontinued
- Any difficulty in achieving a full venous return should be reported immediately to the surgeons, so that they may make any adjustment to the venous cannulation as may be necessary. Venous air should also be reported to the surgeon. It is important that an optimum venous return can be obtained at this stage
- The perfusionist must monitor the ECG at this stage, so that arrhythmias, particularly ventricular fibrillation (VF), may be noted early and action taken to prevent cardiac distension
- Once the aorta has been clamped, the required temperature has been achieved, cardioplegia has been administered, if required, and a steady-state of perfusion has been attained, the first sample for blood gases, electrolytes, ACT, Hb/HCT, and glucose is taken

3. Patient flows

The flow required to meet a patient’s metabolic requirements may need to be modified in certain circumstances (such as the presence of critical illness). Using the patient’s height and weight, the patient’s

surface area is obtained from a standard nomogram, and hence flows calculated for differing levels of metabolic requirement:

Hypothermia	Temperature (°C)	Flow index (l/minute/m^2)
Normothermia	34–37	2.4
Moderate hypothermia	32–34	2.2
Hypothermia	28–32	1.8–2.0
Profound hypothermia	<28	1.6

As a general rule, flows should be reduced with temperature (as metabolic requirement diminishes) and vice versa. While individual cases may require special consideration, it is important to note the following:

Hypothermia is used as a technique in order that flows may be safely reduced. Too high a flow at a reduced temperature may:

- Cause blood damage
- Impede the surgery by flooding the field
- Cause an excessive rise in venous pressure
- Cause warming of the heart when cardioplegia has been used
- Cause underperfusion. Flows should correspond to temperature. Too low a flow during re-warming or at normothermia may lead to serious underperfusion

4. The re-warming phase

The re-warming phase begins only after consultation with the surgeon. On re-warming, appropriate adjustments to gas flows and to blood flows must be made. This is a period during which a rapid drop in S_VO_2 may be experienced. A sample for all parameters should be taken during the mid-warming phase, in order to give sufficient time for any corrective action to be taken before coming off bypass. Final samples should be taken once a core temperature > 35°C has been attained.

Re-warming

- The patient should be re-warmed using the arterial blood temperature and patient core temperature as guides to the rate and extent of re-warming
- The target arterial blood temperature is between 37.5 and 38°C. The upper limit should not be exceeded
- A gradient of 10°C between the water temperature in the heater-chiller unit and the arterial blood should not be exceeded
- Re-warming the patient to 37°C (nasopharyngeal) is usually a maximum, although surgeons vary in this regard
- Appropriate adjustments to gas flows and to blood flows must be made
- The rate of re-warming should be such as to allow time for distribution of heat between core and peripheral tissues, using vasodilators, if needed, to enhance peripheral blood flow and thus heat distribution
- Post-CPB an "after drop" in core temperature occurs as heat is redistributed from core to peripheral tissues; this after drop can be lessened if adequate time is allowed for thorough re-warming

Self assessment

1. Regarding the conduct of CPB:

A Venous drainage should be complete before arterial flow is commenced

B The most common site for arterial cannulation is the ascending aorta

C Good communication between the team is essential for safety

D The ACT should be at least > 400 s before commencing bypass

E The presence of an arterial filter removes the risk of arterial air embolism

Answers: A False; B True; C True; D True; E False

2. When monitoring the patient on CPB:

A. It is essential to monitor central venous pressure (CVP)

B. A rise in CVP may indicate impaired venous drainage

C. It is possible to have a pulsatile arterial trace with adequate pump flow

D. A radial arterial line should always be sited in the left radial artery

E. Absence of urine output means CPB flow is inadequate

Answers: A True; B True; C True; D False; E False

3. Central venous cannulation for CPB:

A. May result in atrial dysrhythmias

B. Should always be via a “two-stage” cannula

C. May be performed with a straight or angled cannula

D. Should always result in SVC and IVC drainage

E. Always drains blood returning from the coronary sinus

Answers: A True; B False; C True; D True; E False

4. Transesophageal echocardiography:

A Is an essential part of the safe conduct of CPB

B Can be reliably used to assess for plaque in the ascending aorta

C Is useful to assess adequacy of de-airing of the heart

D Is risk free

E May be used to assess the correct placement of cannulae

Answers: A False; B False; C True; D False; E True

5. Oxygen consumption on bypass:

A Can be calculated using the Fick equation

B Is not influenced by temperature

C If not matched by oxygen delivery will result in a metabolic acidosis

D Is affected by the level of anesthesia

E Is constant

Answers: A True; B False; C True; D True; E False

Suggested Further Reading

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Chapter 6

Metabolic management during cardiopulmonary bypass

Kevin Collins and **G. Burkhard Mackensen**

> The perfect perfusion to me… is to be allowed to perform the necessary repair, however long that takes and yet leaving my patients looking like they've never been on bypass.
>
> Dr. Norman Shumway, Stanford University

The key to metabolic management during cardiopulmonary bypass (CPB) is the maintenance of adequate blood flow and oxygen delivery to the body's tissues. Utilizing the CPB machine, the perfusionist provides the optimum conditions necessary for operations on the heart, lungs or major vessels, while supporting the patient's physiological and metabolic needs.

CPB-induced perturbations of patient metabolism and corrective interventions

CPB induces a unique set of physiological disturbances. The principal causes of metabolic derangement include:

- fluid priming of the CPB circuit;
- organ hypoperfusion; and
- changes in body temperature.

The causes, management, and monitoring of metabolic parameters during CPB are discussed in this chapter.

CPB primes, hemodilution, and autologous priming

CPB circuit primes

All priming fluids cause hemodilution, which leads to a fall in the hematocrit (HCT), alterations in the volume of distribution of electrolytes, and fluid shifts between the vascular and intercellular compartments. Every attempt should be made to minimize the volume of the CPB circuit. Use of small-diameter tubing and cannulae in the circuit, minimizing the length of circuit tubing, partially priming with autologous blood, and using vacuum-assisted venous drainage all provide easy methods of reducing priming volume.

In the earliest days of cardiac surgery and CPB in the late 1950s, the prime was constituted to provide near normal HCT levels. However, with the advent of the use of hypothermia in the 1960s, intentional hemodilution became standard practice. Hemodilution is principally the result of the need for fluid priming of the CPB circuit, but also arises from the infusion of fluids during surgery and the administration of cardioplegia solution (CPS). Some degree of hemodilution is considered to be beneficial:

- The reduction in blood viscosity minimizes CPB circuit sheer stresses upon blood, thereby lowering hemolysis rates.
- Reduced blood viscosity improves blood flow through capillary networks.

Utilizing weight-adjusted formulas, the desired HCT on CPB can be calculated as outlined in Table 6.1.

Table 6.1 Expected HCT on CPB

HCT on CPB = red cell volume/system volume
Red cell volume = patient blood volume × pre-CPB HCT
System volume = patient blood volume + prime volume
Blood volume:
Adult – male: 70 ml/kg, female: 60 ml/kg
Child–1–10 years: 80 ml/kg, 3–6 months: 85 ml/kg, 0–3 months: 90 ml/kg

Further rationale for the use of hemodilution includes reducing bank blood usage and thus the associated risks of transfusion, as well as respecting the wishes of patients not wanting to receive blood transfusions (e.g. Jehovah’s Witness).

Hemodilution affects the concentration of plasma proteins, which exert an "oncotic pressure," holding water in the vascular compartment and so preventing its accumulation in the interstitial spaces. Plasma proteins also bind a high proportion of drugs and electrolytes, maintaining a balance between their unbound, ionized state and their protein-bound state. Serum albumin (3.5–5.5 g/dl) constitutes 50–70% of the total protein with globulins (2–3.6 g/dl) comprising the bulk of the remainder.

Starches, modified animal colloids or human albumin may be added to CPB primes to increase their effective oncotic pressure. The composition of CPB primes is discussed in detail in Chapter 3.

Autologous priming

Autologous priming (AP) utilizes the patient's blood to partially re-prime the CPB circuit upon initiation of CPB. AP uses normal (antegrade) blood flow (Q) through the CPB circuit to displace the circuit prime with the patient's venous blood while diverting the crystalloid into a sterile bag, potentially reducing the circuit prime by between 250 and 750 ml. During the 10- to 20-second period required for AP, the patient is essentially being exsanguinated and the anesthetist must administer vasoconstrictors as required to maintain blood pressure. Alternatively, partial priming with autologous arterial blood can be achieved by retrograde drainage of 100–400 ml of blood (accounting for the volume of the cannula, tubing, and arterial line filter (ALF)) via the arterial cannula into the cardiotomy reservoir. Low prime volumes using current microcircuitry (including intregral ALFs, cardioplegia sets, and ultrafilters) can range from 1000–1250 ml. AP can dramatically decrease the extent of hypotension, attributed to rapid hemodilution, commonly seen following the initiation of CPB. AP allows for higher HCT levels with slightly higher viscosities at warmer CPB temperatures (32–35°C) and still appears to avoid hemolysis from CPB circuit sheer stresses. AP also aids "normalization" of vascular oncotic pressures, thus decreasing fluid shifts and "third spacing."

CPB flow rates

The perfusionist calculates a CPB blood flow (Q) utilizing the patient's body surface area (BSA) and cardiac index (CI) (see Table 6.2). Insufficient flow can result in inadequate tissue perfusion. Metabolic acidosis during CPB is almost always the result of hypoperfusion leading to inadequate oxygen delivery in order to meet metabolic demands for aerobic respiration. Oxygen consumption (VO_2) is thus a major determinant of CPB flow requirements (see Table 6.3).

Table 6.2 Hemodynamic calculations for CPB

CPB flow (Q) = CI × BSA

BSA = √(body weight (kg) × height (cm)/3600)

CI = CO / BSA

SVR = (MAP – CVP / CO) × 80

BSA, body surface area; CI, cardiac index; CO, cardiac output; CPB, cardiopulmonary bypass; CVP, central venous pressure; Q, blood flow; SVR, systemic vascular resistance; MAP, mean arterial pressure.

Table 6.3 O_2 calculations for CPB

$VO_2 = (S_aO_2 – S_vO_2)\ (1.34)\ (Hb) + (P_aO_2 – P_vO_2)\ (0.003)$

O_2 capacity = (1.34) (Hb) + (0.003) (PO_2)

O_2 content = (1.34) (Hb) (S_aO_2 or S_vO_2) + (0.003) (PO_2)

CPB O_2 consumption = ($aO_2 – vO_2$) (Q l/minute) (10)

CPB O_2 transfer = [($S_aO_2 – S_vO_2$) (1.34) (Hb) (Q ml/minute)]/100

aO_2 content, arterial oxygen content; CPB, cardiopulmonary bypass; Hb, hemoglobin; P_aO_2, oxygen arterial partial pressure; P_vO_2, oxygen venous partial pressure; Q, blood flow; S_aO_2, arterial oxygen saturation; S_vO_2, mixed venous oxygen saturation; vO_2, venous oxygen content.

Hypoperfusion

CPB-related hypoperfusion may be intentional or unintentional. The most common intentional causes of transient periods of hypoperfusion are induced by the cardiac surgeon. Manipulation of the heart may impede venous blood return to the CPB circuit necessitating a reduction in flow. Frequently, the surgeon requests the perfusionist to reduce flow to permit safe application or removal of the aortic cross-clamp, decrease surgical bleeding or to empty and decompress the heart.

Reduction of pump flow, for unintentional reasons, is nearly always caused by poor venous return to the circuit, usually due to a venous cannula that has been advanced too far or surgical distortion of the venae cavae and heart. Malpositioned aortic arterial cannulation, movement of the cannulae after placement or an incorrectly occluded arterial roller pump head may sometimes result in reduced flow.

Temperature and hypothermia

The temperature of the patient while on CPB is one of the most profound determinants of the requirements for perfusion. Systemic O_2 consumption, VO_2, is reduced by approximately 50% for every 7°C reduction in core temperature below normothermia (30°C = 50%, 23°C = 25%, 16°C = 12.5% metabolic demand of the same organ at 37°C; see Table 6.4). As such, relatively small decreases in temperature markedly reduce the requirements for systemic O_2 delivery, making moderate reductions in pump flow or HCT tolerable, such that DO_2 remains sufficient to meet VO_2.

Table 6.4 Classification of hypothermia

Mild: 36–34°C
Moderate: 33–28°C
Severe: 27–22°C
Deep:< 21°C

Left and right shifts in the oxygen–hemoglobin dissociation curve also occur with temperature changes during CPB (see Figure 6.1). At lower temperatures hemoglobin has a greater affinity for binding oxygen, consequently oxygen is also released less readily and the dissociation curve is shifted to the left. At higher temperatures the converse is true and the curve is shifted to the right.

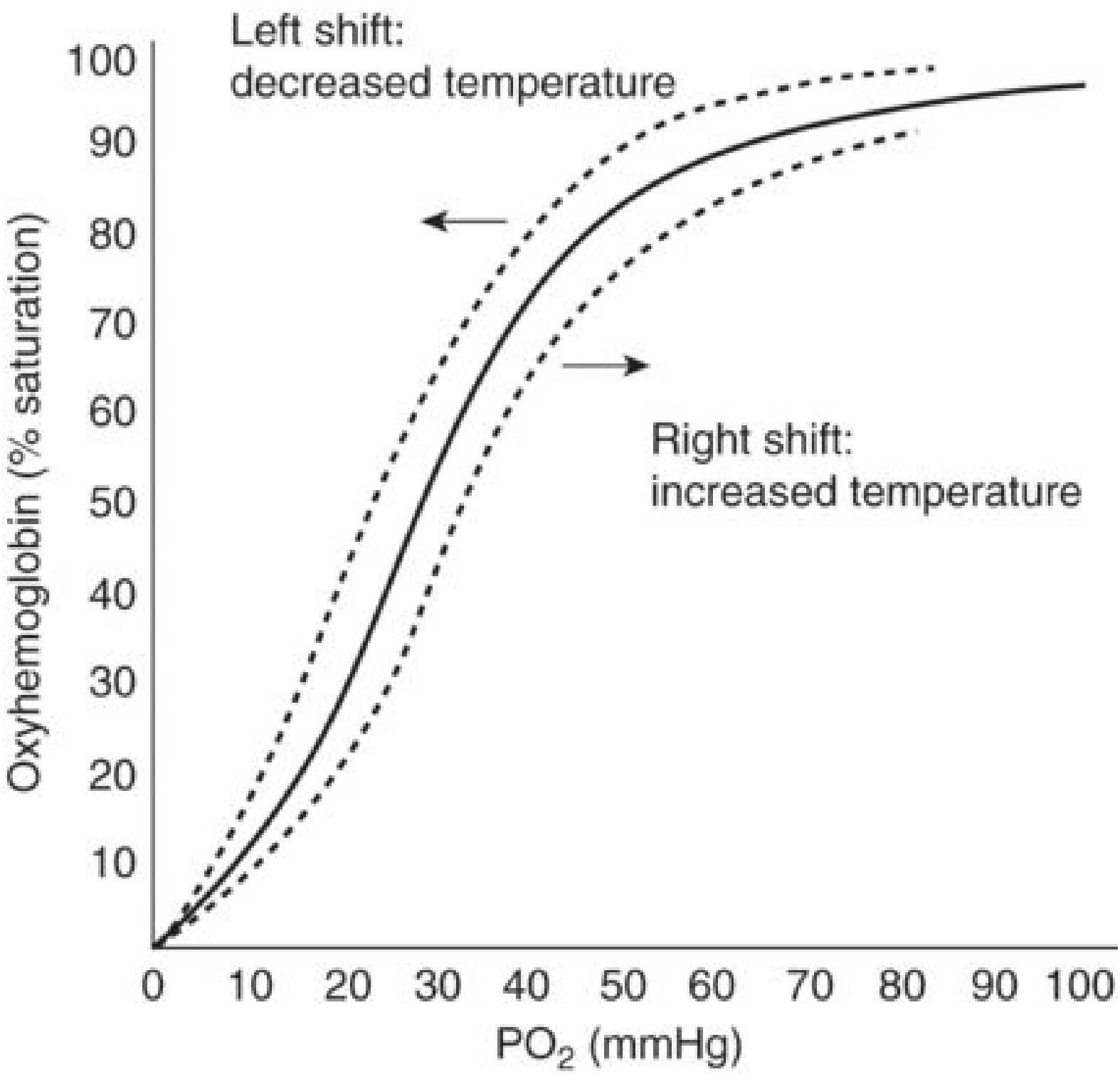

Figure 6.1 Oxyhemoglobin dissociation curve.

Pump flow rate must be adjusted with due consideration to temperature if the metabolic demands for oxygen are to be matched by delivery. Typical flow rates over a range of temperatures are shown in Appendix 5.1.

Deep hypothermic circulatory arrest

Deep hypothermic circulatory arrest (DHCA) is discussed in detail in Chapter 10, but is briefly mentioned here for completeness. Certain cardiac procedures require DHCA, rather than just

conventional mild to moderate hypothermia, usually because the aorta cannot be cross-clamped or total absence of blood flow is required to enable surgical access. DHCA is used to dramatically lower the body's metabolic demand while protecting organs, particularly the brain, during a period in which perfusion is suspended. This technique utilizes severe to deep hypothermia, with or without the use of aortic cross-clamping and delivery of cardioplegia, to facilitate surgery to the left ventricular outflow tract, aortic valve, ascending aorta or great vessels. Pediatric palliative and corrective surgical procedures also frequently necessitate periods of DHCA. Procedurally dictated, intermittent "low-flow" (5–15 ml/kg/minute) states may be employed during DHCA to deliver oxygenated blood to the brain via antegrade cerebral perfusion (ACP) and retrograde cerebral perfusion (RCP). During ACP in adult patients, mean arterial pressure (MAP) should be ≤ 65 mmHg, and during RCP the central venous pressure (CVP) should be ≤ 25 mmHg.

pH, acid–base, blood gases, electrolytes, and hemo/ultrafiltration

pH and acid–base metabolism

The normal pH of arterial blood is 7.4 (± 0.05). Bicarbonate and non-bicarbonate systems play important roles in buffering pH changes.

Bicarbonate system

The bicarbonate buffer system (carbonic acid H_2CO_3 and bicarbonate HCO_3^-) is considered to be the most important mechanism for physiological regulation of pH. It possesses approximately 53% of the total buffering capacity of body fluids. Exogenous sodium bicarbonate is easily administered during CPB. It should be noted that bicarbonate's molecular weight is small enough to allow its passage across the semipermeable fibers of hemofilter systems and may thus be removed with the effluent product or "plasma water waste" if hemofiltration is used during CPB. The simple formula [(body weight (kg) × 0.3)/2] × base deficit = mmol $NaHCO_3^-$ needed to yield base excess equal to 0 is often used when treating persistent acidosis.

Non-bicarbonate buffers

- **Inorganic phosphate buffers** are important in regulating pH in the intracellular and renal tubular fluids. Inorganic phosphates are removed during hemofiltration.

- **Plasma proteins** possess significant buffering capacity because of the ionic nature of their amino acid structure and because of their high plasma concentrations. Plasma proteins are not removed during hemofiltration because of their larger molecular size.
- **Hemoglobin and oxyhemoglobin** play a major role in buffering hydrogen ions at the tissue level. Considered the most important of the non-bicarbonate pH buffers, hemoglobin is not removed during hemofiltration because of the size of the red blood cell.

Metabolic acidosis and alkalosis

Metabolic acidosis is usually due to systemic O_2 delivery (DO_2) during bypass not meeting systemic O_2 demand (VO_2). The options to address this are to increase pump flow or HCT, thereby increasing DO_2, or to reduce VO_2 by decreasing temperature or possibly by increasing depth of anesthesia. Failing this, administration of sodium bicarbonate, or the use of hemofiltration (ultrafiltration) may correct the acidosis.

CPB-related metabolic alkalosis may be due to a reduction in serum potassium levels (e.g. due to increased urine output or hemofiltration) and is best treated by titrated administration of potassium chloride.

Respiratory acidosis and alkalosis

Respiratory acidosis is the result of insufficient removal of CO_2 from the patient's blood by the membrane oxygenator. Increasing the sweep gas rate through the membrane oxygenator will facilitate the transfer or elimination of excess CO_2 from the patient's blood. Conversely, respiratory alkalosis is the result of excessive CO_2 removal.

Alpha-stat and pH-stat strategies for blood gas management

The optimal pH management strategy during hypothermic CPB is as yet undetermined. The two main strategies utilized clinically, alpha-stat and pH-stat, differ in their approach to the acid–base alterations that occur with hypothermia. As blood temperature falls, gas solubility rises and the partial pressure of carbon dioxide decreases (PCO_2 decreases 4.4% for every °C drop in temperature). With alpha-stat management, arterial gas samples are not corrected for sample temperature and the resulting alkalosis remains untreated during cooling; with pH-stat management, arterial blood gas samples are temperature corrected and carbon dioxide is added to the gas inflow of the CPB circuit so that the PCO_2 and hence pH, is corrected to the same levels as during normothermia. The advocates of alpha-stat point to potential benefits in terms of the function of intracellular enzyme systems and the advantage of preserving cerebral autoregulation. Proponents of pH-stat, which results in cerebral vasodilation, cite, as advantages, higher

levels of oxygen delivery to the brain and enhanced distribution of blood flow. However, the higher cerebral blood flows associated with pH-stat also have the potential to carry more gaseous or particulate emboli to the brain.

Alpha-stat management is based on the concept that the dissociation constant, pK, of the histidine imidazole group changes with temperature in a manner nearly identical to physiological blood buffers. Hence, the ionization state (α) of this group stays the same, irrespective of temperature. As the imidazole group's ionization state is a key determinant of intracellular protein function, advocates of alpha-stat management contend that this strategy promotes normal protein charge states and function, even at low temperatures.

The pH-stat approach requires increases in the total carbon dioxide content of the blood as the temperature falls in order to maintain fixed temperature-corrected pH values. The optimal pH of most enzymatic reactions does vary with hypothermia, mostly in accordance with the predictions of the alpha-stat hypothesis. Hence, the relative acidosis of pH-stat would be expected to lower enzymatic reaction rates. Whether this is beneficial in reducing energy consumption, or harmful by impairing key cellular homeostatic mechanisms, is unclear.

Differences in alpha-stat and pH-stat management become progressively greater as temperature is reduced. The effect is quite profound below 25°C, but above 32°C the change in CO_2 solubility is small and of much less clinical and physiological relevance. This is further evident when one appreciates how little CPB time most adult cardiac surgical patients spend at hypothermic temperatures. Most cases are conducted with mild hypothermia and in those much of CPB time is spent transitioning to, or from, those temperatures; the actual time on CPB spent below 32°C may only be 25% of the total CPB time. Thus, although frequently discussed, alpha-stat versus pH-stat management is of little actual relevance in most adult cardiac surgery.

Electrolytes

Potassium (K^+)

Hyperkalemia is the most common electrolyte disturbance during CPB. Potassium levels can be lowered using diuretics, insulin, and dextrose administration, or hemofiltration. The treatment of choice is dictated by the potassium level, the persistence of rise in potassium levels, and the presence or absence of electrophysiological disturbances. Serum potassium levels transiently rise with the administration of cardioplegia and this will usually correct without treatment within a short period after ceasing delivery of cardioplegia. Potassium levels in the range 5.5–6.5 mmol/l can be treated with administration of a

diuretic, usually furosemide 20–40 mg. In some centers, levels between 6.5 and 7 mmol/l are treated using insulin and dextrose infusions. Levels above 7 mmol/l or persistently raised potassium levels can be lowered using "zero balance hemofiltration." A crystalloid solution, typically normal saline, is added to the CPB circuit to maintain circulatory volume and then removed by hemofiltration causing concomitant removal of potassium. As this technique can result in the loss of significant amounts of bicarbonate through the hemofilter, it should be replaced using sodium bicarbonate titrated to blood bicarbonate levels.

The urgency or need to treat hyperkalemia should in part be determined by the presence or absence of electrophysiological disturbance. In the absence of ECG changes, moderate hyperkalemia may not require treatment. If treatment is chosen, its effect should not be longer than the anticipated period of hyperkalemia. It is important to note that during CPB extracellular potassium may rise but typically, even untreated, increases in K^+ levels are nearly always transient, as the extracellular potassium concentration in the plasma is quite small relative to the intracellular capacity for its uptake. Rapid shifts to the intracellular space and urinary excretion often correct K^+ levels quite quickly after CPB.

Hypokalemia, usually less than 4.5 mmol/l, is treated by administration of potassium chloride, normally in 10–20 mmol boluses. It is worth bearing in mind that rapid bolus administration of potassium during CPB may cause transient vasodilatation. Potassium levels alter with temperature. Treatment should thus be undertaken in the context of:

- temperature;
- the rate of rise of the potassium level;
- the persistence of that level; and
- the point during surgery at which it is occurring.

Ideally, potassium is finally corrected before separation from CPB using results of electrolyte measurements taken at a body temperature of not less than 35°C.

Calcium (Ca^{2+})

Calcium levels are reduced by hemodilution, chelation by preservatives in bank blood or by hemofiltration. Significantly low serum Ca^{2+} levels are generally corrected close to the termination of CPB, when the aortic cross-clamp has been removed, a cardiac rhythm has been established, and the temperature is approaching normothermia. One gram (or 3–5 mg/kg) of calcium chloride is usually all that is required to normalize serum ionized calcium levels (1–1.5 mmol/l). Administration of Ca^{2+} may exacerbate reperfusion injury and should be avoided immediately before or after cross-clamp removal.

Timing of administration can be guided by normalization of cardiac conduction indicating adequate reperfusion.

Magnesium (Mg^+)

Magnesium depletion occurs during CPB if hemofiltration is used or if there is high volume diuresis, particularly with loop diuretics. In these situations, a 2 mg bolus of Mg^+ may be added empirically into the circuit after the core temperature has reached 34°C and the aortic cross-clamp has been removed. Ideally, if Mg^+ levels are available, Mg^+ administration should be titrated according to blood levels.

Phosphate

Phosphate levels are commonly low after major cardiac surgery. This frequently occurs in the immediate postoperative period and is associated with significant respiratory and cardiac morbidity. Therefore, phosphate levels should be routinely measured after surgery, especially in patients with a complicated or prolonged intraoperative course, so that appropriate replacement therapy may be started in a timely manner.

Glucose

Glucose levels on CPB tend to increase as a result of the physiological stress response to major surgery. Values may exceed 20 mmol/l in diabetic patients without treatment. Non-diabetic patients' serum glucose levels can also rise; levels of 10–15 mmol/l are not uncommon. Continuous insulin infusions of 5–15 U/hour may be required during CPB. Hyperglycemia is associated with poor patient outcomes. Specifically, perioperative hyperglycemia has been associated with higher incidences of mediastinitis, wound infections, and neurocognitive deficits. There is conflicting literature regarding both the ideal and acceptable intraoperative and postoperative glucose levels. However, recent studies have shown mixed results from attempts at aggressive management of CPB-related hyperglycemia. The results range from favorable outcomes, to little or no association between reducing serum glucose levels and reduction in postoperative complications, to adverse patient outcomes associated with the tight control of CPB-related hyperglycemia. It is generally believed that normal (4.0–5.5 mmol/l) serum glucose levels during CPB are ultimately desirable. Consistent achievement of this goal is very difficult during CPB unless large doses of insulin are given and thus many clinicians will accept moderate hyperglycemia (7–9 mmol/l) as an endpoint to titrate insulin administration. Postoperative hypoglycemia, equally as dangerous and undesirable as hyperglycemia, can result from clinicians "overshooting" in their attempts at serum glucose

reduction. Glucose-free cardioplegia will ease the management of on bypass and postoperative patient glucose levels. Recent literature suggests sick, physiologically compromised hearts are unable to uptake and use glucose for fuel unlike healthy hearts. Elimination of exogenous glucose from the administration of glucose-containing cardioplegia can greatly lower the amounts of on bypass insulin required to achieve normoglycemic serum levels. The goal should be to maintain as near to normal serum glucose levels for each patient.

Lactate

Lactate is a major end product of glucose metabolism and gives an indication of the metabolic status during CPB. Most patients exhibit a progressive increase in plasma lactate during CPB. Lactate levels increase two- to three-fold during normothermic and hypothermic CPB. During periods of hypoperfusion or decreased liver function, usually secondary to hypothermia, serum lactate levels can increase even further (four- to eight-fold). Re-warming the patient and increasing flow rates usually helps to lower lactate levels.

Hemofiltration (ultrafiltration)

This allows selective separation of plasma water and low-molecular-weight solutes from the blood's cellular and plasma protein. Hemofilter membranes are composed of thousands of semipermeable hollow fibers (polysulfone, polyacrylonitrite or cellulose acetate fibers), each with an internal diameter of ~ 200 μm. Hollow fiber pore size determines which plasma solutes will be removed. Pore size usually ranges between 10 and 35 angstroms, removing molecules ≤ 60–20 000 daltons. The sieving coefficient is a measure of hemofilter efficiency and is directly related to solute molecular size. Solutes with weights ≤ 11 000 daltons (Na^+, K^+, Ca^{2+}, Mg^+, urea, creatinine, chloride, phosphorous, HCO_3^-, C3a, C5a, IL-1, IL-6, TNF-α) have a sieving coefficient of 1, indicating they are filtered at the same concentration as they exist in the blood. Larger molecules > 20–60 000 daltons (hemoglobin, globulin, fibrinogen, blood cells, platelets, albumin, and clotting factors) are unable to pass through the hemofilter fiber pores. The hydrostatic pressure differential, or transmembrane pressure (TMP), across the hemofilter rather than the osmotic pressures, as in hemodialysis, results in the separation of solutes and fluids. Application of vacuum to the effluent side of the hemofilter will improve solute and fluid filtration rates (up to 180 ml/minute). TMP (100–500 mmHg) is the mean of the hemofilter inlet (PI) and outlet pressures (PO) plus vacuum (PV): TMP=PI + PO/2 + PV. The combination of these pressures determines the filtration rate.

Drug dilution and loss

Current micro CPB circuits can add as much as 1000–1300 ml of priming fluid to the adult patient's circulating volume. Institutions that do not employ prime-reducing techniques (AP, vacuum-assisted venous drainage and microcircuitry) may have to add 300–600 ml more.

Institution of CPB results in an immediate dilution of drug concentrations. A new equilibrium between protein-bound and free ionized drug concentrations is established. Drug clearance and the intensity of biological effect are proportional to the concentration of free (unbound) drug, thus the pharmacodynamic effects of drugs are not necessarily altered if the concentration of free drug is maintained.

The effect of CPB on drug concentrations is complex and influenced by a number of factors such as temperature and the type of materials used in the CPB circuit; certain types of plastics and coatings on oxygenator membranes are more prone to binding drugs than others. Alterations in renal and hepatic metabolism induced by CPB also have a marked effect on plasma drug concentrations.

Monitoring of metabolic and physiological parameters

Arterial and venous blood gases and electrolytes

In-line real-time blood gas analysis has become the "gold standard" for extracorporeal perfusion. These arterial and venous analyzers utilize disposable sensors that attach directly to the arterial and venous lines of the CPB circuit, providing a luminal surface interface for blood leaving the oxygenator and for blood returning from the patient. Arterial sensors provide pH, PO_2, PCO_2, BE, HCO_3^-, and S_aO_2 data. The venous sensor generally provides HCT, hemoglobin, and mixed venous oxygen saturation (S_vO_2) measurements. Some in-line devices will also provide a continuous calculation of oxygen consumption based on pump flow and the arteriovenous oxygen differential.

If in-line blood gas monitoring is not available, intermittent samples should be taken at 30-minute intervals for analysis. Most blood gas machines provide data on blood gases, acid–base status, hematocrit, hemoglobin, electrolytes, and glucose.

Mixed venous oxygen saturation (S_vO_2)

During CPB S_vO_2 is an indicator of the matching of DO_2 and VO_2. As the margin between systemic O_2 delivery and demand narrows, O_2 extraction increases and S_vO_2 is reduced.

Reduced depth of anesthesia or degree of muscular paralysis by muscle relaxant drugs, low inspired oxygen concentration in the fresh gas flow mixture or anemia all decrease S_vO_2. However, if these parameters have been optimized, low S_vO_2 values generally indicate hypoperfusion and should prompt an increase in pump flow rate to improve oxygen delivery. If the ability to increase flow is limited by venous return, then increasing DO_2 by increasing HCT, or reducing VO_2 by reducing temperature, is indicated. However, the S_vO_2 value should always also be interpreted in the context of core temperature. The solubility and hemoglobin binding affinity of oxygen increases with hypothermia, while organ metabolic demand decreases, resulting in increased S_vO_2 if perfusion is adequate. Venous saturations of 65–75% are typical at temperatures of 37–35°C, 76–85% at temperatures of 34–32°C, and 85–100% at temperatures of 32–16°C.

Self assessment

1. Replacement of potassium in patients with hypokalemia during cardiopulmonary bypass (CPB) should be undertaken with due consideration to:

A. Temperature

B. Rate of rise of potassium level

C. The point during surgery at which it is occurring

D. The patient's acid–base status

E. All the above

Answer: E

2. Circuit primes are composed of either crystalloid, blood-based fluids, or a combination of both. How does the perfusionist determine which prime to utilize?

A. Body surface area and procedure type

B. Ideal body weight and gender

C. Factoring in various physiological variables, each unique case will dictate the components of the circuit prime

D. Lean muscle mass, age, and gender

E. A and D

Answer: C

3. Which statement in regards to hemodilution during CPB is **false**? Hemodilution …

A. Decreases allogeneic transfusions

B. Decreases hemolysis

C. Decreases microvascular blood flow during hypothermic perfusion by increasing blood viscosity

D. Should be limited by minimizing the volume of the CPB circuit thus reducing prime volume

Answer: C

4. Ultrafiltration has been associated with improved hemodynamics and pulmonary function, in addition to its beneficial effects on fluid balance, hemostasis (preservation of coagulation factors and platelets), and blood conservation (reduction in allogeneic blood product transfusions).

A. True

B. False

Answer: A

5. "Cell washing" salvaged blood via cell savers:

A. Discards coagulation factors as irretrievable waste

B. Possibly necessitates the transfusion of fresh frozen plasma if large amounts of a patient's blood is washed and returned

C. Can induce a dilutional coagulopathy

D. A and C

E. All of the above

Answer: E

6. During the course of a cardiac procedure, the rate of blood flow may be reduced or even completely stopped, creating both intermittent and protracted periods of hypoperfusion or no perfusion to one organ or the entire body. This is done to:

A. Accommodate the surgical procedure

B. Decrease the amount of hemolysis

C. Protect the patient from developing cerebral edema

D. Decrease the development of whole body inflammation

E. B, C, and D

Answer: A

7. Hypothermia's major advantages are:

A. The reduction of metabolism

B. The reduction of oxygen consumption during CPB

C. It allows for reduced blood flow rates promoting better surgical exposure and visualization while protecting tissue and end organs

D. A and B

E. All of the above

Answer: E

8. Controversy exists regarding the type of blood gas management strategy to use during CPB. Benefits of both can be argued eloquently as the superior technique. Which statement in regards to alpha or pH-Stat is most appropriate?

A. With alpha-stat management, arterial gas samples are not corrected for sample temperature and the resulting alkalosis remains untreated.

B. pH-stat management leads to higher cerebral blood flow (CBF) but this may have the potential to increase the embolic load to the brain.

C. With pH-stat management, arterial blood gas samples are temperature corrected and carbon dioxide is added to the gas inflow of the CPB circuit to correct the $PaCO_2$ and pH.

D. Differences between alpha-stat and pH-stat management become progressively smaller as temperature is reduced.

E. A, B, and C are correct

Answer: E

9. SvO_2, although commonly used during CPB, provides only one piece to the puzzle of monitoring and proper management of patient metabolism. Which of the following statements are true?

A. A normal or increased SvO_2 value does not ensure adequate delivery of regional oxygen requirements

B. A decreased SvO_2 does not necessarily indicate either inadequate systemic oxygen delivery or increased oxygen consumption

C. Insufficient perfusion, Hgb, and PaO_2 lead to decreased oxygen delivery; inadequate anesthesia or hyperthermia can lead to excessive oxygen consumption

D. A and C

E. All of the above

Answer: E

10. Which statement in regards to the bicarbonate system and non-bicarbonate buffers is correct?

A. Inorganic phosphates, like bicarbonate, are not removed during hemofiltration

B. Plasma proteins are not removed during hemofiltration.

C. The bicarbonate buffer system is considered the least important mechanism for regulation of pH.

D. Hemoglobin does not serve as a pH buffer.

Answer: B

Suggested Further Reading

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Chapter 7

Myocardial protection and cardioplegia

Maurice Hogan and **David Jenkins**

The majority of cardiac operations expose the patient to the risk of myocardial ischemia and subsequent myocyte damage, so this risk must be evaluated beforehand, and a strategy devised to minimize it. Specific decisions which must be made include whether:

- to perform the operation on cardiopulmonary bypass (CPB) or not,
- to maintain cardiac perfusion and allow the heart to continue beating during the operation or not,
- asystolic cardiac arrest is required then how this can be best achieved and maintained.

Deciding on the myocardial protection strategy for a particular operation involves a compromise between obtaining optimal conditions to facilitate surgery, i.e. a bloodless, non-beating heart with enough time to perform the surgery, and limiting myocardial damage. Myocardial damage results from “oxygen debt” due to imbalance between oxygenated blood supply and energy demand. Acute, inadequate myocardial perfusion gives rise to

- myocardial stunning, in which short periods of ischemia followed by reperfusion produce temporary myocardial dysfunction (i.e. hours or days) without myocyte necrosis;
- myocardial infarction, in which “death” of areas of cardiac muscle occurs with irreversible loss of function.

Inadequate perioperative myocardial protection is most likely to result in myocardial stunning, or even infarction depending on the duration of the ischemic period. This may manifest initially as difficulty in separating from CPB due to ventricular dysfunction, needing pharmacological or mechanical support. Subsequently a low cardiac output syndrome may develop, sometimes leading to multiorgan failure. The

myocardial protection strategy that is employed for each patient thus has a major bearing on perioperative morbidity and mortality, and on the overall success of the operation.

Myocardial protection during cardiac surgery has traditionally focused on techniques aimed at limiting the ischemic damage following application of the aortic cross-clamp and consequent cessation of coronary artery blood flow. Myocardial preservation during this ischemic period while the aorta is cross-clamped is achieved by administration of cardioplegia solution to arrest the heart in diastole to minimize myocardial oxygen demand. Unintentional ischemia may, however, also occur before application and/or following removal of the aortic cross-clamp as the consequence of hypotension, coronary spasm, or due to a complication of surgery, e.g. coronary artery embolus or a non-functioning coronary graft. Thus, the optimum approach to myocardial preservation should ideally consider protection of the heart during all phases of the operation and not just the period during which the aorta is cross-clamped and the heart excluded from the circulation.

Myocardial damage during CPB

While established biomarkers of myocardial damage, including troponin I, troponin T, and creatine kinase MB fraction (CK-MB), are highly specific and sensitive for myocardial cell damage, their direct clinical utility post-cardiac surgery is paradoxically limited by their high sensitivity: almost all patients after cardiac surgery will have a rise in serum cardiac biomarkers, but it does seem that the degree of rise correlates well with the extent of myocardial injury. This has proven useful in evaluating new techniques or interventions in cardiac protection, and has also been taken into account in the definition of perioperative myocardial infarction. Following coronary artery bypass graft (CABG) surgery, perioperative myocardial infarction is defined as increases in biomarkers greater than 10 times the 99th percentile upper reference limit, plus either new pathological Q waves or left bundle branch block on the postoperative electrocardiogram, or angiographically documented new graft or native coronary occlusion, or imaging evidence of new loss of viable myocardium. A meta-analysis of studies which looked at CK-MB or troponin rise post coronary artery bypass graft surgery showed that elevation within the first 24 hours was associated with increased risk of intermediate (1 year) and late (3 year plus) mortality.

Damage to the myocardium is more likely to occur in cases with

- prolonged aortic cross-clamp times,
- in patients who are already experiencing acute myocardial ischemia in the immediate preoperative period,

- reoperations,
- combined valve and coronary artery bypass graft surgery,
- and in patients with significantly impaired ventricular function preoperatively.

When the aorta is cross-clamped, perfusion of the coronary arteries ceases and oxygen cannot be delivered to the myocardium. If the heart continues beating, myocardial oxygen demand also continues at its usual level. This results in myocytes metabolizing anaerobically, as their high-energy phosphate stores are depleted. Consequently intracellular acidosis develops due to lactic acid accumulation and this, coupled with the depletion of high-energy phosphate stores, leads to contractile dysfunction. When the cells' energy stores are depleted, they can no longer support active transport of electrolytes across their membrane and this results in membrane breakdown, intracellular edema, and intracellular calcium overload – this stage is irreversible. If the coronary arteries are then subsequently re-perfused following a period of ischemia, then the myocytes may behave in a stunned manner for a period of time before regaining function or not regain function at all, i.e. die. Reperfusion itself can, however, also damage myocytes, as it leads to generation of free radicals, and the sequence of ischemia followed by reperfusion is itself implicated in stunning of the myocardium. This is why myocyte damage is often termed ischemia/reperfusion injury.

Goals and principles of myocardial protection

The goals of any myocardial protection strategy are to prevent or limit myocardial damage during episodes of either deliberate or unintentional ischemia in the perioperative period. The principle is that if myocardial oxygen supply is continually matched to demand, then myocardial damage should not occur. In clinical practice today, the planned intentional ischemia is most commonly protected against using a cardioplegic strategy. The principal determinants of myocardial energy demand, and thus oxygen utilization, are electromechanical activity and left ventricular end-diastolic wall tension (LVEDP) (see Figure 7.1).

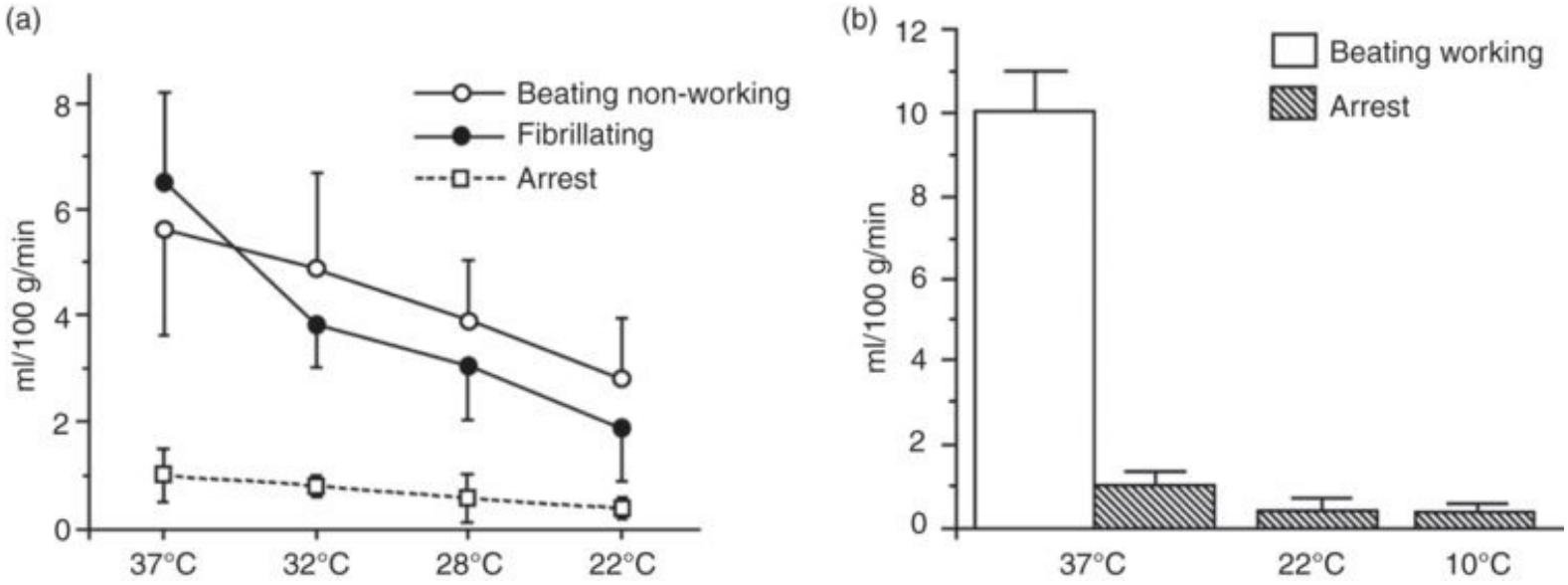

Figure 7.1 Myocardial O_2 demand at various working modes and temperatures.

During diastole, with low LVEDP, myocardial oxygen consumption and energy substrate utilization are minimized. The rapid attainment of diastolic cardiac arrest at the onset of the ischemic period is important and protection is further enhanced if the myocardium is simultaneously cooled as hypothermia reduces basal metabolic rate and reduces myocardial electrical activity.

Myocardial cooling can be achieved by administering cold cardioplegia, packing the heart with ice, cold pericardial lavage, or with temperature-controlled CPB. Care should be taken as prolonged localized hypothermia may actually cause myocardial damage. In contemporary practice antegrade cold blood cardioplegia to rapidly stop electromechanical activity and simultaneously reduce temperature in all myocardial layers has become the preferred method of cooling the heart.

Components of cardioplegia

Cardioplegic solutions provide myocardial protection via a combination of three overlapping mechanisms:

- induction of chemical cardiac arrest,
- myocardial hypothermia, and
- additional protection provided by measures such as the addition of acid–base buffers, energy substrates, or oxygenated blood to the cardioplegia infusion.

Induction of chemical cardiac arrest

Cardioplegia literally means “heart paralysis.” The heart can be arrested in either systole or diastole, but as discussed above, its lowest energy-requiring state is in diastole, so this is universally the preferred state of deliberate arrest. All cells have an electrical gradient or potential difference across their membranes and cardioplegic solutions act by altering the electrical gradient across the cell membrane of myocytes, with the goal of suppressing electrical activity and consequently mechanical contraction. The membrane equilibrium potential of the cardiac myocyte at rest is stable and relatively negative, at approximately minus 90 mV. At this equilibrium the inward depolarizing and outward repolarizing currents are equal in magnitude and there is no net current. This potential is determined by the selective permeability of the cell membrane to ions.

The myocyte cell membrane is ordinarily most permeable to K^+ and relatively impermeable to other ions. Movement of other ions across the membrane is mainly determined by voltage gated channels, which open or close at specific membrane potentials. The resting membrane potential is therefore dominated by the K^+ equilibrium potential according to the K^+ gradient across the cell membrane. The equilibrium potential for any ion may be calculated using the Nernst equation, which in a simplified version states that (e.g. for K^+):

$$E_{mK} = 61.5 \log_{10} (C_o / C_i),$$

where, E_{mK} is the potassium (K^+) equilibrium potential in mV, C_o is the extracellular concentration of K^+, and C_i is the intracellular concentration of K^+. Since the normal value for C_o/C_i for K^+ is 4/140, the K^+ equilibrium potential is calculated as −94 mV. If the extracellular K^+ concentration rises to 20 mmol/l, the value for C_o/C_i changes to 20/140, and the equilibrium potential is then −52 mV. In this way we can appreciate how manipulation of the extracellular environment affects the equilibrium potential of the cardiac myocyte.

Figure 7.2 shows the normal action potential of a cardiac myocyte. Phase 4 represents the resting membrane potential of the cell, and coincides with ventricular diastole. Normally as an action potential propagates through the heart’s conduction system, the myocyte membrane becomes less negative, to approximately −70 mV, and once this threshold potential is reached, this triggers the fast sodium (Na^+) channels to open. This allows Na^+ to rush into the myocyte, and raises the membrane potential further very rapidly, i.e. depolarizes the cell to approximately +20 mV (Phase 0). Almost as soon as the membrane potential becomes positive, these voltage controlled Na^+ channels are closed, and voltage gated K^+ channels open, allowing K^+ to leave the cell, and reducing the membrane potential to +5 mV (Phase 1). At this time, voltage gated calcium (Ca^{2+}) channels in the membrane open and Ca^{2+} enters the myocyte (Phase 2). Calcium influx to the cell results in contraction, and this coincides with ventricular

systole. These Ca^{2+} channels only remain open transiently, and as soon as they close, the membrane potential returns to approximately −90 mV, as K^+ is still able to leave the cell via the voltage gated K^+ channels, and the cell membrane repolarizes. The intracellular calcium is mopped up, and the cell relaxes again.

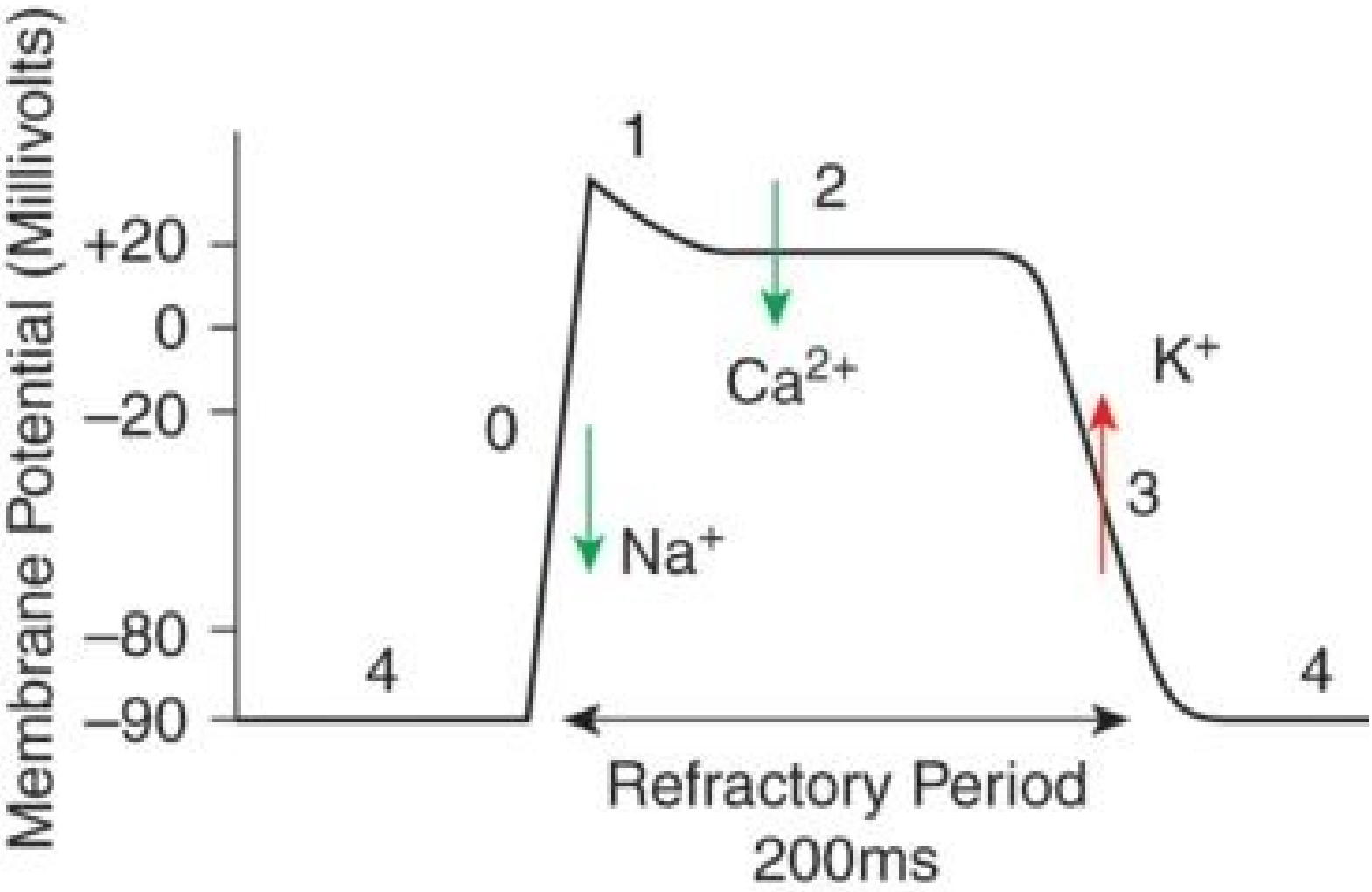

Figure 7.2 Myocardial membrane potential at the 4 phases of the cardiac cycle.

When extracellular cardioplegia with high K^+ (20 mmol/l) displaces blood surrounding the myocytes, the cell membrane potential is increased and it depolarizes more readily, i.e. at a less negative membrane potential. The depolarization causes voltage gated Ca^{2+} to open, transient calcium influx via these channels results in contraction, before they close and the calcium is locked away in the sarcoplasmic reticulum again, and the cell relaxes (diastole). However, the high extracellular potassium concentration of the cardioplegia now prevents repolarization from occurring, so that the cell stays depolarized. When the resting potential approaches −50 mV, Na^+ channels are inactivated resulting in a diastolic arrest of cardiac activity.

Cardioplegia may be classified as either crystalloid-based or blood-based solutions. The crystalloid solutions may be further sub-classified based on their composition and similarity to either the normal

intracellular or extracellular environment (see Table 7.1).

Table 7.1 Composition of a typical extracellular cardioplegia solution (St. Thomas, STh1), a typical intracellular cardioplegia solution (Custodial Histidine-Tryptophan-Ketoglutarate, HTK), and of blood cardioplegia solution (BSTh1)

	STh1	**BSTh1**	**HTK**
K^+ (mmol/l)	20	20	10
Na^+ (mmol/l)	144	142	15
Mg^{2+} (mmol/l)	16	16	4
Ca^{2+} (mmol/l)	2.2	1.7	0.015
HCO_3^-(mmol/l)	Added prior to use	30–40	0
Histidine (mmol/l)	0	0	198
Tryptophan (mmol/l)	0	0	2
Procaine (mmol/l)	1	1	0
pH	5.5–7.0	7.4	7.02–7.20
Hematocrit (%)	0	10–20	0
Osmolarity ($mOsm/kgH_2O$)	300–320	310–330	310
Mannitol (mmol/l)	0	0	30

Initially, in the 1950s, potassium-based cardioplegia solutions were introduced with K^+ concentrations of 200 mM, and while the technique was effective in inducing cardiac arrest, it was associated with myocyte damage and necrosis caused by intracellular calcium overload as a result of membrane depolarization-induced calcium channel activation. It was not until the 1970s that the clinically safe K^+ concentration for cardioplegia solutions was determined to be closer to 20 mM, and since then potassium-based cardioplegia has been the standard solution used in cardiac surgery to arrest the heart. The development of St. Thomas' Hospital cardioplegic solution, essentially by adding potassium (16 mM) and magnesium (16 mM) to Ringer's solution in the 1970s by Hearse and colleagues was a

significant development in cardiac surgery and led to reduced operative mortality and better recovery of cardiac function postoperatively. As the mechanism of myocyte depolarization and contraction outlined above shows, potassium is not the only ion which could be used to manipulate myocyte electrical membrane potential and so affect myocardial contractility. In addition to hyperkalemia, hyponatremia, hypocalcemia, and hypermagnesemia will all ultimately cause diastolic cardiac arrest. Hypercalcemia, if profound enough, may cause systolic cardiac arrest. Bretschneider, working in Germany, developed a calcium-free, low sodium cardioplegia solution, which works by reducing the transmembrane Na^+ gradient sufficiently so that not enough Na^+ can enter the myocyte during phase 0 to cause depolarization, and the myocyte membrane remains hyperpolarized, and arrested in diastole. This solution is known as histidine-tryptophan-ketoglutarate (HTK), Bretschneider's or Custodiol solution, and its components are listed in Table 7.1. It is classified as an intracellular cardioplegia solution as its composition is closer to that of the intracellular environment, in contrast to the K^+ based "extracellular environment-like" solutions. A specific advantage of this solution over the solutions that resemble the extracellular environment is that it may be administered as a single bolus which provides effective protection for a period of over 2 hours. This means that the surgeon can concentrate wholly on the surgical procedure without being interrupted in order to repeatedly administer cardioplegia solution. Disadvantages are that a larger volume is given initially, which can cause hemodilution, and that the low sodium content may also result in systemic hyponatremia, although as serum osmolarity is maintained this may not be clinically significant.

Crystalloid solutions were the first cardioplegia solutions to be widely adopted and both "intracellular" and "extracellular" solutions are associated with excellent results. In the 1970s, however, Buckberg introduced the concept of "blood cardioplegia." The active ingredient of blood cardioplegia solution is still K^+, however it is delivered in a mixture of the patient's own CPB blood and a modified crystalloid cardioplegia solution. The ratio of blood to crystalloid cardioplegia mixed is usually four parts to one, however this can be varied. Purported benefits of blood over crystalloid cardioplegia are:

- reduced systemic hemodilution with repeated administration,
- blood helps maintain oncotic pressure,
- blood contains natural buffers,
- blood is a free radical scavenger, and
- blood can transport and deliver oxygen and remove carbon dioxide.

Blood cardioplegia is now considered by many to be the optimum cardioplegic solution, especially for higher risk patients. One practical drawback, however, is that repeated doses are required, usually at 20

to 30 minute intervals, and this can disrupt the smooth progress of the operation.

Myocardial hypothermia

As Figure 7.1 demonstrates, myocardial oxygen demand decreases with temperature. Myocardial hypothermia has therefore been used as a means of myocardial preservation during cardiac surgery. Prior to the introduction of effective cardioplegia solutions, systemic hypothermia was used to enable surgery on the arrested heart, albeit with poor results. Selective myocardial hypothermia can be very effectively achieved by administration of cold (4°C) cardioplegia. Hypothermia has been implicated in myocardial damage by causing myocardial edema, reducing cell membrane fluidity, and impairing function of transmembrane receptors. Much debate has taken place over the optimum temperature of administration of blood cardioplegia, as hypothermia shifts the oxygen dissociation curve to the left, and means that oxygenated blood cardioplegia is less likely to transfer the oxygen to the myocardial cells when administered cold. Infusion of warm (37°C) blood cardioplegia before and after cold cardioplegic arrest has been shown to preserve myocardial ATP levels. On this basis some surgeons choose to administer a "hot-shot" of cardioplegia prior to releasing the aortic cross-clamp and reperfusing the myocardium. Although reducing myocardial temperature effectively reduces myocardial oxygen demand, the additional benefit of cold blood cardioplegia is only around 10% more than that achieved by chemically induced arrest alone (see Figure 7.1). In a small randomized study comparing cold, warm, and tepid (29°C) blood cardioplegia in patients undergoing CABG surgery, it was shown that the best clinical outcome was achieved with tepid blood cardioplegia. Crystalloid cardioplegia, however, seems to be most effective when administered cold.

Additives to cardioplegia solutions

The main efficacy of all cardioplegia solutions in current use stems from their electrolyte composition and ability to induce rapid diastolic arrest. Many substances have been added to these solutions with a view to fine-tuning the myocardial protectant effect. Procaine has been shown to be effective in stabilizing the cardiac rhythm after cross-clamp removal and reperfusion, decreasing the incidence of ventricular fibrillation. Mannitol is a component of many cardioplegia solutions, and is added to increase the osmolarity of the final solution, with the aim of minimizing fluid transfer and intracellular edema. Albumin and glucose have also been added to some solutions to increase osmolarity. All cardioplegic solutions contain buffering agents, commonly sodium bicarbonate in the case of extracellular and blood-based solutions, and histidine in the case of HTK intracellular solution. Tris-hydroxymethyl aminomethane (THAM) is a buffer agent that, unlike sodium bicarbonate, does not produce carbon

dioxide (CO_2) but rather works by reacting with CO_2, and removing it. A reduction in myocardial pH consequent to ischemia impairs enzyme kinetics and myocardial metabolism. A limited degree of acidosis may be protective following ischemia as it has been suggested that calcium accumulation is inhibited by attenuation of the sodium–hydrogen exchange system in acidosis. Calcium accumulation within myocytes occurs during ischemia, and is detrimental. Magnesium is a very effective physiological anatagonist to calcium, and is added to cardioplegia solutions to block calcium entry into myocytes. Citrate, in the form of citrate-phosphate-dextrose (CPD) is also added to some preparations, to prevent calcium accumulation.

Cardioplegia delivery

In order to induce and maintain diastolic cardiac arrest, cardioplegia solutions must act directly on the myocyte membrane. Practically this means that the solution must reach and surround each individual myocyte, in order to protect it. Thankfully the heart has a vascular network in place which is designed to continually perfuse each myocyte, and in most individuals this can be utilized effectively to deliver the cardioplegia solution. Cardioplegia solutions may be delivered antegrade (i.e. via the coronary arteries), retrograde (i.e. via the coronary sinus, through the venous system of the heart.), or by a combination of both, as demonstrated in Figure 7.3.

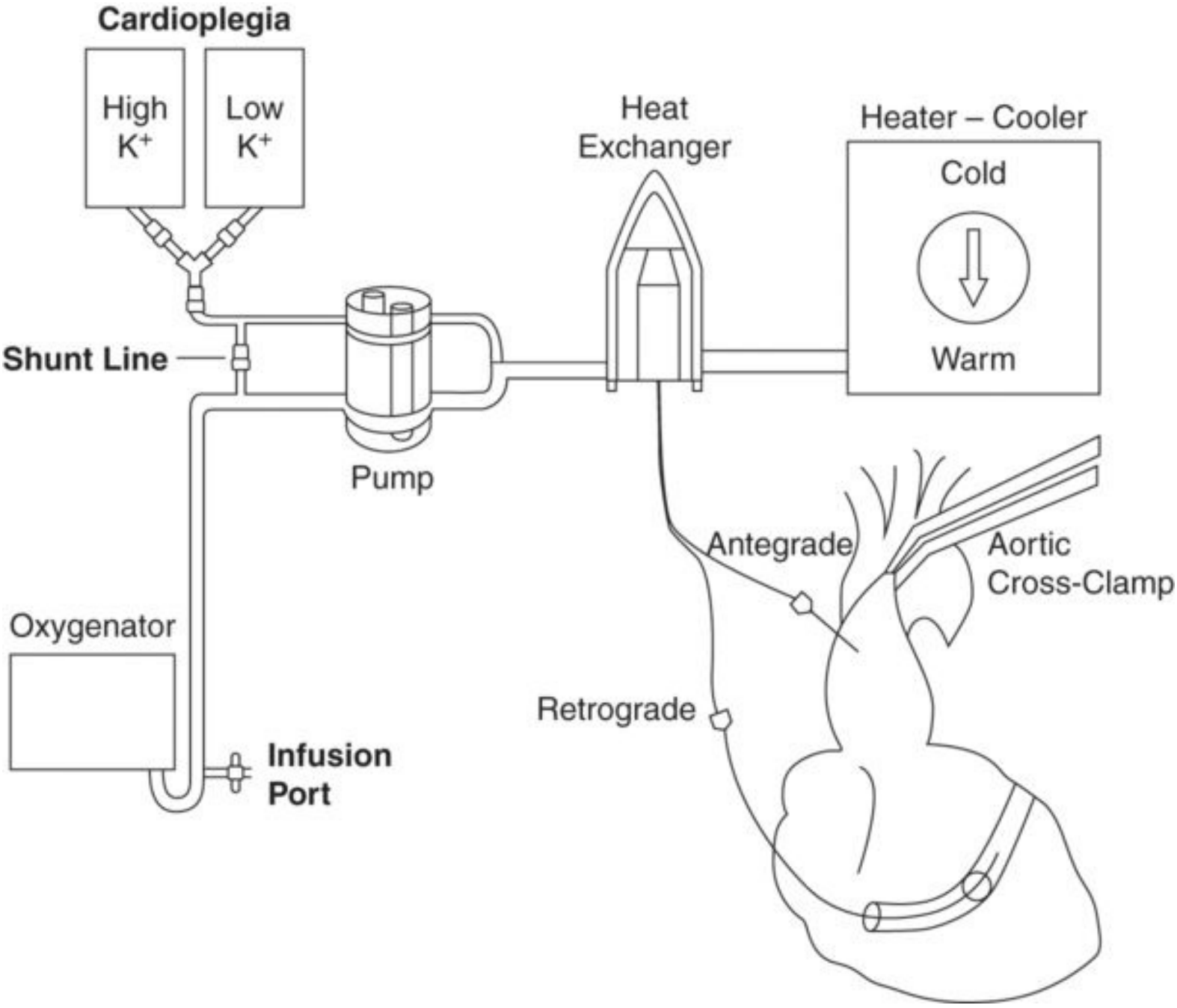

Figure 7.3 Cannulation and set-up for antegrade and retrograde application of cardioplegia.

Antegrade delivery

The standard means of antegrade cardioplegia delivery is to inject the cardioplegia into the aorta, proximal to the aortic clamp immediately after application of the cross-clamp to the ascending aorta. If the aortic valve is competent, then as the solution is delivered, pressure within the aorta will rise and the solution will flow under pressure down the coronary arteries. Antegrade cardioplegia is typically delivered at a pressure of 80–100 mmHg. The pressure can be measured by the perfusionist, and high pressures may predispose to intracellular edema. If this is effective, the ECG will rapidly become asystolic, as electrical activity is abolished. Persistence of electrical activity suggests suboptimal delivery. Common causes include an incompetent aortic valve, allowing the cardioplegia solution to

escape into the left ventricle, or significantly stenosed coronary arteries, which lead to unequal distribution of cardioplegia across the myocardium. If the aorta is being opened, e.g. for aortic root or valve surgery, then cardioplegia can be selectively administered down each of the coronary ostia. Care must be taken not to damage or dissect the coronary ostia.

Retrograde delivery

Where there are concerns about the efficacy of antegrade delivery, e.g. in severe widespread coronary stenosis, redo CABG with partially patent grafts, or acute myocardial infarction then cardioplegia can be administered retrogradely, through the venous system of the heart. To achieve this, the coronary sinus, through which the venous system of the myocardium drains into the right atrium, may be cannulated blindly, under direct vision or under transesophageal echocardiography (TEE) or fluoroscopic guidance, and the cannula secured in place by inflation of a balloon at its distal end. Cardioplegia is delivered at pressures not greater than 40 mmHg, to avoid causing endothelial damage or even perforation of the sinus. The delivery pressure should be monitored continually throughout administration. Retrograde cardioplegia alone is often inadequate to protect the right ventricle, especially if the cannula is inserted too far, and also because of the presence of Thebesian vessels which shunt blood directly into the cardiac chambers. Placement of a coronary sinus catheter does allow for the technique of continuous cardioplegia administration; however, this may lead to a bloody operating field, cause hemodilution as larger volumes are given, and is prone to catheter displacement as the heart is being manipulated to achieve optimal surgical conditions. Retrograde cardioplegia is also ineffective in cases of a persistent left superior vena cava. Overall retrograde delivery is considered inferior to antegrade, however there are situations in which it may be useful and it is often combined with antegrade administration in the same patient in an attempt to ensure optimal distribution of cardioplegia throughout the myocardium.

Non-cardioplegic protection techniques

Intermittent ischemia and reperfusion (cross-clamp/fibrillation)

Intermittent cross-clamping of the aorta combined with the deliberate induction of ventricular fibrillation and moderate systemic hypothermia (30–32°C) is an established means of myocardial management that can be used to perform some cardiac surgery. It is most suited to coronary bypass graft surgery and allows the surgeon to operate on the fibrillating heart, while the aorta is clamped and the patient is on CPB. Induction of fibrillation reduces cardiac motion, thereby facilitating suturing of a distal graft anastomosis

in an ischemic period of 10–15 minutes. The proximal anastomosis to the ascending aorta can then be performed with the heart perfused and beating, and the procedure then repeated for the next graft. This means however that the aorta is repeatedly manipulated and this may predispose to release of emboli if the aorta is atherosclerotic. This technique has been shown in large single center case series to be effective, and is still practiced by some surgeons as their first choice technique for CABG surgery, but is no longer in widespread use. Cardiopulmonary bypass is required for this technique to maintain systemic perfusion, and safe periods of aortic cross-clamping are shorter than with cardioplegic arrest.

Off-pump coronary bypass graft surgery (OPCABG)

Some cardiac surgeons advocate performing CABG surgery on patients without the use of CPB, fashioning the coronary artery grafts while the heart is still beating and maintaining adequate output for systemic perfusion. The goal is to complete the surgery while maintaining both coronary and systemic perfusion. Although this has proven to be a feasible and valid option, consideration to myocardial protection is still relevant perioperatively, and large multi-center randomized trials have failed to show a significant difference in mortality or major morbidity in patients who undergo CABG surgery, either on or off CPB. In order to visualize the coronary arteries and be able to fashion the grafts, the surgeon will often either temporarily occlude the particular coronary artery proximally, so that a bloodless field is created, or alternatively place a shunt temporarily across the intended anastomotic site, thereby reducing bleeding, and also helping to maintain distal coronary perfusion. It has been shown that the use of coronary shunts reduces the rise in biomarkers of myocardial damage (CK-MB, troponin) after off-pump CABG.

Although the heart must keep beating to maintain cardiac output, its motion can be regionally reduced using commercially available stabilizers, which help fix the area of interest and facilitate suturing of the coronary grafts. Occasionally, however, it is not possible to maintain adequate cardiac output and simultaneously perform the surgical procedure, so the operating team must always be prepared to convert the operation and initiate CPB. Another compromise solution is to initiate CPB and then operate on the beating heart, thereby maintaining both cardiac and systemic perfusion.

Preconditioning

Ischemic preconditioning

Although diastolic cardiac arrest induced and maintained by cardioplegic solution administration is the single most effective intervention available to protect the heart from ischemia, not all procedures need to

be performed on a motionless heart, and the deliberate ischemia induced by aortic cross-clamping is not the only perioperative period when the heart is at risk. Additional adjunctive protective strategies based around the concept of preconditioning could possibly benefit cardiac surgical patients whether they are operated on with or without CPB. Ischemic conditioning, first reported by Murry et al., describes an endogenous phenomenon, in which one or more brief episodes of nonlethal ischemia and reperfusion confer protection against a sustained lethal episode of ischemia and reperfusion. The conditioning stimulus can be applied before (ischemic preconditioning) or after the onset of (ischemic post-conditioning) ischemia, or at the transition from sustained ischemia to reperfusion (ischemic post-conditioning). The underlying mechanism of ischemic preconditioning has not been fully elucidated, but main candidate mechanisms suggested involve ion channels (especially K_{ATP}, the adenosine triphosphate (ATP) sensitive potassium channel), G-protein receptor coupled agonists (e.g. opioids, adenosine), protein kinases, and reactive oxygen and nitrogen species. Patients undergoing CABG surgery were found to have reduced troponin levels post op if they were exposed to ischemic preconditioning by short intermittent periods of aortic cross-clamp application and reperfusion, compared to controls. Subsequently it has been found that the ischemic conditioning stimulus can be effective also when applied to a distant organ or limb, and not necessarily to the heart. This has been called remote ischemic preconditioning (RIPC), and has been shown not only to reduce postoperative markers of myocardial damage, but also to improve clinical outcomes, i.e. lower rates of myocardial infarction and mortality at 1 year. The stimulus typically applied consists of three or four cycles of 5 minutes of upper or lower limb ischemia induced by inflation of a blood pressure cuff, followed each time by 5 minutes of reperfusion. This has been shown to provide added myocardial protection to patients undergoing CABG with or without aortic valve surgery. In spite of these promising results from such a seemingly innocuous intervention, RIPC has not yet been integrated into routine clinical practice. Results of a recently completed randomized multi-center study of RIPC on cardiac surgery patients (ERRICA study) may shed further light on the benefits in daily practice.

Pharmacological preconditioning

Ischemia is not the only intervention which can potentially confer protection to myocardial cells from a subsequent ischemic insult. Some drugs, most notably volatile anesthetic agents (e.g. sevoflurane, isoflurane, desflurane) have been shown to reduce myocardial infarct size and troponin release in animal models of myocardial ischemia. Volatile anesthetic agents have also been shown to have a post-conditioning effect and protect the myocardium when administered immediately after prolonged coronary ischemia. The underlying mechanism has not been fully elucidated, but closely resembles those associated

with ischemic preconditioning, giving rise to speculation that there may be a final common pathway of preconditioning stimuli.

While the preclinical and animal evidence of anesthetic preconditioning is consistently favorable, high-grade evidence of clinical benefit in cardiac surgery patients comparing volatile to intravenous anesthesia is scarce, or inconclusive. Large-scale, multi-center, randomized clinical trials are required to determine if use of volatile anesthetic agents in cardiac surgery is clinically beneficial and if so then at what dose, at what time point in relation to ischemia, and for what duration should they be administered? Volatile anesthetic agents are reliable and safe agents and any specific myocardial protection they may offer represents a beneficial side effect of the general anesthesia technique for surgical patients.

The state of general anesthesia itself however, regardless of the agent type used, typically reduces myocardial oxygen demand and so is considered to confer some cardio-protective benefit. On the other hand, it seems that patients who are woken and extubated earlier after cardiac surgery as part of a fast track management program have a lower incidence of postoperative low cardiac output syndrome. Opioid drugs, specifically those which act at the delta receptor, are also credited with having a preconditioning effect, and in the early days of cardiac anesthesia it was believed that high dose opioid administration improved myocardial protection mainly because it was associated with better hemodynamic stability, rather than any specific preconditioning effect.

Minimal access cardiac surgery

Minimal access surgical techniques are used in some centers for both valve surgery and CABG. Mitral and tricuspid valve surgery via a right antero-lateral mini-thoracotomy and aortic valve surgery via a partial sternotomy are the most established techniques. The fundamental benefit of these surgical techniques is that the incision required to access the operative field is minimized, thereby reducing the inflammatory response, facilitating faster wound healing with less pain and infection and more rapid functional recovery. For mini-thoracotomy or port access surgery, the aorta can be cross-clamped externally, using a modified extended clamp (Chitwood clamp, Figure 7.4), which is introduced via a seperate port, thereby leaving as much space as possible through the main surgical incision for access.

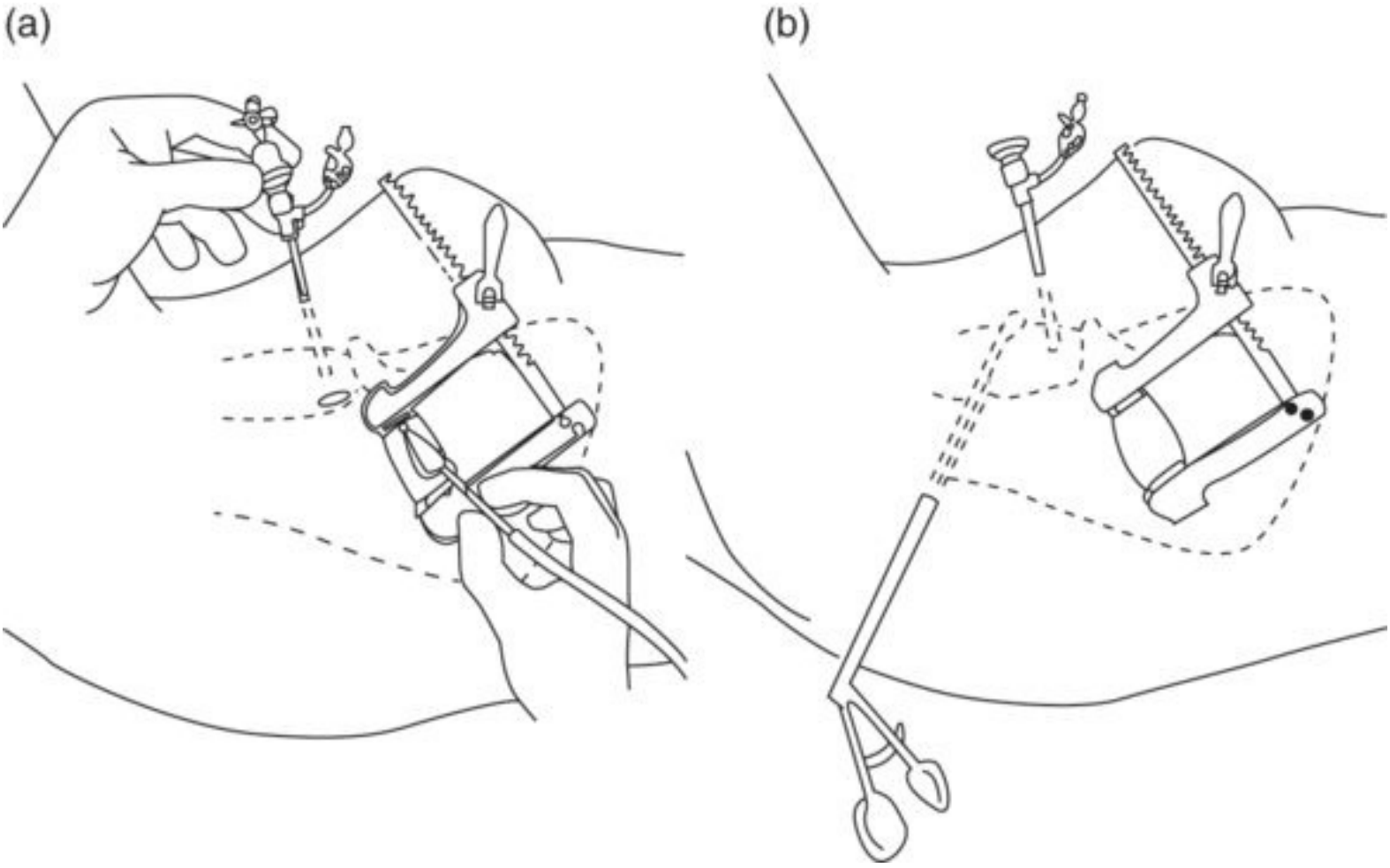

Figure 7.4 Application of Chitwood clamp for aortic cross-clamping through separate access port.

An alternative method is to use an endoclamp, where an inflatable balloon is floated through the aorta, under TEE guidance, usually through a special port in the femoral arterial bypass line. When it is correctly positioned in the ascending aorta, it is inflated, and this occludes the ascending aorta from within, thereby “clamping” it (see Figure 7.5). Cardioplegia can then be given antegrade via a separate cannula through the balloon, into the aortic root. Problems can arise if the balloon moves during the procedure and occludes the aortic arch vessels. TEE monitoring and bilateral upper limb arterial pressure monitoring can alert the team to this event. TEE assessment of aortic regurgitation is especially important in minimally invasive cardiac surgery, as left ventricular distension will not be noticed easily if cardioplegia leaks through an incompetent aortic valve.

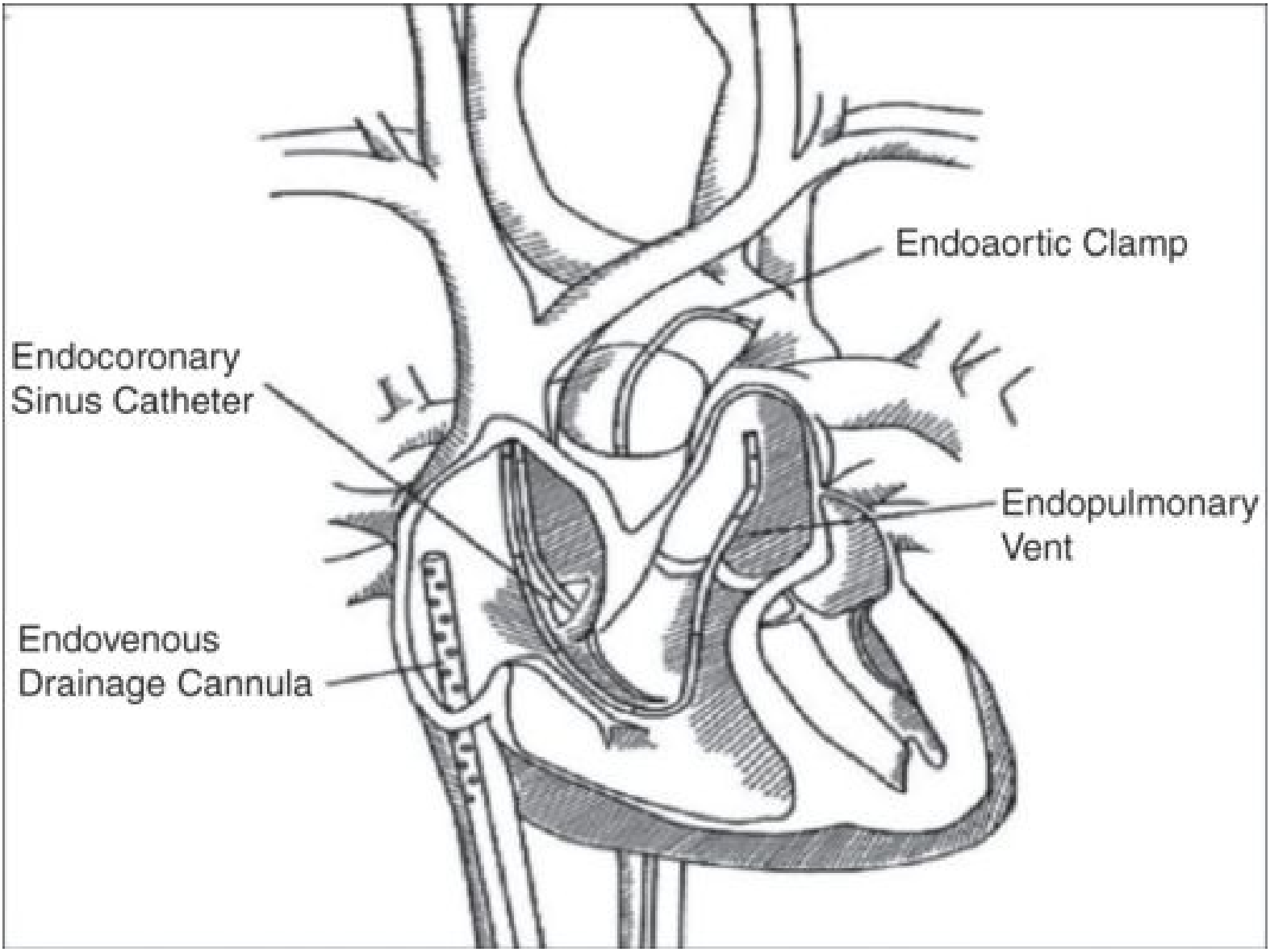

Figure 7.5 Position of endoclamp within the aorta.

HTK crystalloid cardioplegia has been advocated by some specialist mitral valve repair centers, because a single dose can provide effective cardioplegic protection for at least 2 hours. This means that the surgeon can work uninterrupted on the repair, without needing to remove the mitral retractor and give blood cardioplegia every 20 minutes. When the mitral retractor is left in place, the aortic valve can become incompetent, thereby necessitating its removal during cardioplegia administration.

Not all minimally invasive mitral surgeons use HTK cardioplegia, and some still prefer to use blood cardioplegia. Minimally invasive mitral valve surgery can also be performed under fibrillatory arrest and mild to moderate hypothermia, thereby avoiding aortic manipulation and cardioplegic arrest. Particular care must be given to de-airing the heart at the end of the repair, once the cardiotomy incision is closed. Most surgeons will insufflate the chest with carbon dioxide to reduce the significance of any gas emboli; testing competency of the mitral valve by injecting saline into the left ventricle should not be used using the fibrillatory arrest technique, as it is likely to force gas emboli into the aorta.

General perioperative management

Although many of the issues outlined above are specific to particular patients and/or procedures, there are also many general considerations to be taken account of perioperatively, which may have an impact on protecting not just the heart, but also other organs, and consequently outcomes such as major morbidity and mortality.

Management of patients' medications perioperatively is particularly important. The use of beta blockers has been a contentious issue, perioperative initiation can prevent postoperative myocardial ischemic events in patients with significantly increased cardiac risk, but may increase risk for stroke. Perioperative initiation is recommended for patients who are undergoing surgery for coronary artery or vascular disease, who are not already bradycardic or hypotensive. Importantly, withdrawal of beta blockers or other antihypertensive agents (especially alpha antagonists) before surgery can result in extreme hypertension and myocardial ischemia. Continuation of ACE inhibitors and angiotensin receptor anatagonists has been associated with perioperative hypotension, particularly after cardiac bypass, and generally these medications are withheld from the evening prior to surgery. Statins appear to have benefits when continued throughout the perioperative period and should not be withheld from patients already taking them before surgery. Many patients presenting for cardiac surgery take some form of antiplatelet or anticoagulant medication. Almost all of these should be withheld prior to surgery, and if ongoing anticoagulation is required, then the patient should be "bridged," usually with intravenous or subcutaneous heparin. The exception is aspirin alone, which if withdrawn is associated with increased in hospital mortality following CABG surgery. It is important that institutional policies exist to guide the perioperative management of these medications in any hospital performing cardiac surgery, as adherence to best practice guidelines relies largely on ward nursing staff to advise patients and ensure compliance.

In addition to the potential benefits of anesthetic preconditioning from the choice of anesthetic agent, overall conduct of anesthesia is also important. Tachycardia will increase myocardial oxygen demand, and adequate depth of anesthesia and perioperative analgesia can ensure that the sympathetic response to surgery is minimized. The mainstay of perioperative organ protection is adequate perfusion, and as most anesthetic agents have vaso-dilatatory effects, general anesthesia may often be associated with reduced blood pressure. This may be overcome easily in most patients by judicious intravenous fluid administration, or low-dose vasoconstrictor therapy. For certain procedures, especially involving a thoracic rather than sternotomy incision, regional or neuraxial analgesia techniques can be very effective, not just in providing pain relief, but may also effect a degree of sympathetic blockade, which may be beneficial. Catecholamines are often necessary to support cardiac function perioperatively; however, if used inappropriately or gratuitously will increase myocardial demand and worsen outcome. It is accepted

also that perioperative hyperglycemia is associated with worse outcomes for patients, and this should be managed in the operating room and intensive care unit with an intravenous infusion of short-acting insulin, aiming to maintain blood glucose levels in the range 6 to 10 mmol/l.

Summary

Surgery performed under cardioplegic cardiac arrest is associated with excellent patient outcomes, and represents the crux of perioperative myocardial protection strategies. Many aspects of the use of cardioplegia continue to be debated such as type of solution, route of administration, intermittent versus continuous administration, and optimal solution temperature. It is therefore imperative that the surgeon be aware of the fundamental principles and evidence in support of these varying practices so that the optimum mode is chosen for the patient and procedure being performed. Many cardiac operations, however, are now performed without cardioplegic cardiac arrest. The whole team including surgeon, anesthetist, perfusionist, and intensivist play a role in ensuring myocardial protection, whether via cardioplegia or by implementation of adjunctive protection, e.g. via remote ischemic or pharmacologic preconditioning, or simply by attention to good perioperative medicine and appropriate recovery protocols.

Self assessment

1. Which of the following would be the single most effective means of protecting the heart during CPB for aortic valve surgery?

A. Moderate systemic hypothermia.

B. Anesthetic preconditioning with a volatile anesthetic agent.

C. Chemical arrest with blood cardioplegia solution.

D. Fibrillatory arrest.

E. Four cycles of remote ischemic preconditioning performed on a lower limb, 30 minutes prior to surgery.

Answer: C

2. When considering cardioplegia administration for minimally invasive mitral valve surgery via an anterolateral thoracotomy, which of the following is correct?

A. Only retrograde cardioplegia can be administered.

B. Blood cardioplegia may be used.

C. Aortic valve insufficiency does not need to be considered when giving antegrade cardioplegia via an endoaortic balloon delivery system.

D. Antegrade cardioplegia alone is never sufficient and must be combined with retrograde cardioplegia.

E. Migration of the endoaortic balloon distally is least likely to occur during cardioplegia administration.

Answer: B

3. Retrograde cardioplegia:

A. Provides better protection for the right heart than the left heart.

B. Should be administered at pressures of 80–100 mmHg normally for best protection.

C. Given alone provides better protection than antegrade cardioplegia alone.

D. Can be effective in the presence of a persistent left superior vena cava, if the delivery pressure is high enough.

E. Can result in traumatic damage to the coronary sinus.

Answer: E

4. Which of the following electrolyte abnormalities would ultimately result in systolic cardiac arrest?

A. Hypercalcemia.

B. Hyperkalemia.

C. Hypermagnesemia.

D. Hyponatremia.

E. Hypocalcemia.

Answer: A

5. After initial administration of antegrade cardioplegia directly down the coronary ostia during a combined aortic valve replacement and CABG procedure, some electrical activity on the patient's ECG persists. The most appropriate next step in this situation would be to:

A. Ignore the activity and carry on with the surgery, as you are very happy that the coronary ostia were cannulated under direct vision correctly.

B. Cool to 20°C and perform the surgery under deep systemic hypothermia.

C. Ask the perfusionist to administer volatile anesthetic agent throughout the bypass period, and carry on.

D. Give combined retrograde cardioplegia.

E. Ask the perfusionist to increase the potassium concentration of the cardioplegia solution for subsequent doses and carry on.

Answer: D

6. Regarding serum troponin levels after cardiac surgery, which of the following is true:

A. The degree of troponin elevation correlates well with the degree of myocardial damage.

B. Elevated troponin level over ten times the normal range is sufficient alone to diagnose a myocardial infarction after cardiac surgery.

C. Troponin levels are too sensitive and specific to be of use in evaluating myocardial protection techniques for cardiac surgery.

D. Troponin levels are never elevated unless the event is clinically significant.

E. Troponin levels are never elevated after periods of aortic cross-clamping under fibrillatory arrest.

Answer: C

7. Potential benefits of blood over crystalloid cardioplegia include all of the following, except:

A. Tissue oxygen delivery.

B. Free radical scavenging.

C. Reduced systemic hemodilution.

D. Longer interval between doses.

E. Presence of natural buffers.

Correct Answer: D

8. The following substances are added to act as buffers in cardioplegic solutions except:

A. Histidine.

B. Sodium bicarbonate.

C. Tris-hydroxymethyl-aminomethane (THAM).

D. Procaine.

Answer: D

Suggested Further Reading

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Chapter 8

Weaning from cardiopulmonary bypass

Amy Needham and **Christopher P. R. Walker**

The transition from cardiopulmonary bypass (CPB) to normal circulation requires numerous mechanical, physiological, and pharmacological factors to be coordinated efficiently within an extremely short time frame. Thus communication and teamwork between perfusionist, surgeon, and anesthetist are key to success. Weaning from CPB is often a routine process, however pre-existing poor cardiac function or unexpected difficulties perioperatively may make weaning from CPB complex and challenging. Complications encountered during the weaning phase may contribute to significant additional perioperative morbidity.

Preparation

Separation from CPB requires the heart to resume its native, inherent pump function; to achieve a smooth transition cardiac function must be optimized prior to weaning from CPB. Delays in recognizing or treating abnormal physiological parameters prior to cessation of CPB may lead to poor cardiac performance and failure to separate from CPB, or necessitate return to extracorporeal circulatory support. Consequently, anticipation of possible cardiac dysfunction and thorough advance preparation are crucial to the weaning process. A checklist of physiological parameters that should be optimized prior to weaning is recommended (see Table 8.1) and discussed below.

Table 8.1 Preparation for weaning from cardiopulmonary bypass

Warm patient to target temperature
Correct electrolytes and acid–base

Check blood and blood products available

Achieve target hemoglobin

Ensure pulmonary ventilation restarted before coming off CPB

Assess heart rate, rhythm, and conduction

Control arrhythmias

Establish pacing if required

Consider mechanical support (e.g. intra-aortic balloon pump (IABP), assist device) if difficulty predicted

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Temperature

Re-warming to a core temperature of at least 36°C is necessary to wean from CPB. In addition to multiple temperature monitoring sites within the CPB machine, including blood temperature and the temperature of the heat exchanger, body temperature may be monitored at numerous sites including the nasopharynx, esophagus, myocardium, bladder or rectum. Re-warming is not uniform and consideration of which site, or sites, best represents adequate re-warming will vary according to how much the patient has been cooled, the duration of hypothermic bypass, and patient-specific variables such as body surface area. A combination of bladder temperature and the temperature of the venous blood returning to the bypass circuit is particularly valuable when CPB temperature has been below 30°C. Active surface warming using a forced warm air device should be combined with re-warming via the extracorporeal circuit to reduce redistribution of heat from core to peripheral tissues. If re-warming is inadequate, or if the core-surface gradient is greater than 7°C, significant further heat loss may occur during wound closure. Shivering and increased peripheral vascular resistance in the recovery period will result in an unwanted increase in oxygen consumption. Conversely, core temperature should not be allowed to rise above 37°C as this may lead to tachycardia and possibly increase the risk of central nervous system dysfunction.

Electrolytes and acid/base

Electrolyte abnormalities should be corrected before separation from CPB in order to optimize myocyte function. In particular, potassium, magnesium, and calcium must be kept within the normal range.

- **Potassium** (4.0–5.5 mmol l^{-1}) – Hypokalemia can cause arrhythmia and should be treated if below 4 mmol l^{-1}. In many centers potassium is maintained at the “higher” end of the normal range

in order to suppress the development of arrhythmias, to which the heart is particularly susceptible post-CPB. Hyperkalemia can cause conduction abnormalities and impair contractility. Values above 6.0 mmol l^{-1} should serve as an alert to monitor parameters closely and levels above 6.5 mmol l^{-1} should be actively treated before weaning.

- **Calcium** (1.09–1.30 mmol l^{-1}) – The concentration of calcium in the plasma may be reduced if large volumes of citrated blood were given during CPB, leading to impaired contractility and vasodilatation. Ionized calcium should be maintained above 1.1 mmol l^{-1}.
- **Magnesium** (0.80–1.40 mmol l^{-1}) – Low levels of magnesium are associated with dysrhythmia and should be corrected if below 0.8 mmol l^{-1}. It is worth noting that some point-of-care analyzers employ a lower normal range for ionized magnesium, so it is important to check the nature of the measurement and the device normal range before interpreting the result.
- **Glucose** (4.0–7.8 mmol l^{-1}) – Tight glucose control in the postoperative period has been shown by some investigators to improve outcome after cardiac surgery and investigation of its impact in the perioperative phase is ongoing. Extrapolation of the available evidence and majority practice suggest that significant hyperglycemia (> 10 mmol l^{-1}) should be treated with an insulin infusion, although treatment thresholds vary. Hypoglycemia in association with CPB is extremely rare in the absence of liver failure and, if encountered, should be judiciously treated and its cause investigated.
- **Lactate** (0.7–2.5 mmol l^{-1}) – Elevated serum lactate levels are encountered frequently during prolonged episodes of CPB, particularly if there have been periods of low flow or if deep hypothermic circulatory arrest has been employed. Treatment of lactic acidosis per se is not usually instituted, but increasing values must be seen as a potential indicator of inadequate organ perfusion.
- **Metabolic acidosis** – This commonly occurs during CPB and there are numerous approaches to its correction. Some units correct base deficits to baseline whereas the majority of units readily accept base deficits of up to –5 mmol l^{-1}. Most clinicians would treat a base deficit if the deficit is worse than –8 mmol l^{-1}. Between these values the debate about treatment continues.

Hemoglobin concentration

For most patients, the hemoglobin concentration should be above 7.5 g dl^{-1} prior to termination of CPB. If myocardial oxygen supply or whole body oxygen delivery is expected to be impaired post-CPB in low cardiac output states it is preferable to aim for a higher hemoglobin concentration. Similarly, when

bleeding is expected to be an ongoing problem in the post-CPB period a higher target hemoglobin ought to be considered. Co-morbid pathology, particularly coexisting respiratory disease, may also indicate the need for a higher hemoglobin level. In patients with congenital heart disease who remain cyanosed after surgery a higher hemoglobin concentration is essential.

Stored, concentrated red blood cells should be immediately accessible for use in the post-bypass period. Cell-salvaged autologous blood may reduce the need for use of stored, homologous blood in the first instance.

Coagulation

The anticoagulation necessary for CPB, together with the effects of the CPB circuit on the clotting cascade and platelet function, poses a significant risk of bleeding post-CPB. Thus availability of clotting factors and platelets must be assured. Following separation from CPB and reversal of anticoagulants assessment of clotting and platelet function should be performed according to unit protocols (laboratory-based clotting screen, activated clotting time (ACT), heparin assays or thromboelastography (TEG)). Persistent bleeding should initiate consideration of blood product support, informed by coagulation measurements. It is, however, important to emphasize that abnormal clotting assays alone should not initiate blood product administration in the operating theatre if the surgical field does not show evidence of ongoing bleeding.

Fluid replacement

In addition to ready access to blood products, colloid and crystalloid solutions should be immediately available to increase circulating volume when indicated.

Vasoactive drugs

Vasopressors, inotropes, and vasodilators must be immediately to hand if not already in use before or during CPB. The choice of drug(s) should be based on the patient’s myocardial function, vascular tone, and nature of the surgery. The vasoactive support strategy should ideally be agreed by the team before weaning from CPB commences.

Anesthesia

Anesthesia, analgesia, and neuromuscular blockade must be assessed and supplemented as required. Weaning from CPB may require either a change in anesthetic agent (e.g. intravenous to volatile) or an

adjustment to continuing dose delivery. It is vital that anesthesia is maintained continuously on and off CPB and this should be confirmed by the team members.

Cardiac function

Following removal of the aortic cross-clamp adequate reperfusion of the myocardium should ensue. This allows myocytes to replenish metabolic substrates, specifically high-energy phosphates (ATP), and "washes out" the products of anaerobic metabolism and residual cardioplegia before attempting to wean from CPB. Commonly 20 minutes of reperfusion for every hour of ischemic (aortic cross-clamp) time is recommended, although practice is varied. Surgical sequence may accommodate time for myocardial reperfusion – for example, the aortic anastomoses of coronary revascularization grafts may be performed during the reperfusion period.

Cardiac function should be assessed prior to weaning from CPB, focusing primarily on heart rate, rhythm, and contractility. Following CPB, the ventricles are generally less compliant and will not have the normal capacity to increase stroke volume. Therefore, heart rate is usually maintained at 80 to 100 beats per minute to help compensate for this. This "stiff" ventricle phenomenon increases the relative importance of the contribution of synchronous atrial contraction to stroke volume and cardiac output. Thus sinus rhythm is always preferable. Epicardial pacing leads and an external pacemaker should be available immediately, ideally with dual chamber function to allow sequential atrio-ventricular pacing.

Contractility may be assessed with direct visualization of the right ventricle. If in use, transesophageal echocardiography (TEE) enables a more detailed examination of all four chambers of the heart. If any of the cardiac chambers have been opened during the procedure, for example in valve replacement surgery, it is essential to evacuate any air from the heart prior to separation from bypass and this is guided most effectively by TEE.

Predicting difficulty

Occasionally weaning from CPB is difficult and identification of patients who will present a particular challenge allows any additional preparations to be made in advance.

Commonly encountered risk factors for failure to wean from CPB include:

- poor preoperative ventricular function;
- urgent and emergency surgery;
- prolonged aortic cross-clamp time;

- inadequate myocardial protection; and
- incomplete surgical repair.

Several strategies may be considered if weaning from CPB is likely to be difficult. An intra-aortic balloon pump (IABP) may be inserted before the start of surgery in patients with poor ventricular function. Inotropes and vasopressors can be commenced at re-warming or even earlier, ensuring they have cleared the dead-space of administration lines prior to weaning from CPB. Some inotropes require administration of a loading dose (e.g. enoximone, milrinone, levosimendan) – these should ideally be given after aortic unclamping during re-warming. Very dilute solutions of adrenaline (epinephrine) or noradrenaline (norepinephrine) can be prepared to allow small bolus doses to evaluate the responses of the myocardium and circulation.

If sinus rhythm is not established, or supraventricular arrhythmias or ventricular irritability are present despite correction of metabolic parameters, anti-arrhythmic treatments should be considered and given as necessary in advance of any attempts at weaning from CPB. Direct current (DC) cardioversion may be required in isolation or in addition to anti-arrhythmic agents.

Additional invasive monitoring lines, e.g. pulmonary artery catheter or left atrial pressure line, may be prepared, permitting direct measurement of cardiac chamber pressures and calculation of cardiac output and systemic/pulmonary vascular resistances.

Events immediately prior to initiating weaning

Mechanical ventilation

During CPB the lungs are allowed to deflate fully, resulting in widespread alveolar collapse, or to remain slightly inflated at low levels of continuous positive airway pressure. Prior to weaning from CPB full and effective re-inflation of the lungs should be ensured with controlled manual hyperinflation. If one or both pleural cavities are open, direct visualization of the lung(s) is possible and the pleural cavities may be drained of any accumulated fluid. Once satisfactory tidal volumes are achieved, mechanical ventilation is resumed, usually with positive endexpiratory pressure (PEEP). It is prudent to apply tracheo-bronchial suction to the lungs to clear respiratory secretions before ventilation is resumed.

Effective mechanical ventilation of the lungs must be underway prior to weaning from CPB. Ventilation should be initiated when it no longer interferes with surgical maneuver, particularly when there is significant left ventricular ejection; cardiac ejection while on CPB in the presence of a competent aortic valve suggests re-establishment of significant pulmonary blood flow. If the lungs remain

unventilated this pulmonary blood flow will acts as a true right to left shunt, delivering deoxygenated blood to the left ventricle. This deoxygenated blood will then be ejected and mixed with oxygenated blood from the aortic cannula and, depending on the volume of ejected blood, may result in undesirable systemic arterial hypoxia in the latter stages of CPB.

The perfusionist and anesthetist must confirm to each other that effective ventilation has been resumed. The consequence of weaning from CPB without ventilation is the rapid onset of hypoxia and hypercapnia, followed by bradycardia, cardiac failure, and organ damage.

Physiological alarms

Alarm settings for many parameters displayed on anesthetic monitors and ventilators are adjusted or even disabled during CPB. It is vital that physiological monitoring with appropriate alarm settings is re-enabled prior to weaning from CPB. This should be seen as a team responsibility rather than that of an individual, and the anesthetist and perfusionist should specifically confirm that physiological and ventilation monitoring and their alarms have been re-enabled prior to commencing weaning.

Arterial blood gases and electrolytes analysis

Following re-warming, an arterial blood gas and electrolytes sample should be taken and reviewed by the team. In the majority of cases little or no corrective action is required at this stage. The commonest adjustments that need to be made are to acid–base status and potassium levels.

Metabolic acidosis may require treatment. Sodium bicarbonate ($NaHCO_3$) is commonly used to correct the acidosis. Administration of sodium bicarbonate solution, usually into the cardiotomy reservoir of the extracorporeal circuit, generates a substantial amount of intracellular carbon dioxide and is often associated with a reduction in systemic vascular resistance. Although cardiac myocytes are thought to have effective intracellular buffering mechanisms, the administration of a large volume of sodium bicarbonate in a short period may generate paradoxical intracellular acidosis. Clearance of this excess generated carbon dioxide via the oxygenator membrane may take 5–10 minutes. In patients with poor cardiac function, and in particular poor right ventricular function, weaning from CPB should not be attempted until the risk of significant paradoxical intracellular acidosis has passed and the majority of excess carbon dioxide has been cleared.

As previously discussed, serum values of potassium and ionized calcium should be normalized. Magnesium is an increasingly popular anti-arrhythmic agent and may be administered following aortic de-clamping regardless of the baseline serum level. A rapid bolus of $MgSO_4$ can cause vasodilatation; the

systemic vascular resistance should be allowed to recover, or vasoconstrictors administered, prior to weaning from CPB.

De-airing of the heart

Cardiac surgical procedures that require opening of cardiac chambers will inevitably allow introduction of air. Air in the right-sided chambers is usually relatively innocuous as long as its volume is not substantial enough to prevent forward flow and provided there are no defects in the atrial or ventricular septum. Air in the left side is dangerous and presents two major risks:

- cerebral air embolus with postoperative morbidity, ranging from transient confusion to widespread neurological damage; and
- coronary air embolus, which may cause transient and possibly widespread regional ventricular dysfunction and, in the extreme, irreversible myocardial damage.

It is therefore vital that meticulous attention to de-airing is applied. Direct cardiac agitation, syringing of air from left-sided chambers, and venting of the aorta or left-sided chambers is usually undertaken with the patient in a head down position, prior to, and after, aortic unclamping. It is customary to ventilate the lungs during the de-airing process in order to displace air that accumulates in the pulmonary veins. Increased use of TEE by cardiac anesthetists has greatly improved the de-airing process, allowing targeting of air “pockets” and de-airing until the amount of residual intracardiac air is considered acceptable (see Figure 8.1).

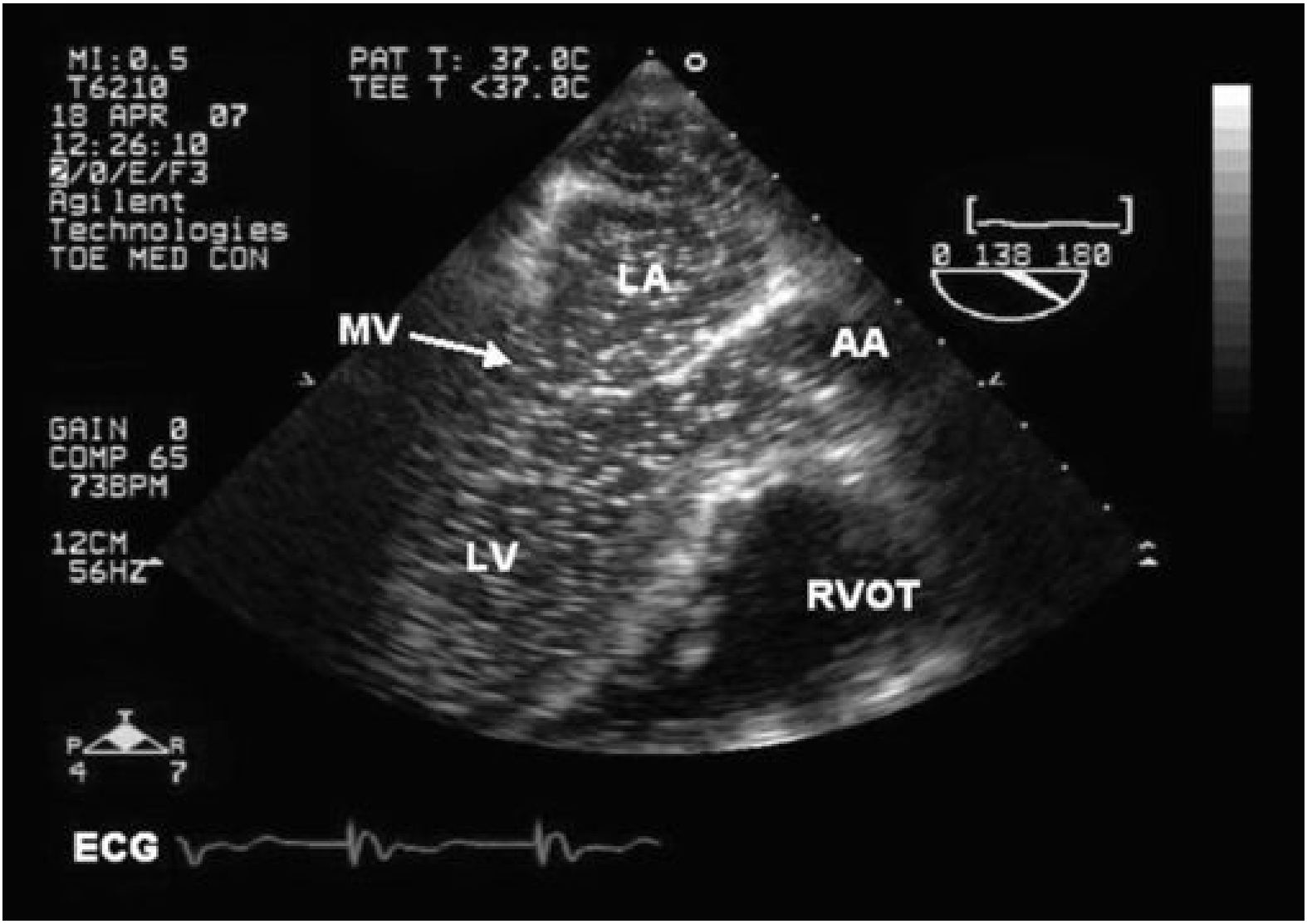

Figure 8.1 Transesophageal echocardiogram (mid-esophageal, left ventricular outflow tract view) showing the heart during de-airing following aortic valve surgery. Air is seen as white speckles throughout the left heart. Of note, there is no air seen in the right heart. AA = ascending aorta; ECG = electrocardiogram; LA = left atrium; LV = left ventricle; MV = mitral valve (arrowed); RVOT = right ventricular outflow tract.

Epicardial pacing

Epicardial pacing is commonly required in the immediate and early post-CPB period. Atrial pacing may be used alone to increase heart rate in patients in sinus rhythm or in a junctional rhythm where atrio-ventricular (A-V) conduction is intact. When possible atrial pacing is preferable to A-V or ventricular pacing. Ventricular pacing may be employed in isolation when there is no effective atrial contraction (e.g. in chronic atrial fibrillation). In cases where A-V synchronization is likely to be helpful and effective sinus rhythm is not yet established, atrial and ventricular epicardial leads should be placed to facilitate sequential A-V pacing.

Appropriate epicardial pacing modes are specifically intended to improve cardiac performance to enable effective weaning from CPB. Commonly pacing is usually set at around 80–90 bpm immediately post-CPB. However, the pacing rate should be determined by patient requirement and not by protocol. When using dual chamber pacing, the standard preset atrio-ventricular interval is 150 ms; however, where increased heart rates are required, the A-V delay should be adjusted accordingly.

If cardiac function and rhythm are satisfactory after weaning from CPB, pacing may not be necessary.

Mechanics of separation from CPB

As soon as cardiovascular, respiratory, and metabolic parameters are within acceptable limits and the patient is adequately re-warmed and ventilated, the perfusionist commences weaning, initially by incrementally occluding the venous return to the CPB circuit, thus allowing the heart to fill with and hence eject blood. The CPB arterial pump flow is simultaneously gradually reduced. As cardiac stroke volume progressively increases to a level suitable for physiological circulation, the venous return pipe is completely occluded, the arterial flow reduced to "off," and the transition from CPB to "normal" circulation completed.

Ideally at this stage the heart should be relatively "relaxed" and the chambers empty with left and right atrial filling pressures low (2–5 mmHg). Circulating volume can be increased as required by infusion of fluid via the aortic cannula (in adults usually in 100-ml aliquots). Current convention tends towards the heart being weaned from CPB with low filling pressures, allowing the ventricles time to adjust to working under the increasing ventricular end-diastolic pressures associated with changes in pre- and afterload.

Weaning from CPB may take just a few seconds in a patient with vigorous cardiac activity who might typically be taken to "half-flow" and then off CPB. In patients with less promising cardiac function, the weaning process may need to be protracted, requiring a period of "partial bypass," that is, low-flow CPB, during which time titration of ventricular volume loading and optimization of inotropes, vasoconstrictors, and cardiac rhythm can be undertaken.

Assessment and adjustment of preload

Central venous pressure is used to reflect and guide the filling volume of the heart. Perfusionists rarely have the opportunity to inspect the heart under direct vision and it may provide considerable information to the surgeon and anesthetist. Normally, only the right ventricle is visible: a relaxed and slightly underfilled right ventricle typically displays inward dimpling of its anterior surface during systole. In

patients with impaired left ventricular function, or if weaning from CPB is proving difficult, direct left atrial pressure or pulmonary artery/pulmonary capillary wedge pressure measurements are helpful. In some centers, all patients presenting for cardiac surgery have both central venous and pulmonary artery catheters placed perioperatively.

TEE helps to assess preload and volume status of the chambers and may be particularly useful in the presence of restrictive ventricular physiology, when higher filling pressures may be encountered at lower ventricular cavity volumes.

Assessment of contractility and inotropic support

Myocardial contractility can be estimated from observing the heart both directly and with TEE looking for coordinated muscle contraction generating an acceptable aortic pulsation and arterial blood pressure. Additionally, a sharp upstroke in the monitored arterial wave (dp/dt) and wide area under the arterial waveform curve may also reflect contractility, but are dependent on pre- and afterload. Quantitative measures of contractility include assessment of cardiac output with thermodilution or alternative techniques; these provide an estimation of stroke volume. The information that TEE can provide about ventricular function may be observational and qualitative, but evolving technology can provide readily interpretable quantitative echocardiographic analysis of cardiac output and myocardial contractility.

Inotropic support should be adjusted using all the information available about the patient's cardiovascular function. The strategies employed are considered below and generally guided by institutional and local team practice. Inotropic support should, if possible, be optimized prior to weaning from CPB, thus presenting the patient with borderline cardiac function with optimal conditions for a successful transition from CPB.

Assessment of afterload

Commonly systemic vascular resistance (SVR) is assumed to be low following CPB because of the systemic inflammatory response accompanying CPB and hemodilution. Patients at risk of a profound inflammatory response include those with long CPB times, long aortic cross-clamp times, complex cardiac surgery, and previous exposure to CPB. Commonly short-acting vasoconstrictors (e.g. metaraminol, phenylephrine) are administered during CPB and in the weaning phase. Similarly, infusions of noradrenaline (norepinephrine) or vasopressin may be used to maintain SVR in the weaning and post-CPB periods.

An estimate of systemic vascular resistance can be obtained while on CPB using the equation:

[MAP (mmHg) – RA (mmHg)]/pump flow (1/min) = SVR (Wood units)

This is accurate unless there is additional native cardiac output, in which case the equation will overestimate the SVR, since the denominator will be falsely low. Wood units of vascular resistance are converted to more commonly used international units (dyn.s cm^{-5}) by multiplying the Wood unit value by 80.

Normal values for SVR are 900–1200 dyn.s cm^{-5}. Units of SVR are sometimes indexed to body surface area.

Optimal SVR for weaning from CPB needs to be considered according to individual pathophysiology. However, the following considerations generally apply:

- patients with dilated, poorly functioning left ventricles exhibiting a low ejection fraction (< 30%) are thought to benefit from lower range SVR values;
- patients with coronary disease with residual, flow-limiting lesions or with left ventricular hypertrophy with small cavity size, but normal cardiac outputs, are thought to benefit from SVR values higher than normal; and
- coexisting disease in other organs, particularly cerebral or renal, may also dictate the requirement for higher SVR in order to maintain adequate perfusion pressures to these organs.

Consideration must also be given to the anesthesia regimen used. Use of volatile anesthetic agents, prior to and during extracorporeal circulation, may result in a dose-dependent reduction in SVR (700–900 dyn.s cm^{-5}). Total intravenous anesthesia, e.g. using propofol infusion, may also exert a dose-dependent effect on SVR, similar to that seen with volatile agents.

The role of TEE in weaning from CPB

There is a wide variation in the use of TEE in adult cardiac surgery, ranging from routine to highly selective. TEE can be an extremely valuable tool informing decision making if difficulties are encountered when weaning from CPB.

In the event of failed weaning from CPB, TEE is also a useful real-time modality for guiding the placement of mechanical support devices. The tip of an intra-aortic balloon pump can be visualized directly with TEE, as can the placement of ECMO cannulae. The effectiveness of ventricular assist devices can be assessed and adjustments to therapy made under TEE guidance.

A detailed discussion of the role of TEE is beyond the scope of this chapter. A summary of the key benefits of TEE in weaning from CPB is given in Table 8.2.

Table 8.2 Key benefits of TEE when weaning from CPB

Confirm adequate de-airing
Guide filling of heart and manipulation of preload
Confirm valve position and function
Identify paraprosthetic leaks
Identify patient–prosthesis mismatch
Identify outflow tract obstruction, e.g. systolic anterior motion of mitral valve (SAM)
Identify coronary artery obstruction, e.g. secondary to atheromatous embolism/complication of surgery
Display aortic dissection following aortic decannulation
Identify intracardiac shunts
Identify regional wall motion abnormalities
Diagnose ventricular systolic and diastolic dysfunction
Guide inotropic support
Identify pericardial and pleural collections
Guide placement of mechanical support devices

Reversal of anticoagulation

Protamine is used to reverse heparin anticoagulation after successful transition from CPB to physiological circulation. Practice of heparin reversal varies among centers:

- a fixed dose of protamine based on the patient's weight (usually 3–4 mg kg^{-1}) can be given regardless of the heparin dose; or
- the protamine dose is titrated to the amount of heparin given, usually 1.0–1.3 mg protamine for each 100 units of heparin administered.

The venous cannulae are removed prior to protamine administration and the arterial cannula is removed before, during or after protamine delivery according to local practice. Preload can be supported during

protamine administration by titrating fluid administration from the extracorporeal circuit while the arterial cannula is still *in situ*.

Protamine administration may be associated with cardiovascular instability. This is generally limited to mild or moderate vasodilatation and mild negative inotropic effects, which are usually attenuated by slow administration of protamine over 5–15 minutes. More severe adverse reactions to protamine may be seen in patients with existing pulmonary hypertension, due to pulmonary vasoconstriction or in those with previous exposure to protamine. In a small number of patients adverse hemodynamic responses may be unexpectedly severe due to anaphylactoid or, in extreme cases, anaphylactic responses to protamine or the protamine–heparin complex. These rare but severe responses will require escalation of inotropic and vasoconstrictor support. Use of pulmonary vasodilators may be necessary and, in exceptional cases, re-heparinization and return to CPB may be the only course of action available to support cardiorespiratory function and allow time for recovery from this reaction.

Failure to achieve satisfactory weaning from CPB

Reinstitution of CPB

Inadequate hemodynamic performance when attempting to wean from CPB should prompt the consideration of a return to CPB, particularly if such deterioration is catastrophic or unexpected.

Reinstitution of CPB should not necessarily be viewed as an adverse event. Inevitably it will result in a prolongation of the total CPB time but it will allow:

- escalation of monitoring (e.g. left atrial line or pulmonary artery catheter placement);
- time for optimization of drug therapies;
- fine adjustment of hematocrit, acid–base, and electrolyte status;
- checking the integrity of the surgery (e.g. kinked coronary bypass grafts, paraprosthetic leaks);
- identification of other reversible causes of myocardial failure.

It is occasionally necessary to return to CPB due to major bleeding, such as dehiscence of a surgical anastamosis, correction of which might not be possible off CPB.

An intra-aortic balloon pump (IABP) may be inserted during this period and the team should have a low threshold for its deployment if there is persistent myocardial failure not readily reversed by less invasive measures.

Vasopressors and inotropes – choices in weaning from CPB

Administration of inotropes and/or vasopressor infusion may be indicated following assessment of preload, SVR and myocardial contractility, and optimization of heart rate, rhythm, and preload. The choice of agent should balance the effect of improved organ perfusion with the potential increase in myocardial oxygen demand and arrhythmias that accompany inotrope usage. Drugs should be titrated to effect and patients monitored using an appropriate combination of pulmonary artery catheter, echocardiography, blood gas analysis, and assessments of end-organ perfusion such as urine output. If several different drugs are required the use of pulmonary artery catheters becomes more essential to guide their rational use. Increasingly newer non-invasive cardiac output monitors based on pulse contour analysis are being used perioperatively, but cardiac output studies using a pulmonary artery catheter and thermodilution remain the gold standard. Pulse contour analysis estimation of cardiac output is not possible if an IABP is in use.

Hypotension caused by reduction in SVR post-CPB may result in impaired coronary blood flow and myocardial ischemia. In this situation, a vasopressor such as noradrenaline or vasopressin is indicated.

Low cardiac output syndrome after CPB is multifactorial, but potential causes include pre-existing ventricular dysfunction, residual myocardial ischemia, inadequate myocardial protection, prolonged cross-clamp time with reperfusion injury, arrhythmias, activation of inflammatory cascades, and imperfect surgical repair. Reversible causes for cardiac failure should be identified, treated appropriately, and inotropic support instituted as necessary.

There are considerable variations in pharmacological strategies employed by cardiothoracic teams in weaning from CPB. As yet there is no clear evidence for the use of any one drug or combination of drugs over any other.

Drugs to be considered for acute hemodynamic support during weaning from CPB are outlined below.

Adrenaline (epinephrine)

Adrenaline has both alpha and beta adrenoceptor activity leading to increased intracellular cyclic AMP and protein kinase C activity. Adrenaline increases cardiac output by increasing contractility and heart rate, and is frequently employed where moderate to severely impaired cardiac contractility is present. It may be used during weaning as single, small bolus injections to rapidly stimulate increased ventricular contractility. At high continuous infusion doses it may cause considerable vasoconstriction and raise serum lactate concentrations.

Dopamine

Dopamine is a naturally occurring catecholamine that binds to dopaminergic receptors as well as to alpha and beta adrenergic receptors. Beta effects tend to predominate at low doses with alpha effects more prominent at high doses. Dopamine increases cardiac output by increasing heart rate and contractility; however, at higher doses blood pressure may be increased by raising systemic vascular resistance with no increase in cardiac output. Dopamine is generally used with more mild impairment of hemodynamic performance, but its use is declining in the face of more targeted inotrope strategies now available with newer drugs. There is no evidence to confirm the role of dopamine as a "renal protective drug."

Dobutamine

A synthetic catecholamine and derivative of isoprenaline, dobutamine possesses strong affinity for beta adrenoceptors with little alpha activity. Contractility and heart rate are increased along with a reduction in systemic vascular resistance, leading to a rise in cardiac output. At higher doses the effects on heart rate and increased oxygen consumption and demand tend to predominate and may limit its use in moderate to severe cardiac failure. Its use in weaning from CPB appears to have waned with the availability of phosphodiesterase-III inhibitors.

Milrinone, enoximone

Often referred to as "inodilators," these are bipyridine phosphodiesterase-III (PDE III) inhibitors, which exert their effects by inhibiting the breakdown of intracellular cyclic AMP and thus increasing stores of the high-energy phosphate, ATP. PDE III inhibitors improve contractility and may cause systemic and pulmonary vasodilatation. They appear to be associated with a lower incidence of tachycardia and arrhythmia than beta agonists and tolerance or tachyphylaxis do not occur, but they may need to be administered concurrently with a vasoconstrictor. Cardiac output increases without a significant increase in myocardial oxygen consumption and demand. PDE III inhibitors are also positive lusitropes, enhancing diastolic relaxation of the myocardium. This improves myocardial perfusion and performance as it shifts down Starling's Curve. Splanchnic perfusion may be increased. There is evidence that prophylactic use of PDE III inhibitors prior to separation from CPB improves the chances of successful weaning and reduces the incidence of low cardiac output syndrome postoperatively.

Noradrenaline (norepinephrine)

This is a naturally occurring catecholamine with predominantly alpha-adrenergic effects and lesser beta-receptor activity. Alpha-1 receptors are G-protein coupled and increase phospholipase C and intracellular calcium concentration resulting in smooth muscle contraction and vasoconstriction. Noradrenaline may be useful when the SVR is low or to counter the vasodilatory effects of phosphodiesterase-III inhibitors. Disadvantages of using noradrenaline include an increase in pulmonary vascular resistance, and effects on the perfusion of the kidneys, gut, and extremities, potentially resulting in hypoperfusion or overt ischemia depending on the dose used.

Vasopressin

Also known as anti-diuretic hormone (ADH) or argipressin, vasopressin is a naturally occurring peptide hormone synthesized from a prohormone released from the hypothalamus. Vasopressin acts on a family of vasopressin receptors (also known as AVPR receptors). V1 receptors are G-protein coupled receptors expressed on vasculature smooth muscle, which activate a phosphatidyl-inositol-calcium signaling pathway resulting in vasoconstriction. However, stimulation of the V1 receptors in the coronary and pulmonary vasculature causes release of nitric oxide and vasodilation. The action of vasopressin is independent of adrenoreceptors so may be useful in conjuction with noradrenaline for low SVR states. Vasopressin also has renal (V2 receptors increasing retention of water) and central effects (V3 receptors influencing the release of adrenocorticotrophic hormone (ACTH)).

Levosimendan

This is a relatively new drug with inodilator properties mediated by calcium sensitization of troponin C and the opening of potassium channels on the sarcolemma of vascular smooth muscle cells. Levosimendan is also thought to confer cardioprotection via its action on mitochondrial potassium channels in the cardiomyocytes. Hemodynamics are improved without a significant increase in myocardial oxygen consumption. Clinical effects persist beyond drug discontinuation due to the formation of active metabolites and are not attenuated by concomitant beta blockade. Levosimedan may precipitate a fall in blood pressure so should be used with caution in severe hypotension. Clinical trials have demonstrated improvements in both left and right ventricular function and overall hemodynamic state and also improved renal function, decreased length of intensive care stay, and a reduction in 30-day mortality when compared to the use of other inotropes. Despite its apparent favorable profile the use of levosimendan remains limited, most likely due to the availability of and familiarity with cheaper alternatives.

Calcium

Calcium chloride may be given as a bolus dose in the event of ventricular dilation and poor function on immediately separating from CPB. Calcium has both positive inotropic and vasopressor effects and may stabilize hemodynamics or improve them until another inotrope takes effect. However, controversy exists as to whether calcium should be used in the setting of myocardial ischemia as increased intracellular calcium may contribute to cell injury and death.

Glyceryl trinitrate

Glyceryl trinitrate (GTN) is an organic nitrate that is converted to nitric oxide and promotes venodilation at low dose and both venous and arterial dilation at higher doses. It may be used post-CPB to control hypertension, decreasing myocardial wall tension and oxygen consumption, and protecting the integrity of vascular suture lines.

Nitric oxide

Nitric oxide (NO) is an endogenous molecule produced by nitric oxide synathase using L-arginine as a substrate. It acts on vascular smooth muscle by stimulating guanylate cyclase, producing cGMP and a phosphorylation cascade leading to smooth muscle relaxation and vasodilation.

Inhaled nitric oxide may be used as a selective pulmonary vasodilator in the context of pulmonary hypertension in order to preserve right heart function. Nitric oxide is aerosolized into the inspiratory limb of the breathing circuit and the dose titrated up to a maximum of 40 ppm. As the drug is delivered directly to the pulmonary vasculature systemic hypotension is limited. Exposure to prolonged high concentrations of nitric oxide results in methemoglobinemia and pulmonary edema. The drug is weaned in a stepwise fashion to avoid hypertensive rebound phenomena. Nitric oxide may be used post-lung transplantation in an attempt to attenuate the acute lung injury induced by ischemia and reperfusion.

Mechanical support

After failure to separate from and thus returning to CPB, attention is directed towards the adequacy of the surgical repair and optimizing hemodynamics while allowing myocardial recovery from insults such as air emboli and the effects of reperfusion. Despite appropriate measures, in a small number of cases ventricular function remains insufficient to maintain adequate organ perfusion. In these circumstances mechanical strategies may be employed to facilitate separation from CPB. Once out of the operating room there may be improved cardiac performance with time, or this time can allow consideration for further

surgery. Strategies are discussed briefly here and mechanical support is described in greater detail in Chapters 9 and 14.

Chest splinting

Sternal closure increases intrathoracic pressure and can adversely affect ventricular filling, effects which are magnified in a poorly functioning, dilated, and edematous ventricle. A period where the chest is left open with subsequent delayed sternal closure may be beneficial. The sternal wound should be dressed and the risks of mediastinal infection countered until definitive closure, which ideally should happen within 48 hours of the original procedure.

Intra-aortic balloon counterpulsation

The intra-aortic balloon pump (IABP) is a balloon-tipped device which is positioned within the descending aorta, the tip just distal to the origin of the left subclavian artery. Inflation of the balloon coincides with diastole, timed with the dichrotic notch on the arterial waveform or alternatively the T-wave on the electrocardiogram. The benefits of arterial counterpulsation lie with the augmented coronary flow and oxygen delivery that occurs as blood is displaced proximally in the aorta by the inflated balloon, and the decrease in left ventricular afterload that occurs during balloon deflation, thus reducing myocardial oxygen demand. Although the benefits of IABP in cardiogenic shock post myocardial infarction have recently been challenged, they remain a first-line mechanical strategy to assist separation from CPB. Insertion is preferably percutaneous and via the femoral artery, but in the context of small caliber, stenotic or tortuous femoral arteries, subclavian or axillary approaches may be possible, but rarely used.

Ventricular assist devices

Ventricular assist devices (VADs) may be applied to either or both ventricles to support a failing heart and preserve organ perfusion. These mechanical devices were originally designed as a temporary bridge to recovery, and later used as a bridge to transplant. As technology has advanced VADs are increasingly being used as destination therapy. Few data exist to support the use of VAD over ECMO in the setting of failure to separate from CPB. The decision to implement either technique should be based on center-specific expertise and experience. VADs are described more extensively in Chapter 9.

Veno-arterial extracorporeal membrane oxygenation

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is a means of mechanically supporting the heart (and lungs) using a modified CPB circuit. ECMO may continue for a period of days to weeks until myocardial recovery or as a bridge to VAD or transplant. Vessel cannulation may be either central, requiring sternotomy, or peripheral, but is most likely central in the context of cardiac surgery. The decision to commence VA ECMO or implant a ventricular assist device depends on patient requirement (single or biventricular failure) and institutional experience. The main benefits of VA ECMO over VAD are that the single VA ECMO circuit supports both ventricles and also the lungs, and can be more rapidly initiated since cannulae are already *in situ* and only a change of circuit is required. Although historically ECMO has been complicated by a high incidence of coagulopathy, technical advances with the circuitry, oxygenators, and newer centrifugal pumps have helped to reduce hemolysis, improve gas exchange, and limit inflammation and thrombus formation. The use of ECMO is discussed further in Chapter 14.

Self assessment

1. With regard to preparing to wean a patient off CPB, which of the following are true statements?

A. Core temperature should be 37.5°C (normal body temperature) or greater

B. Hemoglobin concentration should be 9 g/dl or greater

C. In many centers the acceptable base deficit is ideally between 0 and −5

D. A low potassium level will protect the heart from arrhythmias, so should not be treated just before separating from CPB

Answer: C

2. Which of the following statements are true?

A. Mechanical ventilation of the lungs should only be recommenced after flow from the CPB system has been stopped as positive pressure ventilation reduces venous return to the heart

B. Weaning from CPB is achieved by initially increasing venous drainage from the heart and simultaneously reducing the bypass pump flow rate

C. The central venous pressure can be a useful guide to the degree of filling of the heart during the process of weaning from CPB

D. Weaning from CPB is achieved by gradually reducing the venous return from the patient to the bypass system, while simultaneously reducing the bypass flow rate and so reducing flow in the arterial

limb of the bypass circuit

Answers: A False; B False; C True; D True

3. Which of the following may help to improve cardiac performance? (select one or more statements)

A. Allowing a period of reperfusion of the heart after removal of the aortic cross-clamp and before attempting separation from CPB

B. Maintaining a slow heart rate (50 to 60 beats/minute) to reduce energy use by the myocardium while weaning from CPB

C. Use of an intra-aortic balloon pump to augment coronary blood flow

D. Pacing the atrium at a rate of 80 to 100 beats/minute

Answers: A True; B False; C True; D True

4. Common causes of failure to wean from CPB include: (select one or more)

A. Inadequately corrected metabolic abnormalities, e.g. acid–base status

B. Prolonged aortic cross-clamp duration

C. Poor preoperative ventricular function

D. Inadequate myocardial preservation technique

Answers: A True; B True; C; True; D True

Suggested Further Reading

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Chapter 9

Mechanical circulatory support

Kirsty Dempster and **Steven Tsui**

The introduction of cardiopulmonary bypass (CPB) in 1953 for the closure of an atrial septal defect marked the dawn of using machines to provide a circulation. While incremental refinements to CPB were being made during the ensuing decade, developmental work had already begun with other forms of mechanical circulatory support (MCS). In 1966, a patient who failed to wean from CPB due to post-cardiotomy shock was successfully bridged-to-recovery with a temporary left ventricular assist device (LVAD). Two years later, a patient with cardiogenic shock was salvaged with an intra-aortic balloon pump. Research on the total artificial heart (TAH) also commenced in the late 1960s.

There is now a wide range of options available to support the failing circulation and this chapter will focus on some of these options (see Table 9.1). The decision whether to proceed to MCS depends on the etiology of the heart failure and on the likely long-term treatment strategy. Which method of MCS is deployed depends on the rapidity of onset of heart failure, its potential reversibility, its severity, and the anticipated duration of support required.

Table 9.1 Types of mechanical circulatory support

- Cardiopulmonary bypass (CPB)
- Extracorporeal membrane oxygenation (ECMO)
- Intra-aortic balloon pump (IABP)
- Ventricular assist devices (VADs)
- Total artificial heart (TAH)
- Aortic compression devices

- Cardiac compression devices

Intra-aortic balloon counterpulsation

The intra-aortic balloon pump (IABP) is the most commonly used device for circulatory support (see Table 9.2). The intra-aortic balloon (IAB) catheter has two channels: one for the passage of helium gas used to inflate and deflate the balloon; the other for direct monitoring of the arterial blood pressure inside the aortic lumen. The IAB catheter is usually inserted in a retrograde fashion via the femoral artery. A sheathless insertion technique causes less obstruction to distal limb perfusion than one that is inserted via a large-bore sheath in the artery. Occasionally, in patients with severe aorto-iliac disease who have undergone open heart surgery, the balloon catheter is inserted antegrade via the ascending aorta. The IAB catheter is positioned in the descending thoracic aorta, the balloon segment of the catheter lying just distal to the origin of the left subclavian artery.

Table 9.2 Indications for IABP

Ischemic myocardium	• Unstable angina despite maximal medical therapy • Ischemia-induced ventricular arrhythmia • Elective support in high-risk percutaneous coronary interventions
Structural complications of acute myocardial infarction	• Ventricular septal defect • Acute mitral valve regurgitation
Cardiogenic shock	• Post myocardial infarction • Acute myocarditis • Acute deterioration of chronic heart failure • Post-cardiotomy • Primary graft failure of the donor heart following heart transplant

The balloon is rapidly inflated at the end of ventricular systole, just as the aortic valve closes, generating a surge in aortic pressure during ventricular diastole. Just before ventricular systole, the balloon is rapidly deflated, reducing the aortic pressure against which the left ventricle has to eject. The timing of balloon inflation and deflation can be triggered automatically by the patient's ECG (ECG trigger), the aortic pressure waveform (pressure trigger), the atrial and/or ventricular pacing signal from a pacemaker (A-pacing or V-pacing trigger) or at a fixed rate by the IABP console (internal trigger). The combined effects on cardiovascular physiology are listed in Table 9.3.

Table 9.3 Beneficial effects of IABP

Balloon deflation during ventricular systole	• Reduces left ventricular afterload • Reduces peak LV wall stress and LV stroke work • Decreases myocardial oxygen demand • Reduces mitral valve regurgitation • Increases LV ejection fraction
Balloon inflation during ventricular diastole	• Increases coronary perfusion pressure • Augments coronary blood flow • Improves myocardial oxygen delivery • Improves end-organ perfusion, e.g. kidneys, liver, etc.
Overall effects	• Augments cardiac output • Reduces pulmonary capillary wedge pressure • Relieves pulmonary congestion and tendency for edema

Management of the IABP patient

The frequency and magnitude of balloon augmentation can be controlled via the balloon pump console. The inflation ratio refers to the number of balloon inflations to the number of QRS complexes and can be set at 1:1, 1:2 or 1:3 (see Figure 9.1a–c). The magnitude of augmentation can range from 10% to 100%.

Figure 9.1d shows the console tracing from an IABP set at 50% augmentation. During normal use, maximal IABP support is provided with a 1:1 inflation ratio at 100% augmentation. The timing of the inflation/deflation triggers should be checked regularly and adjusted when required to optimize the support provided. Current consoles have an "*Autopilot*" mode which uses an algorithm to automatically select the best ECG lead and trigger source to optimize the inflation and deflation timing. To reduce thrombo-embolic risks associated with an IAB catheter, systemic anticoagulation with unfractionated heparin infusion is advised, aiming for an activated partial thromboplastin time ratio (APR) of 1.5 to 2.0. Distal limb perfusion must be examined regularly and distal pulses checked either by palpation or with a hand-held Doppler probe.

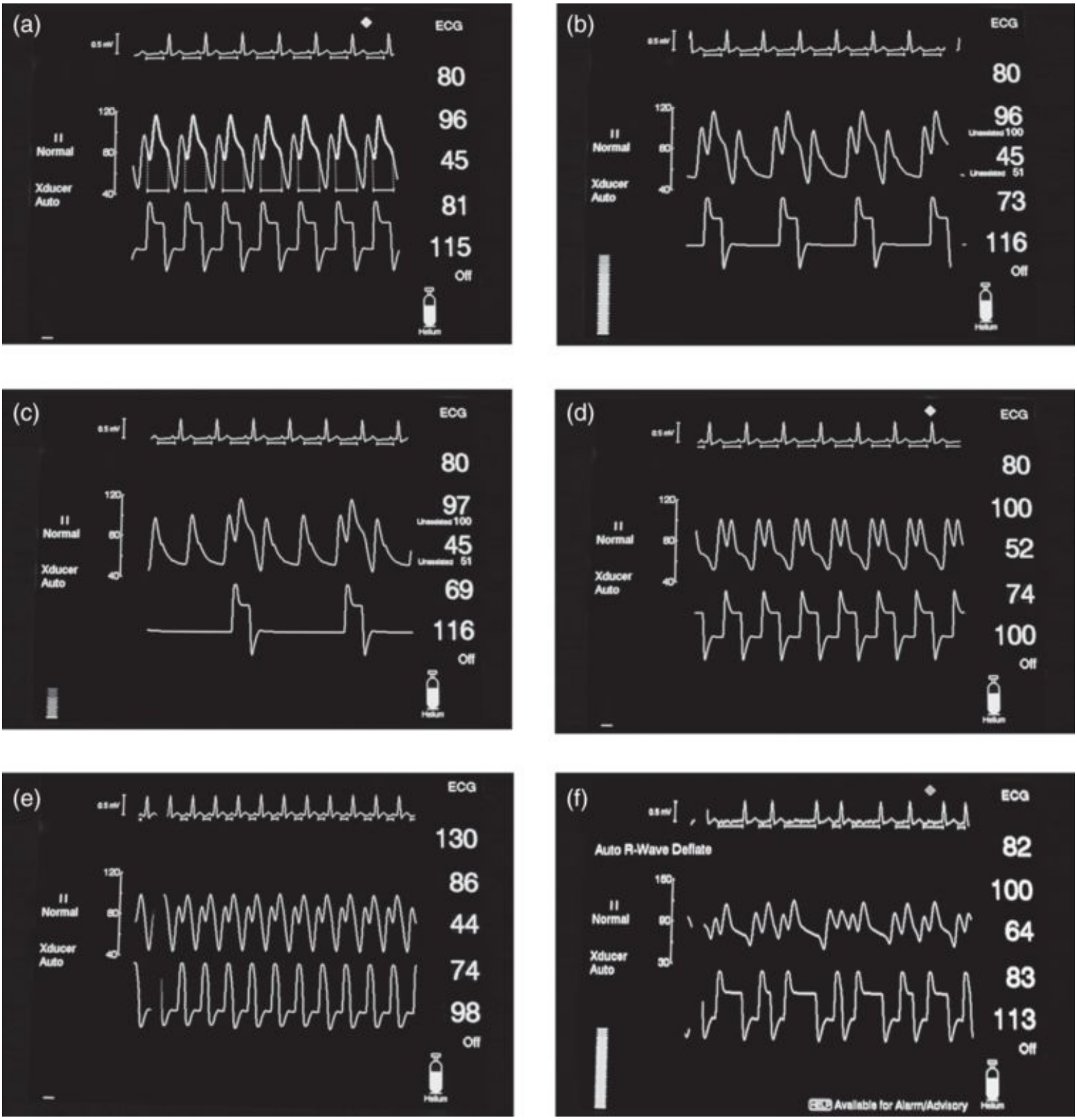

Figure 9.1 Intra-aortic balloon console tracings. The screen displays the ECG trace at the top, the intra-aortic pressure waveform in the center, and balloon inflation/deflation at the bottom. (a) Full IABP augmentation with inflation 1:1 and inflation interval highlighted, showing correct balloon inflation at the dicrotic notch of the arterial pressure trace. (b & c) Full augmentation with inflation ratio of 1:2 and 1:3 respectively. (d) Balloon augmentation set at 50%. (e) IABP on full support but showing diminished effectiveness due to tachycardia. (f) Auto R-wave deflate mode for a patient in AF.

The effectiveness of IABP augmentation is diminished when there is excessive tachycardia (> 120 bpm) or when the cardiac rhythm becomes irregular, e.g. atrial fibrillation (see Figure 9.1e–f). Therefore, inotropic support should be moderated to minimize the occurrence of such rhythm disturbances. Invasive hemodynamic monitoring is indispensable and provides the best assessment of the adequacy of circulatory support. A Swan–Ganz pulmonary artery flotation catheter can provide important hemodynamic information including left ventricular preload (pulmonary capillary wedge pressure), left ventricular afterload (systemic vascular resistance), right ventricular afterload (pulmonary vascular resistance), and cardiac output, as well as providing information on the adequacy of systemic oxygen delivery (mixed venous oxygen saturation or SvO_2). When cardiac function begins to recover, the inotrope dose should be reduced before IABP support is weaned. If the cardiac index is maintained above 2.2 l min^{-1} m^{-2} with acceptable preload (pulmonary capillary wedge pressure < 15 mmHg), attempts can be made to wean the IABP. Firstly, the IAB augmentation is reduced to 50% for 2–4 hours. The inflation ratio is then reduced from 1:1 to 1:2 for another 2–4 hours and then to 1:3 before the balloon catheter is removed. The IABP must be switched off and the catheter completely deflated just prior to removal. Heparin infusion should be discontinued at the start of the weaning process so that coagulation is normalized by the time the IAB catheter is ready for removal.

Complications of IABP use

Major vascular complications can occur in up to 15% of patients treated with an IABP. Femoral insertion of an IAB catheter may not be possible in 5% of patients, because of a tortuous or diseased ilio-femoral system. During insertion, vascular injury can lead to dissection, rupture or hemorrhage. Once *in situ*, distal limb ischemia can result from a combination of peripheral vasoconstriction and low cardiac output state or thromboembolism. Malpositioning of an IAB catheter may result in obstruction of visceral or renal arteries, making a visual check on catheter position via chest radiography essential.

In the operating room, placement is usually facilitated with the use of transesophageal echocardiography, which can also give an indication of the presence of atherosclerotic disease in the descending thoracic aorta.

Other complications can include infection, thrombocytopenia, and rupture of the IAB catheter. Helium is used as the driving gas for IAB inflation because of its high blood solubility, so reducing the risks from gaseous emboli in the event of balloon rupture. If the IAB ruptures, blood can be seen to track down the gas channel of the balloon catheter. Whenever this is observed, the IABP counterpulsation must be stopped immediately and the catheter removed.

Ventricular assist devices

Severe heart failure refractory to medical management and IABP support has an appalling prognosis. Inadequate systemic perfusion gives rise to end-organ dysfunction and metabolic acidosis, while excessive back-pressure from the failing left and right ventricles results in pulmonary edema and systemic venous congestion respectively. Ventricular assist devices (VADs) can be used to augment perfusion and relieve congestion, potentially reversing the damaging effects of severe heart failure.

VADs are mechanical blood pumps that can provide either left, right or biventricular support. A left ventricular assist device (LVAD) withdraws oxygenated blood from the left atrium or left ventricle, and returns it to the aorta; a right ventricular assist device (RVAD) withdraws venous blood from the right atrium or right ventricle, and returns it to the pulmonary artery. In general, it is preferable to cannulate the ventricle as VAD inflow as this configuration provides superior ventricular decompression, avoids ventricular stasis, and affords higher VAD flow rates.

The output of an LVAD is dependent on adequate right ventricular function to deliver sufficient blood flow across the lungs and into the left heart chambers for the LVAD to pump. Likewise, an RVAD can only provide benefit if the native left ventricle can generate enough stroke work to cope with the pulmonary blood flow produced by the RVAD. If both native ventricles are failing, two VADs are required in order to provide biventricular assistance to support the circulation.

Principles of assist devices

In its simplest form, emergency short-term VAD support can be provided by any blood pump (e.g. a Biomedicus centrifugal pump) and a couple of vascular cannulae: one for inflow from the heart to the pump; the other for outflow return from the pump to the aorta or pulmonary artery. In the absence of specialist VAD equipment, such a set-up can be lifesaving and used to maintain the circulation for hours or days.

There is, however, a growing number of temporary devices specifically intended for use as a VAD. These systems consist of blood pumps that are less traumatic to the blood components, and have cannulae that are designed to provide more secure attachment to the heart chambers with superior flow characteristics. Temporary VAD systems are intended for short-term circulatory support in the intensive care unit for days or weeks. Long-term VAD systems are designed to provide circulatory support for months or years. Continual improvements in implantable VADs are enabling patients to be discharged from hospital and treated as out-patients, often with a relatively normal quality of life.

The fate of patients receiving a VAD depends on the underlying cause of the cardiac dysfunction and its reversibility. In some cases of post-cardiotomy shock and fulminant myocarditis, cardiac function

recovers after a period of circulatory support and the VAD can be weaned and removed, a process known as “bridge to recovery.” Unfortunately, in the majority of cases of chronic heart failure, e.g. ischemic or dilated cardiomyopathies, the myocardial dysfunction is unlikely to be reversible. Occasionally, a VAD is required for these patients who are usually already waiting for a heart transplant because of deteriorating cardiac status. Here the VAD is used to buy time for the patient until a suitable donor heart can be found, a process called “bridge to transplant” or BTT. For selected patients with advanced heart failure who are not transplant candidates, implantable VAD can be offered as a permanent support, a process sometimes called “destination therapy” or DT.

The VAD decision making process

The key decisions of which patient to support with a VAD, when to insert a VAD, whether the patient requires LVAD alone or biventricular assist device (BiVAD), and which VAD system to use are often difficult ones to make. They are influenced by a number of factors including the acuity of onset and the severity of heart failure, patient comorbidities, transplant waiting times, device and resource availability, and institutional experience.

Up until a few years ago, patients with heart failure were stratified according to the New York Heart Association (NYHA) functional classification, with Class I describing patients with cardiac disease but no symptoms or physical limitations, and Class IV describing patients in advanced heart failure with symtoms at rest who are often bedbound. However, among those patients with Class IV heart failure symptoms, there remained a very broad spectrum of pateints ranging from those who are stable on oral therapy to those who may be pre-terminal on inotropic support. The treatment strategy required varied according to the severity of heart failure. Therefore, it was necessary to further sub-classify patients with advanced heart failure.

The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) was established as a mandatory registry for all patients receiving an implantable mechanical circulatory support device (MCSD) in the USA. Based on patient characteristics at the time of device implantation and outcome analysis, seven profiles have been defined to further stratify patients in advanced heart failure, with Profile 1 being the most severely ill. NYHA Class IV patients are now subdivided into Profiles 1–6 while those in NYHA Class IIIb are described as Profile 7 (see Table 9.4).

Table 9.4 INTERMACS Level of limitation at time of implant

INTERMACS profile	Description	Time frame for definitive intervention
Profile 1	Critical cardiogenic shock	Emergency intervention within hours

Profile 2	Progressive decline	Urgent intervention within days
Profile 3	Stable but inotrope dependent	Elective intervention within days/weeks
Profile 4	Resting symptoms	Elective interventions within months
Profile 5	Exertion intolerant	Variable urgency, maintain nutrition and organ function
Profile 6	Exertion limited	Variable urgency, maintain nutrition and organ function
Profile 7	Advanced NYHA III	Transplant or MCSD may not be currently indicated

Profile 1 consists of decompensated patients with precarious hemodynamics and life-threatening hypoperfusion refractory to escalating inotropic support. There is worsening acidosis and rising lactate associated with oliguria and derangement of hepatic and renal functions, sometimes described as “crash and burn.” Unless circulatory support is provided within hours, irreversible shock will most likely follow. Due to the decompensated state of these patients, the use of implantantable devices in INTERMACS Profile 1 patients tend to result in a higher 30-day mortality (see Figure 9.2). For some of the sickest patients, despite restoring normal systemic perfusion, the function of some injured end organs may not recover and the patient does not survive. When there are significant uncertainties about the viability of a decompensated patient, a temporary MCSD may be deployed to see whether the shock state is reversible before more durable treatment options are considered. This approach is sometimes described as “bridge to decision.”

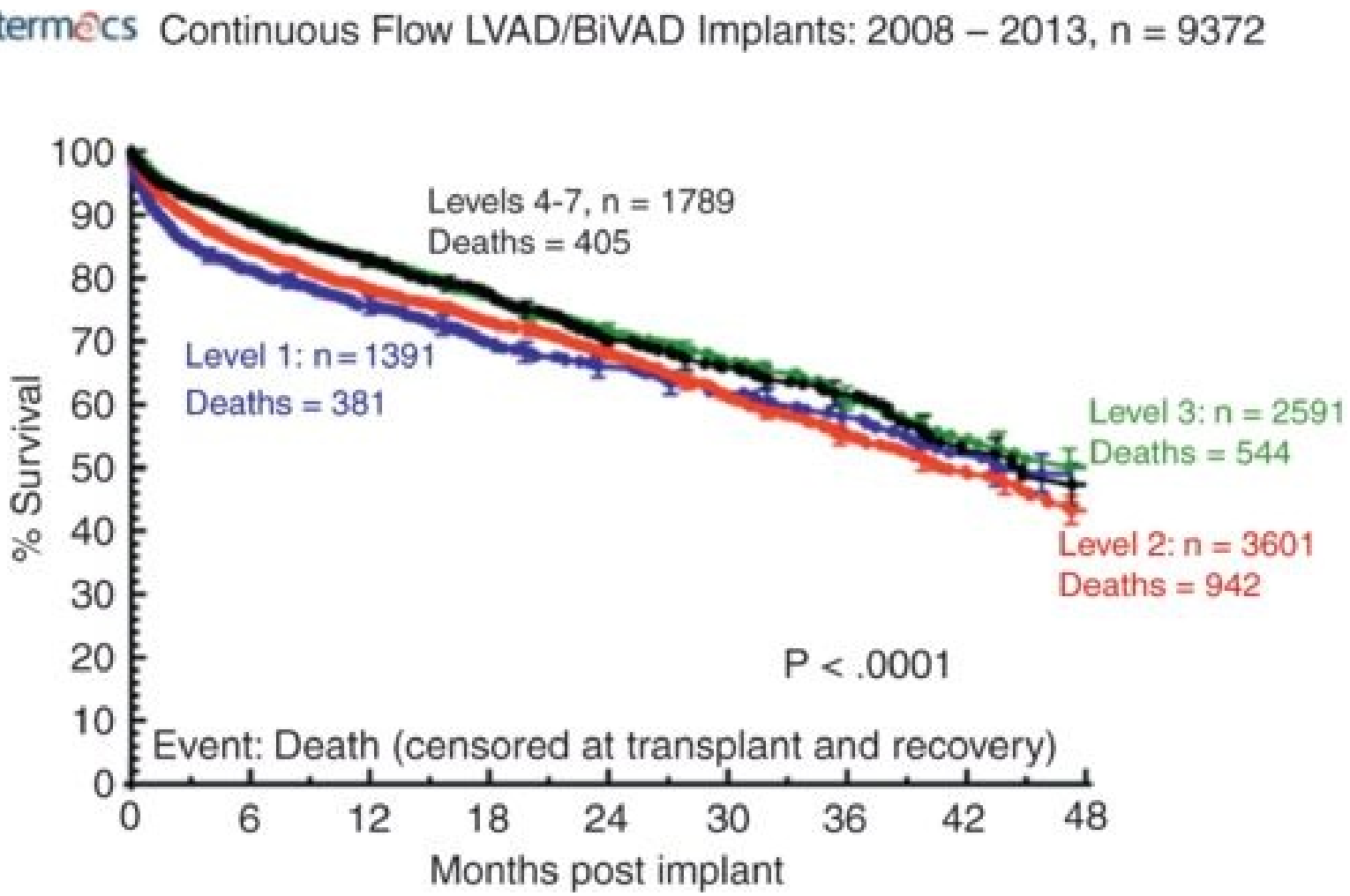

Figure 9.2 Actuarial survival after continuous-flow LVAD implant, stratified by INTERMACS level at implant.

(from Kirklin,J, Naftel D, Pagani F, et al. Sixth INTERMACS annual report: A 10,000-patient database. The Journal of Heart and Lung Transplantation 2014; 33: 555–64).

Profile 2 describes patients with progressive decline in nutritional status, renal function, and/or fluid retention despite ongoing or escalating inotropes. Urgent intervention with MCSD is indicated to avoid further deterioration.

Profile 3 describes patients who are dependent on moderate levels of inotropic support but remain stable clinically and biochemically. In countries where waiting times for an urgent heart transplant is reasonable, this might be the more straightforward treatment option and a lower risk approach. However, close monitoring of hemodynamic and biochemical trends must be available to detect any subtle decline into INTERMACS Profile 2 as soon as possible in order to minimize potential increases in the risks associated with interventions using MCSDs.

Ventricular tachy-arrhythmia is an ominous sign and should prompt an earlier decision for VAD insertion. Since the “bridging” period to a transplant can range from months to sometimes over a year, these patients should be implanted with a long-term VAD so that they can be discharged home. Currently,

there are several wearable or portable VAD systems that allow patients independent mobility during VAD support with reasonable quality of life.

Currently, there is insufficient evidence to support the use of MCSDs in INTERMACS **Profile 4–7** patients. Earlier implantation of LVADs in these ambulatory patients does not confer superior post-implant survival when compared with inotrope-dependent INTERMACS Profile 3 patients. A number of prospective studies are currently underway to explore whether the use of implantable LVADs in Profile 4–7 patients could be justified.

There are certain patients who would otherwise be transplant candidates except for one or more serious, but potentially reversible, complications of advanced heart failure, e.g. pulmonary hypertension, renal dysfunction. Unless such complication(s) could be reversed, these patients are not transplantable and they will invariably die from their heart failure. Elevated pulmonary vascular resistance due to left ventricular failure and pulmonary venous congestion often revert to normal levels with mechanical unloading of the left ventricle using an implantable LVAD. When systemic perfusion is improved using MCS, renal dysfunction due to chronic low cardiac output state can sometimes be reversed. The use of LVAD implantation in these patients is sometimes described as “bridge to candidacy.”

Patients presenting with acute cardiogenic shock refractory to medical therapy have an appalling prognosis. The common causes of heart failure are listed in Table 9.5. Over the last decade, temporary MCSDs have been increasingly used to support such patients in order to maintain systemic perfusion while recovery of cardiac function is awaited. Those patients in whom cardiac function recovers sufficiently to be weaned from mechanical circulatory support tend to do so within 5–7 days. For those with insufficient cardiac recovery, a decision has to be made between escalating to longer-term devices, i.e. “bridge to bridge,” or treatment withdrawal and death. Cardiac arrested patients undergoing cardiopulmonary resuscitation can also be placed on peripheral extracorporeal life support to maintain systemic circulation while further cardiac and neurological assessment could be carried out. For patients with acute cardiogenic shock requiring treatment with temporary MCSDs, the overall survival to discharge is approximately 30–40%.

Table 9.5 Common causes of cardiogenic shock

Acute MI shock *(5–8% of acute myocardial infarction)*
Post-cardiotomy *(1–4% after cardiac surgery)*
Post-HTx. primary graft failure
Miscellaneous

Malignant ventricular arrhythmia
Post-partum cardiomyopathy
Fulminant myocarditis
Poisoning, e.g. beta blocker overdose

Between 1 and 4% of patients fail to wean off CPB after cardiac surgery despite support with an IABP escalating inotrope doses. The idea of bridging these patients with a MCSD is very attractive as the recovery of cardiac function post-cardiotomy is possible. However, as cardiac surgical patients get older and have an increased number of co-morbidities the knowledge of contraindications for a VAD insertion after cardiac surgery is essential (see Table 9.6).

Table 9.6 Contraindications to the use of VADs post-cardiotomy

Age > 65–70 years
Uncontrollable bleeding
Intractable metabolic acidosis
Other comorbidities
Pre-existing neurological impairment
Severe cerebral vascular disease
Severe peripheral vascular disease
Advanced chronic pulmonary disease
Chronic renal failure
Chronic liver disease
Recent malignancy

Types of ventricular assist devices

Technical developments in mechanical circulatory support have progressed rapidly over the last 10 years. There is now a large range of systems available for clinical use. These can be classified into temporary systems and long-term systems. The earliest "*first generation*" devices were based on a volume displacement mechanism and generated pulsatile blood flow. These devices were bulky in design, noisy in operation, and had limited durability. As a result, most of the newer devices have moved to rotary

blood pump technology with a single moving part. These can either be of an axial flow design or a centrifugal configuration. Implantable LVADs with mechanical bearings are referred to as “second generation” LVADs while those with magnetic levitation or hydrodynamic bearings are referred to as “third generation” (see Table 9.7). Continuous flow devices are generally more compact, silent in operation, and more durable.

Table 9.7 Classification and examples of VAD systems

Temporary devices	Thoratec CentriMag Impella 2.5; CP; 5.0; LD TandemHeart

Longer-term devices	• Pulsatile (1st generation or volume displacement)
	  • Thoratec PVAD
	  • Berlin Heart Excor
	  • Abiomed AB5000
	• Continuous flow (2nd generation)
	  • Micromed HeartAssist 5
	  • Jarvik 2000
	  • Thoratec HeartMate II
	• Continuous flow (3rd generation)
	  • Berlin Heart Incor
	  • Terumo DuraHeart
	  • HeartWare HVAD
	  • Thoratec HeartMate III

In the HeartMate II study, patients with end-stage heart failure were randomized to undergo implantation of the pulsatile Thoratec Heartmate XVE or a continuous flow Thoratec HeartMate II. Patients implanted with the continuous flow LVAD had superior actuarial survival rates at 2 years and

significantly lower adverse event rates. Following the publication of these results, the use of 1st generation LVAD has all but ceased.

A full description of all available devices is beyond the scope of this book. A few selected examples of commonly available VADs that are in clinical use are briefly described below.

Thoratec CentriMag

The Thoratec CentriMag is a continuous flow extracorporeal system comprised of a single-use polycarbonate centrifugal pump, a motor, and a primary drive console (see Figures 9.3 and 9.4). It is intended for short-term left, right or biventricular support of up to 30 days' duration. The Thoratec CentriMag is designed to operate without mechanical bearings or seals, which are components known to contribute to hemolysis and thrombus formation. The magnetically levitated pump impeller achieves rotation with no friction or wear at speeds of 1500 rpm to 5500 rpm, providing flow rates of up to 9.9 l/minute in vitro. In vivo, flows of 5.0–6.0 l/minute are regularly achieved.

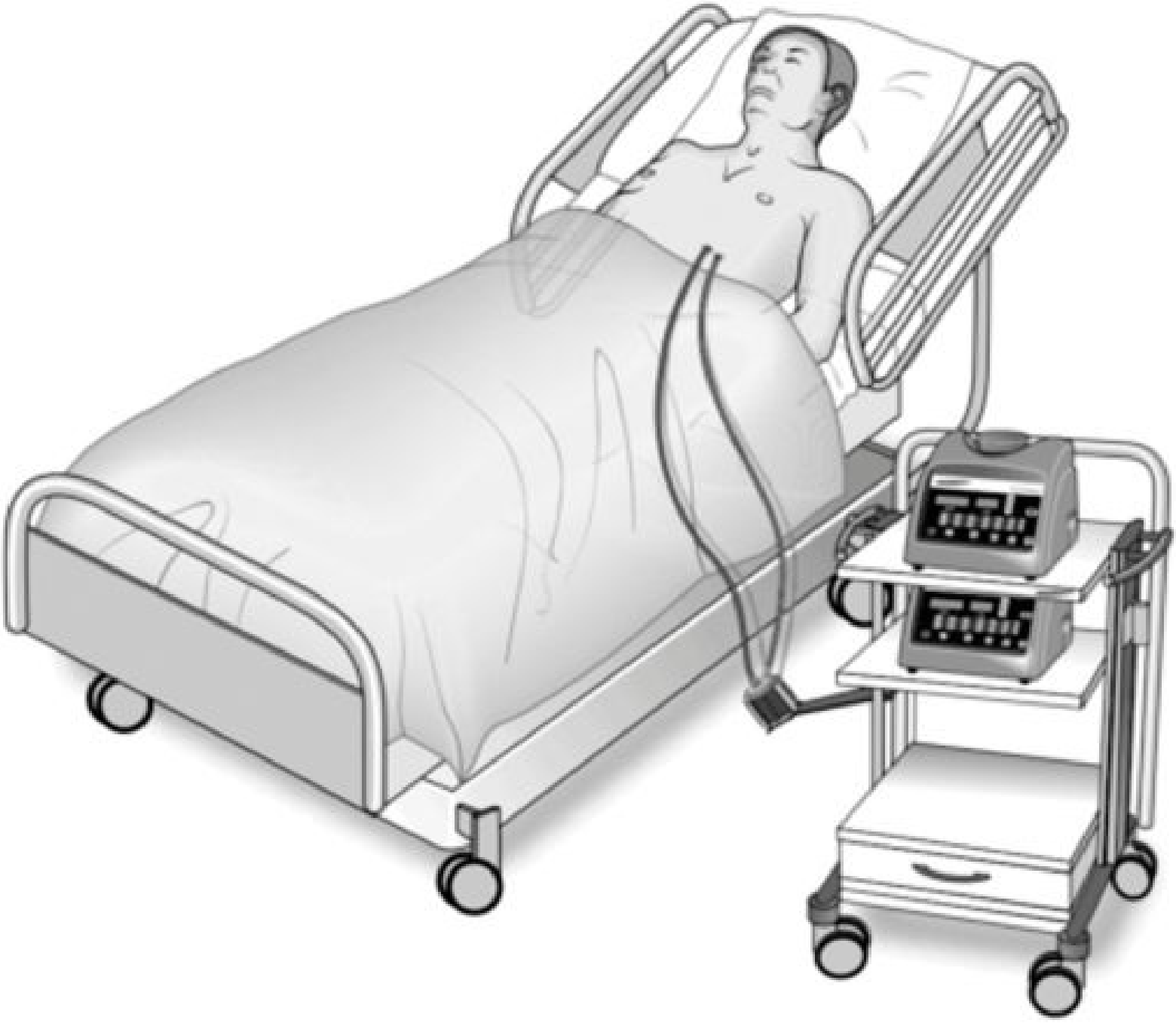

Figure 9.3 Thoratec CentriMag Primary Console and patient.

(Reprinted with the permission of Thoratec Corporation)

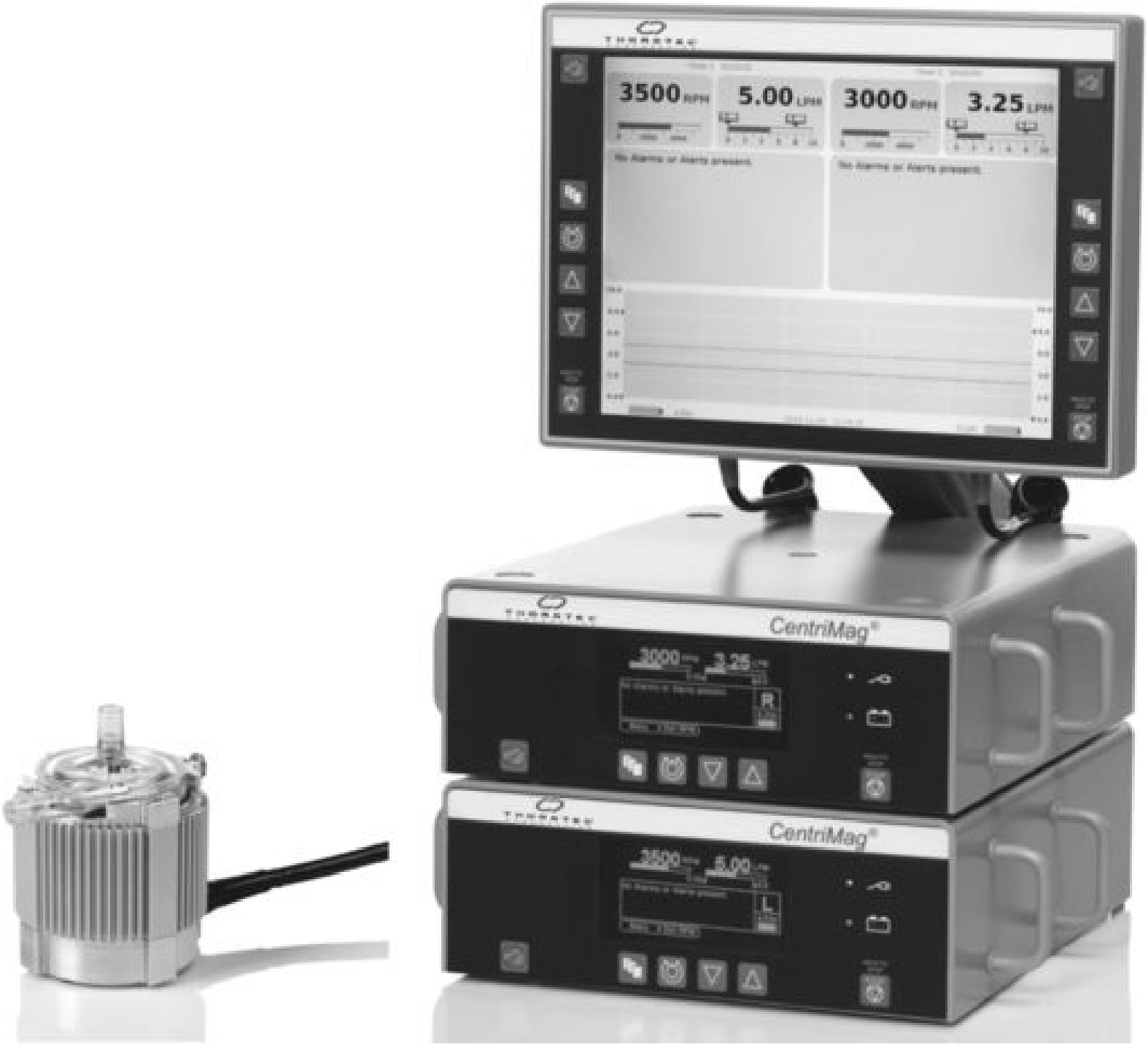

Figure 9.4 Thoratec CentriMag Pump, Motor, and new Primary Drive Console.

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The inflow and outflow cannulae can be rapidly inserted into the beating heart and great vessels with or without CPB (see Figure 9.5). Other clinical equipment such as a membrane oxygenator or hemofilter can be spliced into the system. Although patients supported with the CentriMag are kept on the intensive care unit, they can be allowed to move around the bed space and can undergo physiotherapy (Figure 9.6). Because of its simplicity and versatility, the CentriMag is rapidly becoming the most widely adopted temporary MCSD at many centers. It is also being used as either stand alone VAD or as part of an ECMO system, to stabilize patients for transport to an advanced heart failure center for further treatment.

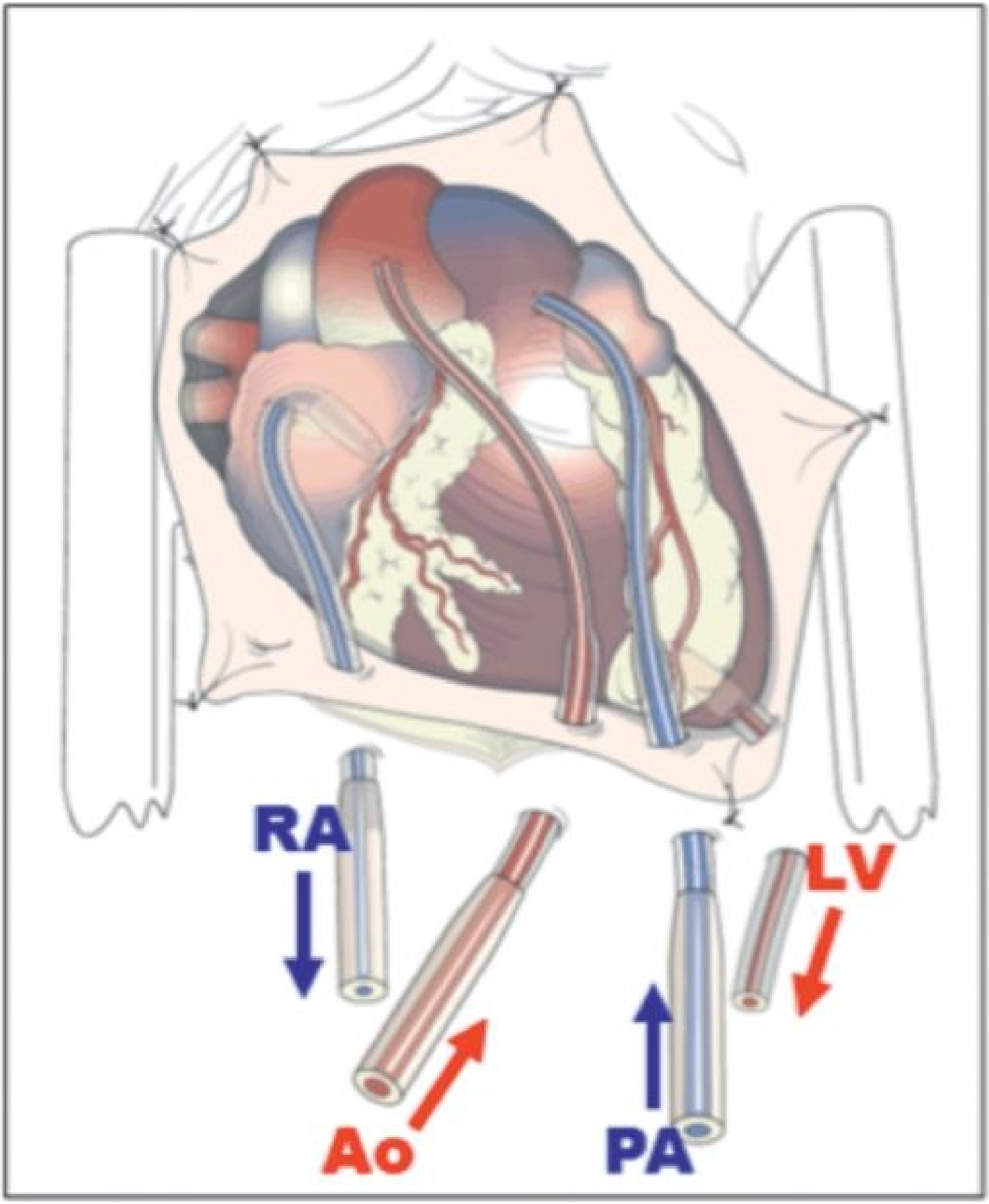

Figure 9.5 Cannulation of the heart for biventricular support with the LVAD inflow cannula in the LV apex and the outflow cannula returning blood to the ascending aorta. The RVAD inflow cannula takes

blood from the right atrium and returns it to the pulmonary artery. The cannulae are tunneled through the skin to allow for chest closure.

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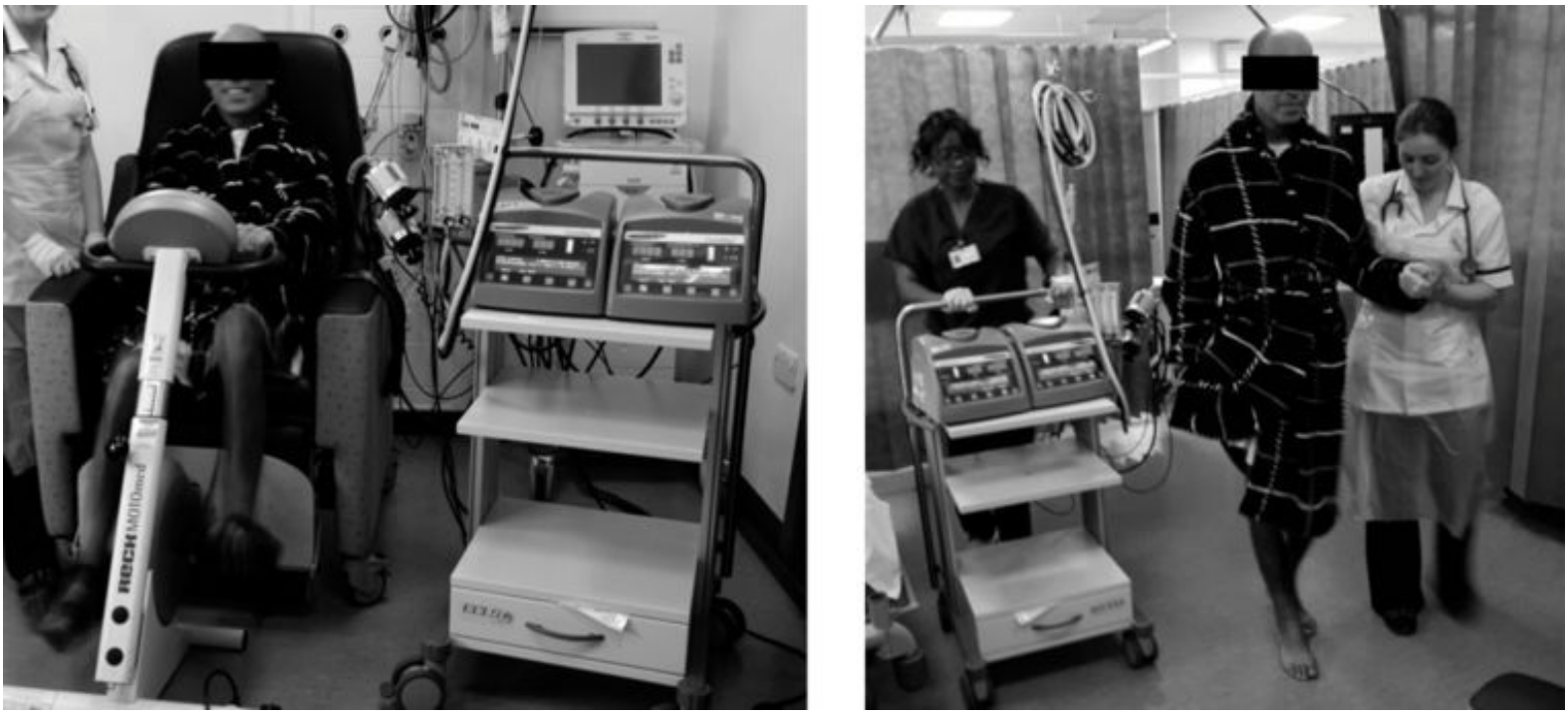

Figure 9.6 Patients on CentriMag BiVAD support can undergo physical therapy and mobilize out of bed.

HeartMate II

The HeartMate II is by far the most widely used long-term implantable LVAD with over 18 000 implants worldwide. It is a high-speed, axial flow blood pump weighing 300 g and measuring approximately 4 cm in diameter and 8 cm in length. As such, it is suitable for implantation in a wide range of patients, including small adult females and selected children.

The internal pump surfaces are made of smooth, polished titanium. A rotor within the pump contains a magnet and is rotated by the electromotive force generated by the integral magnetic motor in the housing (see Figure 9.7). The rotor spins on ceramic bearings and propels the blood from the inflow cannula sited in the LV apex to the ascending aorta. The pump speed can vary from 6000 to 15000 rpm, providing blood flow of up to 10 l/minute.

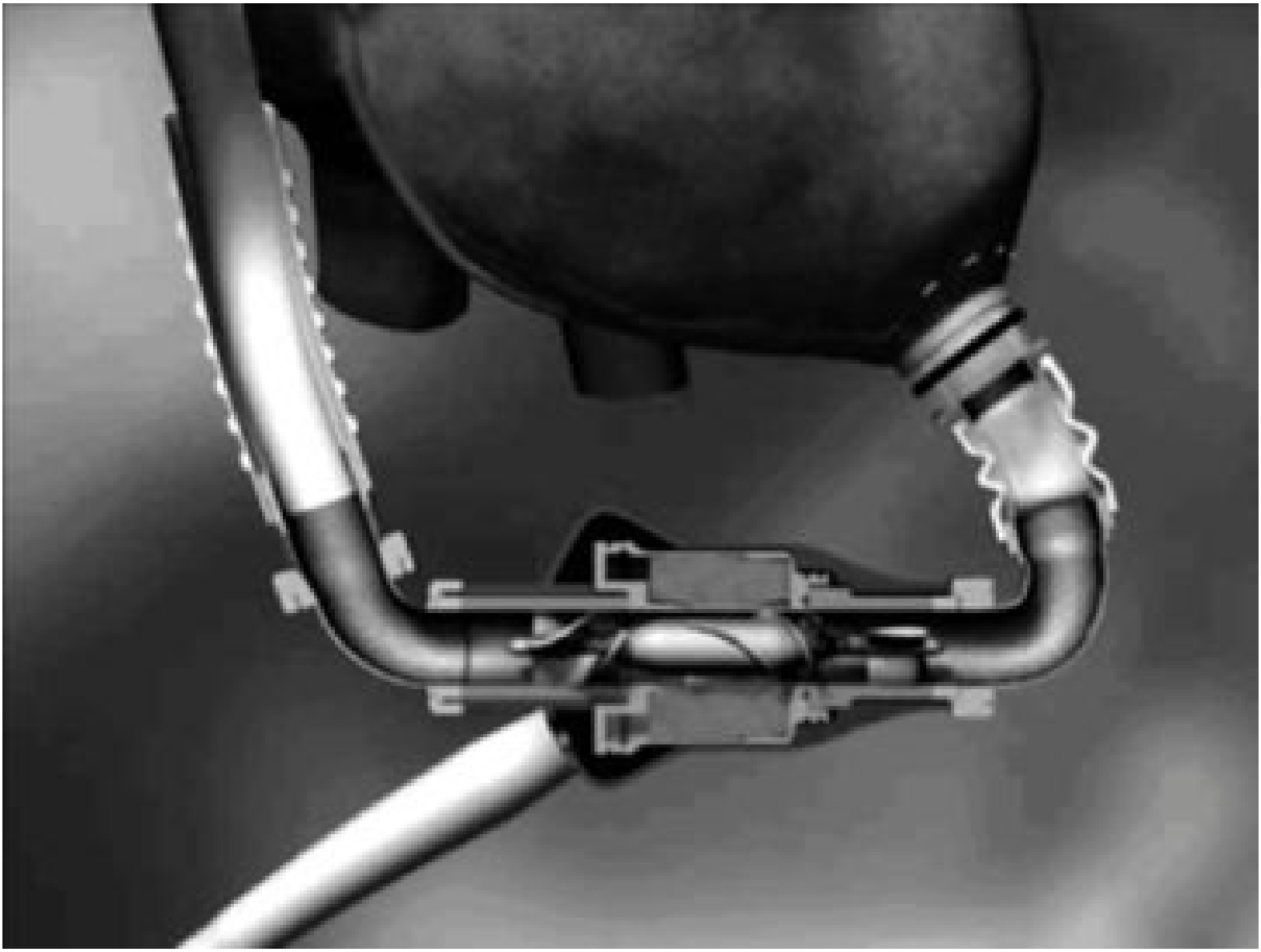

Figure 9.7 Cutaway view of Thoratec HeartMate II showing inflow cannula in the left ventricle, rotor, magnetic motor and ceramic bearings, and outflow towards ascending aorta.

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External equipment includes a system controller, power module, system monitor, universal battery charger, rechargeable batteries, and battery clips. The system controller continuously monitors and controls the implanted pump and shows information regarding alarm conditions (see Figure 9.8).

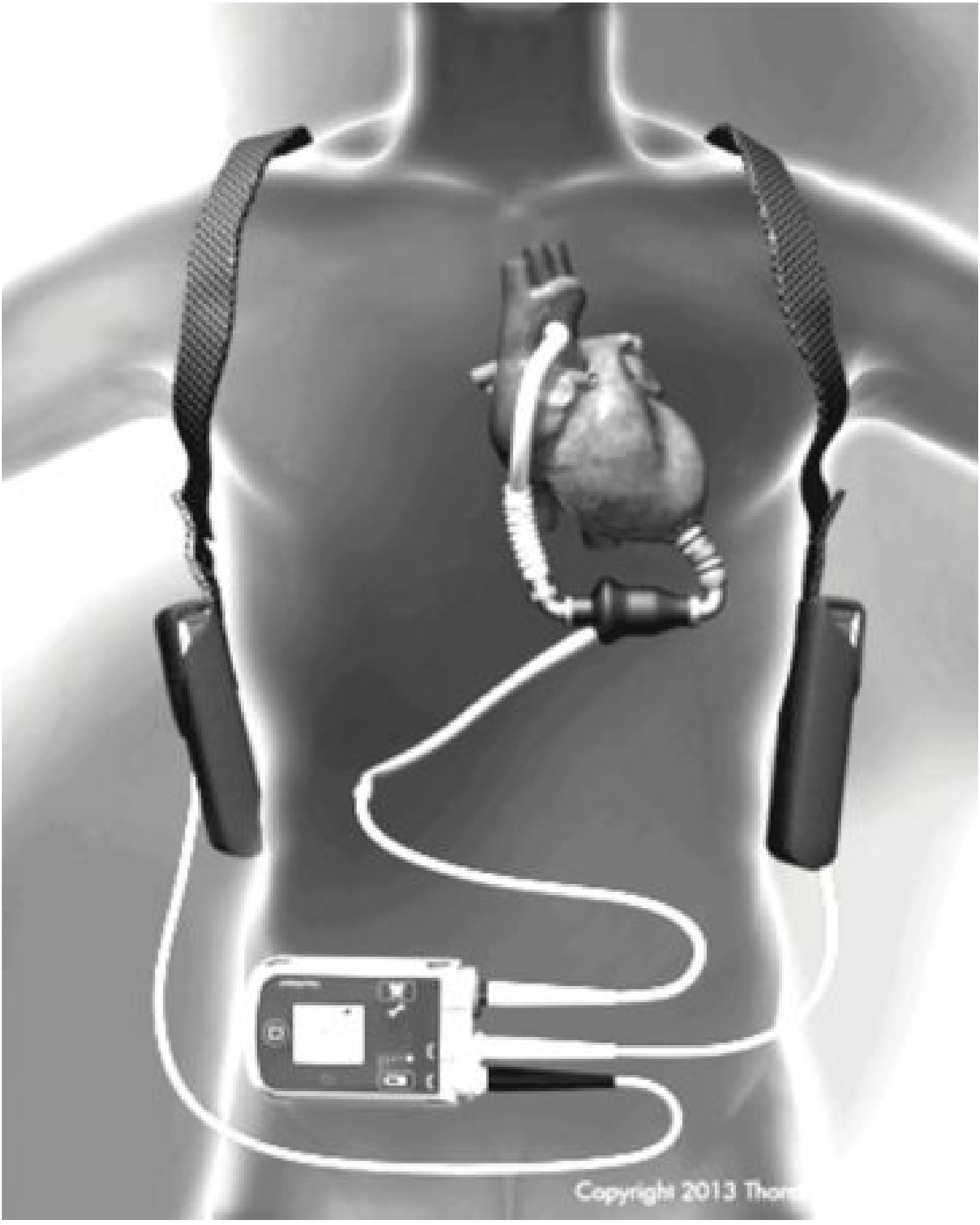

Figure 9.8 Diagram of the configuration of the Thoratec HeartMate II showing implanted pump, percutaneous lead, external system controller, and batteries.

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The power module provides AC power and acts as an interface between the system monitor and the implanted pump. The power module and power module patient cable allows the system to be operated by AC power. Alternatively, patients can connect to batteries, which permits the system to be operated for up to 10 hours.

HeartWare HVAD

The HeartWare HVAD is a third generation long-term implantable VAD. It consists of a small centrifugal blood pump with a wide bladed impeller suspended by a combination of passive magnetic and hydrodynamic forces. The lack of a mechanical bearing contributes to its blood compatibility and durability. Its integrated inflow cannula design results in a compact pump weighing 160 g and an implant volume of only 50 ml allowing intra-pericardial placement even in smaller patients (see Figures 9.9 and 9.10). It operates at between 1800 and 4000 rpm and can generate flows of up to 10 l/minute. The system is managed by an external controller which can be powered from the AC adapter, DC adapter (car power) or from batteries which allow at least 12 hours of patient activity. Due to its small size, two HeartWare HVADs have even been implanted simultaneously in patients with biventricular failure as biventricular support (see Figure 9.11). Currently, the use of the HeartWare HVAD as BiVAD support is an off-label indication.

Figure 9.9 HeartWare HVAD pump integrated sintered inflow cannula, driveline, and sewing ring used to attach the pump to the left ventricle.

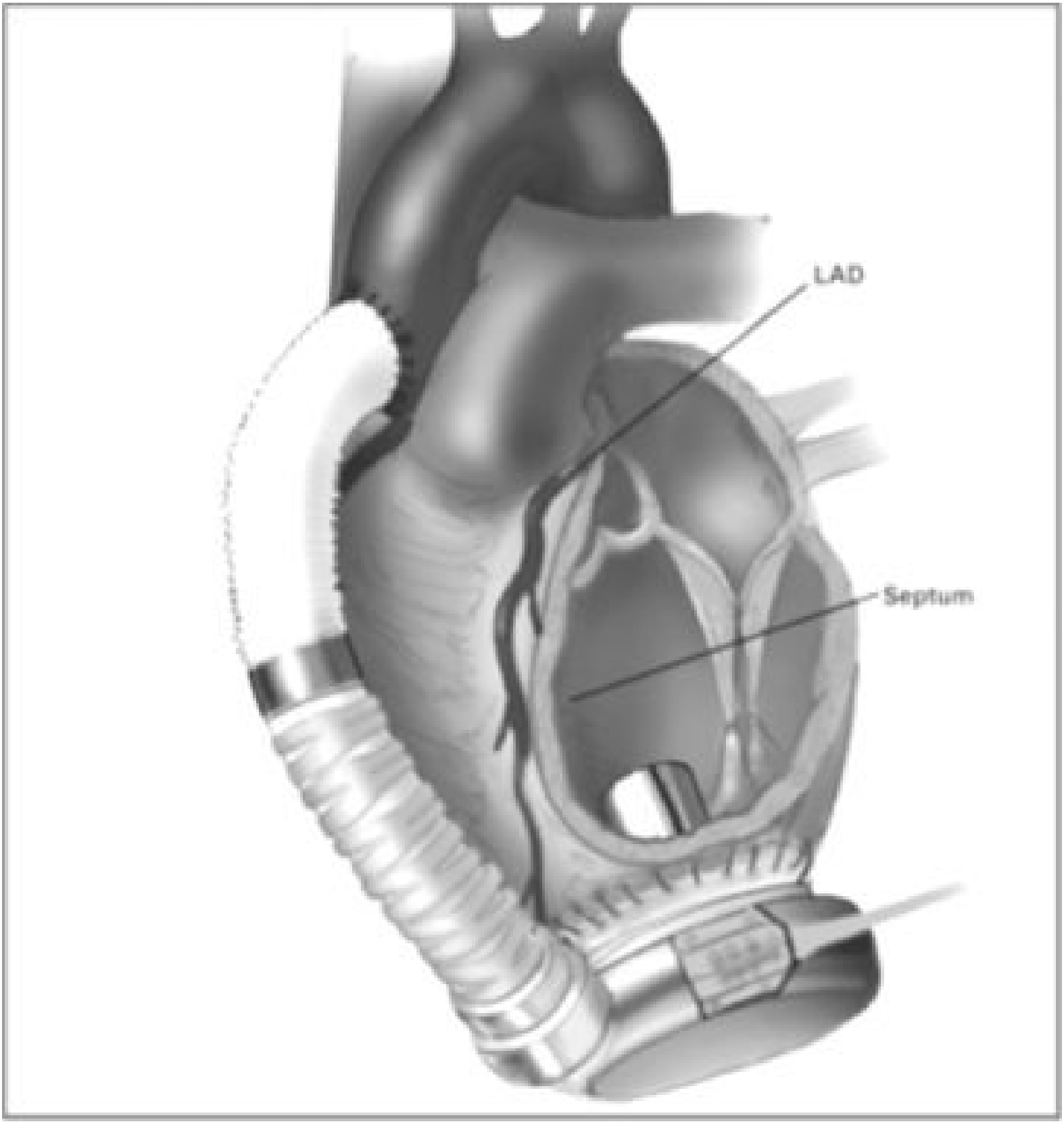

Figure 9.10 Diagram of HeartWare HVAD showing inflow drainage from left ventricular apex and outflow graft anastomosed to ascending aorta.

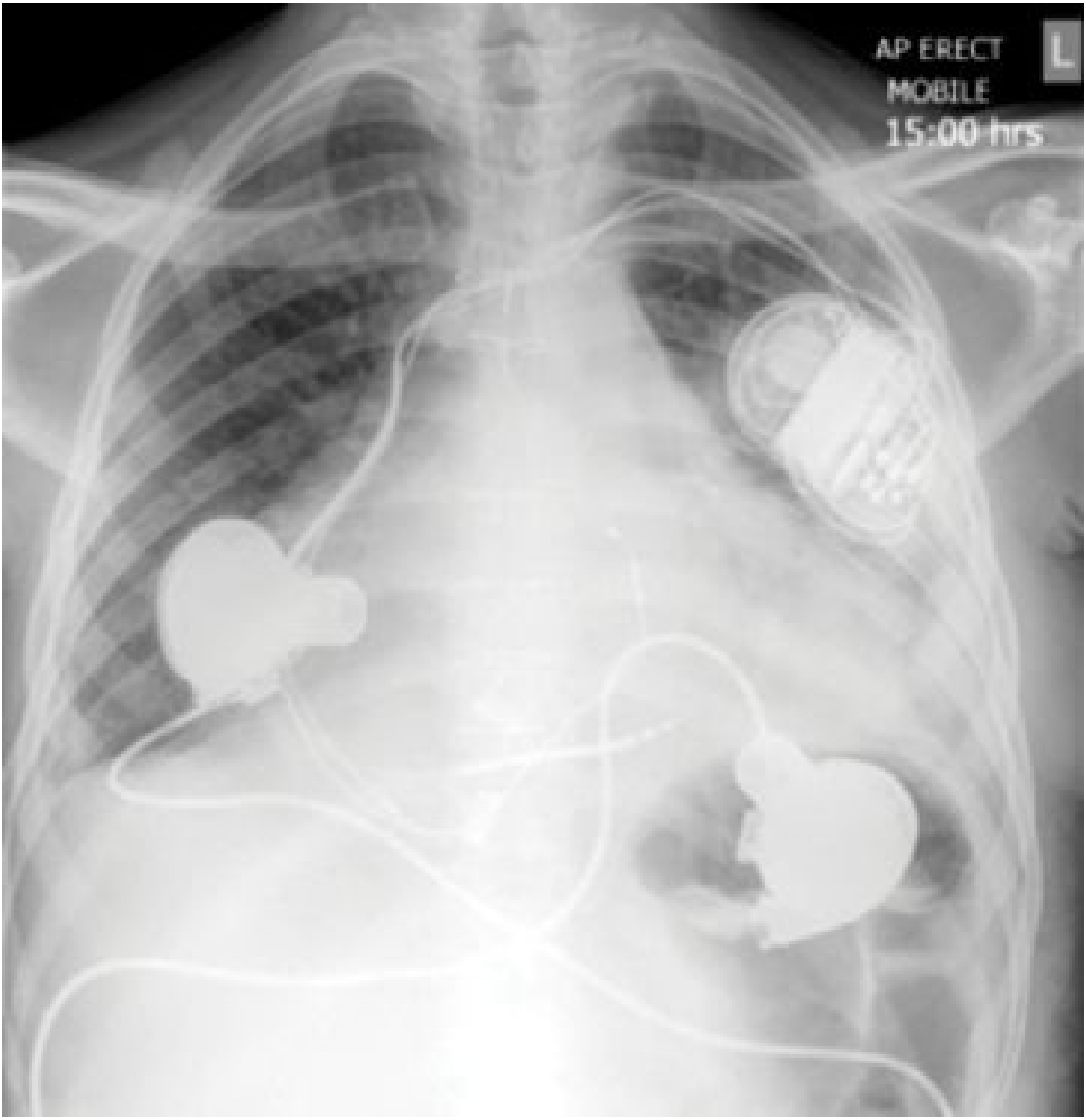

Figure 9.11 Chest X-ray of a patient implanted with two HeartWare HVADs in the left ventricle apex and the right atrium respectively as BiVAD support.

VAD patient management

Preoperative management

Patients requiring a VAD implant are probably among the sickest of patients to undergo cardiac surgery. They have severe heart failure and are either in impending or established end-organ failure. A low cardiac output state coupled with systemic venous congestion result in compromised organ perfusion. The kidneys become refractory to diuretic therapy and hepatic dysfunction manifests as coagulation abnormalities. The lungs are stiff from pulmonary congestion increasing the work of breathing and many patients are grossly fluid overloaded.

If the stability of the patient permits, a period of *preoperative* optimization in the ICU prior to VAD implant can be highly beneficial. Inotropic therapy should be rationalized to reduce the risk of arrhythmias and a period of IABP support helps augment end-organ perfusion. Low-dose vitamin K can normalize elevated prothrombin time, which in turn reduces the risk of perioperative hemorrhage.

Continuous veno-venous hemofiltration (CVVH) is the most expeditious way of reducing excessive intravascular volume and total body water content. Patients with chronic heart failure with CVP > 20 mmHg are often grossly edematous. The aim is to normalize the preload and bring the CVP towards 10–12 mmHg. In practice, CVVH can be used to achieve a negative balance of 600–1000 ml per hour until the target CVP is reached. In these patients, it is not uncommon to remove 7–10 l of fluid in the first 24 hours of CVVH. As the venous pressure begins to normalize, excessive fluid from the third spaces returns to the intravascular compartment and peripheral edema resolves. Finally, by normalizing an elevated preload, the over-stretched ventricles and atrio-ventricular valves are allowed to return to more physiological dimensions, often resulting in reductions in functional regurgitation of the atrio-ventricular valves.

The combined use of IABP and CVVH support in fluid overloaded patients in a low cardiac output state often results in augmentation of cardiac output and tissue oxygen delivery, as measured by improvements in mixed venous oxygen saturations.

Perioperative management

The perioperative strategy should be aimed at minimizing further insult to these sick patients during VAD implantation, targeting those areas that are known to result in serious morbidities and mortality. Perhaps the most unpredictable and dangerous complication following LVAD implantation is right ventricular failure. It is therefore imperative to pay particular attention to factors that might contribute to this complication (see Table 9.8). The other commonly encountered problem is early postoperative hemorrhage.

Table 9.8 Factors contributing to right ventricular failure following LVAD

Right ventricular dysfunction

- Right ventricular ischemia
- Deviation of the inter-ventricular septum to the left
- Air embolism into the right coronary artery
- Right ventricular volume overload

Functional regurgitation of tricuspid valve

Elevated pulmonary vascular resistance

- Atelectasis
- Metabolic acidosis
- Pulmonary vasospasm

Broad-spectrum prophylactic antibiotics and antifungal agents are adminstered at induction of anesthesia (see Table 9.9). Transesophageal echocardiography (TEE) is used to confirm aortic valve competence and exclude the presence of a patent foramen ovale or an atrial septal defect. If present, they require surgical closure at the time of VAD implant in order to prevent a right to left shunt following decompression of the left-sided chambers with an LVAD. If CPB is used, the lungs can be kept ventilated throughout the bypass period with the addition of nitric oxide at 5–10 parts per million (ppm) to minimize atelectasis and pulmonary vasoconstriction respectively. We would also advocate bypass to be normothermic, using hemofiltration (ultrafiltration) to maintain hemoglobin > 100 g/l and base excess within ± 2 mEq/l. The VAD cannulae are implanted into a beating heart, avoiding aortic cross-clamping and cardiac ischemia. The pericardial space is flooded with carbon dioxide to displace air, so that gas bubbles entrained into cardiac chambers can dissolve more readily. The right ventricle is supported with an infusion of dopamine at 5 μg/kg/minute. The heart rate is optimized with temporary pacing at 90–100 bpm. Systemic vascular resistance is maintained between 800 and 1000 dyne sec cm^{-5} using an infusion of vasopressin or with an α-agonist. TEE is used to confirm good positioning of the ventricular outflow cannula and to guide de-airing of the heart before finally attempting to wean from bypass. However, CPB is not always necessary for implanting the newer generations of LVADs. There is growing interest in off-pump LVAD implants with minimally invasive techniques via a small anterior thoracotomy and a mini-sternotomy incision. Early experience suggests that LVAD implant with such approaches can

be accomplished safely with negligible blood loss and has the potential to avoid CPB-related adverse events.

Table 9.9 Perioperative LVAD patient management

Broad-spectrum prophylactic antibiotics and antifungal agents
Transesophageal echocardiography • Confirm aortic valve competence • Exclude patent foramen ovale and ASD • Confirm de-airing • Check LVAD cannula position • Confirm decompression of LA and LV during LVAD support • Monitor right ventricular and tricuspid valve function when weaning from CPB

If using CPB:
• Normothermic CPB
• Continuous ventilation of the lungs with nitric oxide at 10 ppm
• Filtration on CPB and maintain
  • Hb > 100 g/l
  • Base excess ± 2 mEq/l
• No aortic cross-clamp during VAD cannulae implant
• Pericardial CO_2

Dopamine infusion at 5 μg/kg/minute or appropriate inotropic support for right ventricle
Vasopressin infusion for SVR

The perioperative management strategy is summarized in Table 9.9.

Weaning from CPB with VAD support

In order to wean from CPB, the heart is filled to a CVP of 8–10 mmHg. Once TEE confirms that the left-sided cardiac chambers are sufficiently filled, the LVAD is initiated at the lowest possible setting. As the LVAD flow rate increases, CPB is gradually reduced, taking care not to overdistend the right ventricle. It is sometimes necessary to supplement the LVAD output with CPB flows of 1 – 2 l/minute for the first 20–30 minutes before complete weaning. TEE is used to confirm satisfactory LVAD cannula position and left heart decompression. TEE is particularly useful in determining the adequacy of LV filling and monitoring the response of the RV as CPB support is weaned; collapse of the LV wall around the LVAD cannula, or septal distortion, are readily observed by TEE and indicate that the balance between the set LVAD flow rate and cardiac filling needs to be addressed and that RV function may need to be further optimized.

If LVAD flows of 2.2 l/minute/m^2 could not be achieved with CVP < 15 mmHg, adequacy of tissue perfusion should be assessed with mixed venous oxygen saturation measurement (SvO_2). Not infrequently, patients suffering from chronic heart failure are already accustomed to a low cardiac output state and a cardiac index of 1.8 l/minute/m^2 may be quite acceptable provided that the SvO_2 is satisfactory (> preimplant SvO_2). Otherwise, additional measures to augment LVAD flows have to be considered.

As mentioned earlier, the output of a LVAD is dependent upon adequate right ventricular function to deliver enough blood flow across the lungs to the left-sided cardiac chambers and LVAD inflow. If LVAD flows are inadequate and the left heart appears empty on TEE despite a full right heart, this is either due to right ventricular failure, elevated pulmonary artery resistance, or a combination of both. These can either be treated with low-dose infusions of adrenaline and a phosphodiesterase inhibitor or with inhaled iloprost, respectively. However, unless LVAD flows improve readily, CPB should be reinstituted early to avoid development of metabolic acidosis from prolonged systemic hypoperfusion. Under these circumstances, the early addition of a RVAD is advisable to provide biventricular support.

Postoperative management of VAD patients

At the end of the VAD implant procedure, careful hemostasis is crucial in order to minimize hemorrhage. An effective closed drainage system is essential in preventing mediastinal and pump pocket collections. Some surgeons close the pericardial sac or place a surgical membrane between the sternum and the mediastinum to facilitate subsequent re-sternotomy and re-entry. The percutaneous cannulae or driveline must be secured to minimize movement and trauma to the exit site(s). This is the best way to encourage tissue healing onto the driveline and minimize exit site infections.

Once returned to the intensive care unit, VAD patients must be closely monitored for early complications (see Table 9.10). Antibiotic prophylaxis is continued for 48 hours. Coagulation defects should be corrected without waiting for signs of significant bleeding. Right ventricular (RV) function often

remains precarious in the first few days following LVAD implantation. RV failure can be precipitated by excessive LVAD flow rate and/or elevated pulmonary vascular resistance (PVR). Therefore, it is prudent to limit the LVAD flow rate in the first few days in order to avoid overwhelming the RV or shifting the ventricular septum to the left and distorting RV dynamics. Furthermore, it is essential to avoid factors that may precipitate increases in PVR, e.g. hypoxia and acidosis.

Table 9.10 Common complications of VAD support

Perioperative hemorrhage
Right ventricular failure
Cerebral vascular events • Metabolic • Embolic • Hemorrhagic
Infection
Hemolysis
Thromoembolism
Mechanical pump failure

Anticoagulation is usually omitted in the first 24 hours and is only introduced when the patient has stopped bleeding (< 30 ml/hour for 3 consecutive hours). Most institutions commence with an infusion of unfractionated heparin and this is continued for 5–7 days before warfarin is commenced. The actual anticoagulation/antiplatelet regime is device specific and also unit specific.

Rising right atrial pressure coupled with a fall in pump flow rate are signs of tamponade or impending RV failure. The latter can be confirmed with TEE, which demonstrates full right-sided cardiac chambers with empty left-sided chambers. The atrial and ventricular septa are seen to bulge towards the left and these are often accompanied by tricuspid valve regurgitation. Under these circumstances, it is important not to increase the preload further with more fluid transfusions. Immediate treatment consists of a combination of inotropic support for the RV and pulmonary vasodilators. These may include adrenaline (up to 0.1 μg/kg/minute), enoximone (5 μg/kg/minute), nitric oxide (up to 20 parts per million), and/or

nebulized iloprost (9.9 µg 3 hourly). If the situation does not respond readily to these measures, early consideration should be given to the addition of a RVAD.

Long-term care

Long-term support of a VAD patient relies on a multidisciplinary team approach. Dieticians are involved from the preoperative period to ensure that nutritional status is optimized. Most patients would have been immobile for a long period of time and will require intensive postoperative physiotherapy to facilitate their physical rehabilitation. Anticoagulation therapy has to be closely monitored to reduce the risk of thromboembolic and hemorrhagic complications. The patient will need to be taught how to care for their driveline exit site to minimize the risk of infection. The patient will also need to be trained in all aspects of operating and maintaining their VAD system, allowing them the freedom and independence to leave the hospital and return to a normal life. Actuarial survival with LVAD support at 1 and 2 years are now 80% and 70% respectively (see Figure 9.2), and fast approaching post-transplant survivals. As a result, LVAD as destination therapy has become a good alternative for patients with severe heart failure who are not eligible for heart transplantation.

Self assessment

1. Intra-aortic balloon inflation during ventricular diastole:

A. Reduces left ventricular afterload

B. Augments coronary blood flow

C. Increases LV ejection

Answer: B

2. An RVAD returns blood to the:

A. Pulmonary artery

B. LV apex

C. Aorta

Answer: A

3. HeartWare HVAD is:

A. Pulsatile

B. Continuous flow

Answer: B

Suggested Further Reading

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Chapter 10

Deep hypothermic circulatory arrest

Joseph E. Arrowsmith and **Charles W. Hogue**

The majority of cardiac surgical procedures are accomplished using cardioplegia-induced cardiac arrest, with cardiopulmonary bypass (CPB) to maintain perfusion to other organs. However, in certain situations the nature of the surgical procedure or the pathology of the underlying condition necessitates complete cessation of blood flow. For example safe removal of large tumors encroaching on vascular structures requires provision of a bloodless field to enable dissection, or operations on the aorta itself may preclude application of a cross-clamp because of the pathological anatomy. Preservation of organ function during the period of total circulatory arrest can be achieved by reducing the core temperature of the body. The technique of core cooling combined with cessation of blood flow is termed “deep hypothermic circulatory arrest” (DHCA).

DHCA provides excellent operating conditions, albeit of limited duration, while ameliorating the major adverse consequences of organ ischemia. During DHCA the brain is the organ most vulnerable to injury, but may be protected if cooled to reduce its metabolic activity and hence oxygen requirements to a minimum before and during the period of arrest. Similarly, preservation of the function of other organs, less susceptible to ischemic damage, may be afforded by core cooling. DHCA owes its existence to two overlapping eras; a brief period in the early 1950s when hypothermia was used as the sole method for organ protection during surgery, and the current epoch of CPB heralded by Gibbon in 1953. Subsequent modifications to the basic technique have extended both the duration of “safe” circulatory arrest and the range of surgical indications.

Historical roots

In pioneering work during the 1940s and early 1950s, Bigelow demonstrated that a reduction in body temperature to 30°C increased the period of 'safe' cerebral ischemia from 3 to 10 minutes – time enough for expeditious intracardiac surgery. Using cold rubber blankets for surface cooling, Lewis was the first to successfully use hypothermic inflow occlusion in cardiac surgery. The use of an iced water bath for cooling proved more practical and was adopted with considerable success, notably in London by Sir Thomas Holmes Sellors. The types of procedures that could be undertaken during inflow occlusion, however, were limited to atrial septal defect repair, valvotomy, and valvectomy. Despite spectacular successes, the incidence of death and complications such as hypothermia-induced ventricular fibrillation, hemorrhage, myocardial failure, and neurological injury were high by today's standards.

Although CPB-induced hypothermia and DHCA in the management of aortic arch pathology had been described in the 1960s, it was not until the mid-1970s that the technique was demonstrated to be a relatively simple and safe approach for aortic arch surgery. DHCA, either alone or in combination with other strategies, has remained the mainstay of brain protection during aortic surgery. In addition to being used to facilitate pulmonary vascular surgery and the repair of congenital cardiac lesions, DHCA is also used in neurosurgery and urological surgery (Table 10.1).

Table 10.1 Applications of deep hypothermic circulatory arrest

Cardiothoracic surgery	Thoracic aortic surgery
	Pulmonary (thrombo)endarterectomy
	Complex pediatric reconstructions
Neurosurgery	Basilar artery aneurysm surgery
	Cerebral tumor resection
	Intracranial arteriovenous malformation resection
Other	Caval mass resection (e.g. renal cell carcinoma)
	Resection of extraperitoneal tumors with atriocaval extension

Pathophysiology of hypothermia

In animals which maintain body temperature in a tight range, homeotherms, thermoregulation occurs as a result of the dynamic balance between heat production (thermogenesis) and heat loss. Stimulation of cutaneous cold receptors and temperature-sensitive neurons in the hypothalamus activates sympathetic autonomic (vasoconstriction), endocrine, adaptive behavioral, and extrapyramidal (shivering) mechanisms to maintain core temperature. Hypothermia – defined as a core temperature < 35°C – occurs when heat losses overwhelm thermoregulatory mechanisms (e.g. during cold immersion) or when thermoregulation is impaired by pathological conditions (e.g. stroke, trauma, endocrinopathy, sepsis, autonomic neuropathy, uremia) or drugs (e.g. anesthetic agents, barbiturates, benzodiazepines, phenothiazines, ethanol). Thanks to the early work of Currie and Rosomoff, and experience gained from managing accidental hypothermia, the physiological effects of hypothermia are well known (Table 10.2). An understanding of both normal physiological and pathological responses is essential when using deliberate or therapeutic hypothermia.

Table 10.2 The pathophysiology of hypothermia

	Mild (33–35°C)	**Moderate(28–33°C)**	**Severe (< 28°C)**
Neurological	Confusion Amnesia Apathy Impaired judgment	Depressed consciousness	Pupillary dilatation Coma Loss of autoregulation
Neuromuscular	Shivering Ataxia Dysarthria	Muscle & joint stiffening	Muscle rigor
Cardiovascular	Tachycardia Vasoconstriction Increased BP, CO	Bradycardia Increased SVR Decreased cardiac output ECG changes: J (Osborn) waves QRS broadening ST elevation/depression T-wave inversion	Severe bradycardia Asystole Ventricular fibrillation

		AV block QT prolongation	
Respiratory	Tachypnea Left-shift HbO_2 curve	Bradypnea Bronchospasm Bronchorrhea	Lactic acidosis Right-shift HbO_2 curve
Renal/metabolic	ADH resistance Cold-induced diuresis	Reduced glomerular filtration rate (GFR) Reduced H^+ & glucose reabsorption	Metabolic acidosis
Hematology	Increased blood viscosity & hemoconcentration (2% increase in hemacrit/°C) Coagulopathy – inhibition of intrinsic/extrinsic pathway enzymes, platelet activation, thrombocytopenia (liver sequestration) Leukocyte depletion, impaired neutrophil function & bacterial phagocytosis		
Gastrointestinal		Reduced motility Acute pancreatitis	Ileus Gastric ulcers Hepatic dysfunction

Practical considerations

Preoperative assessment is similar to that for any other major cardiac surgical procedure. Because DHCA is commonly used in emergency, lifesaving procedures it may not be possible to undertake the usual battery of "routine" preoperative investigations. The presence of significant comorbidities (e.g. coronary artery disease, cerebrovascular disease, renal insufficiency, diabetes mellitus) should be anticipated on the basis of the clinical history and physical examination.

Anesthesia

Standard arterial, central venous, and peripheral venous access is required in all cases. In anticipation of division of the innominate vein to improve surgical access, venous cannulae should be sited in the right

arm or in a femoral vein. Cannulation of the right radial artery and a femoral artery permits arterial pressure monitoring both proximal and distal to the aortic arch. Cannulation of a femoral artery also serves as an anatomical marker for the surgeon should an intra-aortic balloon pump be required on separation from CPB. Whilst not considered mandatory, pulmonary artery catheterization may aid management immediately post-CPB and in the early postoperative period. Where available, and in the absence of contraindications, transesophageal echocardiography (TEE) may be used to assess aortic valvular function, monitor cardiac function, and assist with cardiac de-airing.

Accurate temperature monitoring – at two or more anatomical sites – is crucial. Nasopharyngeal or tympanic membrane temperature monitoring provides an indication of brain temperature, whereas rectal or bladder temperature monitoring provides an indication of body core temperature. While these devices are accurate at *steady-state* it should be borne in mind that, during both cooling and warming, thermal gradients may be generated in tissues and monitored temperature may lag behind actual tissue temperature by 2–5°C.

The choice of anesthetic drugs is largely a matter of personal and institutional preference. In theory, using propofol and opioid-based anesthesia in preference to volatile anesthetic agents, reduces cerebral metabolism without uncoupling flow-metabolism relationships. The impact of hypothermia on drug metabolism and elimination should be considered and drug infusion rates adjusted accordingly. In particular, it should be borne in mind that the blood solubility of volatile agents increases as temperature falls, increasing the time required to achieve equilibrium at the effect-site.

The long duration of surgery with DHCA mandates careful attention to the prevention of pressure sores and inadvertent damage to the eyes, nerve plexuses, peripheral nerves, and pressure points. Cannulation sites, three-way taps, monitoring lines, the endotracheal tube connector, electrical monitoring cables, and the TEE probe should be padded to prevent pressure necrosis of the skin.

All measures should be taken to facilitate re-warming and prevent “after-drop” hypothermia following the termination of CPB. The use of a heated mattress, sterile forced-air blanket, and intravenous fluid warmer should be considered in all cases.

Extracorporeal circulation

The nature of DHCA requires modifications to be made to the standard extracorporeal circuit:

- Infusion bags for the storage of heparinized blood during hemodilution (see below).
- Use of a centrifugal pump – in preference to a roller pump – to reduce damage to the cellular components of the circulation and reduce hemolysis.

- Incorporation of a hemofilter to permit hemoconcentration during re-warming.
- Incorporation of a leukocyte-depleting arterial line filter (see below).
- Selection of a cardiotomy reservoir of sufficient capacity to accommodate the circulating volume during exsanguination immediately before DHCA. An additional reservoir may be required when managing morbidly obese patients.
- Arteriovenous bypass and accessory arterial lines – to permit retrograde or selective antegrade cerebral perfusion (see below).
- An efficient heat exchanger. Assuming that human tissue has an average specific heat capacity of 3.5 kJ kg^{-1} $°C^{-1}$ (0.83 kcal kg^{-1} $°C^{-1}$), the energy required to warm a 70-kg adult from 20°C to 37°C is at least 4.2 MJ (1000 kcal) – the energy required to raise the temperature of 12.5 l of water from 20°C to 100°C.
- Consideration of the use of heparin-bonded circuits. This is advocated in cases requiring prolonged CPB, despite conclusive evidence of benefit.

Surgical considerations

In some cases, such as acute "Type A" aortic dissection, femoral, innominate or right axillary, arterial cannulation may initially be necessary together with femoral venous cannulation. Femoro-femoral or axillo-femoral CPB permits systemic cooling prior to sternotomy and affords a degree of organ protection should chest opening be accompanied by inadvertent damage to the aorta or heart and exsanguination. After completion of the aortic repair, placement of the arterial line directly into the prosthetic graft restores anterograde flow. Cannulation of the mid or distal aortic arch may be required in cases of degenerative aortic aneurysm to reduce the risk of atheroembolism associated with retrograde flow via femoral arterial cannulation.

The choice of venous drainage site and cannula is largely dictated by surgical preference and the degree of surgical access required. For example: bicaval cannulation is required if retrograde cerebral perfusion (RCP) is to be used with reversal of blood flow in the superior vena cava. If anterograde cerebral perfusion is to be used with selective arterial cannulation of the carotid arterial circulation then adequate cerebral venous drainage must be ensured, again using bicaval cannulation, to optimize cerebral perfusion pressure and prevent cerebral edema. Removal of a renal tumor from the inferior vena cava requires the use of a right atrial basket, in preference to a caval or two-stage cannula, to permit full visualization of the cava and to prevent dislodged fragments of tumor from becoming impacted in the pulmonary circulation.

The use of DHCA during surgery of the distal aorta via left thoractomy presents several problems. Access to the proximal aorta is limited and femoral arterial cannulation may be required initially. Access to the right atrium typically requires an extensive thoracotomy that traverses the sternum. Alternatively, venous drainage may be achieved using pulmonary artery cannulation or a long femoral cannula advanced into the right atrium.

Cardiopulmonary bypass: cooling

Following anticoagulation, CPB is instituted with a constant flow rate of 2.4 l min^{-1} m^{-2} and cooling immediately commenced with a cooling unit to blood temperature gradient of < 10°C. Vasoconstrictors (e.g. phenylephrine, metaraminol) or vasodilators (e.g. glyceryl trinitrate, sodium nitroprusside or isoflurane) are used to ensure a mean arterial pressure (MAP) of 50–60 mmHg. As much of the planned procedure as possible is carried out *during* the cooling phase *prior* to DHCA in order to minimize the duration of circulatory arrest.

Cooling continues until brain (e.g. nasopharyngeal) and core body (e.g. bladder) temperatures have equilibrated at the target temperature for 10–15 minutes. In some centers continuous monitoring of the EEG, evoked potentials or jugular venous saturation is used as a guide to the adequacy of cerebral cooling.

Circulatory arrest

As stated earlier, every effort should be made to reduce the period of ischemia. For this reason preparation of any prosthetic grafts and as much surgical dissection as possible should be undertaken during the period of cooling. The CPB pump is then stopped, intravenous infusions stopped and the patient partially exsanguinated into the venous reservoir. Once isolated from the patient, blood within the extracorporeal circuit is recirculated via a connection between the arterial and venous lines in order to prevent stagnation and clotting. The surgical repair proceeds with heed to the duration of circulatory arrest.

Safe duration of DHCA

Determining the duration of DHCA that any particular patient will tolerate without sustaining disabling neurological injury remains, at best, an inexact science. Current practice makes it difficult to separate the neurological risks of the prolonged CPB, reperfusion and re-warming, all unavoidable consequences of DHCA, from those of DHCA alone. The incidence of neurological injury rises sharply when DHCA

exceeds 40 minutes. On the basis of animal experimentation and clinical observation, unmodified DHCA is typically limited to no more than 60 minutes at 18°C. Frustratingly, while some patients appear to tolerate DHCA > 60 minutes without apparent injury, others sustain major brain injury after < 20 minutes DHCA (see Figure 10.1).

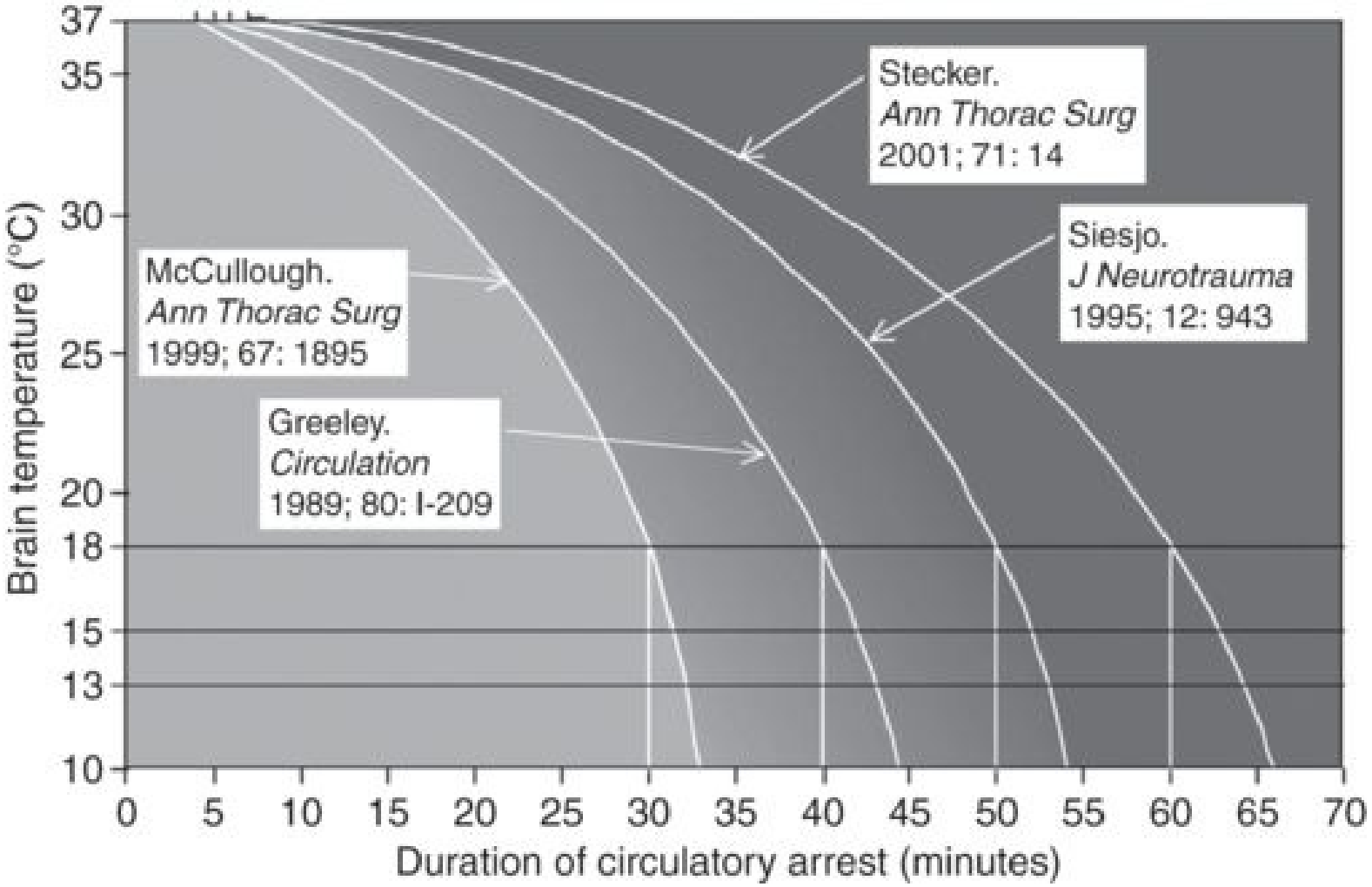

Figure 10.1 The effect of brain temperature on reported safe duration of deep hypothermic circulatory arrest.

Cardiopulmonary bypass: re-warming

Re-warming should be instituted following a planned rate of rise of core temperature. Excessively rapid re-warming, accompanied by a rise in cerebral arteriovenous O_2 difference, is known to worsen neurological outcome. In patients undergoing coronary artery bypass surgery, maintaining a temperature gradient of < 2°C between inflow temperature and brain (nasopharyngeal) temperature has been shown to improve cognitive outcome. Because hyperthermia is known to exacerbate neuronal injury, inflow temperature should not exceed 37°C and CPB terminated when core body temperature reaches 35.5–36.5°C. A significant “after-drop” is inevitable and patients are commonly admitted to the intensive care

unit with temperatures as low as 32°C. Using a slow rate of re-warming with adequate time for even distribution of heat between core and peripheral tissues helps to reduce the extent of this after-drop.

During the period of re-warming attention should be given to the correction of metabolic abnormalities, particularly the metabolic acidosis that inevitably accompanies reperfusion following circulatory arrest. Correction of acid–base balance may require the titrated administration of sodium bicarbonate or use of hemofiltration (ultrafiltration).

Hemostasis

Prolonged CPB and hypothermia produce a coagulopathy. Hemostasis is facilitated by meticulous surgery, the use of predonated autologous blood, and administration of donor blood components under the guidance of laboratory tests of coagulation and thromboelastography. Despite safety concerns, antifibrinolytic agents (e.g. tranexamic acid, ε aminocaproic acid) and aprotinin have been shown to be efficacious in aortic arch surgery with DHCA. Recently published and widely publicized studies reporting a high incidence of adverse effects associated with aprotinin use in *adult* patients undergoing coronary revascularization and high-risk cardiac surgery have, however, prompted withdrawal of the drug.

Neuroprotection during DHCA

Although hypothermia is the principal neuroprotectant during DHCA, additional strategies may be employed to reduce the likelihood of neurological injury (Table 10.3). These include: acid–base management strategy, hemodilution, leukodepletion, and glycemic control. Surgical maneuvers, such as intermittent cerebral perfusion, selective antegrade cerebral perfusion (SACP), and retrograde cerebral perfusion (RCP), may also be used to both protect the brain and extend the operating time available to the surgeon.

Table 10.3 Neuroprotectant strategies during DHCA

Anesthesia	Glycemic control
	External cranial cooling
	Neurological monitoring
	Cerebrospinal fluid drainage
	Pharmacological neuroprotection

Perfusion	Acid–base management strategy
	Hemodilution
	Leukocyte depletion
Surgical	Intermittent cerebral perfusion
	Selective antegrade cerebral perfusion (SACP)
	Retrograde cerebral perfusion (RCP)

Hypothermia

Cerebral metabolism decreases by 6–7% for every 1°C fall in temperature below 37°C, with consciousness and autoregulation being lost at 30°C and 25°C respectively. At temperatures < 20°C, ischemic tolerance is around ten times that at normothermia. While some authors maintain that the electroencephalograph (EEG) becomes isoelectric at this temperature, it is evident that a significant number of patients have measurable EEG activity at < 18°C. In addition to its effects on the metabolic rate, hypothermia appears to reduce lipid peroxidation, neuronal calcium entry, membrane depolarization, the production of superoxide anions, and the release of excitotoxic amino acids.

In many centers, placing ice packs or an ice-cold water jacket around the head after induction of anesthesia is used to augment cerebral cooling. The extent to which extracranial cooling influences brain temperature and neurological outcome in humans remains undocumented. Use of the procedure is justified on the basis of an absence of significant adverse effects and limited evidence derived from animal experimentation (see Figure 10.2).

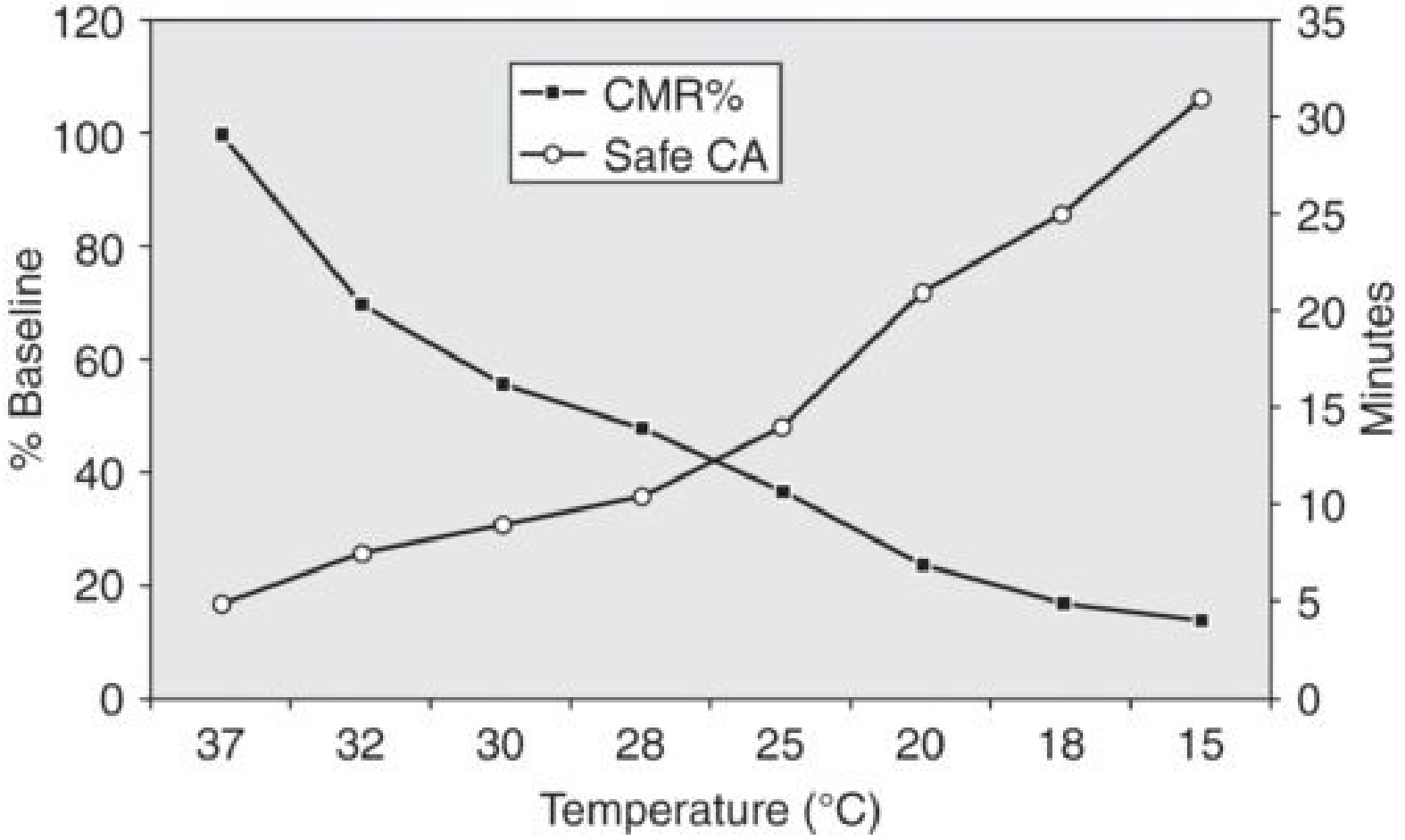

Figure 10.2 The effect of temperature on cerebral metabolic rate (CMR%) and duration of safe circulatory arrest (CA).

Data derived from McCullough *et al*. *Ann Thorac Surg* 1999;67(6):1895–9 and Kern *et al*. *Ann Thorac Surg* 1993;56(6):1366–72.

Hemodilution

The combination of vasoconstriction, increased plasma viscosity, and reduced erythrocyte plasticity secondary to hypothermia leads to impairment of the microcirculation and ischemia. Progressive hemodilution during hypothermic CPB, typically to a hematocrit of 0.18–0.20, is thought to partially alleviate this phenomenon. In some centers, a degree of normovolemic hemodilution is undertaken prior to the onset of CPB. The optimal hematocrit for a particular individual at a specific temperature remains unclear. Gross anemia (i.e. hematocrit < 0.10) may, however, result in inadequate oxygen delivery to tissues, particularly during re-warming.

Acid–base management

Hypothermia increases the solubility of gases (e.g. N_2, O_2, and CO_2) and volatile anesthetic agents in blood. While the total content of any particular gas in a blood sample remains constant, hypothermia shifts

the equilibrium between dissolved and undissolved gas, leading to an increase in the former, which in turn reduces the partial pressure of the gas. When analyzed at 37°C, a “normal” blood sample taken during hypothermia reveals ‘normal’ results, whereas correction of these results for body temperature reveals reduced PaO_2 and $PaCO_2$, and alkalosis. Maintaining $PaCO_2$ within the normal range on the basis of analysis at 37 °C is termed *α-stat* management, whereas maintaining a normal $PaCO_2$ (and pH) on the basis of “temperature-corrected” analysis is termed *pH-stat* management. This is discussed further in Chapter 6.

When cerebral perfusion pressure (CPP), PaO_2, and $PaCO_2$ are maintained within the physiological range, autoregulation couples cerebral blood flow (CBF) to cerebral metabolic rate ($CMRO_2$). Cerebral autoregulation is obtunded by profound hypothermia and hypercarbia. At $PaCO_2$ > 10 kPa the classical autoregulation “plateau” is abolished and CBF becomes ‘pressure-passive’ – dictated solely by CPP. Alpha-stat management preserves cerebral autoregulation and thus CBF decreases during hypothermia. In contrast pH-stat management results in cerebral hyperperfusion, which in turn increases O_2 delivery and ensures more rapid and homogeneous brain cooling, albeit at the expense of increased cerebral microembolic load.

In the piglet model of DHCA, pH-stat management improves neurological outcome. In human neonates undergoing DHCA for repair of congenital heart defects, pH-stat management prior to circulatory arrest appears to be associated with fewer complications than alpha-stat management and better developmental outcome. In adults, however, the superiority of one strategy over another in the setting of DHCA remains unproven. Currently α-stat management is used in most adult centers – presumably on the basis of superior cognitive outcome following hypothermic CPB.

Retrograde cerebral perfusion (RCP)

Reversing the direction of blood flow in the superior vena cava (SVC) has been advocated as a means of improving brain protection during DHCA and extended the period of “safe” DHCA. Following the onset of CPB, the cavae are snared and arterial blood directed into the SVC via an arteriovenous shunt constructed in the CPB circuit. Pump flows of 150–700 ml min^{-1} are advocated to maintain a mean perfusion pressure of ~ 25 mmHg. The putative advantages of RCP include continuous cerebral cooling, cerebral substrate delivery, and expulsion of air, particulates, and toxic metabolites. The absence of blood flow detectable by transcranial Doppler (TCD) sonography in the middle cerebral arteries of a small, but significant, number of patients subjected to RCP may explain conflicting evidence of efficacy. In addition, significant extracranial shunting via the external jugular veins may occur during RCP.

Interestingly, the use of multi-modal neurological monitoring to guide RCP delivery at pressures as high as 40 mmHg, considered by many surgeons to be harmful, has been shown to be safe.

Antegrade cerebral perfusion (ACP)

Selective hypothermic brain perfusion permits surgery to be conducted at lesser degrees of systemic hypothermia (e.g. 22–25°C); reducing the time required for cooling and re-warming, and thus the total duration of CPB. ACP typically requires greater mobilization of the epiaortic vessels and division of the innominate vein. Following the onset of circulatory arrest, the aortic arch is opened and balloon-tipped arterial cannulae advanced into the innominate and left carotid artery ostia (see Figure 10.3). The left subclavian artery is clamped and arterial flow commenced at 10–20 ml/kg to maintain a perfusion pressure – measured in the right radial artery – of 50–70 mmHg. Alternative approaches include cannulation of the right subclavian artery and hemicerebral perfusion via the innominate artery alone. The technique provides more “physiological” cerebral perfusion but has the disadvantage of increasing operative time and carries the risk of atheroembolism and microembolism. In a recently published series of 501 consecutive patients undergoing aortic arch surgery with DHCA (25°C) and ACP (14°C), Khaladj et al. reported an overall mortality of 11.6% and permanent neurological deficit rate of 9.6%.

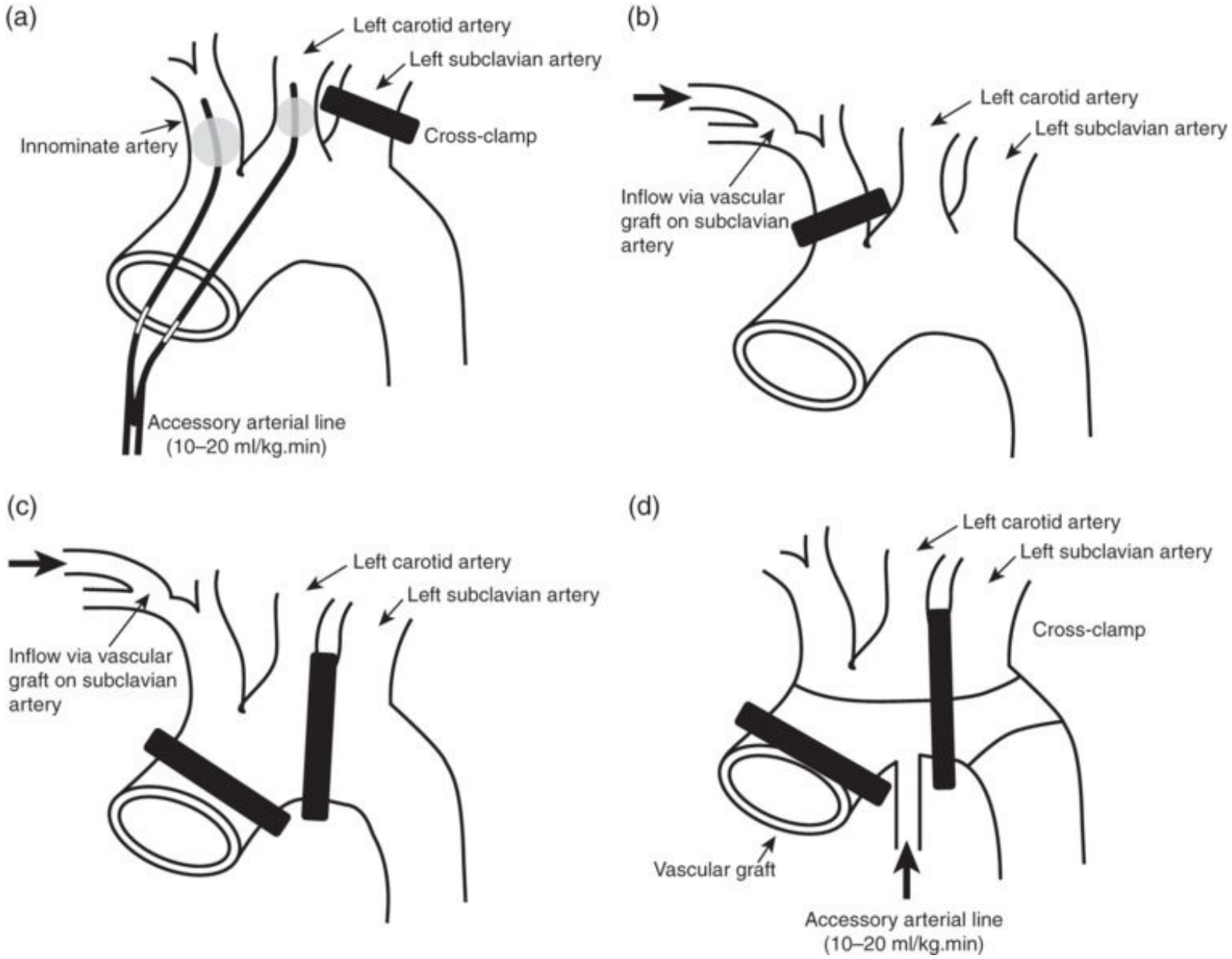

Figure 10.3 Examples of selective antegrade cerebral perfusion techniques. (a) Direct cannulation of the innominate and left carotid arteries. (b) Hemicranial perfusion via a left subclavian artery graft. (c) Bilateral cranial perfusion via a left subclavian artery graft. (d) Bilateral cranial perfusion via a sidearm on vascular graft.

In some instances intermittent, rather than continuous, ACP is considered more practicable or expeditious. In a piglet model of DHCA, one minute of reperfusion for every 15 minutes of DHCA has been found to be sufficient to provide normal metabolic and microscopic cerebral recovery.

In a retrospective, two-center study of patients undergoing “non-complex” aortic arch reconstruction, Milewski et al. compared the efficacy of RCP and ACP. Patients undergoing DHCA with RCP in Philadelphia, USA (n=682) were compared with patients undergoing moderate hypothermic circulatory arrest (MHCA) with bilateral ACP in Bologna, Italy (n=94). As expected, cerebral ischemic times were significantly longer in the DHCA/RCP group and visceral ischemic times significantly longer in the MHCA/ACP group. There were no significant differences in either the primary (death, neurological

deficit) or secondary (new renal failure, acute myocardial infarction, prolonged mechanical ventilation, reoperation for bleeding) outcomes. The authors concluded that both techniques afforded excellent organ protection for aortic reconstruction of < 45 minutes' duration.

Leukocyte depletion

The use of leukocyte-depleting arterial line filters is reported to moderate the systemic inflammatory response to CPB, reduce reperfusion injury, and reduce postoperative infective complications. Evidence for cerebral protection by leukocyte depletion is lacking in humans, and animal experimentation has yielded conflicting results. Interestingly, perfusate modification in a piglet model of DHCA has been shown to improve neurological outcome. Furthermore, the removal of leukocytes and calcium, and the addition of magnesium, O_2, CO_2, mannitol, and a Na^+/H^+ exchange inhibitor to the CPB prime during circulatory arrest were found to improve myocardial function.

Glycemic control

Insulin resistance and hyperglycemia are common consequences of cardiac surgery and hypothermia. In animal models, hyperglycemia worsens outcome after cerebral infarction. While tight glycemic control during cardiac surgery appears to reduce mortality and infective complications, any neuroprotective effect remains unproven and carries the risk of inadvertent hypoglycemia and hypokalemia.

Pharmacological neuroprotection

At present no drug is specifically licensed for neuroprotection during cardiac surgery. Over the last four decades a wide variety of compounds, many with very promising preclinical pharmacological profiles, have been evaluated in the setting of cardiac surgery. These include anesthetic agents (barbiturates, propofol, volatile agents), calcium channel blockers, immunomodulators (corticosteroids, ciclosporin), amino acid receptor antagonists (magnesium, remacemide), glutamate-release inhibitors (lignocaine, fosphenytoin), antiproteases (aprotinin, nafamostat), and free radical scavengers (mannitol, desferrioxamine, allopurinol).

In many centers thiopental 15–30 mg/kg continues to be administered before DHCA despite the absence of any objective evidence of efficacy. The widely held belief that thiopental reduces neurological injury in conventional cardiac surgery is not borne out by the evidence, although there is some suggestion that it reduces overall mortality. In a recent review of 11 diverse "best evidence" publications, Al-

Hashimi et al. concluded that thiopental was indeed neuroprotective in the setting of DHCA and that timing of administration was “crucial.”

Animal evidence suggests that the administration of corticosteroids (e.g. methylprednisolone 15 mg/kg) prior to DHCA affords a degree of neuroprotection. The recent demonstration of neuroprotection by sodium valproate in a canine model of DHCA has prompted a randomized trial in humans.

Spinal cord protection

Surgery involving the descending thoracic aorta may interrupt blood flow to the spinal cord via the anterior spinal artery (artery of Adamkiewicz) and cause paraplegia. Although drainage of cerebrospinal fluid (CSF) has long been proposed as a means of improving spinal cord perfusion, debate continues as to its efficacy. One early study suggested that postoperative hypotension, rather than avoidance of CSF drainage, was the only predictor of paraplegia. More recently, however, CSF drainage has been shown to reduce the incidence of paraplegia or paraparesis by 80% in a randomized study of 145 patients undergoing thoracoabdominal aortic aneurysm repair. An alternative approach to spinal cord protection is the continuous infusion of ice-cold saline into the epidural space. Despite reports of efficacy the technique has not been widely adopted.

Neurological monitoring

Until recently, the use of monitors of cerebral substrate delivery or neurological function (see Table 10.4) has largely been confined to specialist centers, researchers, and enthusiasts. It goes without saying that a monitor must prompt a corrective intervention *before* the onset of irreversible neurological injury to be of any use. Cost and lack of level 1 A evidence of efficacy means neurological monitoring has yet to be universally adopted as “standard of care.”

Table 10.4 Neurological monitoring

Clinical	Arterial pressure
	Central venous pressure
	CPB pump flow rate
	Arterial oxygen saturation
	Temperature
	Hemoglobin concentration

	Pupil size
	Arterial Pco_2
Substrate delivery	Transcranial Doppler sonography
	Near infrared spectroscopy
	Jugular venous oxygen saturation
Cerebral activity	Electroencephalography
	Somatosensory evoked potentials
	Auditory evoked potentials
	Motor evoked potentials
Other	Epiaortic ultrasound
	Transesophageal echocardiography

Substrate delivery

Fiberoptic jugular venous oxygen saturation (Sjo_2) monitoring provides a continuous measure of the global balance between cerebral oxygen supply and demand. The normal range for Sjo_2 is quoted to be 55–75%, but may be as high as 85% in some normal individuals. Sjo_2 < 50% is regarded as being indicative of inadequate cerebral oxygenation. A normal or near-normal Sjo_2 value may, however, mask regional cerebral ischemia; thus Sjo_2 monitoring has high specificity but low sensitivity for the detection of cerebral ischemia. Sjo_2 monitoring has been used to assess the adequacy of cerebral cooling prior to DHCA. Low Sjo_2 prior to the onset of DHCA is associated with adverse neurological outcome. Sjo_2 monitoring may also be used to monitor the adequacy of SACP.

In contrast to measuring cerebral Sao_2 and Sjo_2, which provide a measure of global cerebral oxygen delivery and consumption, cerebral near infrared spectroscopy (NIRS) allows measurement of a region of tissue containing arteries, capillaries. and (predominantly) veins (see Figure 10.4). Despite a lack of evidence of efficacy in adult cardiac surgery, NIRS is widely used in DHCA to assess cerebral oxygenation during cooling, DHCA, and re-warming.

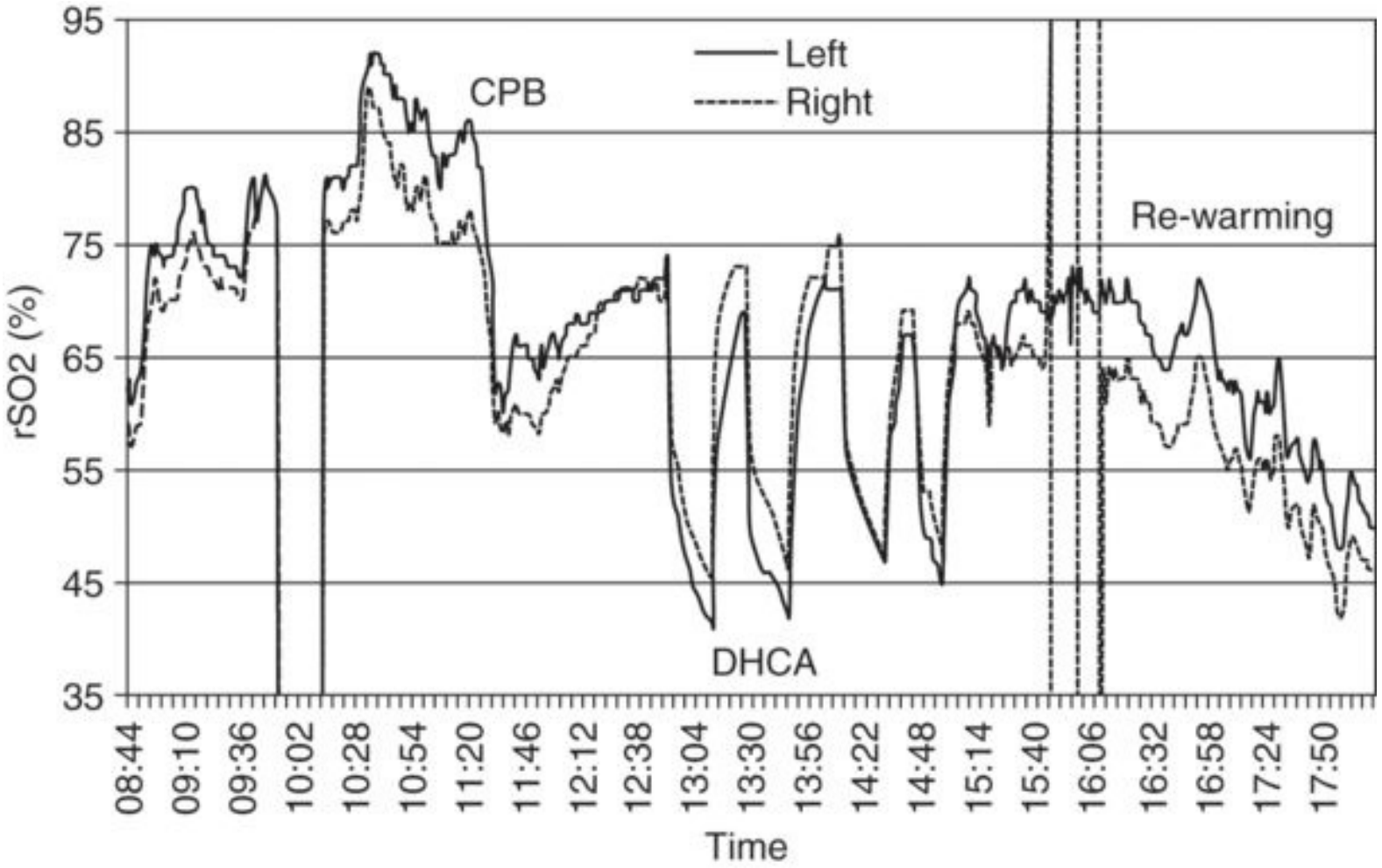

Figure 10.4 Near infrared spectroscopy monitoring during pulmonary thromboendarterectomy. Significant cerebral desaturation is seen at the onset of CPB, during four periods of deep hypothermic circulatory arrest (DHCA), and during re-warming.

Transcranial Doppler (TCD) sonography has been mainly used as a surrogate measure of CBF and a means for detecting microemboli. In the setting of DHCA it has been used to monitor the adequacy of SACP, and to assess CBF autoregulation after surgery.

Neurological function

Qualitative and quantitative electroencephalography (EEG) has been used in cardiac surgery for over five decades and has long been considered the "gold standard" for the detection of cerebral ischemia. Unfortunately a consistent and reproducible EEG descriptor of reversible cerebral injury has remained frustratingly elusive. Although a sensitive indicator of neuronal injury, its use is complicated by the fact that hypothermia and virtually every anesthetic drug have profound influences on neuroelectrophysiology. Below 28°C there is progressive slowing until the EEG becomes isoelectric – a phenomenon used to assess the adequacy of cooling prior to DHCA. The temperature at which EEG activity is lost is subject

to considerable inter-patient variation and is typically *higher* during the cooling phase than during re-warming.

Evoked potential monitoring encompasses a number of techniques that measure the response of the nervous system to external stimulation. Sensory evoked potential monitoring techniques measure the cortical or brainstem responses to auditory, visual, spinal cord or somatic stimulation. Motor evoked potential (MEP) monitoring techniques measure the spinal cord or compound muscle action potential response to cortical stimulation. Abolition of specific components of somatosensory evoked potentials (SSEPs) and brainstem auditory evoked potentials (BAEPs) have been used as a measure of cooling prior to DHCA.

Postoperative care

Postoperative care is similar to that for any patient undergoing cardiac surgery. Every effort should be made to prevent secondary brain injury; hyperthermia, hypoxemia, hypotension, and hypoperfusion should be aggressively treated. Even mild degrees of hyperthermia, a common occurrence after cardiac surgery, have been shown to be detrimental after DHCA.

Outcome

The risks associated with DHCA are largely determined by the pathology being treated, the duration of CPB, the presence of significant comorbidities, and the urgency of surgery.

Neurological

Surgery with DHCA carries a finite risk of neurological injury. The type and pattern of neurological injury seen in neonates after DHCA appears to differ from that seen in older children and adults. In neonates the predominant lesion is neuronal apoptosis in the hippocampus and the gray matter of the cerebral cortex. Seizures and choreoathetosis are by far the most common clinical manifestations of neurological injury. By contrast, selective neuronal necrosis and infarction (i.e. stroke) in the cerebellum, striatum, and neocortex are the predominant lesions in non-neonates.

In a study of 656 patients undergoing DHCA, Svensson et al. reported an overall stroke rate of 7%. Univariate predictors of stroke included advanced age, a history of cerebrovascular disease, DHCA duration, CPB duration, and concurrent descending thoracic aortic repair. In a study of 200 patients

operated upon using DHCA between 1985 and 1992, Ergin et al. reported an in-hospital mortality of 15% and stroke rate of 11%. Age > 60 years, emergency surgery, new neurological symptoms at presentation, and permanent postoperative neurological deficits were found to be significant predictors of operative mortality. Stroke was more common in older patients and when the aorta was found to contain thrombus or atheroma.

The impact of DHCA and cerebral perfusion strategies on postoperative cognitive function has been examined in two recently published prospective studies. In a study of 74 patients undergoing pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension, the Papworth group found that cognitive outcomes in patients randomized to DHCA plus ACP were no different from those randomized to DHCA alone. Similarly, in a study of patients undergoing either ascending aortic surgery without DHCA (n=33) or aortic arch surgery with DHCA (n=29), the Yale University group reported that overall cognitive function was preserved and similar in both groups. The authors concluded that cumulative DHCA duration < 40 minutes effectively preserves cognitive function.

Non-neurological

In a retrospective study of 116 patients undergoing thoracic aortic surgery with moderately hypothermic CPB (MHCPB 28°C) or DHCA (15°C), Harrington et al. reported that duration of CPB, rather than degree of hypothermia, was the primary predictor of postoperative hemorrhagic complications. Profound hypothermia, *per se*, did not appear to be an independent risk factor for renal impairment, early pulmonary dysfunction or prolonged intensive care unit stay.

Self assessment

1. Deep hypothermic circulatory arrest may be helpful in the following types of surgery:

A. Basilar artery aneurysm

B. Hypernephroma

C. Pulmonary embolectomy

D. Pneumonectomy

E. Arterial switch

Answers: A True; B True; C False; D False; E True

2. Normal adaptive responses to mild hypothermia includes:

A. Vasodilatation

B. Hyperactivity

C. Tachypnea

D. Diuresis

E. Hypertension

Answers: A False; B False; C True; D True; E True

3. Concerning retrograde cerebral perfusion (RCP)

A. Bicaval cannulation is required

B. Circulatory arrest can be safely used at 30°C

C. Pump flows of 50–150 ml min^{-1} are used

D. Perfusion pressures of 25–40 mmHg are considered safe

E. Transcranial Doppler may not detect any cerebral blood flow

Answers: A True; B False; C False; D True; E True

4. The following have been demonstrated to improve neurological outcome following deep hypothermic circulatory arrest (DHCA)

A. Thiopental 1 g IV at the onset of CPB

B. Use of aprotinin by infusion

C. Use of cerebral near infrared spectroscopy

D. Use of selective antegrade cerebral perfusion

E. Tight glycemic control during re-warming

Answer: A False; B False; C False; D False; E False

5. Putative predictors of stroke in adults following deep hypothermic circulatory arrest (DHCA) include:

A. Atheroma of the proximal aorta

B. Previous stroke

C. Duration of CPB

D. Diabetes mellitus

E. Emergency surgery

Answers: A True; B True; C True; D False; E True

Suggested Further Reading

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Chapter 11

Organ damage during cardiopulmonary bypass

Christopher C. C. Hudson and **Sherif Assaad**

Cardiopulmonary bypass (CPB) is an essential component of the majority of cardiac surgical cases. It serves four primary purposes:

1. gas exchange,
2. systemic circulation,
3. diversion of blood from the heart to provide a bloodless surgical field, and
4. temperature modulation.

Unfortunately, CPB is not benign: it is associated with significant adverse physiological disturbances that can result in end-organ damage and death. In this chapter, we will review the underlying pathophysiological mechanisms leading to end-organ damage during CPB, followed by a discussion of organ-specific effects.

Pathophysiology of organ damage

Organ damage during CPB is multifactorial. The full breadth of this topic is sufficient to fill entire textbooks: this chapter will present a synopsis of the following key mechanisms:

1. Blood–surface interface
2. Systemic inflammatory response (SIRS)
3. Ischemia-reperfusion injury

4. Endotoxins
5. Embolism
6. Non-pulsatile flow
7. Hemodilutional anemia
8. Temperature

Blood–surface interface

Contact of blood with the foreign surfaces of the CPB circuit disrupts the delicate homeostatic balance maintained by the vascular endothelial system. This causes profound physiological disturbance in homeostasis mediating thrombotic, hemorrhagic, and inflammatory reactions ultimately leading to tissue injury. A variety of options are available to minimize this robust response:

1. Centrifugal pumps
2. Surface-coated circuits (heparin and phosphorylcholine)
3. Membrane oxygenators
4. Minimal circuit length
5. Cell salvage (rather than cardiotomy suction)
6. Hemofiltration
7. Leukocyte-depleting filter
8. Medications (heparin, heparin-substitutes, antifibrinolytics)

The remainder of this section will explain in further detail the pathophysiological consequences of CPB.

Systemic inflammatory response

Systemic inflammatory response (SIRS) associated with cardiac surgery is a complex process. As Figure 11.1 demonstrates its pathophysiology can be subdivided into (1) initiation, (2) mediators, and (3) cellular injury.

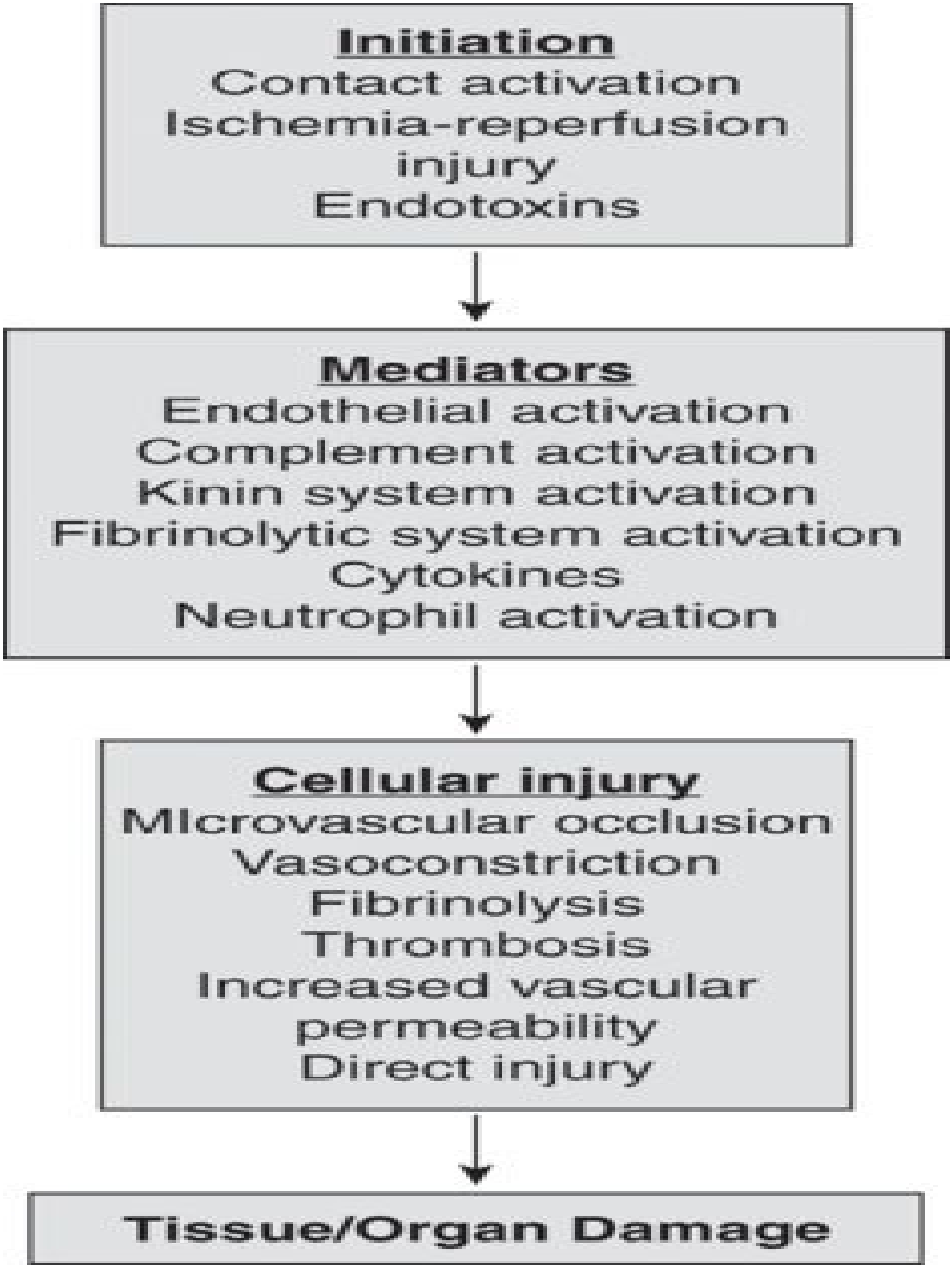
Initiation
Contact activation
Ischemia-reperfusion injury
Endotoxins
Mediators
Endothelial activation
Complement activation
Kinin system activation
Fibrinolytic system activation
Cytokines
Neutrophil activation
Cellular injury
MIcrovascular occlusion
Vasoconstriction
Fibrinolysis
Thrombosis
Increased vascular permeability
Direct injury
Tissue/Organ Damage

Figure 11.1 Overview of systemic inflammatory response to CPB.

Initiation

SIRS is incited by a number of factors, including the interaction of blood with the foreign surfaces of the CPB circuit (i.e. contact activation), altered blood flow patterns (i.e. non-pulsatile flow), ischemia-reperfusion injury, and endotoxins.

Initiation results from a multitude of cellular-mediated processes including:

1. Endothelial activation
2. Complement activation
3. Kinin system activation
4. Fibrinolytic system activation
5. Synthesis of cytokines
6. Neutrophil activation

1. Endothelial activation

The endothelium lines the interior surface of blood and lymphatic vessels. Physiologically, the endothelium plays a dynamic protective role by: (1) selectively controlling passage of material and white blood cells into and out of the circulation, (2) inhibiting clot formation by secreting anticoagulants such as tissue plasminogen activator (tPA), thrombomodulin, and heparin-like substances, and (3) causing local vasodilation through nitric oxide and prostacyclin. Activation or disruption of the endothelial layer leads to a cascade of events including recruitment and release of immune cells, and release of inflammatory cytokines, procoagulant factors, and vasoactive agents. This results in further direct and indirect injury.

2. Complement activation

An essential component of the immune system, the complement system consists of over 30 plasma proteins that are involved in chemoattraction, activation, opsonization, and cell lysis. Activation of the system can occur via either the “classical” or “alternative” pathways. The two complement pathways are shown in Figure 11.2. The classical pathway involves the activation of C1 by an antibody–antigen complex. The alternative pathway does not require an antibody for its activation: C3 fragments free-floating in serum attach directly to antigens, endotoxins, or foreign surfaces (otherwise known as contact activation). The common step linking both pathways is the cleavage of C3. Cleavage of C3 to its activated form C3a stimulates the release of histamine and other inflammatory mediators from mast cells, eosinophils, and

basophils. This results in smooth muscle constriction and an increase in vascular permeability. C5a is a potent chemotactic factor for neutrophils as it promotes their aggregation, adhesion, and activation. C3b and C5b interact on cell membranes with components C6–C9 to form a "membrane attack complex," which activates platelets and "punches" holes in cell membranes.

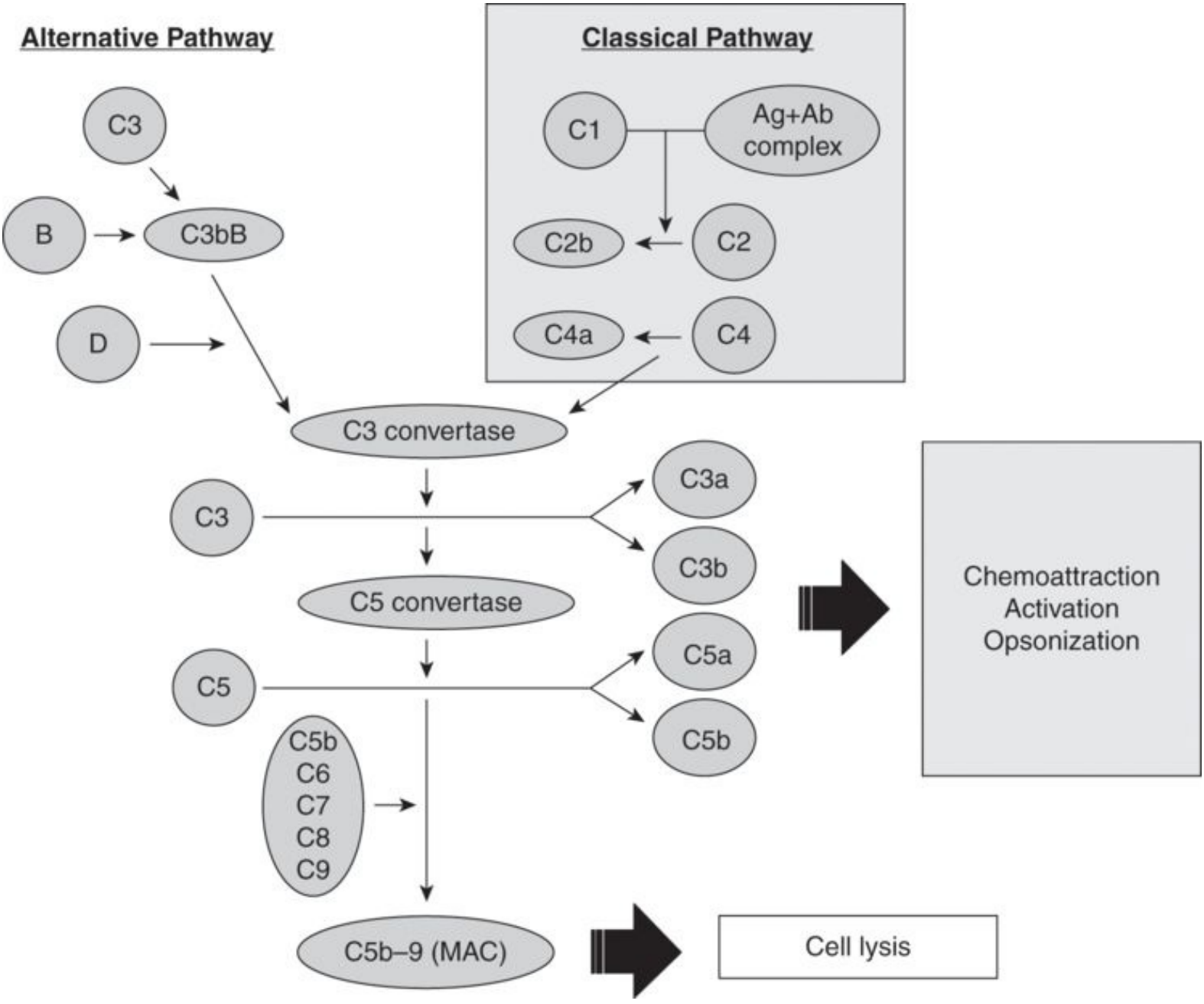

Figure 11.2 Diagram of the alternative and classical complement pathways. Abbreviations: Ag+Ab = antigen + antibody; MAC = membrane attack complex.

This process is rapid: plasma levels of activated complement factors rise within 2 minutes of the onset of bypass, and a second rise can be detected after release of the aortic cross-clamp and re-warming. Levels decline postoperatively and generally return to normal 18–48 hours postoperatively.

3. Kinin system activation

Initiated by contact with anionic surfaces, the initial step of the kinin system is activation of factor XII to factor XIIa (see Figure 11.3). In the presence of high-molecular-weight kininogen (HMWK), factor XIIa activates plasma prekallikrein to kallikrein. Kallikrein has five main actions:

i. accelerates and activates plasma prekallikrein via a positive feedback loop;

ii. cleaves HMWK to release bradykinin (a potent vasodilator that increases vascular permeability);

iii. activates complement system C3 and C5;

iv. activates the fibrinolytic pathway by stimulating tissue plasminogen activator; and

v. activates the sympathoadrenal system.

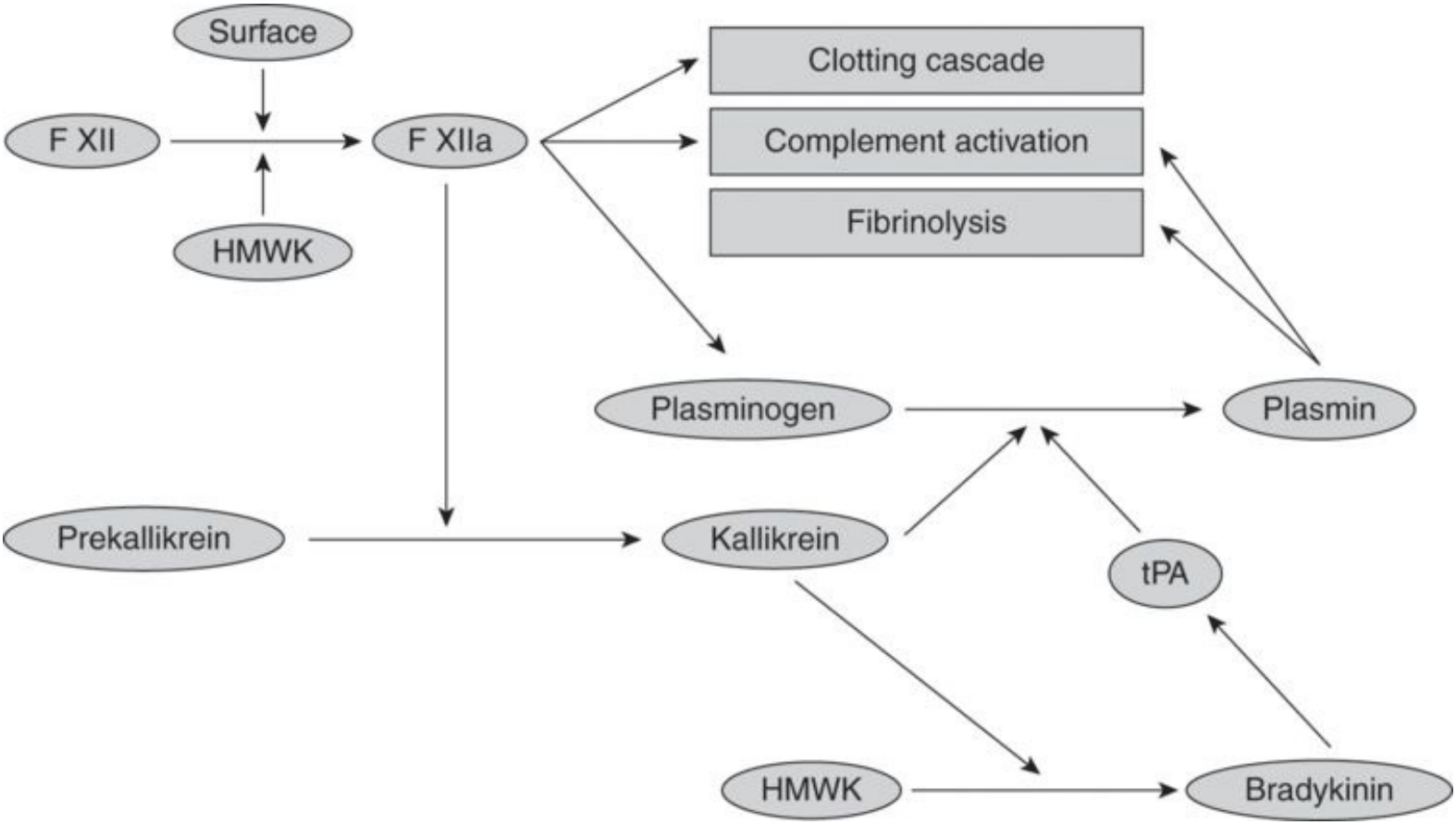

Figure 11.3 Diagram of kinin, clotting, and fibrinolytic system. Abbreviations: tPA = tissue plasminogen activator; HMWK = high-molecular-weight kininogen.

4. Fibrinolytic system activation

Exposure of blood to the artificial surface of the CPB circuit, temperature changes, medications, mechanical trauma, or blood products trigger fibrin clot formation, resulting in activation of the fibrinolytic system. The fibrin clots are continuously proteolytically digested into fibrin degradation products (FDPs) by plasmin (see Figure 11.3). Plasmin production is upregulated via two pathways:

i. Bradykinin upregulates tissue plasminogen activator (tPA), which in turn converts plasminogen to plasmin. tPA levels peak with 30 minutes of CPB and return to baseline within 24 hours.

ii. Kallikrein and HMWK upregulate urokinase, which activates urokinase plasminogen activator (uPA), which in turns converts plasminogen to plasmin.

Intravascular fibrin clots lead to impaired microcirculation and hypoxic cellular damage. FDPs compete with thrombin and slow down clotting by inhibiting the conversion of fibrinogen to fibrin. The net effect is endothelial and platelet dysfunction.

5. Synthesis of cytokines

Cytokines are soluble proteins released by immune cells and endothelial cells in response to local injury and play a critical role in the pathophysiology of inflammation. Cytokines are important messengers in the immune system: they attract immune cells to areas of injury and enhance their function. In addition, they stimulate further expression of procoagulant and fibrinolytic enzymes. Proinflammatory cytokines tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, IL-8, and IL10 are all elevated during CPB. Excessive levels of cytokines lead to uncontrolled systemic inflammation causing tissue damage.

6. Neutrophil activation

Recruitment and activation of neutrophils occurs in response to local endothelial damage and cytokine release, resulting in leukocyte adhesion. Leukocytes cause local damage via three main mechanisms:

i. aggregation with platelets to cause local microvascular occlusion and ischemia,

ii. release of proinflammatory cytokines,

iii. release of leukotrienes causing increased vascular permeability and vasoconstriction. In addition, dissolution of neutrophil–platelet aggregates can lead to ischemia-reperfusion injury.

Cellular injury

Described throughout the previous text, the mechanisms for cellular and organ injury are:

1. Microvascular occlusion

2. Vasoconstriction

3. Fibrinolysis

4. Thrombosis

5. Increased vascular permeability (“local edema”)

6. Direct injury from immune system, oxygen free radicals, and cytokines

Ischemia-reperfusion injury

Ischemia-reperfusion injury is a term used to describe the cellular injury that occurs on resumption of normal perfusion to an organ after a period of relative or complete ischemia. During ischemia, there are a multitude of cellular changes including:

1. altered membrane potential,

2. increase in intracellular calcium (Ca^{2+}),

3. increase in hypoxanthine,

4. decrease in adenosine triphosphate (ATP),

5. cellular acidosis, and

6. edema.

Upon reperfusion, a cascade of mechanisms occurs that may contribute to further cell death due to alteration in calcium handling, oxygen free radical production, and hypoxanthine accumulation.

Altered calcium handling

During ischemia, there is an increase in intracellular Ca^{2+}, primarily due to failure of ATP-dependent cellular calcium pumps. On reperfusion, there is an increase in both intracellular and mitochondrial Ca^{2+} secondary to entry via L-type Ca^{2+} channels and alterations of sarcoplasmic reticulum Ca^{2+} cycling. Increased Ca^{2+} can lead to cell death by hypercontracture (via interaction of actin and myosin) and opening of mitochondrial permeability transition (MPT) pores. Although the exact mechanism is unknown, induction of MPT pores causes an increase in mitochondrial permeability, disrupting the electrochemical gradient essential for ATP production. This process ultimately leads to cell death.

Oxygen free radical production

Low levels of oxygen free radicals and oxidants are normal and play essential roles in cellular homeostasis. However, on reperfusion of ischemic tissue, large quantities of oxygen free radicals are generated, overwhelming the endogenous scavenging systems. Oxygen free radicals have several detrimental effects including:

i. inhibition of ATP-dependent Ca^{2+} pumps causing increased intracellular Ca^{2+};

ii. lipid peroxidation resulting in cell membrane breakdown and edema; and

iii. promotion of neutrophil transmigration and activation.

Neutrophils are the final mediators of ischemia-reperfusion injury by the production of toxic chemicals generated during the metabolism of oxygen, and by the secretion of proteolytic enzymes released from granules stored in their cytoplasm.

Hypoxanthine accumulation

During ischemia, energy generation using high-energy phosphates (ATP) creates the metabolite hypoxanthine. Normally, hypoxanthine is metabolized by the enzyme xanthine dehydrogenase. However, following rapid reperfusion with increased oxygen availability, xanthine dehydrogenase is converted to xanthine oxidase. As a result, molecular oxygen is converted into highly reactive superoxide and hydroxyl radicals. Furthermore, nitric oxide produced during reperfusion reacts with superoxide to produce the potent free radical peroxynitrite. These free radicals attack and damage cellular components.

Endotoxins

Another well-described phenomenon associated with SIRS is a rise in plasma endotoxin levels during CPB. Endotoxins are lipopolysaccharides derived from the cell membranes of gram-negative bacteria. Endotoxins are produced by intestinal flora and are normally confined to the intestinal lumen by a barrier of endothelial cells. The most prominent hypothesis is that during CPB, hypoperfusion of the intestines leads to increased endothelial permeability, allowing translocation of endotoxins into the portal circulation. Lipopolysaccharides invoke potent inflammatory and immunological reactions, including macrophage activation and cytokine generation (TNF, IL-6, and IL-8).

Embolism

Intraoperative emboli during cardiac surgery can arise from many sources. With aortic manipulation (e.g. cannulation and cross-clamping), atheromatous plaques can become dislodged and scatter systemically. Interaction between the CPB circuit and blood, stagnation within the CPB circuit, direct tissue damage (i.e. to bone marrow), and introduction of homologous transfused blood can all result in microemboli. These emboli may be composed of a variety of biological products or aggregates including fibrin/fibrinogen, platelets, lipids, and protein. Gas emboli can originate from the CPB apparatus or be entrapped directly from the surgical field. Lastly, emboli can be composed of foreign material, such as plastic from the CPB circuit tubing, components of surgical items (e.g. fibers, plastics, metals), and bone

wax. Emboli cause acute disruption of blood flow, leading to upstream ischemia and eventual cell death. The extent of damage is contingent on the territory supplied by the affected vessels and the duration of ischemia.

Non-pulsatile flow

Most cardiac centers employ non-pulsatile roller or centrifugal pumps to drive circulation during CPB. Though the exact mechanism is not fully understood, it is believed that non-pulsatile laminar flow, as opposed to physiological pulsatile flow, causes deterioration of microcirculatory perfusion. The net result of this derangement is an increase in endotoxins, increase in endogenous vasoconstrictors, and platelet activation leading to local cellular damage. On the other hand, roller pumps designed to rotate at varying speeds can achieve pulsatile flow in an appropriately configured CPB circuit. It has the advantage of delivering more energy to the microcirculation. Theoretically this should result in preservation of the microcirculation, improvement of the blood flow to the vital organs, and attenuation of the systemic inflammatory response. Despite these potential advantages, the use of pulsatile flow during CPB is still controversial among surgeons because of the absence of clinical data showing any clinically significant benefits and the perception that pulsatile CPB is more technically challenging to provide.

Hemodilutional anemia

Hemodilutional anemia is an inevitable consequence of CPB, given the current practice of priming the CPB circuit with non-blood components. There are advantages and disadvantages to hemodilution. The main advantage is reduced blood viscosity improving microvascular flow. The main disadvantage of excessive hemodilution is increased risk of compromising oxygen delivery at the tissue level, leading to ischemic organ injury.

Temperature

Thermoregulation is an essential homeostatic process: regulation of core body temperature at 37°C is one of the functions of the hypothalamus, ensuring optimal physiological conditions. During CPB, the physiological balance is altered, leading to a multitude of injuries. Hypothermic strategies are often employed during CPB to provide organ protection. The application of hypothermia (< 34°C) during CPB has been in practice during coronary artery bypass grafting and valvular heart disease for over half a century. The primary mechanism is a reduction in metabolic rate and oxygen consumption, but other

possible benefits include attenuation of excitatory neurotransmitters (particularly glutamate), preservation of phosphate stores, and reduction in cytokine release and inflammation.

Extremes of temperature and rapid re-warming can nullify the beneficial effects of mild hypothermia. The main detriments of very low temperatures are decreased macro- and microvascular blood flow and increased blood viscosity. In addition, hypothermia can lead to leukocyte activation, endotoxin release, and production of TNF. All the aforementioned mechanisms can lead to perioperative organ damage. Both rapid re-warming and inadvertent hyperthermia during CPB can cause organ damage. The mechanism of this damage includes production of free radicals, intracellular acidosis, increase in excitatory amino acid neurotransmitters, and hyperemia. Despite the theoretical advantages of hypothermia during CPB, studies have failed to show a clinical advantage of hypothermia in respect to cerebral protection during CPB. In fact, no difference between CPB utilizing hypothermia or normothermia (> 34°C), with respect to mortality rate, stroke, cognitive decline, myocardial infarction, use of inotropic support or intra-aortic balloon pump, infections, atrial fibrillation or acute kidney injury has been conclusively demonstrated. In contrast, hypothermia was associated with coagulopathy, increased risk of transfusions, impaired drug metabolism, and longer periods of bypass time. The release of markers of myocardial injury during CPB seems to be independent of the temperature used.

Alterations in organ perfusion

The transition from physiological circulation to CPB represents a major change to the homeostasis of the body. This is secondary to changes in the type of circulation from pulsatile to non-pulsatile flow and in the temperature of the body from normothermia to hypothermic circulation. This transition leads to alterations in distribution of blood flow and oxygen delivery to the organs (see Figure 11.4a). Furthermore, tissue oxygen delivery is influenced to a large extent by CPB flow rate (see Figure 11.4b). Organ dysfunction may, thus, be in part attributed to these changes in the regional distribution of blood flow and the dependence of oxygen delivery on the maintenance of adequate CPB flow rates. Also, the initiation of the SIRS contributes to many of these complications. Table 11.1 summarizes a list of complications post-cardiac surgery. Cerebral and renal complications are discussed in further detail in Chapters 12 and 13 respectively.

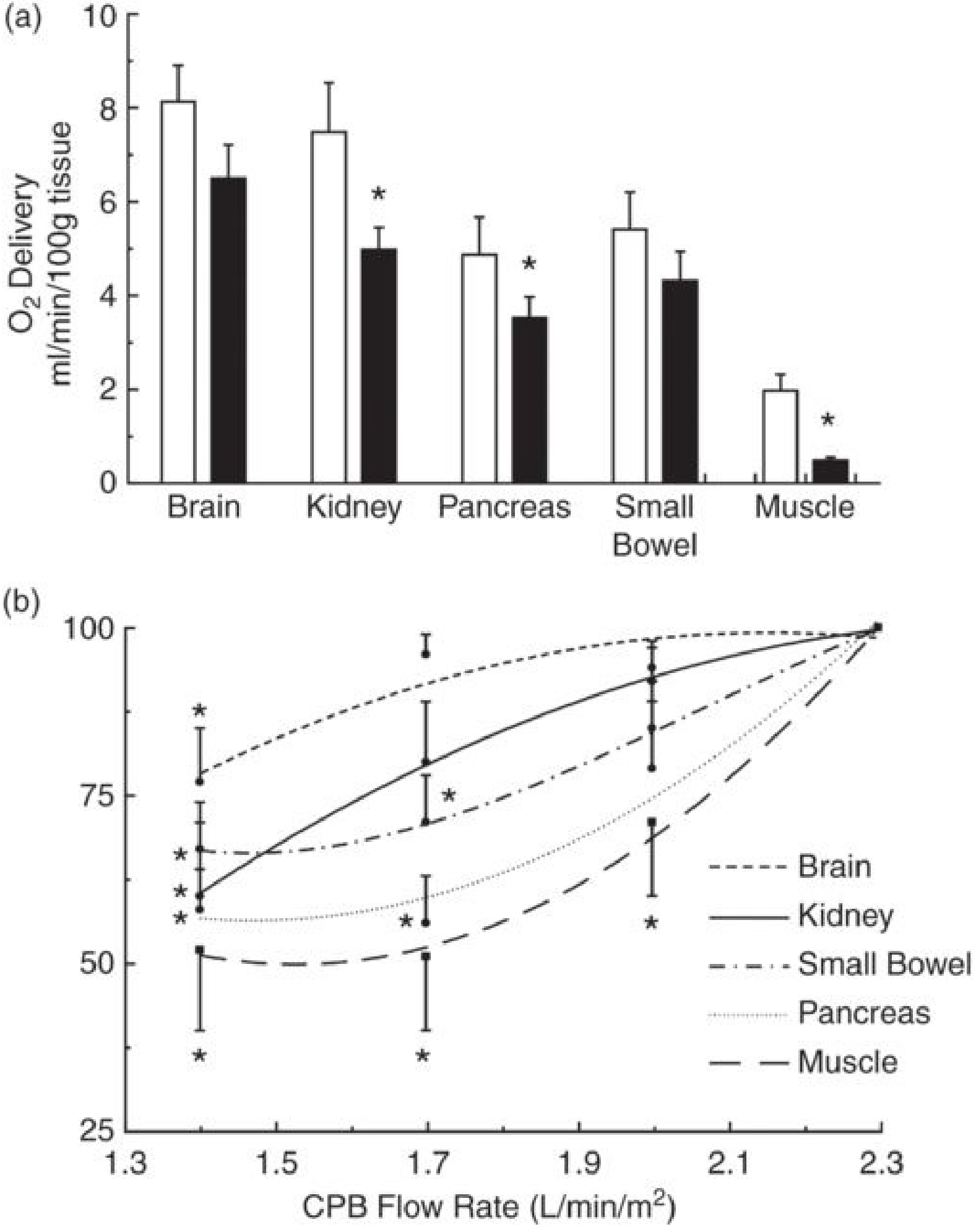

Figure 11.4 (a) Regional O_2 delivery with onset of cardiopulmonary bypass. (Adapted from Boston

and Cook. Ann Thorac Surg 2001.) (b) Change in organ DO_2 with changes in CPB flow rate.

(Adapted from Boston and Cook. Ann Thorac Surg 2001.)

Table 11.1 Complications after cardiac surgery: first time coronary artery bypass in the United States of America (utilizing cardiopulmonary bypass)

Renal failure	3.1%
Stroke or coma	2.8%
Gastrointestinal complications	2.5%
Re-op for bleeding	2.3%
Sternal infections	1.4%
Peri-op myocardial infarction	1.1%
Acute respiratory distress syndrome	0.9%
Dialysis	0.9%
Multisystem failure	0.6%

Society of Thoracic Surgeons, 1997 Database; 161 018 patients.

Adapted from Hessel EA, 2nd. Abdominal organ injury after cardiac surgery. Semin Cardiothorac Vasc Anesth, 2004; 8(3): 243–63.

Gastrointestinal dysfunction

Gastrointestinal (GI) complications post-cardiac surgery are relatively uncommon with an incidence of 2–4%, but when they occur, they are associated with a mortality rate of 15–60%. This represents about 11 times (range 4–32 times) the mortality in patients not experiencing GI complications. Despite improvements in the surgical techniques, and perfusion strategies during CPB, the incidence and the mortality rates have not changed in the last two decades. The clinical assessment of patients with GI complications is often delayed because patients might be sedated, partially unresponsive, mechanically ventilated or the classical symptoms and signs are masked by other cardiac and pulmonary complications. A list of common GI complications is summarized in Table 11. 2.

Table 11.2 Visceral complications after cardiac surgery: incidence and mortality (review of 1675

visceral complications from 34 series)

	Incidence (%)	Mortality (%)
Gastrointestinal bleeding	30.7	26.9
Ischemic bowel	17.7	71.3
Pancreatitis	11.2	27.5
Cholecystitis	10.9	26.9
Paralytic ileus	4.5	10.8
Perforated peptic ulcer	4.2	43.8
Hepatic failure	3.5	74.4
Diverticulitis	2.6	17.1
Small bowel obstruction	2.0	18.5
Pseudo-obstruction of colon	1.9	21.4

Adapted from Hessel EA, 2nd. Abdominal organ injury after cardiac surgery. Semin Cardiothorac Vasc Anesth, 2004; 8(3): 243–63.

Pathogenesis of GI complications

1. Depressed systemic hemodynamics: CPB causes profound reductions in blood flow for several hours postoperatively in the splanchnic circulation and thus leads to reduced perfusion of the GI tract and associated organs. Severe intestinal ischemia may occur during CPB even when the indices of global body perfusion remain normal. This may be due to the release of a variety of endogenous vasoactive factors, such as vasopressin, catecholamines and thromboxanes, during CPB, and to the administration of vasopressor drugs to maintain perfusion pressure, leading to a redistribution of regional blood flow away from the mucosa of the GI tract.

2. SIRS: The combination of reduced splanchnic blood flow and the CPB-induced SIRS reduce the efficacy of both the absorptive and barrier functions of the GI tract. The increase in gastrointestinal mucosal permeability results in the translocation of bacterial endotoxins from the GI tract into the bloodstream, amplifying SIRS and subsequent further organ damage.

3. Atheroembolism.

4. Prolonged mechanical ventilation > 24 hours: Mechanical ventilation using large tidal volumes with high airway pressures may lead to release of proinflammatory cytokines. In conjunction with stimulation of the sympathetic nervous system and decreased cardiac output, which are also often associated with mechanical ventilation, this may result in splanchnic hypoperfusion and mucosal injury.

Table 11.3 gives an overview of the risk factors for GI complications.

Table 11.3 Risk factors associated with GI complications post-cardiac surgery

Preoperative	Age > 75 years History of congestive heart failure or ejection fraction < 40% Renal insufficiency Increased preoperative total bilirubin > 1.2 mg/dl Preoperative partial thromboplastin time (PTT) > 37 seconds Type of cardiac surgery • Emergency • Reoperations • Valve or combined procedures • Cardiac transplantation
Intraoperative	Intraoperative circulatory failure CPB duration > 100 minutes Aortic cross-clamp duration > 55 minutes Transfusion of packed red blood cells
Postoperative	Low cardiac output Use of inotropes or vasopressors or intra-aortic balloon pump (IABP) Reoperation for bleeding

	Loss of normal sinus rhythm
	Ventilation > 24 hours
	Intensive care unit stay > 1 day

Specific GI complications

1. GI bleeding

Bleeding from the upper GI tract is far more common than bleeding from the lower GI tract. Although a history of peptic ulcer was considered as a risk factor, routine prophylaxis with antacids or histamine2 receptor antagonists is not recommended. Lower GI tract bleeding is usually associated with bowel ischemia or pre-existing large bowel disease.

2. Bowel ischemia/perforation

Bowel ischemia after cardiac surgery is one of the most serious complications in the postoperative period. It accounts for 18% of all GI complications and is associated with a mortality rate of 71%. It is more common in advanced age, females, emergency surgery, combined cardiac surgery, end-stage renal disease, prolonged bypass, and perioperative use of IABP and vasopressors. The earliest presenting signs are progressive metabolic acidosis, leukocytosis, and ileus. Early diagnosis and intervention, e.g. using colonoscopy, CT scan, angiography and laparotomy, may be lifesaving.

3. Hepatic dysfunction

Hepatic metabolism is reduced during CPB in conjunction with the reduction in splanchnic blood flow. Hepatic blood flow has been reported to decrease by 19% after CPB is commenced. There may be a transient rise in the levels of hepatic enzymes measured in the blood, which usually peaks early in the postoperative period. Clinically evident jaundice is only apparent in a small number of patients, although bilirubin levels rise in about 20% of cases. Moderate or severe degrees of hepatic dysfunction are rare and usually occur in concert with multiorgan failure.

Risk factors for hepatic dysfunction post-cardiac surgery include female gender, congestive heart failure, valvular heart surgery, combined surgical procedures, hematomas, and transfusions. Consequences of hepatic dysfunction relevant to CPB specifically include:

- Impaired drug metabolism
- Reduced plasma protein concentrations leading to reduced plasma oncotic pressure and alteration in the volume of distribution of drugs

- Impaired coagulation due to reduction in production of clotting factors
- Impaired ability to generate heat and regulate temperature

Cholecystitis, in the absence of gallstones, may also occur postoperatively in 0.2–0.5% of all cardiac surgical patients. The gall bladder distends and the stasis of bile leads to inflammation of the gall bladder. It carries a mortality rate of 25–45% once diagnosed, despite aggressive treatment.

4. Pancreatitis

Overt pancreatitis, characterized by a rise in serum amylase to over 1000 IU/l, occurs in 0.1–1% of cases following cardiac surgery and accounts for 11% of GI complications. Uncomplicated pancreatitis carries a mortality of 5–10%, but cases that progress to necrotizing pancreatitis or to the development of a pancreatic abscess or a pseudocyst usually result in death. Lesser degrees of pancreatic cellular injury with mild elevations in serum amylase concentrations are, however, common. The etiology is probably related to perioperative reduction in splanchnic blood flow causing pancreatic ischemia. Hyperamylasemia is a risk factor for death even in the absence of overt pancreatitis and considered as a marker for splanchnic ischemia, which may cause pancreatitis. The incidence of pancreatitis is 30-fold higher after heart transplantation compared to other types of cardiac surgery. Calcium administration, frequently used to treat intraoperative hypotension, has not clearly been identified as an independent risk factor.

5. Pulmonary dysfunction

Pulmonary complications remain the leading cause of post-cardiac surgery morbidity with an incidence of 7.5% and a mortality rate of 21%, resulting in prolonged hospital stay and increase in cost. The spectrum of pulmonary complications ranges from atelectasis to acute respiratory distress syndrome (ARDS). The incidence of post-CPB ARDS is < 2%. The mortality rate associated with post-CPB ARDS, however, is > 50%.

Causes of postoperative respiratory failure are:

- Atelectasis
- Increase in lung water content as a result of increased capillary permeability caused by SIRS
- Impaired hemodynamics in the immediate postoperative period
- Additional fluid load during CPB
- Alteration in the production of surfactant, particularly during the period of lung collapse during CPB and as a result of SIRS causing decreased static and dynamic lung compliance

- Transfusion-related acute lung injury (TRALI)
- Altered chest wall mechanics resulting from sternotomy: Median sternotomy results in more than 50% reduction in vital capacity (VC) and forced expiration (FEV1) from preoperative values. These changes last for about 4 months postoperatively and are caused by discoordinated rib cage expansion following sternotomy, pleural effusion, and pain. The use of the internal thoracic artery for grafts exacerbates these changes. There was no difference between on-pump versus off-pump surgery in regard to these changes except that CPB may be associated with the release of bronchoconstricting mediators causing an increase in expiratory resistance
- Pneumothorax or hemothorax
- Phrenic nerve injury impairing diaphragmatic function

Although some of the factors listed above relate to cardiac surgery in general and are not specific to CPB, the overall effect is the development of intrapulmonary shunts that cause a mismatch between ventilation and perfusion. This manifests as a higher inspired oxygen concentration being required to maintain an acceptable level of blood oxygenation. This mismatch tends to resolve gradually postoperatively, but patients may require supportive measures such as the application of PEEP during mechanical ventilation or continuous positive airway pressure (CPAP) when spontaneously breathing until resolution occurs. In mechanically ventilated patients, tidal volume in excess of 10 ml/kg was found to be a risk factor for organ failure and prolonged intensive care unit stay. Diuretics, as an adjunct to careful fluid balancing, may help to reduce interstitial lung water. In hemodynamically stable patients, with adequate gas exchange and no evidence of neurological insults or bleeding, adequate pain control and early extubation (within 4–6 hours) allow early ambulation and the ability to cough and clear pulmonary secretions, which reduces the incidence of pulmonary complications.

6. Myocardial dysfunction

The period of CPB during cardiac surgery can be divided into three phases:

- Onset of CPB until application of the cross-clamp
- The period of cross-clamping and cardioplegic or fibrillatory arrest
- The reperfusion period following removal of the cross-clamp and ultimately separation from CPB.

During these periods the heart is subjected to injury from microemboli, the inflammatory products of SIRS, regional hypoperfusion, complete ischemia, and finally reperfusion injury. The injurious effects

incurred from these insults, together with the potential for inadequate myocardial protection and distension of the flaccid heart during the period of cross-clamping, result in myocardial edema and reduced ventricular contractility, which may persist into the postoperative period. Furthermore, if the heart is subject to excessive preload or high afterload during weaning from CPB, left ventricular end-diastolic volume, myocardial wall stress, and oxygen consumption are all increased, further contributing to deterioration in cardiac function.

Off-pump coronary artery bypass graft (OPCABG) avoids the need for cross-clamping of the aorta and for cardioplegia, which are both essential during CABG with CPB. In theory, this should minimize the risk of global myocardial ischemia and myocardial stunning. In practice, the incidence of myocardial infarction is similar following OPCABG and CABG with CPB. OPCABG, however, is associated with a more rapid recovery of myocardial oxidative metabolism and this leads to more rapid replenishment of myocardial high-energy phosphates such as ATP and theoretically should result in better myocardial function in the early post revascularization phase.

Therapeutic strategies

A number of strategies have been employed to ameliorate the extent of the SIRS seen during CPB.

Pharmacological

Steroids

The administration of pre-CPB corticosteroids attenuates the inflammatory response mainly by inhibiting the release of the inflammatory cytokines IL-6 and IL-8 and enhancing the release of the anti-inflammatory cytokine IL-10. In one study this was associated with a decrease in the intensive care unit and hospital stay and in the incidence of postoperative atrial fibrillation. These potential benefits did not translate into survival benefits or a reduction in the cardiac or pulmonary complications; on the contrary, there was an increase in the incidence of gastrointestinal bleeding and hyperglycemia requiring insulin infusion. The routine administration of prophylactic corticosteroids is thus not recommended.

Antiplatelet agents (aspirin and clopidogrel)

The combined use of aspirin and clopidogrel after on-pump CABG and OPCABG has been increasing recently owing to the beneficial effects of the combined therapy on graft patency and the high incidence of

aspirin resistance in the postoperative period, rendering aspirin alone as an insufficient therapy in certain circumstances.

Statins

Statins are used in the treatment of hypercholesterolemia. They also have anti-inflammatory effects with reduction in post-CPB renal and cerebrovascular complications. Statins may have a potential benefit on graft patency and reduction in mortality and equivocal benefit on reduction of postoperative atrial fibrillation. For these reasons, continuation of perioperative statins is recommended.

Tranexamic acid (TXA)

TXA is an antifibrinolytic drug, which is administered intravenously to reduce postoperative bleeding and blood transfusion requirement following CPB. Recently, it has been used during OPCABG with the same beneficial results without an increase in the incidence of postoperative myocardial infarction, stroke or pulmonary embolism.

Angiotensin converting enzyme inhibitors (ACE-I)

ACE-I are antihypertensive agents that are used as an adjunct in the treatment of heart failure with beneficial effects on cardiac remodeling. They have anti-inflammatory effects as shown by attenuation of IL-6 rise in the postoperative period and antifibrinolytic effects that might decrease the incidence of graft thrombosis. Long-term survival benefits and reduction in cardiac adverse events are still controversial specifically in patients with normal ejection fraction.

Perfusion

Heparin-bonded circuitry can be used with the intention of reducing the degree of complement activation, but has proven to be less effective in attenuating coagulation disorders or fibrinolysis.

Hemofiltration/ultrafiltration (convection and osmosis under hydrostatic pressure) has been incorporated into the circuit to remove low-molecular-weight substances from plasma with the aim of reducing the circulating levels of proinflammatory mediators. Current techniques have proven to be more effective in the pediatric than the adult population.

Leukocyte-depleting filters are often incorporated into the CPB circuit to reduce the number of circulating activated white cells. Their value is presently unclear, but leukocyte depletion may have a protective effect in reducing the severity of lung, renal, and myocardial injury observed post-CPB. The

most consistent benefit is found in higher risk patients with pre-existing lung disease, ventricular dysfunction or undergoing procedures with prolonged duration on CPB. Leukocytes in allogenic blood transfusions have important immunomodulatory effects in the recipient. The use of leukocyte-depleted stored blood has been shown to decrease mortality in some patients who undergo CPB. This is predominantly due to a decrease in non-cardiac causes of death, in particular multiorgan failure.

Maintaining ventilation and pulmonary artery perfusion during CPB decreases the incidence of postoperative atelectasis and lung ischemia-reperfusion injury and hence decreases the incidence of post-CPB pulmonary dysfunction. Although this strategy has been associated with lesser inflammatory and proteolytic response, its clinical benefit is still to be proven.

CPB versus OPCABG

Off-pump CABG is an alternative technique for coronary revascularization, which is still controversial and highly dependent on institutional preference. Clinical reports have shown that oxidative stress and markers of inflammation (particularly IL-8, IL-6, TNF, and E-selectin) are significantly reduced during OPCABG when compared to CABG performed on CPB. OPCABG has also been shown to be associated with a reduction in blood transfusion. Full heparinization may be avoided during OPCABG and this, together with the avoidance of hemodilution by the priming volume required for CPB, may be more important in reducing transfusion requirements than any advantageous effects from ameliorating SIRS. Despite these potential advantages, large-scale studies failed to show long-term survival benefits at 1–3 years or neuropsychological outcome benefits after OPCABG compared to on-pump CABG. On the contrary, OPCABG patients have poorer graft patency at 1 year. There is limited evidence that OPCABG surgery has significant benefits over cardiac surgery with CPB in preventing GI complications.

Quality of life

The ultimate measure of the success of a medical intervention is its ability to improve the quality of life for patients. There is much evidence to show that both mental and physical health are improved after cardiac surgery and, furthermore, studies comparing quality of life after cardiac surgery with CPB or OPCABG yield similar results. This is a testament to the fact that CPB provides a safe and effective means for performing cardiac operations.

Self assessment

1. Which of the following is **NOT** a cause of organ damage during CPB?

A. Endotoxins

B. Blood–surface interface

C. Ischemia-reperfusion

D. Exotoxins

E. Embolism

Answer: D

2. Which of the following is **NOT** a cellular-mediated process of the systemic inflammatory response (SIRS)?

A. Complement activation

B. Kinin system activation

C. Proerythroblastic activation

D. Neutrophil activation

E. Fibrinolytic system activation

Answer: C

3. Which of the following proinflammatory cytokines are elevated during CPB?

A. IL-2

B. IL-1

C. IL-7

D. IL-11

E. IL-12

Answer: B

4. Which of the following complications has the highest incidence post-cardiac surgery?

A. Reoperation for bleeding

B. Pulmonary complications

C. Stroke

D. Renal failure

Answer: B

5. Median sternotomy results in reduction of forced vital capacity and first second forced expiratory volume by:

A. Less than 10%

B. Less than 20%

C. More than 50%

D. More than 80%

Answer: C

6. When compared to on-pump coronary artery bypass surgery, off-pump coronary artery bypass surgery has a lower incidence of neurological complications

A. True

B. False

Answer: B

7. In coronary artery bypass surgery performed through median sternotomy, the advantage of off-pump compared to on-pump surgery is:

A. Better graft patency

B. Higher neuropsychological outcome benefits

C. Reduction in transfusion requirements

D. Lower pulmonary complications

Answer: C

Suggested Further Reading

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Chapter 12

Cerebral morbidity in adult cardiac surgery

David J. Cook and **Sean M. Bruggink**

Neurological complications in adult cardiac surgery

Postoperative brain injury has been a focus of attention since the inception of cardiac surgery. In the last decade, approximately 3000 English-language articles have been published in this area. However, there has been only a modest decrease in the incidence of stroke or encephalopathy. The syndrome of cognitive dysfunction may be more prevalent today than 20 years ago: McKhann, comparing stroke incidence in 1994 (2.9%) versus that in 2004 at Johns Hopkins Hospital in Baltimore found a greater incidence in 2004 (4.5%). This is presumably because of the increasing average age of patients presenting for cardiac surgery and hence greater level of pre-existing disease in the more recent group of patients. A great deal, however, has been learned about brain physiology and mechanisms of injury in cardiac surgery; changes in practice have occurred that are probably making neurological outcomes better than might be predicted, given the increasing age and associated medical conditions prevalent in the surgical population.

In the 1980s and 1990s, a large number of physiological and clinical studies were conducted that better characterized brain physiology and function during cardiac surgery and cardiopulmonary bypass (CPB). The physiological variables that were investigated as possible causes of perioperative brain injury included mean arterial pressure (MAP), body temperature, hematocrit (HCT), bypass pump flow rate, the use of pulsatile flow, and CO_2 management. During this same period pharmacological and physiological interventions and changes in surgical technique were also investigated with an eye to reducing neurological morbidity. While many of those investigations can be faulted for being statistically underpowered, two decades of research have not led to either a brain protectant drug or device that has become part of our routine practice and substantially improved neurological outcomes. In fact, there is

little evidence that intraoperative maneuvers aimed at manipulating physiological parameters (in the absence of gross mismanagement) are an independent determinant of neurological outcome.

Cerebral physiology during CPB

The results of a large number of investigations can be best summarized by saying that in adults, over the range of conditions in which nearly all CPB is conducted, the determinants of cerebral blood flow and metabolism are the same as those under non-bypass conditions.

CPB may profoundly affect cerebral blood flow (CBF) and cerebral metabolic rate of oxygen consumption ($CMRO_2$), but these changes are qualitatively no different from those that would occur under non-CPB conditions; the effects are simply quantitatively greater. During CPB conducted above 27°C, which constitutes about 90% of adult surgery, brain physiology is straightforward and predictable. However, when bypass is conducted under moderately to profoundly hypothermic conditions some of these relationships change, primarily because of the non-linearity of changes in $CMRO_2$ and because of hypothermia-induced vasoparesis.

The determinants of cerebral perfusion during CPB are, in order of importance:

- mean arterial blood pressure;
- hematocrit;
- cerebral metabolism; and
- P_aCO_2.

Laminar blood flow as opposed to pulsatile perfusion does not compromise CBF, nor does pump flow rate when considered independently of its effect on MAP.

In the past there was considerable confusion over the effect of mean arterial pressure on cerebral perfusion during CPB. This arose from the poor design of studies conducted in the 1980s and a failure to appreciate the profound effect that changes in HCT have on cerebral blood flow. At least two very prominent studies from the 1980s concluded that CBF was independent of MAP, down to MAPs as low as 30–40 mmHg during CPB. This conclusion was based on pooling very few measurements of CBF from large numbers of patients. Because the measurements were conducted at multiple MAP, temperature, HCT, and $PaCO_2$ conditions, in multiple patients, a great deal of scatter was demonstrated in the data. When regression analysis relating MAP and CBF was performed on the widely scattered data, no relationship between MAP and CBF could be identified. The study design was thus not adequate to test the hypothesis and the conclusion was misleading.

The other primary source of confusion about the relationship between MAP and CBF arose from a failure to appreciate the profound effect of HCT on CBF. A variety of investigations determined CBF before CPB. Then during CPB, at a significantly lower MAP (below 55 mmHg), CBF measurements were repeated and found to be nearly the same as CBF at a higher MAP prior to CPB. These studies failed to take into account the fact that significant hemodilution occurs during CPB and that this reduces blood viscosity and increases CBF. This was well elucidated by Plöchl, Cook and colleagues who randomized exposure to varying MAP in dogs during CPB at 33°C and found that, while CBF was increased for any given degree of hemodilution, CBF and cerebral oxygen delivery decreased when MAP fell below approximately 55 mmHg (see Figure 12.1).

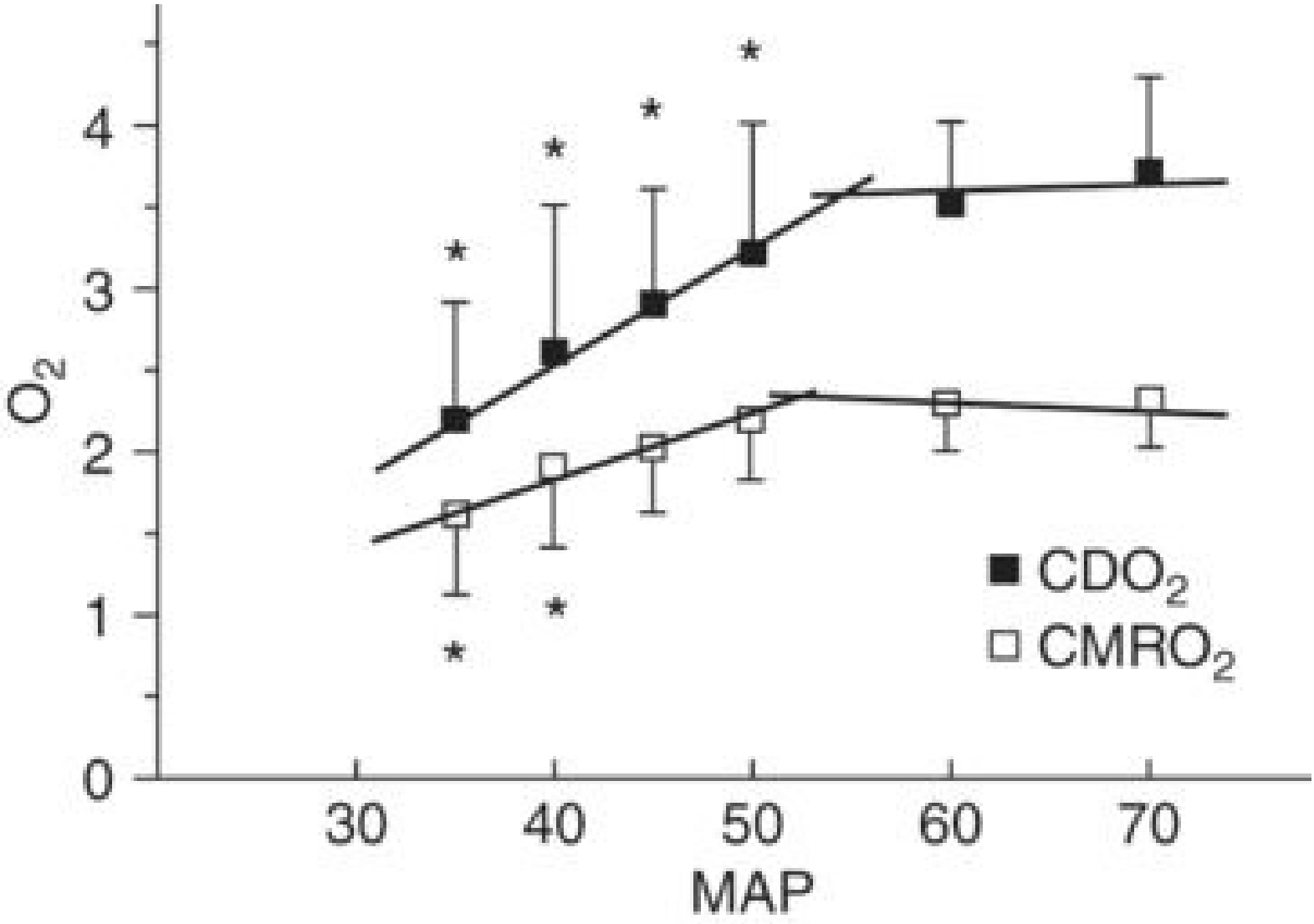

Figure 12.1 Cerebral oxygen delivery (CDO_2) and cerebral oxygen consumption ($CMRO_2$) versus mean arterial pressure (MAP) during cardiopulmonary bypass (CPB) at 33°C. Values for oxygen delivery (on ordinate in ml/100 g per minute) are the mean ± standard deviation (*P < 0.05 versus MAP of 60 mmHg by repeated-measure analysis of variance followed by Student-Neuman-Keuls test)

(From Plöchl W, Cook DJ, Orszulak TA, *et al*. Critical cerebral perfusion pressure during tepid heart surgery in dogs. *Ann Thorac Surg* 1998;66: 118–124, with permission.)

After MAP and HCT, cerebral metabolism is a primary determinant of cerebral blood flow. Over the temperature range in which most adult bypass is conducted, 27°C to 37°C, there is a clear relationship between temperature, $CMRO_2$, and CBF. Below 25°C, the relationships become much more complex. If all other variables (primarily MAP, HCT, and CO_2) are controlled, a 10°C decrease in temperature reduces $CMRO_2$ by about 60% and this is associated with a 50% reduction in CBF.

P_aCO_2 is an independent determinant of CBF during bypass. However, during most adult cardiac surgery the effect of P_aCO_2 is relatively small. If all other variables are controlled, every 1 torr increase or decrease in P_aCO_2 alters CBF approximately 3%. As such, between 32°C and 37°C the maximal effect of CO_2 on CBF is about 15%. The effect of CO_2 and alpha-stat/pH-stat strategies becomes increasingly relevant below 27°C, but it is a minor consideration above 32°C.

Cerebral physiology during CPB has been somewhat difficult to determine because so many variables are subject to change simultaneously and some of the physiological variables interact. This is particularly notable in the interactions of HCT, MAP, and CBF. The interaction of variables leads to confusion about the effect of pump flow on CBF. Some literature has reported that cerebral perfusion is dependent on pump flow. This misunderstanding arose from the failure to appreciate that pump flow, like cardiac output, is a primary determinant of mean arterial pressure. While decreases or increases in CBF may be seen when pump flow is increased or decreased, this is really only clearly demonstrated below or near the autoregulatory threshold: above a MAP of approximately 55 mmHg, increases in pump flow do not increase CBF, while below about 55 mmHg reductions in pump flow result in reductions in MAP that in course lead to reductions in CBF. This was well demonstrated in an animal study by Sadahiro (see Figure 12.2).

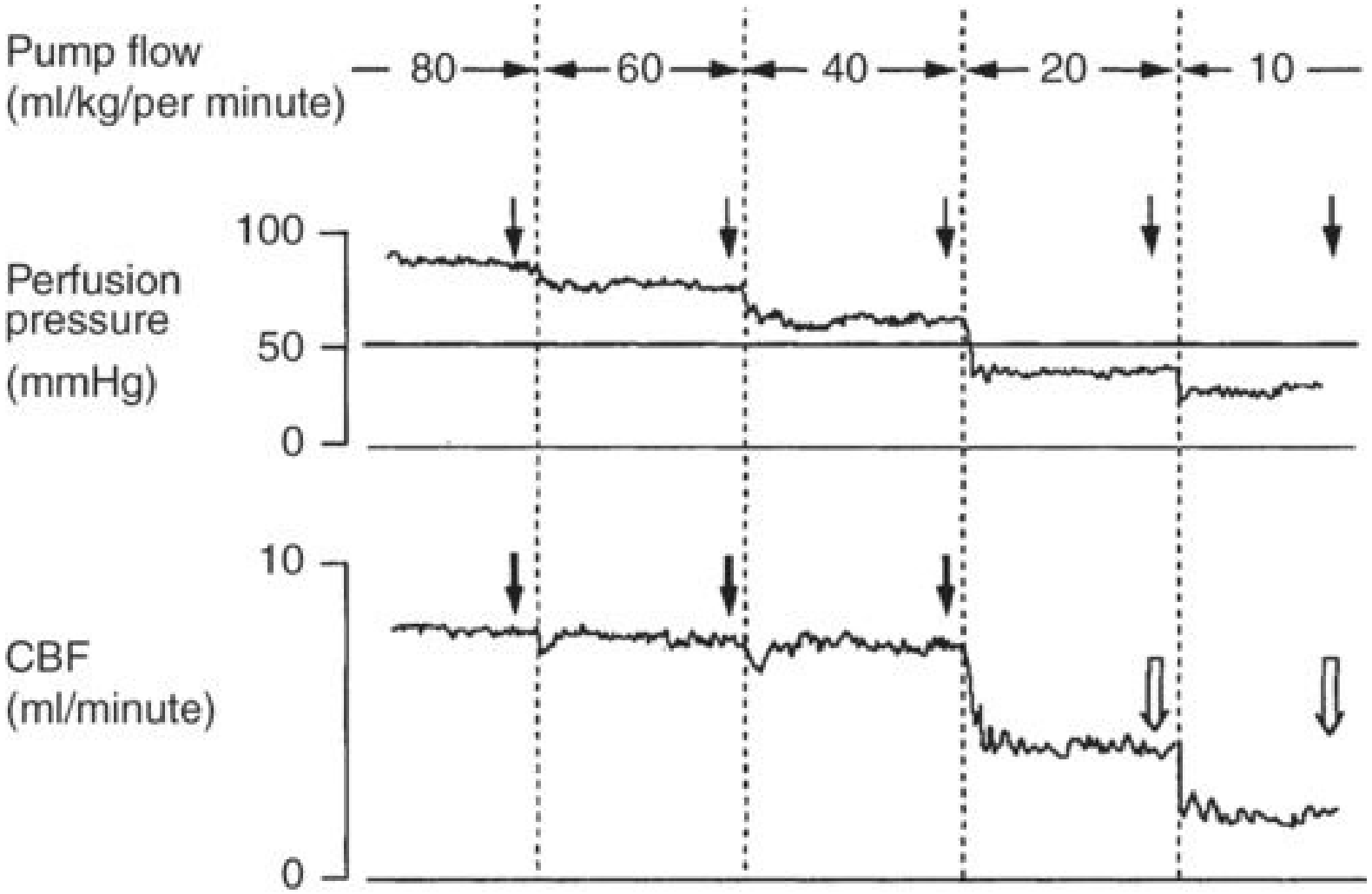

Figure 12.2 Continuous monitoring of perfusion pressure and CBF during perfusion flow rates from 80 to 10 ml/kg/minute. Arrows indicate the point at which the relationship between CBF and perfusion pressure was evaluated. Black arrows show the presence of an autoregulatory response with CBF returning to its prior level after an initial drop. White arrows show the loss of a vascular response

(From Sadahiro M, Haneda K, Mohri H. Experimental study of cerebral autoregulation during cardiopulmonary bypass with or without pulsatile perfusion. *J Thorac Cardiovasc Surg* 1994;108: 446–454, with permission.)

The dependence of CBF on pump flow is seen only when pump flow is too low to generate a MAP above the autoregulatory threshold. In humans and in animals, the independence of CBF from pump flow between 1.2 and 2.3 l/minute/m^2 at a stable MAP has been well shown at 27°C (see Table 12.1).

Table 12.1 Effect of pump flow on cerebral perfusion

30 adult patients, CPB at 27°C	**High flow**	**Low flow**
Pump flow (l/minute/m^2)	2.3 ± 0.1	1.2 ± 0.1
MAP (mmHg)	63 ± 9	62 ± 6

CBF (ml/100 g/minute)	29 ± 7	30 ± 8

From Cook DJ, *et al*. *Cardiothorac Anesth* 1997; 11:415–9 with permission.

Pulsatile flow appears to have no effect on cerebral blood flow during CPB independent of any effect of pulsatility on MAP.

Intraoperative ischemia and physiological management

Of the strokes caused in the operating room, watershed infarcts constitute the minority of cerebral ischemic events. When available, neuroimaging usually demonstrates embolic events and associated regional hypoperfusion. This is probably why, in spite of intensive clinical and laboratory study, it has been difficult to show that physiological variables, such as temperature or perfusion pressure, during CPB are independent determinants of neurological outcome. For intraoperative strokes it is more likely that these variables modulate the severity of injury that occurs subsequent to a cerebral embolic event. Because of the frequency of cerebral ischemic events, physiological management remains a relevant part of practice even if it does not prevent most strokes.

Effect of perfusion pressure

Through much of the 1980s the surgical, and some of the anesthesia literature, indicated that the cerebral autoregulatory threshold was shifted leftward during bypass such that lower mean arterial pressures (35–40 mmHg) were capable of maintaining normal cerebral blood flow. This was incorrect. Although hemodilution associated with CPB increases cerebral blood flow for any given mean arterial pressure, the autoregulatory curve still “breaks” at a pressure of approximately 55 mmHg; below this level cerebral blood flow is compromised. A combination of well-conducted laboratory investigations, the clinical investigation by Gold and colleagues showing better composite cardiac and neurological outcomes at higher mean arterial pressures, and a better understanding of cerebral autoregulation in diabetic and hypertensive patients as well as the elderly have led clinical practice to maintain MAPs above 55–60 mmHg during CPB. Rather than preventing watershed infarcts, this practice presumably helps to maintain cerebral perfusion in the presence of carotid, cerebral, and penetrating vessel disease and supports collateral flow and perfusion of the peri-ischemic region when embolic events do occur.

Effect of temperature

Given the profound effects of temperature on cerebral oxygen demand and the widely held belief in the neuroprotective effect of hypothermia, it was reasonable to expect that absolute CPB temperature would be identified as a primary determinant of cognitive outcome. However, this has not been the case in randomized or non-randomized trials. Although there are “multiple” publications investigating the effect of perioperative temperature management on neurological outcomes, the weight of the evidence is far weaker than would be expected. This is not to say that perioperative temperature management is unimportant, only that the best evidence of an effect of a hypothermic management on neurological outcome is quite weak. While the debate over the relative benefits of hypothermic versus normothermic bypass remains unresolved, more detailed examination of the influence of re-warming rate and postoperative temperature in determining cognitive outcomes have produced interesting results.

Data from the 2001 Grigore’s study randomizing patients to different intraoperative temperature management regimens was reported again when a subset of that negative outcome trial was re-analyzed taking into account the effect of the rate of re-warming on cognitive outcomes. In this re-analysis slow re-warming was associated with a beneficial effect on cognitive performance compared to conventional re-warming.

The simplest improvement in clinical practice relating to temperature management during CPB followed the first documentation of cerebral hyperthermia in 1996. Cook et al. showed that brain temperature was systematically underestimated during CPB and that cerebral temperature can approach 40°C during re-warming, a period associated with a great number of embolic events. From this observation, closer monitoring of nasopharyngeal and perfusate temperature and prevention of hyperthermia during CPB have become a standard part of intraoperative care.

Effect of glucose control

Maintaining blood glucose in the normal range is more a matter of not doing harm than actually doing something to prevent or reverse ischemic injury. The experimental stroke literature clearly demonstrates that hyperglycemia, like hyperthermia, worsens neurological outcome in the event of an ischemic insult. While maintaining perioperative normoglycemia will not independently determine the incidence of perioperative stroke, it is very likely to moderate its severity when ischemia does occur.

Effect of other measures

Few other intraoperative interventions hypothesized to improve neurological outcome have found their way into clinical practice. A range of different classes of drugs have been tried including aprotinin,

complement inhibitors, steroids, barbiturates, propofol, xenon, calcium channel antagonists, and magnesium, to name but a few. None has proved efficacious in a sufficiently powered clinical trial.

Perioperative stroke

Stroke is one of the most devastating complications following adult cardiac surgery. Literature from the 1960s and 1970s indicates that the incidence of stroke was approximately 2–4%. When one looks at very large populations, reports from the last 5 years demonstrate that this is largely unchanged. The overwhelming risk factor for stroke is physiological age, particularly manifest as atherosclerotic disease. In the 1990s a great deal of attention was paid to whether physiological variables were responsible for neurological outcomes, but none of these studies produced compelling evidence. With the rapid expansion of echocardiography and transcranial Doppler studies, attention shifted towards intraoperative embolization as the primary etiology of perioperative stroke and cognitive dysfunction.

While difficult to measure, due to lack of a concurrent control group, improvements in surgical technique have probably restricted the rise in the incidence of stroke, which would have been anticipated in the ageing population of patients, with more complex medical conditions, presenting for cardiac surgery. Thus, even if the overall stroke incidence in cardiac surgery is relatively unchanged, at least it has not risen to the levels that outcome models would predict. Recognition of the importance of embolic stroke has led to increased care in handling of the ascending aorta. Transcranial Doppler, echocardiographic, and neuroimaging data all point to the ascending aorta as the primary source of emboli leading to intraoperative stroke. Measures that probably reduce intraoperative embolization include intraoperative imaging of the ascending aorta to assess the optimal site (i.e. area with minimal atherosclerosis) for cross-clamp application, single application of the aortic clamp, femoral cannulation, all-arterial grafting, and off-pump techniques that eliminate ascending aorta instrumentation. However, even with excellent surgical management of the ascending aorta there still remains a substantial incidence of perioperative brain injury.

Use of Epiaortic scanning

Epiaortic scanning is a relatively low-cost intervention that may help to reduce the incidence of strokes due to embolization of atheromatous plaque displaced by surgical manipulation of the ascending aorta. Epiaortic scanning has been demonstrated to be more sensitive than digital palpation for identifying normal aorta for cannulation or cross-clamp application. Hangler and colleagues used epiaortic scanning to guide their management of the ascending aorta in 352 CABG patients and reduced their stroke rate from

4.4% to 2.9% when compared to historical data. In a study of 909 CABG patients by Yamaguchi and colleagues, the authors identified 196 patients for whom aortic manipulation might be unsafe and thus total arterial grafting using an off-pump technique was employed. The remaining 713 patients either had off-pump or traditional on-pump CABG and their aortic manipulation was guided by epiaortic scanning. No in-hospital strokes were identified in any patients, suggesting that risk of embolic stroke from aortic cannulation and cross-clamping is greatly reduced when epiaortic scanning is used. In cardiac operating rooms, equipment for epiaortic scanning is typically readily available given the widespread application of TEE. However, using epiaortic scanning to its full potential requires skill in the interpretation of the aortic ultrasound images, as well as surgeons willing to alter their approach to the ascending aorta when faced with severe atherosclerotic disease.

Off-pump CABG

Off-pump CABG (OPCABG) evolved from minimally invasive surgery and a desire to eliminate any morbidity associated with CPB. There was an expectation that elimination of CPB would dramatically reduce the number of perioperative strokes. Interestingly, this has not been fully borne out. Stroke rates vary greatly in cardiac surgical reports depending on the patient population and the type of surgery; however, in single institution CABG surgery, aortic “no-touch techniques” or off-pump surgery seem to only moderately reduce stroke risk. In a large-scale study of over 16 000 patients, Bucerius described a stroke rate of 3.9% in CABG with conventional bypass versus 2.5% in the off-pump group. A similar effect of off-pump surgery is identified by Peel and colleagues who, in a study population of almost 3300 off-pump and 7300 on-pump CABG, found a stroke rate of 1.35% in off-pump and 2.4% in on-pump CABG (see Figure 12.3). This effect of eliminating aortic cannulation, about a 1% decrease in stroke incidence, is similar to that described in a meta-analysis of off-pump surgery results, as well as the stroke reduction identified with surgical management guided by epiaortic scanning. This moderately small, but meaningful effect is important because it indicates that more than half of perioperative strokes may not be related to intraoperative embolization from the aorta. The limited neuroimaging data available support this: brain imaging shows a 30% incidence of subclinical cerebral ischemic events in OPCABG.

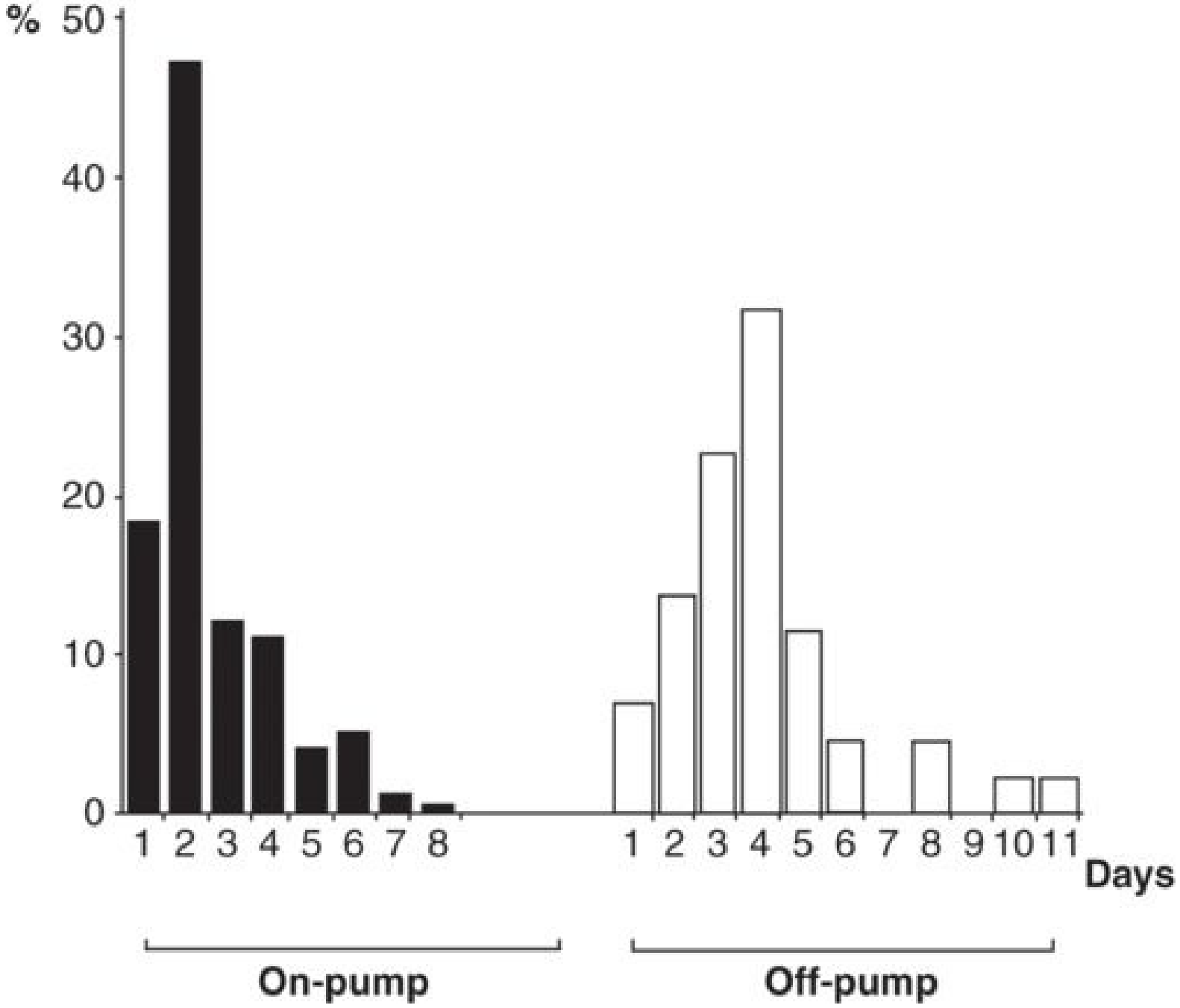

Figure 12.3 Chronological distribution of the onset of postoperative stroke for on-pump and off-pump CABG

(From Garrett K, Peel MHS, Sotiris C, *et al*. Chronological distribution of stroke after minimally invasive versus conventional coronary artery bypass. *J Am Coll Cardiol* 2004;43: 752–6, with permission.)

Aortic "No-Touch" or total arterial grafting

Although avoiding cannulation of the ascending aorta is associated with a stroke reduction of approximately 1% in OPCABG, many OPCABG cases still involve a side-biting aortic cross-clamp, which has been implicated as a source for embolic debris. Newer OPCABG techniques using total arterial conduits with bilateral internal thoracic arterial conduits do not require proximal aortic

anastomosis so are viewed as the most practical way of reducing embolization from aortic manipulation. While theoretically advantageous, this technique is often insufficient at providing conduits of adequate length to address all areas requiring revascularization. While graft extension with free grafts is helpful, supplementation with additional grafts (requiring proximal aortic anastomoses) is often required to achieve complete revascularization. Newer devices such as the HEARTSTRING proximal seal system (Guidant Corporation) allow formation of proximal aortic anastomosis without the application of aortic cross-clamping. A study published by Emmert and colleagues in 2011 compared 4314 patients undergoing either on-pump or OPCABG. The OPCABG group was further subdivided into patients that received a proximal side clamp or the HEARTSTRING system. It is unclear as to how the authors divided the OPCABG group into proximal side clamp or HEARTSTRING cohorts. Patients receiving total arterial grafting without aortic manipulation acted as a control. There was a net 1% stroke reduction when comparing the on-pump and OPCABG groups. However, the subgroup using the HEARTSTRING system had a 0.7% stroke rate vs 2.3% for the traditional side-biting clamp. The 0.7% stroke rate is similar to that seen with the total arterial graft group (0.8%). This data suggests that perhaps stroke reduction can be obtained during OPCABG using techniques that avoid side-biting clamps on the proximal aorta. While off-pump techniques or total arterial revascularization are not suitable for all patients or all surgeons, there is clear evidence that they are advantageous and should probably be considered whenever practical. There is also data to suggest that strokes that occur with off-pump and on-pump CABG have different timing.

Timing of cardiac surgery-related stroke

Given the low incidence of perioperative stroke, the vast majority of clinical studies have been retrospective to attain study populations of sufficient size. They typically have relied on data identifying a diagnosis of stroke recorded on discharge and have rarely identified the timing of an adverse cerebral event. However, one of the most important publications on perioperative stroke in cardiac surgery demonstrated that more than 50% of perioperative strokes occurred postoperatively (see Figure 12.4). This has been confirmed in at least three subsequent investigations from other institutions. In one retrospective study of 10 573 patients, nearly 73% of strokes occurred after the patient had woken from surgery without neurological deficit. The implications of this observation have not been fully appreciated and are important because the etiology and prevention of early and delayed stroke are likely to be different. As such, current bias towards intraoperative interventions would have an impact on less than 50% of the strokes observed in practice.

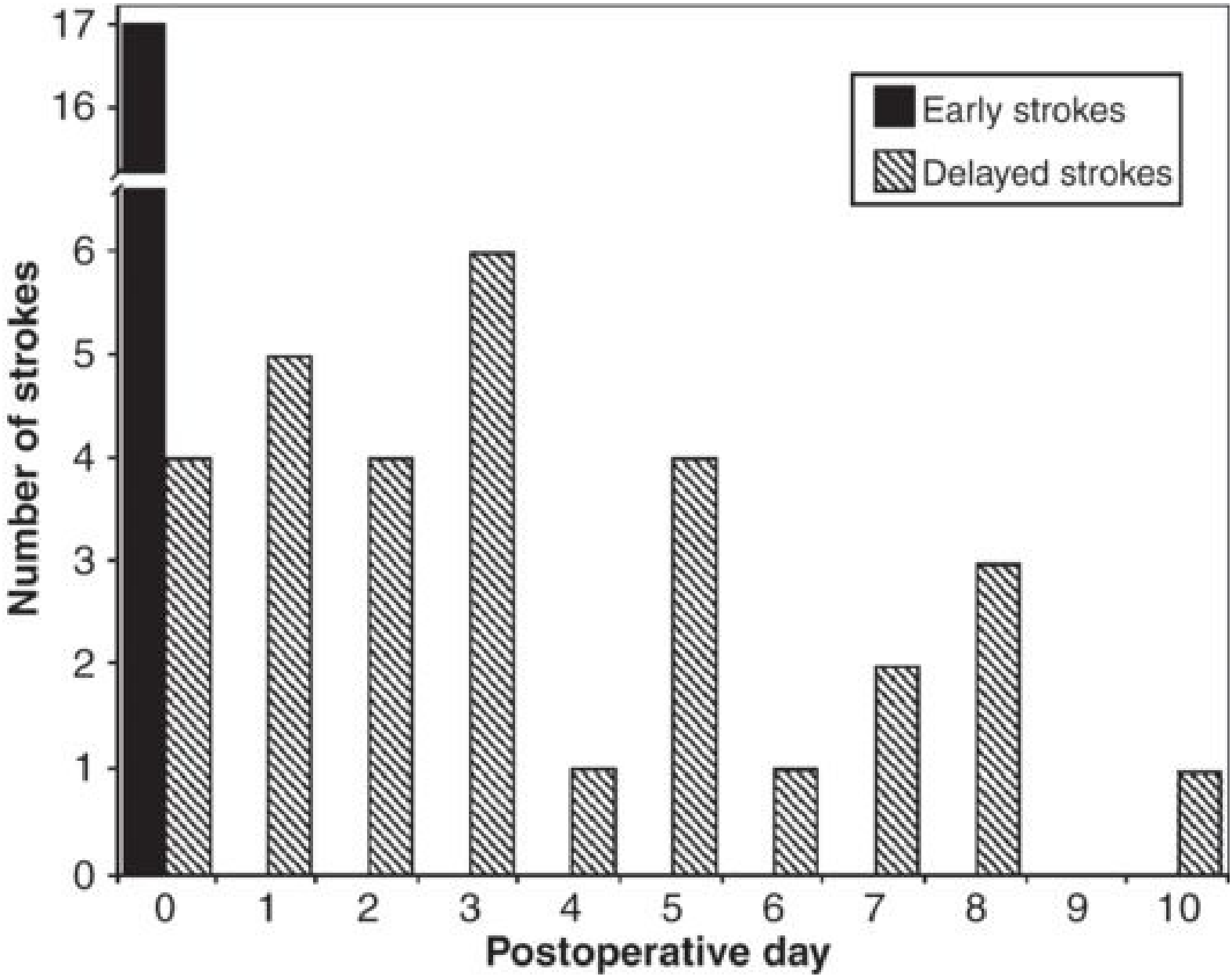

Figure 12.4 Number of strokes detected immediately after surgery (early strokes) and after initial uneventful neurological recovery (delayed strokes) by day neurological event was detected. Note: postoperative day 0 refers to day of surgery, which begins after arrival in intensive care unit

(Hogue CW Jr, Murphy SF, Schechtman KB, Dávila-Román VG. Risk factors for early or delayed stroke after cardiac surgery. Circulation 1999; 100: 642–647, © 1999 American Heart Association, Inc.)

Using multivariate analysis in a study population of 1172 patients, Zingone and colleagues found that early strokes were significantly more frequent in patients with ascending aortic atherosclerosis while delayed strokes were most strongly predicted by patient age. Reinforcing this was their observation that aortic scanning and changing surgical technique had far greater impact on early stroke than on delayed stroke. A conclusion of this study was that for the majority of late strokes a plausible mechanism different from aortogenic embolism could be identified: in their study, the most prominent mechanisms were

postoperative CPR and atrial fibrillation (AF). Comparison of stroke data in on-pump and off-pump CABG is also supportive of precipitating events. Peel and colleagues looked at stroke timing in on-pump and off-pump CABG patients and found that on-pump CABG was associated with earlier events than off-pump CABG.

The origin of delayed strokes may also be embolic, but relatively little research has gone into investigating their etiology or prevention. Apart from rarer interventions such as ventricular assist devices or cardiac arrest with CPR, postoperative stroke might result from aortic plaques, which become unstable at the time of surgery, aortic suture lines or disruption of the aortic surface, or embolism of cardiac thrombi resulting from “sludging” in the left atrium due to AF or generalized left atrial enlargement.

In the geriatric general cardiology population, AF has a high incidence of associated stroke with clot formation in the left atrium, occurring early after the onset of AF. In cardiac surgical patients, the overall incidence of AF is about 25% and in some populations the incidence of new-onset AF can be as high as 60%. Data from a variety of sources indicate that postoperative AF may be responsible for at least 30% of late strokes. In studies separating early and late strokes, multivariate analysis consistently shows that postoperative AF is an independent predictor of late stroke and has been reported to be associated with a six-fold increase in stroke risk, on average most likely to occur on postoperative day 3 or 4. In addition to the thromboembolic risk from an atrium in fibrillation, postoperative stroke may also result from thrombus formation associated with regional wall motion abnormalities, or from thrombus originating on left heart suture lines. This is more likely in low cardiac output states. Prophylactic postoperative therapy with antiplatelet drugs, such as aspirin, may thus improve neurological as well as cardiac outcomes in certain groups of cardiac surgical patients (see Figure 12.5).

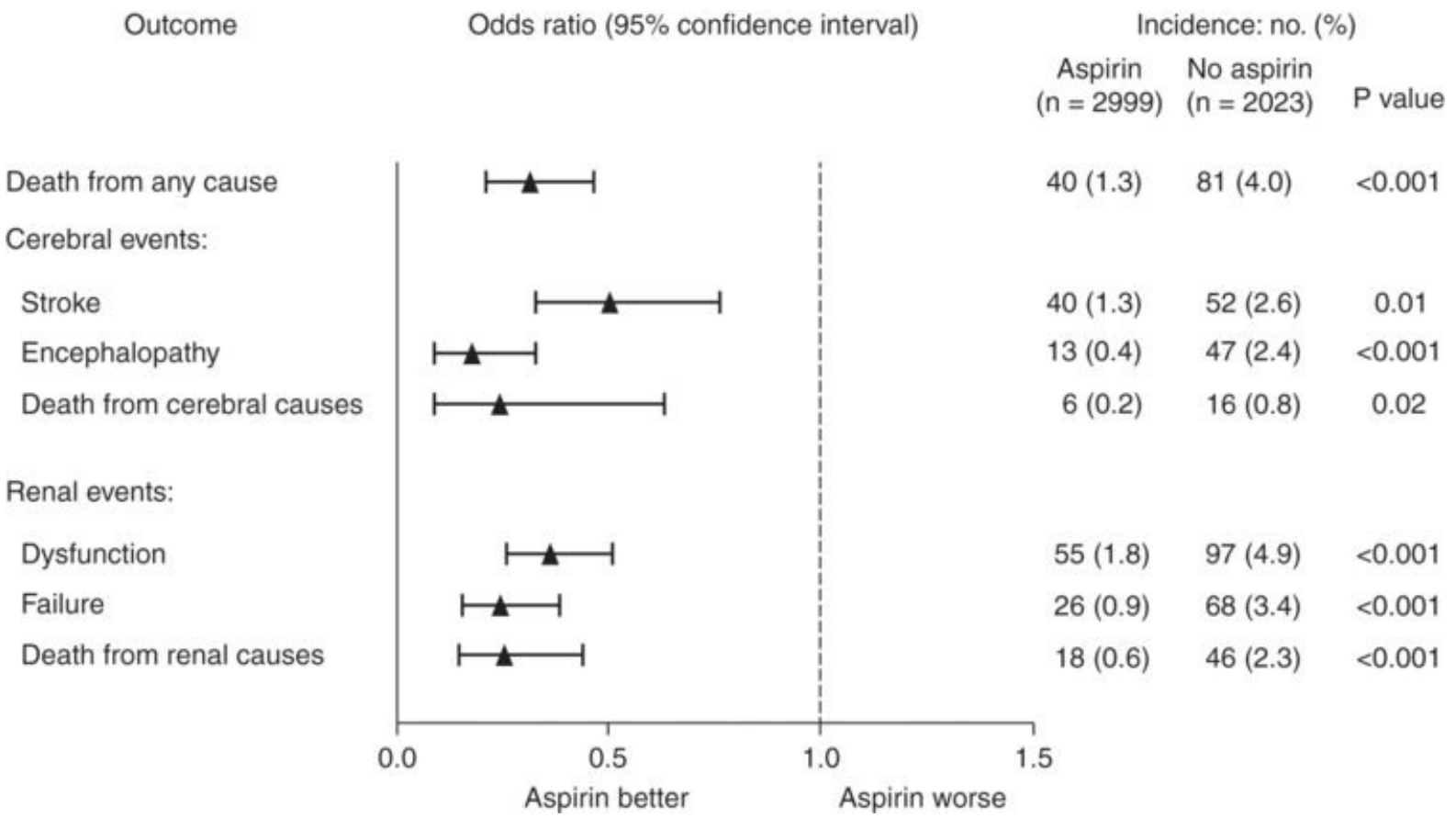

Figure 12.5 Fatal and non-fatal ischemic outcomes among patients who received aspirin within the first 48 hours and patients who did not. The number of patients at risk varied with the type of outcome, since outcomes occurring within 48 hours after surgery were excluded from the analysis. A total of 73 patients had multiple causes of death

(Modified with permission from Mangano DT, *et al*. *N Engl J Med* 2002;347: 1309–17, figure 1.)

Stroke risk in the general population

History of a prior cerebral ischemic event is one of the most powerful predictors of perioperative stroke in cardiac surgery. In the study by Hogue and coworkers, prior stroke increases the risk of an early perioperative stroke by almost 12-fold and the risk of a delayed stroke by nearly 28-fold, which suggests that delayed stroke may be more related to patient-intrinsic risk factors than specific intraoperative events (see Table 12.2).

Table 12.2 Strokes classified depending on whether the neurological deficit was identified either immediately after surgery (early events) or after initial uneventful neurological recovery (delayed events)

Variable	Odds ratio (95% CI)	*P*
Early strokes		
History of stroke	11.6	<0.001

Female sex	6.9	0.004
Ascending aorta atherosclerosis	2.0	0.004
CPB time	1.1	0.005
Delayed strokes		
History of stroke	27.6	<0.0001
Diabetes	2.8	0.008
Female sex	2.4	0.028
Low cardiac output syndrome and atrial fibrillation	1.7	0.033
Ascending aorta atherosclerosis	1.4	0.047

Odds ratio reflects risk of stroke with increase in a single level in the aortic scan results. The odds of an increase of 2 levels (e.g. normal to moderate/severe) is the square of the reported odds ratio.

From Hogue CW, *et al*. *Circulation* 1999; 100: 642–7, table 6 with permission.

Risk factors for stroke include:

- Hypertension
- Atrial fibrillation
- Diabetes
- Prior stroke

The practice of cardiology concentrates the highest risk general population patients under its care and often refers those of greater risk to cardiac surgery. As such, the risk of stroke and renal disease is progressively distilled and concentrated from general internal medicine to cardiology and then into the cardiac surgical population.

The American Heart Association provides population statistics for major cardiovascular disorders and the 2008 report identifies an overall stroke prevalence of 2.6% in the general population. The prevalence of stroke in 60- to 79-year-olds is about 6.3% and close to 13% in those aged over 80. Even more specific for understanding neurological injury in cardiac surgery is the incidence of annual hospital stroke admissions for diabetic and non-diabetic patients (see Figure 12.6), which shows that for diabetic

patients over age 65 their annual likelihood of hospital admission for stroke is 3–7%. This population data places the incidence of perioperative stroke in an important light. It indicates that the likelihood of perioperative stroke (generally thought of as 2–4% in moderate-risk patients) is nearly identical to the annual risk in the general population. This is not to say that cardiac surgery is not responsible for strokes; however, it is helpful to consider that the perioperative experience may be precipitating the existing stroke risk. If we think of cardiac surgery as precipitating pre-existing, population-based risk, very important parallels between neurological and renal dysfunction following cardiac surgery are evident.

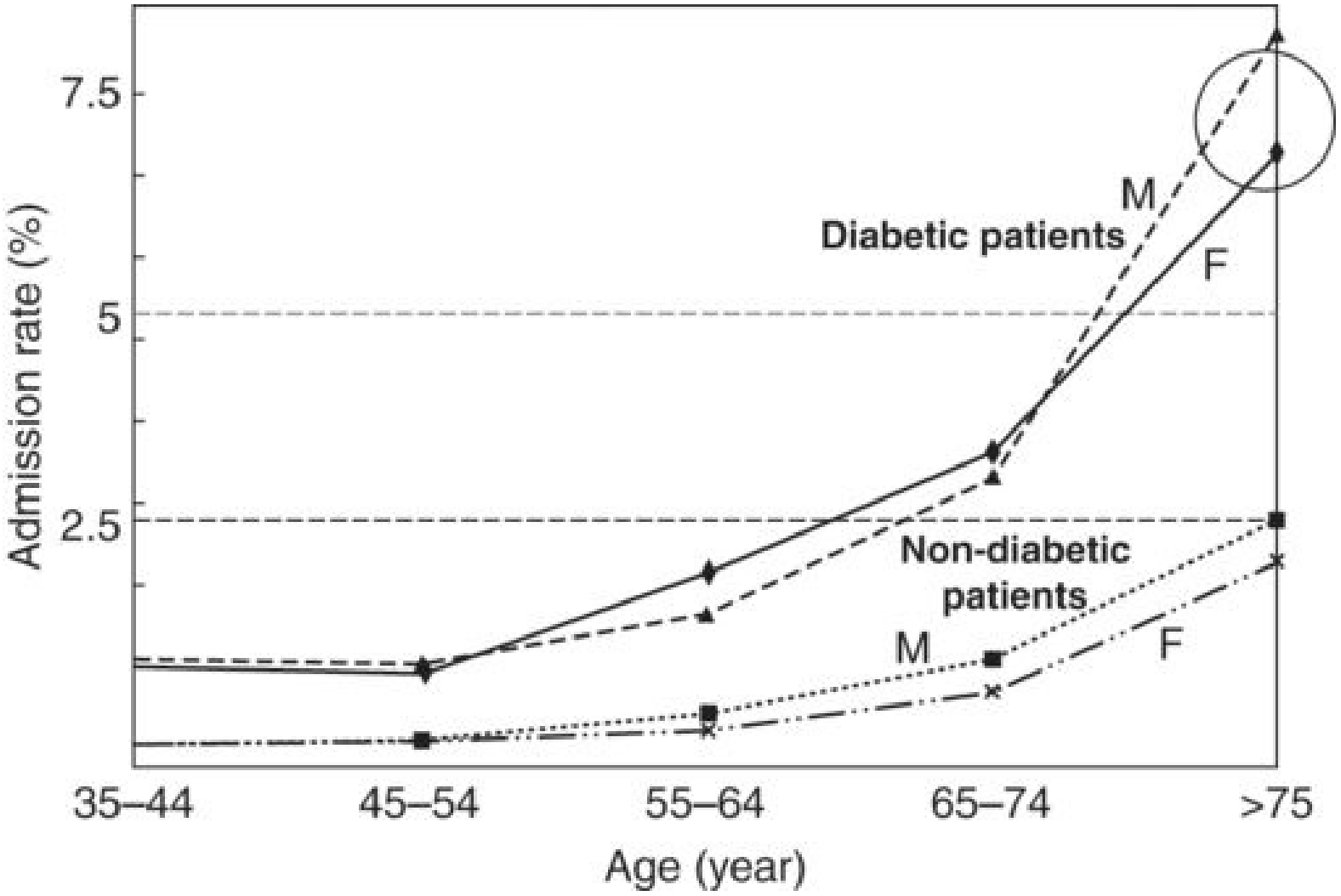

Figure 12.6 Age- and sex-specific annual admission rates for cerebrovascular disease (CVD) in patients with and without diabetes in the general UK population

(Modified with permission from Currie CJ, Morgan, CL, Gill L, Stott NCH, Peters JR. *Stroke* 1997; 28: 1142–6, © 1997 American Heart Association, Inc., figure 1.)

In the general population, those who have had transient ischemic attacks (TIAs) have an approximately 50% chance of stroke within the next 6 months and an approximately 10% risk of another stroke within 2 years. In fact, the predictive value of prior stroke on all major adverse cardiovascular outcomes is profound, particularly in low-income patients. Table 12.3 shows the high incidence of

recurrent stroke and mortality from cardiovascular causes in those who have had a prior stroke. These are the population-based risks independent of hospitalization, interventional cardiology or cardiac surgery.

Table 12.3 Cumulative occurrence of secondary events in Medicare sample by cohort and type of secondary event

Time since initially identified event (years)	**Stroke cohort (n = 1518) type of secondary event (%)**		
	AMI	Stroke	OVD
0.5	0.7	3.7	0
1	1.6	6.2	0
2	3.4	10.8	0.3
3	5.1	12.2	1.8

AMI = acute myocardial infarction; OVD = other vascular death.

Modified with permission from Vickrey BG, *et al*. *Stroke* 2002; 33: 901–6, table 4.

While cardiac surgeons are reluctant to take patients to the operating room with recent stroke (primarily because of hemorrhagic risk), the clinical implications of a history of cerebrovascular events are underappreciated. A Cleveland Clinic study analyzed 126 patients with prior stroke undergoing cardiac surgery. It demonstrated that 17% of patients who had had a stroke within 3 months before surgery had a new perioperative stroke while those with prior stroke more than 3 months before surgery had a 12% incidence of new perioperative stroke. In patients with perioperative strokes, those with a more recent history of stroke appeared to be more sensitive to perioperative hypotension than those with more remote events, suggesting persistent cerebral vulnerability of these patients to hemodynamic instability.

Placing cardiac surgical stroke in the context of the stroke risk in the general population strongly suggests that:

- The most profound determinant of neurological outcome is the patient's previous medical history rather than a specific intraoperative event.
- A large proportion of adverse outcomes may result from the precipitation or triggering of patient risk factors by events in the perioperative period.

Neurocognitive outcomes after cardiac surgery

If we think of perioperative stroke as being intimately related to pre-existing population-based risk, similar observations can be made for postoperative cognitive change. Post-cardiac surgical cognitive decline has been an area of intense interest in the previous decade. Depending on the assessment tools, study timing, and design, the incidence of early postoperative cognitive change is 35–85% with longer-term dysfunction seen in up to 10–30% of patients. It has also been suggested that the perioperative cardiac surgical experience was responsible for worsened cognitive status up to 5 years following surgery.

Because cognitive change is far more frequent than stroke, it became the endpoint of many outcomes trials in the last several years. However, no intervention has resulted in a clinically meaningful reduction in its incidence. The most likely intervention to reduce cognitive injury should be off-pump surgery because exposure to CPB and instrumentation of the ascending aorta is eliminated. However, randomized studies with sufficient numbers of patients have failed to show a clinically meaningful effect. The trial by Van Dijk randomized patients to on- or off-pump CABG. At 3-month follow-up 21% of off-pump and 29% of on-pump patients showed cognitive decline, while at 1 year follow-up decline had occurred in 31% of off-pump and 34% of on-pump patients (see Table 12.4). Most studies have concluded that off-pump CABG has better cognitive outcomes, but the differences between groups appear to be so small as to be of limited clinical importance.

Table 12.4 Randomized 142 off-pump, 139 on-pump CABG cognitive assessment at 3 and 12 months

Incidence of cognitive decline (%)	**3 months (P = 0.15)**	**12 months (P = 0.69)**
Off-pump	21	30.8
On-pump	29	33.6

From Van Dijk D, *et al*. *JAMA* 2002; 287(11): 1405–12 with permission.

Several other observations place cognitive change following cardiac surgery in a perspective suggesting origins outside of perioperative injury. Firstly, there is an incidence of cognitive change after major non-cardiac surgery. While of a lower incidence, the character of the cognitive change is the same and in these other types of surgery there is no CPB and little or no risk of cerebral ischemia. Secondly, long-term cognitive outcomes in percutaneous coronary intervention (PCI) patients appear to be no different from those in patients undergoing CABG (see Table 12.5).

Table 12.5 Mean changes in z-scores for coronary artery bypass graft patients and PCI controls for the eight cognitive domains

Domain	Baseline to 3 months: CABG vs. controls	3 to 12 months: CABG vs. controls
Verbal memory	P > 0.017	ns
Visual memory	ns	ns
Language	ns	ns
Attention	ns	ns
Visuoconstruction	ns	ns
Psychomotor	ns	ns
Motor speed	ns	ns
Executive	ns	ns

From Selnes OA, *et al*. *Ann Thorac Surg* 2003; 75(5): 1377–84 with permission.

This is important because CABG and PCI patients are very closely matched for patient (or population) risk factors of age, atherosclerosis, diabetes, and hypertension. If cognitive outcomes at 1 year are the same in these PCI and CABG populations, it suggests that the longer-term cognitive changes described following cardiac surgery are probably an expression of chronic brain changes related to those comorbidities rather than the cardiac surgery itself. Cook and colleagues used diffusion MRI and cognitive testing to document perioperative cerebral ischemia in cardiac surgical patients. They found that approximately 30% of patients showed ischemic changes indicative of postoperative cerebral embolization; however, there was no relationship between perioperative ischemic events and either in-hospital or postdischarge cognitive dysfunction (see Figure 12.7). The incidence of cognitive dysfunction was exactly the same whether or not patients had experienced a cerebral ischemic event. Furthermore, MRI data was suggestive that the cognitive decline was more a function of chronic ischemic microvascular disease than of a perioperative event. This would be consistent with growing neurology literature on chronic organic brain disease, cognition, and occult cerebral ischemia in the general elderly population.

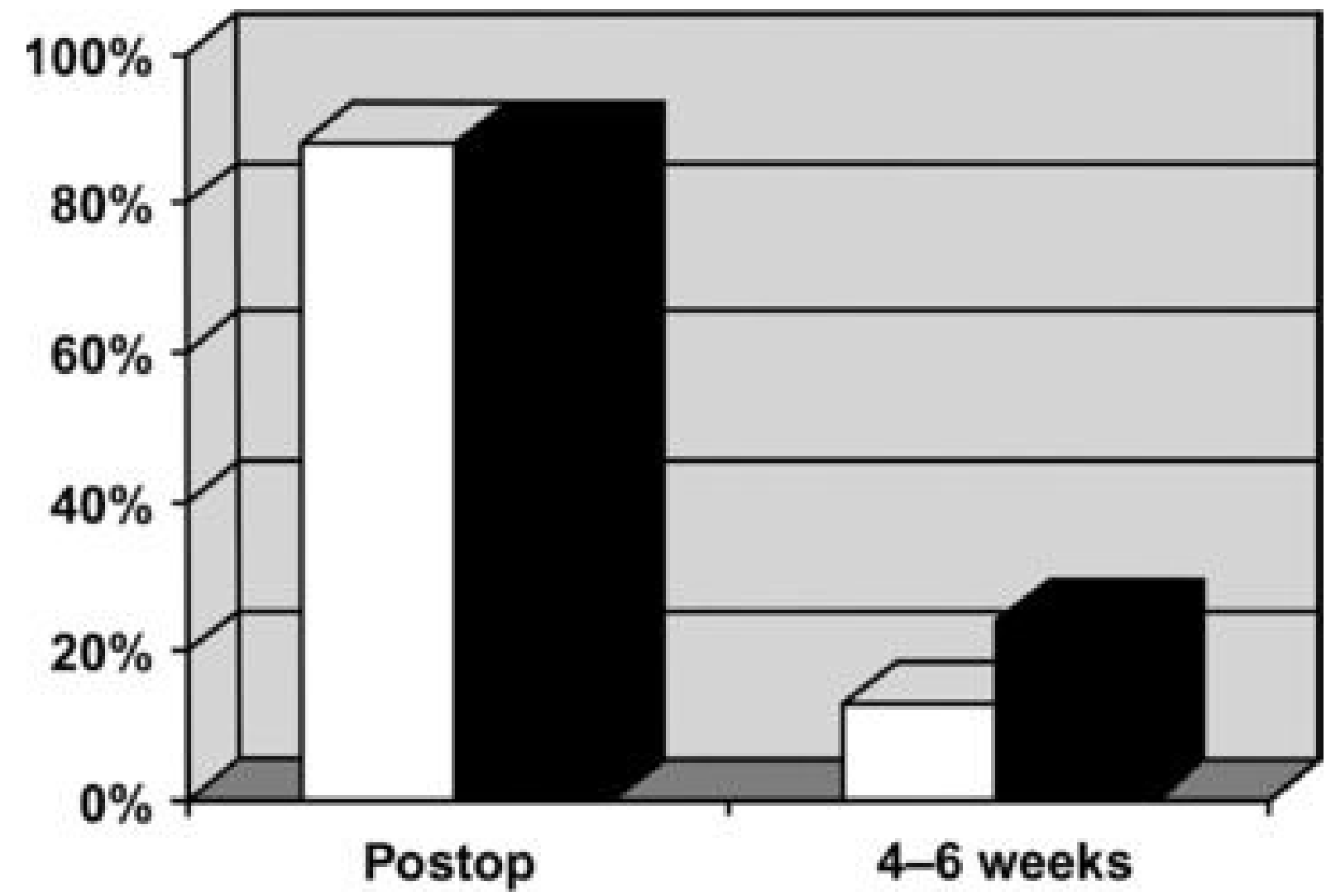

Figure 12.7 Incidence of cognitive decline in cardiac surgery patients with and without acute cerebral ischemia (□ = ischemia; ■ = no ischemia.), $P < 0.05$

(From Cook DJ, *et al*. Post-cardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. *Ann Thorac Surg* 2007; 83: 1389–95, figure 2, with permission.)

Two large studies have used neuroimaging to identify the incidence of occult cerebral ischemia in older cardiology patients: The Cardiovascular Health Survey conducted more than 3000 cerebral MRIs in community cardiology patients and the Rotterdam Scan Study carried out more than 1000 MRIs. These studies found that approximately 20–40% of the general population over 60 years of age have evidence of occult, small-vessel cerebral infarction (see Figure 12.8). This appears to be the result of penetrating vessel disease due to chronic hypertension, diabetes, and atherosclerotic disease. Separate studies have linked this type of chronic small-vessel ischemia to vascular dementia and cognitive change. As such, the cognitive changes seen following cardiac surgery may be the manifestation of underlying chronic brain disease unmasked in the perioperative period by drugs, metabolic changes, sleep deprivation, and environmental changes rather than an expression of a perioperative insult. From this perspective it would

also follow that cognitive declines seen 5 years after surgery are the evolution of underlying chronic brain disease rather than the evolution of an insult occurring in the perioperative period.

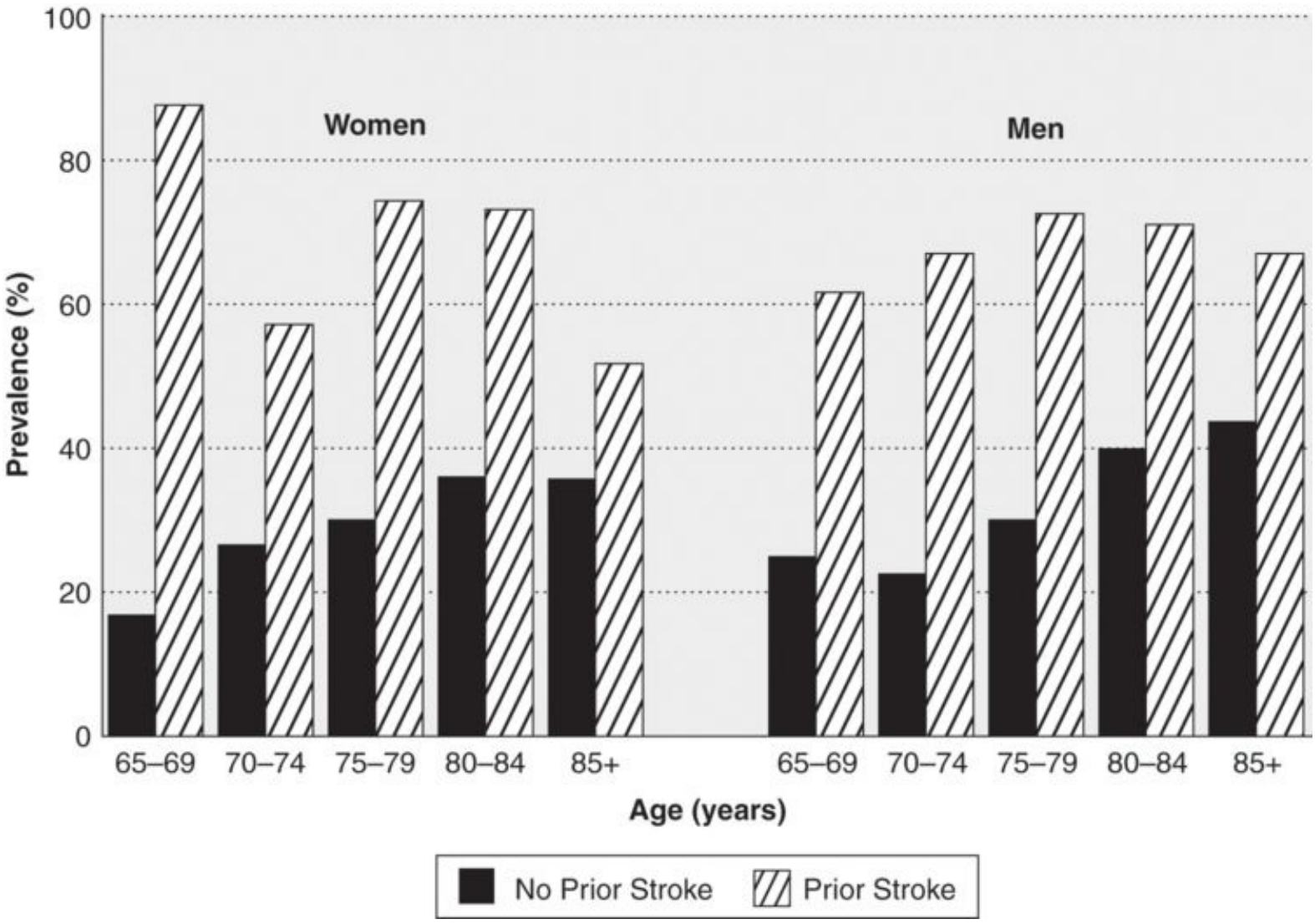

Figure 12.8 Prevalence of MRI infarct by sex, age, and prior stroke. Association with age was significant at $P < 0.0001$ in men and women without prior stroke; sex association was not significant in those without prevalent stroke ($P > 0.1$). Neither sex nor age associations were significant in those with prior stroke

(From Price TR, *et al*. *Stroke* 1997; 28: 1158–64, figure 1, with permission.)

Self assessment

1. Research over the past decade indicates what percentage of strokes associated with cardiac surgery occur in the early postoperative period?

A. 10%

B. 20%

C. 30%

D. 40%

E. 50%

Answer: E

2. Which of the following is false?

A. Flow from the CPB machine is a primary determinant of visceral blood flow

B. Brain perfusion is independent of pump flow if the cerebral perfusion pressure is above the autoregulatory threshold

C. The lower limits of cerebral autoregulation are shifted leftward with moderate hypothermia (27–32°C)

D. Pulsatility is not an important determinant of cerebral blood flow

Answer: C

3. The decrease in mean arterial pressure with transition onto CPB is primarily a function of which of the following:

A. A total pump flow less than is common in the intact circulation

B. Humoral responses that result in vasodilatation

C. Acute hemodilution

D. Loss of arterial pulsatility

E. Sudden change in concentration of anesthetic levels

Answer: C

4. Off-pump surgery combined with a complete “no-touch” technique for the ascending aorta (all arterial grafting, no proximal anastomoses) is associated with about a 90% decrease in perioperative stroke relative to on-pump CABG with proximal anastomoses?

A. True

B. False

Answer: B

5. Which of the following statements about CPB temperature are false?

A. The reductions in cerebral oxygen demand with decreasing temperatures are relatively predictable

B. The differences between alpha- and pH-stat management grow progressively greater as temperature is reduced

C. Cardiopulmonary bypass conducted at 33–35°C has not been associated with increases in neurological injury relative to routine adult cases conducted below 30°C

D. A 5°C reduction in temperature more than offsets the decrease in whole body systemic oxygen delivery associated with modest hemodilution (Hct=24–26%) if pump flows are greater than 2.2 l/minute/m^2

E. Nasopharyngeal temperature typically overestimates the arterial inflow temperature

Answer: E

6. Which of the following statements about neurocognitive outcomes following cardiac surgery are false?

A. The rate of bypass re-warming is clearly demonstrated to determine these outcomes

B. Adverse neurocognitive outcomes typically get better over the weeks following surgery

C. Adverse neurological outcomes has shown no correlation with diffusion MRI evidence of ischemia

D. There is a clear association between age and adverse neurocognitive outcomes

E. Neuromonitoring has not been demonstrated to impact this adverse event

Answer: A

Suggested Further Reading

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Chapter 13

Acute kidney injury (AKI) in cardiac surgery

Robert C. Albright Jr.

The incidence of perioperative renal injury appears to be increasing in the ever more complex elderly population presenting for cardiac surgery. More often than not acute kidney injury (AKI) is associated with well-defined risk factors that precede the surgical event. AKI complicates cardiovascular surgery in as many as 30% of all procedures, leading to dramatically worse outcomes, including increased mortality and substantial financial cost.

The incidence of AKI requiring dialysis among patients who undergo coronary artery bypass grafting alone is roughly 1%. However, when valve surgery or coronary artery bypass grafting and valve surgery occur concomitantly, the risks of AKI requiring dialysis are 1.7 and 3.3%, respectively. The risks for AKI rise substantially if there is pre-existing chronic kidney disease (CKD), which afflicts as many as 30 million people in the USA.

Definitions

Lack of a universally accepted definition of the syndrome of acute renal failure has hampered the study, understanding, management, and prevention of this disastrous complication. The complexities of the accompanying fluid, electrolyte, acid–base, and azotemic solute accumulation have led to approximately 50 different diagnostic criteria for acute renal failure to be cited in the literature.

A subgroup of intensivists and critical care nephrologists has formed the AKI Outcomes and Quality Study Group. This group has agreed upon a new definition of acute renal injury, acute kidney injury (AKI) which replaces the term “acute renal failure” and enhances the recent Risk, Injury, Failure, Loss, End-stage (“RIFLE”) criteria.

AKI is generally defined as an abrupt decline in kidney function over less than 48 hours with an increase in serum creatinine of 0.3 mg/dl (greater than 25 μmol/l) or a 50% increase over baseline, accompanying a urine output of less than 0.5 ml/kg/hour.

- **Stage I –** An increase in serum creatinine of greater than 0.3 mg/dl or greater than 150% increase in baseline and urine output of 0.5 ml/kg/hour for 6 hours.
- **Stage II –** A serum creatinine increase of greater than 200–300% over baseline with concomitant decreased urine output to < 0.5 ml/kg/hour for the past 12 hours.
- **Stage III –** An increase in serum creatinine greater than 300% over baseline, or an absolute level of greater than 4 mg/dl, accompanying a urine output of < 0.3 ml/kg/hour) for the past 12 hours. Also included within the stage III definition would be any patient who requires renal replacement therapy.

However, even this new definition is limited by the utilization of increasing creatinine as the serum marker of decreased renal function (decreased glomerular filtration rate, GFR). Increased serum creatinine is well known to lag significantly behind the development of acute injury, and is confounded by its dependence on tubular secretion and relationship to muscle mass and catabolism. Biomarkers of AKI, including serum and urine neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin C, interleukin 17 (IL-17) and kidney injury marker-1 (KIM-1), are relatively new markers of kidney injury and poor kidney function. NGAL has been shown to be an excellent predictor of AKI in the pediatric population, specifically in the cardiovascular surgical population. Serum and urinary increases in NGAL preceded increase in creatinine by over 2 days. Recent data has suggested that NGAL may also be of value in adult perioperative patients.

Outcomes associated with AKI

It is difficult to overstate the negative clinical impact of AKI on outcome after cardiovascular surgery. Any AKI occurring in the perioperative period carries an accompanying mortality rate of 15–30%, increasing substantially to at least 50% when dialysis is required. In fact, an adjusted covariant-independent observation of an eight-fold increase in death rate has been reported among a large cohort of cardiovascular surgical patients (see Table 13.1).

Table 13.1 Influence of renal dysfunction and AKI on the incidence (%) of mortality and duration of intensive care unit and hospital stay (LOS) (in days) after coronary revascularization

	Mortality (%)	ICU LOS (days)	Hospital LOS (days)
Normal renal function	0.9	3.1	10.6
Renal dysfunction	19.0	6.5	18.2
AKI	63.0	14.9	28.8

Adapted from Mangano CM, Diamonstone LS, Ramsey JG, *et al*. Renal dysfunction after myocardial revascularization: risk factors, adverse outcomes and hospital utilization. *Ann Intern Med* 1998; 128: 194–203.

Even slight decreases in GFR imply an increased mortality risk: an increased mortality risk of four- to five-fold with any increase in serum creatinine has been reported among patients followed for 1 year. A 30% decrease in GFR during the perioperative period is associated with a 6% overall morality over the subsequent year, as compared with 0.4% mortality without an accompanying AKI. When dialysis is required for AKI, recovery of renal function sufficient to discontinue chronic dialysis occurs in less than half of these patients. This obviously leads to a dramatic decrease in quality of life and longevity (20% mortality rate per year).

The cause of death associated with AKI is most often infection. In fact, approximately 58% of patients with AKI requiring perioperative dialysis in the cardiovascular surgery arena have a diagnosis of sepsis as compared to 3.3% of those without AKI. Whether the sepsis was the cause or result of the AKI is not determined in these studies.

The risks for bleeding, wound complications, and nutritional compromise are also increased among patients with AKI.

Risk factors for AKI

Generally, the risk factors for developing AKI can be separated into those that are patient related versus those that are procedure related. Patient-related factors are predominant, once again emphasizing the overwhelming consequences of the ageing population with their concomitant increased burden of chronic illness. The most important patient-related issue predicting AKI is pre-existing chronic kidney disease. There is an overall 10–20% risk of AKI requiring dialysis among cardiac surgical patients with a serum creatinine preoperatively of 2–4 mg/dl, and the risk of requiring dialysis increases to nearly 28% with a preoperative serum creatinine of greater than 4 mg/dl.

The proportional impact of pre-existing subclinical renal insufficiency is extremely well illustrated by the decade-old study by Chertow. In a study of 43 000 patients, Chertow used multivariate analysis to identify independent risk factors for dialysis in cardiac surgical patients. A fraction of his data is presented in Table 13.2. Of greatest importance is the profound effect of moderately reduced creatinine clearance (CrCl) on the likelihood of postoperative dialysis. In this study, approximately 60% had a CrCl less than 80 ml/minute resulting in an odds ratio for dialysis similar to the odds ratio for dialysis in patients who have had prior heart surgery. The weight of the numbers is astonishing. Anesthetists and surgeons think of prior heart surgery as a profound risk factor, but Chertow demonstrates that moderate decreases in preoperative CrCl are as potent a predictor of postoperative dialysis. Even more important, there are five times as many patients with subclinical renal insufficiency as those who undergo redo operations. Given the "normal" declines in CrCl seen as adults age from 65 to 80 years, the importance of this risk factor cannot be overestimated.

Table 13.2 Laboratory evaluation of acute kidney injury

	Prerenal	**Intrinsic renal**	**Postrenal**
BUN/Cr ratio	> 20	10–20	10–20
Urine specific gravity	> 1.020	~ 1.010	> 1.010 early, < 1.0101 late
Uosmol (mosmol/kg)	> 350	~ 300	> 400 early, ~ 300 late
U Na (mEq/l)	< 20	> 30	< 20 early, > 40 late
FE Na (%)	< 1*	> 2–3	< 1 early, > 3 late
U Cr/P Cr ratio	≥ 40	≤ 20	> 40 early, ≤ 20 late
Urine microscopy	Normal, hyaline casts	ATN: dark granular casts, hyaline casts, renal epithelial cells/casts GN: RBCs, dysmorphic RBCs (> 20%), RBC casts, WBC/WBC casts, proteinuria AIN: urine eosinophilia,	

	WBC, WBC casts, hyaline casts (consider CES)

AIN = acute interstitial nephritis; ATN = acute tubular necrosis; BUN = blood urea nitrogen; CES = cholesterol emboli syndrome; Cr = creatinine; FE Na = fractional excretion of sodium (calculated as: U Na/P Na × P Cr/U Cr × 100); GN = glomerulonephritis; P Cr = plasma creatinine; P Na = plasma sodium; U Cr = urinary creatinine; U Na = urinary sodium; Uosmol = urinary osmolality.

* Falsely low FE Na seen occasionally with acute GN, radiocontrast nephropathy, rhabdomyolysis.

Other associated patient-related risk factors include pre-existing diabetes mellitus, female gender, increasing age, preoperative congestive heart failure, peripheral vascular disease, preoperative balloon pump requirements, chronic obstructive pulmonary disease, emergency surgery, anemia, and, although somewhat controversial, decreased serum ferritin level.

Whether on-pump versus off-pump cardiac surgery may lead to increased risk for AKI has continued to spur controversy. A meta-analysis of randomized controlled trials (4819 patients) determined a 40% relative risk reduction of AKI when defined as an increase in serum creatinine greater than 50% at 30 days. However, no difference was noted in the combined risk of death, MI, stroke or in the requirements for new dialysis (13%). Long-term renal outcomes have recently been published, showing no long-term benefit from off-pump CABG versus on-pump CABG. Subset analysis suggested a potential benefit among CKD patients managed with an off-pump strategy; however this has yet to be proven in a randomized prospective fashion. Difficulties in weaning from CPB and postoperative intra-aortic balloon pump (IABP) are intuitive additional risks for AKI.

No single etiological factor is responsible for the development of postoperative AKI, but a number of related factors certainly interact to contribute to cause renal injury.

Etiology of AKI

In this context, the principal etiological factors are reduction in renal blood flow during CPB, the mediators generated by the systemic inflammatory response syndrome (SIRS) accompanying CPB, and the translocation of endotoxins from the gastrointestinal tract.

Under normal circumstances blood flow to the kidney remains constant despite variations in blood pressure in the range from 80 to 200 mmHg; the kidney thus autoregulates its blood supply. The kidney receives approximately 20% of the total cardiac output (about 1 l/minute). Oxygen delivery thus exceeds

80 ml/minute/100 g tissue. The distribution of blood flow within the kidney is not uniform, with the cortex receiving more than 90% of total blood flow.

Oxygen consumption, however, is less than 10% of total body utilization, and thus there is a low arteriovenous oxygen content difference (1.5 ml oxygen per 100 ml blood). The low oxygen extraction by the kidney suggests that supply exceeds demand and that there should be an adequate oxygen reserve. However, the kidney is highly sensitive to reduction in perfusion, with AKI being a frequent complication of hypotension. The sensitivity of the kidney to damage as a result of hypoperfusion, despite its low overall oxygen consumption, is related to the physiological gradient of intrarenal oxygenation. Within the kidney the cortex and medulla have widely disparate blood flows and patterns of oxygen extraction.

Although a high percentage of blood goes to the cortex (about 5 ml/minute/g), the cortex extracts only about 18% of total oxygen delivered to it. On the other hand, the medullary region has a far smaller blood flow (0.03 ml/minute/g), but has a far greater extraction (about 79% of the delivered oxygen), as a result of the high oxygen requirement for tubular reabsorption of sodium and chloride ions.

Medullary oxygenation is normally strictly balanced by a series of control mechanisms, which match regional oxygen supply and consumption. Failure of these controls renders the outer medullary region susceptible to acute or repeated episodes of hypoxic injury, which may lead to acute tubular necrosis (ATN).

Hypoxia and renal damage

The differing requirements of cortex and medulla for blood flow and oxygen result in an oxygen tension in the cortex of about 50 mmHg higher than that of the inner medulla. This explains why renal tubules are extremely vulnerable to hypoxic injury and why ATN can be induced by as little as a 40–50% decrease in renal blood flow.

SIRS and endotoxins

Many of the inflammatory mediators generated by the SIRS associated with CPB are potentially damaging to the kidney. Injury by these mediators results from direct cellular effects, their ability to directly cause vasoconstriction and so impair blood flow, and by their effects on endothelial function in general. For example, during CPB the production of nitric oxide, a smooth muscle relaxant produced by endothelial cells, is reduced and the production of endothelin-1, a potent vasoconstrictor, is increased.

Whilst endotoxins may be directly nephrotoxic, the associated inflammatory responses to circulating endotoxins, in particular the generation of the proinflammatory cytokines such as TNF, mediate further renal damage.

Prevention of AKI

General measures that have been proven to prevent AKI include adequate preoperative hydration, avoidance of nephrotoxins (particularly radiocontrast dye and non-steroidal anti-inflammatory drugs (NSAIDs)) and optimization of hemodynamic parameters.

Disappointingly, there is no evidence-supported specific fluid or vasopressor strategy which can be endorsed. Crystalloids, as opposed to colloids, have shown no distinct benefits in preventing AKI when determining IV fluid strategies. However, Hydroxy-Ethyl-Starch has been associated with an increase in sepsis-associated mortality among patients undergoing CABG.

Unfortunately, pharmacological interventions as a whole have been disappointing in their ability to prevent AKI. Diuretics, including loop diuretics and mannitol, have been evaluated in multiple trials. Most of these have not been controlled or randomized. Treatment with diuretics is often initiated in response to a decrease in urinary flow or clinical signs of volume overload; these situations may be harbingers of/or associated with AKI, but may also be due to decreased effective circulating volume, poor cardiac output or, rarely, urinary tract obstruction. Clearly, diuretics would not be expected to be successful therapeutic interventions specifically for AKI in these situations. Electrolyte imbalance, metabolic alkalosis, and renal tubular damage are all associated with diuretics, leading to concerns about increasing clinical risk with their use.

Studies that have evaluated preoperative use of loop diuretics have shown no benefit in their ability to prevent, correct or shorten the duration of AKI. A non-randomized trial of immediate postoperative utilization of a “cocktail” of mannitol and furosemide compared to furosemide alone among patients deemed high risk for AKI (creatinine > 2 mg/dl) demonstrated a 50% decrease in risk of permanent dialysis. However, this study did not control for severity of illness, perioperative events, IABP use or administration of vasopressor drugs. Small series have suggested a benefit from utilization of mannitol in the pediatric population at a dose of 0.5 g/kg body weight. It has been proposed that this is due to mannitol’s non-diuretic “free radical scavenger” effect.

Angiotensin converting enzyme inhibitor (ACE-i) or angiotensin receptor blocker (ARB) agent use in the perioperative time frame remains controversial. While a prospective observational trial showed a postoperative decrease in AKI, there is a preponderance of retrospective data suggesting an increased AKI incidence with their continuation during the perioperative period.

Statin use in the early postoperative time frame has been shown to decrease the risk of AKI. This data will need long-term follow up before their use becomes clinically acceptable for this purpose.

Dopamine, utilized at its “renal dose” of 1–3 μg/kg/minute, has long been widely accepted as an agent for the prevention and treatment of AKI. However, recent randomized trials have disproven its

benefit. Whether it may have a role in truly diuretic-resistant volume overload, due to its proximal renal tubular natriuretic effects, remains controversial.

Fenoldapam is a more specific dopaminergic agent that has been proposed as an alternative to dopamine. Unfortunately, a controlled trial among patients with chronic kidney disease (CKD) undergoing CABG receiving presurgical angiography showed that the agent failed to prevent AKI, nor did its use reduce 30–day mortality, dialysis requirements or decrease re-hospitalization rates.

N-acetylcysteine has shown some promise in trials in preventing radiocontrast nephrotoxicity. However, a randomized, controlled trial of approximately 300 CKD patients undergoing CABG at high risk for AKI revealed no benefit of *N*-acetylcysteine.

Natriuretic peptides are theoretically attractive as agents for the prevention of AKI. Synthetic atrial natriuretic peptide (ANP), anaritide, and a synthetic brain natriuretic peptide, neseritide, have been studied in the context of AKI and congestive heart failure. The ability of these agents to prevent AKI, decrease mortality rates, and lessen the clinical severity of AKI in multiple models (sepsis, ischemia, toxin exposure) has been demonstrated in animals. Unfortunately, a randomized, double-blind controlled human trial of patients undergoing CABG with or without mitral valve repair showed no clinically meaningful benefit. Natriuretic peptides have also failed to prevent AKI among patients with congestive heart failure.

Theophylline, anti-oxidant supplements (selenium, zinc, vitamin C, and vitamin B1), dexamethasone, pentoxyphyline, clonidine, and diltiazem have also been evaluated as preventative agents. Unfortunately, none of these agents proved superior to standard care/placebo therapy with respect to prevention of AKI.

Finally, prophylactic dialysis has been proposed for patients with pre-existing advanced kidney disease. Mortality and prolonged requirement for dialysis was studied among a very small, non-controlled cohort of patients treated with prophylactic dialysis (serum creatinine preoperatively greater than 2.5 mg/dl). Mortality decreased from 30% to 5% and 30–day dialysis requirement was less common in the interventional arm. This controversial approach has yet to be replicated.

Management of dialysis-dependent patients

Patients with CKD who are already dialysis dependent on presentation for cardiac surgery should be dialysed close to the time of operation; generally this is best done in the 1–2 days preceding surgery, to optimize their metabolic and circulatory volume status. Arrangements should also be made for dialysis to re-commence in the early postoperative period. These patients may benefit from intraoperative hemofiltration/ultrafiltration while on CPB to maintain acid–base and electrolytes within normal limits,

particularly to remove the potassium load imposed by cardioplegia administration. Hemofiltration/ultrafiltration may be required in the immediate postoperative period to manage fluid balance as well as biochemical parameters.

In the immediate postoperative period, hemofiltration/ultrafiltration provides a temporizing measure in these patients until they are sufficiently stable to be re-established on their usual dialysis regimen.

Management of patients with non-dialysis-dependent CKD

Patients with evidence of chronic renal impairment, but who do not have sufficiently advanced renal disease to warrant dialysis, may benefit from intraoperative hemofiltration/ultrafiltration while on CPB to optimize acid–base and electrolyte status during surgery. Such patients, as discussed above, have a high likelihood of developing AKI in the postoperative period and may require renal replacement therapy postoperatively until their renal function returns to a viable level.

Therapy for AKI

Supportive therapy for AKI includes avoidance of further nephrotoxins and optimization of ventilation, perfusion, and hemodynamic parameters. Timely management of acid–base and electrolyte abnormalities and ensuring the adequacy of circulating volume are priorities.

Hyperkalemia

Hyperkalemia commonly complicates AKI and may be immediately life-threatening. Emergency treatment of hyperkalemia includes the myocyte membrane-stabilizing effects of calcium chloride or gluconate initially, followed by attempts to reduce plasma potassium levels by shifting potassium from the extracellular space to the intracellular space. Infusion of insulin and dextrose, administration of bicarbonate, and possibly the utilization of beta agonists are first-line approaches. Enhanced renal excretion of potassium in AKI may be facilitated by loop diuretics, but only after ensuring the adequacy of intravascular volume. Administration of colonic binding resins such as polystyrene sulfonate by enema or orally with sorbitol has historically been an accepted clinical practice for use in less acute situations. Recently, documented cases of colonic necrosis associated with the use of binding resins, as well as lack of relative clinical efficacy, have dampened enthusiasm for their use. In the perioperative setting failure to

correct hyperkalemia relatively rapidly, particularly if associated with oliguria, requires the institution of hemofiltration or ultrafiltration.

The metabolic acidosis associated with AKI is commonly due to decreased tissue perfusion and consequent lactic acidosis. Treatment of the underlying pathophysiology is the preferred therapy. The acidosis associated with AKI may initially be exacerbated by accumulation of phosphates, sulfates, and other organic anions. Severe acidemia (pH < 7.1) may derange adrenergic receptor function, promote pulmonary vasoconstriction, and dramatically increase minute ventilation requirements. Therapy specifically to correct severe acidosis using sodium bicarbonate may thus be justified. Dialysis supplies massive amounts of bicarbonate via conductive means, i.e., transfer across the dialysis membrane, and is an extremely efficient means of supplementing bicarbonate without sodium and volume overload.

Hyponatremia and hypernatremia

Management of hypo- or hypernatremia becomes nearly impossible without adequate renal function. Severe dysnatremia with associated encephalopathy may require dialytic therapy when complicating oliguric AKI. The rate of correction of plasma sodium disturbance needs to be carefully considered, and often continuous dialysis modalities may be best. When medical management fails and/or volume overload occurs, renal replacement therapy may be required.

Oliguria

Use of high-dose diuretics has been advocated by some to convert oliguric to non-oliguric renal failure. In general, these strategies have not been found to decrease mortality, hospitalization or requirements for long-term dialysis. In fact, patients treated with diuretics who are successfully converted from oliguric to non-oliguric renal failure, but who subsequently go on to require dialysis, have increased mortality risk as opposed to oliguric patients started on dialysis within the first 48 hours of nephrology consultation. This calls into question the “automatic” use of diuretics in oliguric AKI, an important shift in common clinical practice. Whether “resting the kidney” occurs with the use of loop diuretics remains controversial. Evaluation of effective circulating volume is critical in AKI, and use of diuretics without clinical signs of volume overload should be questioned.

Renal replacement therapy

Renal replacement therapy is generally recommended when volume status cannot be medically managed and/or severe metabolic derangements are manifest, including hyperkalemia, severe hyper- or

hyponatremia, and severe metabolic acidosis. Additionally, severe azotemia/uremia may be a relative indication for initiation of renal replacement therapy. Clinical signs indicative of the need for initiation of dialysis, with respect to complicated azotemia, include pericardial effusion, pleural rub, bleeding issues (uremic platelet defect), and encephalopathy, which cannot be absolutely attributed to other etiologies. A BUN level of > 100 mg/dl has been clinically adopted as a point at which dialysis should be strongly entertained. The evidence to support this practice is, however, not terribly rigorous by modern standards, and needs to be interpreted within the overall clinical context.

Timing of initiation of renal replacement therapy (continuous or intermittent) remains somewhat empirical. Many experts recommend early intervention, citing decreased requirements for long-term dialysis and more rapid correction of azotemia/uremia and metabolic derangements as sound rationale. However, accounting for whether improvement is the result of early intervention with renal replacement therapy, or would have occurred spontaneously with simpler supportive measures, becomes much more difficult as dialytic modalities are initiated early in the clinical course of AKI.

The choice of intermittent versus continuous renal replacement modalities remains very controversial. Hypothetically, continuous renal replacement therapy, which allows for “online” volume management, solute control, potential management of “cytokinemia,” and easier titration of vasopressors, seems intuitively to be a better choice. However, randomized trials have failed to demonstrate a benefit of continuous renal replacement therapy over intermittent hemodialysis among all critically ill patients, particularly among those post cardiovascular surgery.

Conclusion

AKI complicating cardiovascular surgery portends a grave outcome both acutely and in the long term. As non-remediable demography and pre-existing illnesses play such a large role in the development of intra- and perioperative kidney injury, appropriate preoperative counseling of patients and their families regarding these risks is critically important. All efforts should be undertaken to prevent adverse outcomes by maximizing general supportive measures and specifically avoiding nephrotoxins. Application of panels of biomarkers of AKI may offer some hope of earlier recognition and intervention. Prompt initiation of medical and extracorporeal therapy, coordination of care among the multiple care teams, and avoidance of further iatrogenic complications will maximize positive outcomes among these high-risk patients.

Self assessment

1. Which of the following statements regarding the outcomes of acute kidney injury (AKI) is true?

A. Mortality risk for any degree of AKI is increased by four- to five-fold at 1 year

B. AKI – no matter the severity, is associated with an 80% mortality risk

C. Permanent dialysis complicates only 10% of those patients who require dialysis for AKI post cardiovascular (CV) surgery

D. Mortality associated with AKI post CV surgery is most often attributed to bleeding

Answer: A

2. A 65-year-old male has made little urine for the 48 hours post a combined redo CABG and AVR. His procedure was complicated by prolonged bypass time, inability to wean from the bypass circuit, and placement of an intra-aortic balloon pump. He is hypotensive and requiring pressors. Overall for the past 48 hours he is net volume positive by 5 liters. A bedside ECHO shows IVC distention. His oxygenation is acceptable on 40% Fio2 and PEEP of 5 cm water. No new infiltrates are noted on CXR. His creatinine has risen from 1.8 mg/dl pre-op to 3 mg/dl over the past 48 hours. His urine shows an osmolality of 314 mOsm/l, urine sodium of 45 mEq/l, and muddy brown casts. What is the best approach to this situation?

A. IV 0.9% saline solution 5 l over the next 24 hours

B. IV furosemide 100 mg and initiate an infusion

C. Maximize perfusion, investigate etiology of suboptimal hemodynamics

D. IV dopamine at renal dose

Answer: C

3. A 72-year-old female is having crescendo (progressively worsening) angina and has both circumflex and left anterior descending artery (LAD) lesions requiring CABG. She has CKD with a GFR of 35 ml/minute. Which statement is correct?

A. IV loop diuretics will prevent AKI if given during bypass

B. IV dopamine in the perioperative time period will prevent AKI

C. Off-pump CABG will ensure long-term improved renal function

D. Avoidance of high-dose NSAIDs and COX-2 inhibitors will prevent renal vasoconstriction in the perioperative time frame

Answer: D

4. Hyperkalemia develops in an 89-year-old male with AKI and oliguria. Which of the following contributed to his hyperkalemia?

A. His iatrogenic respiratory alkalosis

B. Lactic acidemia with a pH of 7.11

C. Furosemide

D. Nasogastric suction of 4 l of gastric contents

Answer: B

5. All of the following are indications for emergent initiation of dialysis except for which of these?

A. Severe hyperkalemia with ECG changes in the setting of diuretic-unresponsive oliguria and AKI

B. Diuretic-unresponsive AKI with asymptomatic azotemia (BUN > 100 mg/dl)

C. Impaired oxygenation in the setting of intravascular volume overload and diuretic-unresponsive AKI

D. Refractory acidemia (pH < 7.15) despite maximal general and hemodynamic support in the setting of oliguric AKI

Answer: B

Suggested Further Reading

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Chapter 14

Extracorporeal membrane oxygenation

Loreta Grecu

Extracorporeal membrane oxygenation (ECMO) is an advanced resuscitation method for cardiac or pulmonary failure that can be life-sustaining when conventional treatment options have been exhausted. ECMO is not actually therapeutic, but rather a method of supporting the patient to allow time for healing to occur, or as a temporizing measure in anticipation of a reparatory surgical procedure, a mechanical assist device or organ transplantation.

ECMO is not simple or cheap, and requires a host of well-coordinated human, technological, and institutional resources. Costs associated with ECMO are estimated at approximately $116 000 for a 6-month period. As such, ECMO should not be used indiscriminately, but rather it should be reserved for cases where there is hope for a meaningful recovery.

History and results

ECMO has its roots in cardiopulmonary bypass (CPB), and has since evolved towards a longer duration of support from days to weeks. Its use is indicated for oxygenation deficiencies, carbon dioxide removal, as well as for various cardiac deficiencies requiring prolonged support. ECMO as a technique has changed substantially since its first experimental use in the 1960s, to successful clinical use in adults in 1972 and in neonates in 1976. Up until the 1990s the best outcomes were obtained in neonates (with survival around 88%) and the pediatric population, with poor outcomes reported in adult patients.

Today’s ECMO has built upon this foundation, thanks to the groundbreaking work of Robert H. Bartlett whose work significantly changed the way we provide care for patients with no other hope of survival. In 1979 and 1994, the ECMO-associated mortality for adults was 90% and 77%, respectively. Now, 30 years later, the results of the CESAR (conventional ventilation or ECMO for severe adult

respiratory failure) trial demonstrate a significant improvement in survival (from 47% to 63%) in patients treated with ECMO. The use of ECMO during the recent outbreak of H1N1-related acute respiratory distress syndrome (ARDS) reiterated these promising results with a survival rate of 60–70%. The outcomes of ECMO for cardiac failure are less promising, with survival rates of 20–43%, depending on the specific indication. Most studies in patients who undergo ECMO-associated cardiopulmonary resuscitation versus routine resuscitation demonstrate approximately 20% increased survival rates and improved neurological outcome. Unfortunately, randomized trials in the adult population are rare, so more prospective studies will be needed to fully evaluate its best use. It is of paramount importance that clinicians remember that ECMO should not be used to prolong dying, but rather to extend life.

Early ECMO machines were cumbersome and only capable of partial cardiac support. Subsequent advances, such as the development of centrifugal pumps, and advances in membrane technology have led to the development of more compact devices with better performance characteristics in terms of blood flow and gas exchange (see Figure 14.1). This has in turn led to the improved outcomes being noted in pulmonary, cardiac, and combined pathologies.

Figure 14.1 ECMO system including the console and the blender.

ECMO nomenclature is controversial, as there are authors who disagree with a definition that seems comprehensive, but not specific. As such, the term extracorporeal life support (ECLS) has been proposed and used, however in practice and in the literature these terms are used interchangeably. There are proponents of further taxonomic distinctions based on the indications for device use, such that care for respiratory- and cardiac-failure patients should be performed by different specialists, and in different intensive care units rather than aggregated due to technical convenience.

It is important to understand that despite technical advances in the field, the ability to make decisions for such complex cases requires a thorough understanding of how the device functions (and dysfunctions!), as well as communication with the various stakeholders involved. This can vary among institutions, but often includes intensivists, surgeons, cardiologists, pulmonologists, perfusionists, respiratory therapists, and nurses.

The Extracorporeal Life Support Organization (ELSO) is an international consortium of health care professionals and scientists. ELSO's goal is to gather data regarding the use of ECMO around the world and to provide support to institutions that are dedicated to using ECMO as a method of resuscitation for their patients. ELSO aims to foster innovation, provide guidelines, expertise, clinical support, and aid with forming a community of practitioners with interest in the field.

Indications and contraindications

ECMO can be used for both respiratory, as well as cardiac, failure depending on its configuration (see below). It is commonly used in neonatal pathology such as meconium aspiration, respiratory distress syndrome, congenital diaphragmatic hernia, persistent pulmonary hypertension, as well as cardiac pathology that will necessitate surgical correction. For adults, indications and contraindications are differentiated based on the primary organ failure as outlined in Table 14.1.

Table 14.1 Indications and contraindications for the use of ECMO in respiratory and cardiac failure

Absolute indications	
Respiratory indications	Cardiac indications
• Severe respiratory failure with hypoxemia that is unresponsive to ventilator optimization such as ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2 /FiO2 of < 100 mmHg • Severe ARDS • Uncompensated hypercapnia with acidemia • Severe air-leak syndromes • Prolonged high pressure ventilation • Pneumonia • Post-lung transplant • Trauma	• Cardiogenic shock • Cardiac arrest • Pre/post heart transplant • As a bridge to ventricular assist device (VAD) or transplant • Inability to wean from cardiopulmonary bypass (CPB) • Cardiomyopathy • Myocarditis • Acute coronary syndrome • Sepsis • Drug overdose

Relative contraindications

- High pressure ventilation with high FiO_2 for more than 7 days
- For patients with cardiac dysfunction if the use of ventricular assist devices/transplantation are contraindicated
- Neurologic dysfunction: such as recent brain hemorrhage, severe irreversible brain injury
- Untreatable metastatic cancer
- Significant co-morbid disease such as advanced cirrhosis, renal failure
- Advanced age (although the age limit is not clearly defined)
- Un-witnessed cardiac arrest
- Morbid obesity
- Significant aortic valve incompetence
- Inadequate social support

Absolute contraindications

- If the pulmonary or cardiac failure is considered irreversible
- Conditions that do not allow anticoagulation

Configuration

ECMO evolved from CPB technology, with similar features that include:

- draining of the right atrium,
- pump-controlled blood flow,
- membrane oxygenator-mediated gas exchange,
- heat exchanger, and
- pressure monitors.

The main differences between ECMO and CPB are that ECMO does not have a venous reservoir or an arterial filter and the level of anticoagulation required for ECMO circuits is lower than that used for conventional CPB. The other major difference relates to the intended duration and setting of use: ECMO is mainly used in the ICU for days to weeks, as compared to CPB, which is typically used in the operating room for a matter of hours.

Broadly speaking, ECMO is a circuit that allows blood to be drained from a large vein and pumped back to the patient, via either a large vein or an artery, after passing through a gas exchanger for oxygenation and carbon dioxide removal and a heat exchanger for temperature regulation. Cannulae with the biggest possible diameter are preferred, and are usually placed percutaneously using the Seldinger technique and imaging guidance.

ECMO has two possible configurations, namely veno-venous (VV) used mainly for respiratory support, and veno-arterial (VA) that is employed for cardiac support. These basic configurations are shown in Figure 14.2 and 14.3.

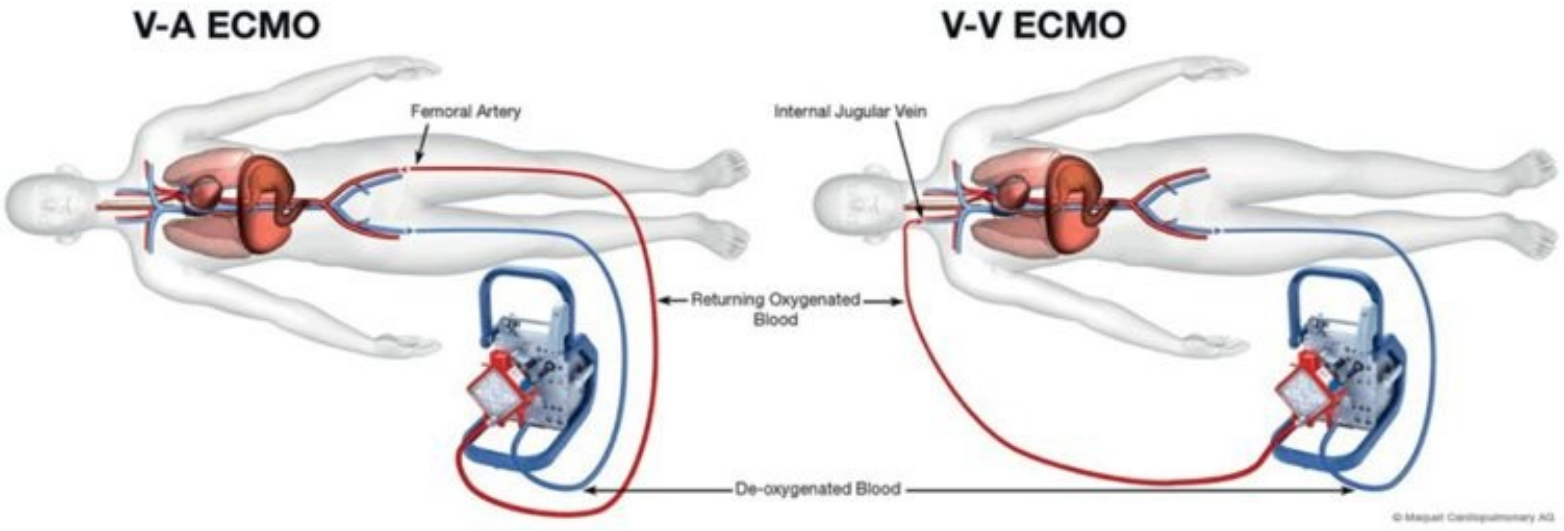

Figure 14.2 Flow principles of VA and V V ECMO.

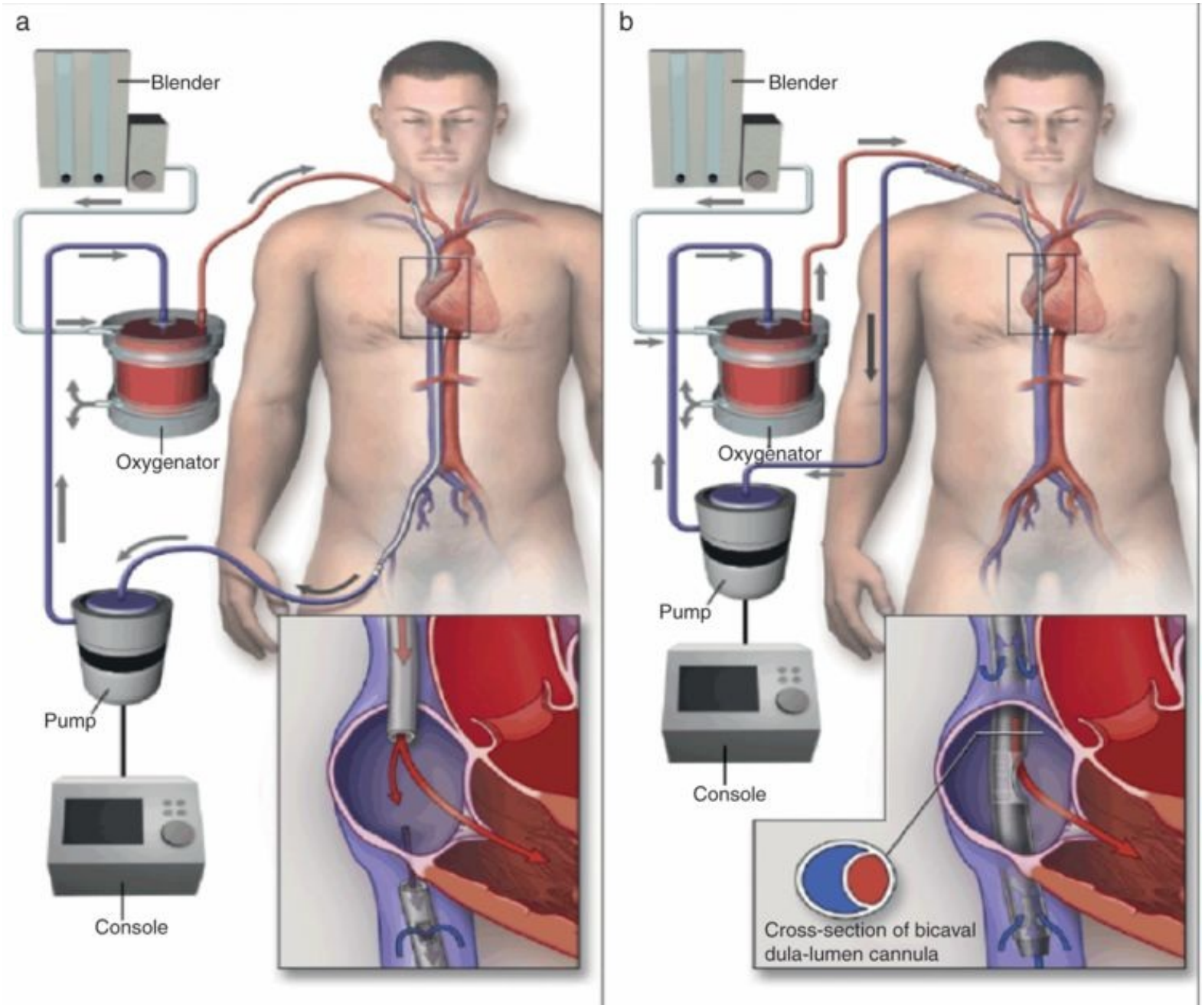

Figure 14.3 Veno-venous ECMO. (a) Two sites cannulation. (b) Single site cannulation.

From [NEJM. Extracorporeal membrane oxygenation for ARDS in adults, Brodie D., Bacchetta M., 2011; 356 (20): 1905–14] Copyright © (2014) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Using VV ECMO, the gas exchange membrane is in series with the intrinsic lung, and is therefore able to provide gas exchange, and ultimately respiratory support. In VA ECMO, the gas exchange membrane is in parallel with the intrinsic lung, and the ECMO system provides replacement for both cardiac and pulmonary function. Both configurations provide respiratory support, but only the VA allows for hemodynamic support.

VV ECMO

Common cannulation sites for VV ECMO are the femoral vein (extending into the inferior vena cava) for drainage and jugular vein (extended into the right atrium) for return (see Figure 14.3). Some oxygenated blood, immediately after being reinfused through the jugular vein cannula, is immediately withdrawn directly through the femoral cannula without reaching the systemic circulation. This phenomenon is known as recirculation. Currently, there is a double-lumen cannula available for single site cannulation with drainage and infusion ports manufactured specifically in order to minimize recirculation. However, in this configuration only up to 5 l/minute flow can be supplied. In patients who require higher flows (e.g. in sepsis) a second cannula may be required in order to optimize gas exchange. If the lungs are not contributing to the gas exchange, blood flows of 3.0–6.0 l/minute may be required to achieve an oxygen saturation (SaO_2) between 86% and 92%, since some mixing of the oxygenated and deoxygenated blood occurs.

VA ECMO

VA ECMO is instituted by either cannulating a femoral vein (commonly) or the right atrium for drainage, and the femoral artery or ascending aorta (for central cannulation, see below) for blood return. One of the adverse effects associated with femoral artery cannulation is distal limb ischemia, which can be improved, if not totally resolved, by using an additional arterial cannula distal to the femoral artery to create a shunt to the distal extremity. Peripheral cannulation rather than central cannulation of the atrium is preferred, mainly due to the fact that it can be instituted rapidly at the bedside, with minimal or no sedation required. The disadvantage of peripheral cannulation is that the proximal aortic arch vessels, including the coronaries, will be perfused by retrograde blood flow from the ECMO circuit that is mixed with blood originating from the patient's intrinsic cardiac output. If the patient has coexisting respiratory dysfunction, it is highly likely that the oxygen concentration of this mixed blood varies substantially from that of the ECMO output, at the location of the arterial cannula, which is beyond the distal aortic arch. Therefore it is important to monitor oxygenation from the right radial artery in order to more accurately assess oxygenation provided to the heart and brain.

Central cannulation is an acceptable alternative, and is convenient in cardiac surgery patients who are being converted to ECMO from CPB. In this situation, the arch vessels as well as the rest of the body are perfused in an antegrade fashion. An intra-aortic balloon pump (IABP) can also be incorporated to aid with left ventricular output, prevent ventricular distention, and possibly ameliorate myocardial stunning. Disadvantages of central cannulation are increased risk of bleeding and infection due to an open chest. Tunneled cannulae that allow for the chest to be completely closed have recently become available; however these do come at an increased cost.

One of the most pressing issues during VA ECMO is the need for close monitoring of left ventricular function, either by observing the arterial waveform for pulsatility or with frequent echocardiographic examinations. Inadequate emptying of the left side of the heart due to poor left ventricular function can lead to dangerous left ventricular distention by blood flowing from the right ventricle and bronchial circulation into the left ventricle. Inotropes and IABP counterpulsation (only in conjunction with central arterial cannulation) can be used to reduce distention. In refractory cases the left ventricle may need to be "vented," similar to what is done during on-pump cardiac surgery, in order to prevent further myocardial damage.

Components of the ECMO circuit

There are several components of the circuitry that are essential for this system to function, including the console, the pump, the membrane oxygenator, and the blender. The circuit has a drainage limb that takes the blood into the pump, a limb that circulates blood from the pump to the membrane oxygenator, and the return portion that circulates the oxygenated blood past the oxygenator to the body. The pump generates a negative pressure to withdraw blood from the body and a positive pressure to aid with blood return towards the body.

The pump

Since ECMO evolved from the CPB circuitry, the pumps initially utilized were roller pumps. Nowadays most institutions use centrifugal pumps for the ECMO circuitry (see Figure 14.4). The advantages of centrifugal pumps are purported to be:

- small size,
- low priming volume (32 ml),
- fast spinning, up to 5000 revolutions per minute,
- less blood trauma,
- less platelet activation, and
- less pronounced inflammatory response.

Roller pumps are afterload independent and may cause microemboli of tubing debris. Centrifugal pumps are both preload and afterload dependent, so a flow sensor must be introduced into the circuit, since the

correlation between the pump speed and the blood flow is not constant. Hemolysis is a real concern, but with evolving pumps, it seems to be less of an issue.

Figure 14.4 Centrifugal pump.

The membrane oxygenator

Several types of membranes have been used for ECMO: silicone, microporous hollow fiber, and poly-methylpentene (PMP) hollow fiber membranes. The disadvantages with the first two include poor efficiency, pulmonary injury, higher transfusion requirement, and plasma leak. The PMP oxygenator is commonly used today, and is a true hollow fiber in which blood and gas are totally separated by the membrane (see Figure 14.5). The advantage is a longer duration of use, and lower incidence of hemolysis. Its role is to allow deoxygenated blood with a high CO_2 concentration to enter through one side and to let the CO_2 diffuse from blood into the gas phase and O_2 to diffuse into the blood, so that oxygenated blood with a lower CO_2 concentration exits through the other side (see Figure 14.6). A

constant flow of fresh gas (known as sweep gas) is administered into the oxygenator to facilitate O_2 and CO_2 exchange. The concentration and flow rate of the sweep gas are titrated via the blender (see Figure 14.7), guided by the patient's arterial blood gases.

Figure 14.5 Membrane oxygenator and cross-section.

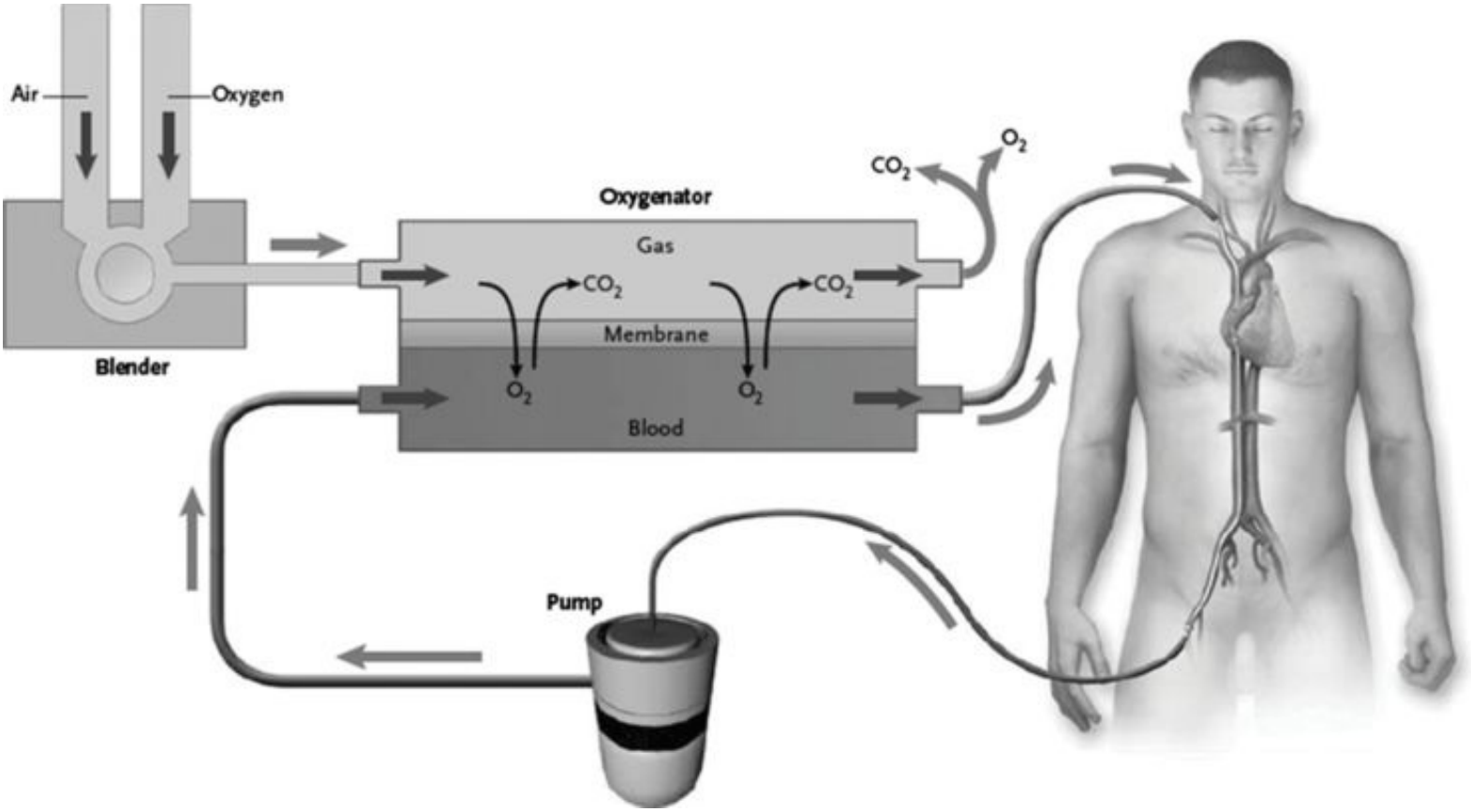

Figure 14.6 From [NEJM. Extracorporeal membrane oxygenation for ARDS in adults. Brodie D, Bacchetta M., 2011; 356 (20): 1905–14]

Figure 14.7 Gas blender.

The O_2 concentration and the blood flow rate control O_2 exchange, while the sweep gas flow rate and gas diffusion gradient control CO_2 elimination. Care must be taken when starting ECMO to avoid a very rapid decrease in CO_2, and thus negatively affect cerebral blood flow due to respiratory alkalosis. Commonly the sweep gas flow required to maintain a normal acid–base balance is 1 to 2 times higher than the blood flow.

Console, heater/cooler unit, access ports, bridge

The console allows for parameter adjustments such as blood flow in order to achieve optimal hemodynamic as well as respiratory parameters. The heater aids with temperature control, thus patients can be either warmed or cooled depending on the specific clinical circumstances. Access ports are used for priming the circuit, blood sampling, drug administration, pressure monitoring and, probably most importantly, de-airing of the circuit. The bridge is an additional connection between the inflow and

outflow limbs of the circuit, but it is not used ubiquitously since it may increase the risk of leaks or disconnections. The bridge can be used in de-airing because it allows for the patient to be temporarily excluded from the circuit, while there is still blood flow through the rest of the tubing.

Safety

By definition, patients requiring ECMO are critically ill and cannot maintain essential life functions independently. As such, circuit dysfunction and obstruction must be avoided at all costs. The circuit contains several inherent mechanisms that are essential for the safety of the patient.

- The air bubble detector is usually located in the post-membrane limb of the circuit. If triggered, forward flow through the pump will cease and alarms will sound.
- Changes in circuitry pressure are a sensitive early warning sign when thrombosis is developing. Pressure monitoring at several points throughout the circuit is important.
- Temperature monitors, and continuous venous oxygen monitors are useful safety elements that ensure the functionality of the circuit.

Maintenance

Once the patient is connected to the ECMO circuit, blood flow rate through the system is adjusted to optimize both hemodynamic as well as respiratory parameters with arterial oxygen saturation > 90%, venous oxygen saturation > 70–80%, and adequate end-organ and tissue perfusion. The physiological goals during ECMO are summarized in Table 14.2.

Table 14.2 ECMO maintenance

Parameter	Goal
Anticoagulation	ACT > 120sec
Hemodynamics	Inotropes/vasopressors
Ventilation	Lung protective ventilation strategy
Sedation	As required
Nutrition	Essential

Antibiotics	As required, as guided by microbiology
Blood products	As required secondary to bleeding or hemolysis
Fluid management	Aim for euvlemia
Physical therapy	Important

Each system should be addressed individually and taken in context of the entire clinical picture to ensure that end-organ perfusion is adequate. Frequent monitoring of labs, vital signs, and invasive hemodynamic parameters is warranted.

Anticoagulation is essential to maintaining a properly functioning ECMO circuit and preventing life-threatening thrombosis. Unfractionated heparin is the most common means of anticoagulation and is delivered as a continuous infusion titrated to achieve an activated clotted time (ACT) of 180–210 seconds, or even lower if bleeding occurs. Alternatively, plasma activated prothrombin time (aPTT) with values of 1.5 times normal are used in some centers.

Hemoglobin and platelet levels should be closely monitored. Platelets are typically consumed due to activation secondary to contact with the large foreign surface of the ECMO circuit. Acceptable platelet levels are > 100 000/mm^3 in the first 48 hours and > 50 000/mm^3 thereafter; however levels as low as > 20 000/mm^3 are tolerated in the absence of bleeding. Clinicians have to remain aware that decreasing platelets, while common on ECMO, may also be due to heparin-induced thrombocytopenia (HIT). A low threshold for testing for HIT should be maintained, and if needed a serotonin-release assay should be obtained. If positive, heparin has to be discontinued and anticoagulation switched to direct thrombin inhibitors or other non-heparin agents. There is no established consensus for optimum or threshold hemoglobin levels in patients on ECMO. Clinicians must maintain a balance between the advantage of blood transfusion in terms of increased oxygen delivery and the risks of frequent blood transfusions, including worse outcomes and increased risk of death.

For patients on VV ECMO, cardiovascular support should be provided as clinically indicated by using vasopressors and/or inotropes. Often vasopressor requirements decrease after ECMO initiation.

Optimum ventilator management for patients on ECMO has not been clearly determined, just as it still remains unclear what the best approach to patients with ARDS is. Commonly, a lung protective strategy with limitation of inspired oxygen concentration, pulmonary pressures, and tidal volumes of 4 ml/kg, or 4 cc/kg; ideal body weight are employed to minimize the risk of ventilator-associated lung injury and oxygen toxicity. Most institutions use positive end expiratory pressure (PEEP) of 10–15 cm. As the patient improves the ventilatory settings need to be adjusted accordingly. Other authors suggest that

ventilation is unnecessary, and the patients should be extubated and permitted to breathe spontaneously while on ECMO.

Nutrition and physical therapy are essential for the recovery of a critically ill patient. Antibiotics are frequently used.

Careful fluid management is essential as by the time they are accepted for ECMO most patients are massively fluid overloaded due to the resuscitation efforts at the beginning of the disease process. Aggressive diuresis, as tolerated by blood pressure and ECMO flow, is frequently necessary. In a number of cases continuous veno-venous ultrafiltration can be added to the circuit to achieve a more restrictive fluid management strategy.

When starting on ECMO patients are usually heavily sedated. As the condition improves, the sedation level can often be decreased to enable the patient to participate in their care and allow neurological monitoring. The drugs used must be carefully chosen. Propofol is highly lipophilic and therefore almost totally absorbed by the membrane; morphine and midazolam dosages must also be escalated during ECMO, although the reasons for this are not fully apparent.

Weaning

Weaning should be considered when there are signs of patient improvement. This can be in the form of improved radiographic appearance or respiratory parameters (including lung compliance) for VV ECMO. In VA ECMO, increased pulsatility observed on the arterial line tracing may represent improvement in myocardial contractility and function. Serial echocardiography can also be used to determine the appropriateness of weaning.

VV ECMO is weaned by terminating the sweep gas flow through the membrane oxygenator. The patient is observed for several hours while ventilator settings are adjusted to compensate for the increased burden and to ensure that both oxygenation and ventilation are adequate, while the blood flow through the ECMO circuit is gradually decreased.

VA ECMO usually is weaned in a more rapid fashion, since there is a higher incidence of thrombus formation in the circuit. VA ECMO weaning is typically done in the operating room with transesophageal echocardiography available to closely monitor cardiac function. Inotropes may be adjusted to ensure adequate cardiac function as both the drainage and infusion lines are clamped. If the venous and the arterial cannulae are flushed with heparinized saline and the ECMO circuit is recirculated through the bridge between the arterial and venous limb, cardiac function can be assessed adequately before making the decision to terminate ECMO support. Once the patient is completely off ECMO support, cannulae are

removed and hemostasis is achieved by compression at the insertion site. If needed, a small dose of protamine may be used to reverse the action of heparin.

Complications

The most extensive list of ECMO-associated complications is maintained by ELSO, which collects self-reported data from a multitude of tertiary centers (see Table 14.3). The list of possible complications is extensive and most authors separate them into circuit-related and patient-related complications, with non-survivors usually having a higher rate of complications than survivors.

Table 14.3 Complications of ECMO: data from ELSO registry report 2012

Event	Rate for respiratory ECLS in adults (%)	Rate for cardiac ECLS in adults (%)
Directly related to ECMO circuit		
Oxygenator failure	16.1	15.1
Tubing rupture	0.3	0.2
Pump malfunction	2.1	0.7
Cannula problems	7.7	4.4
Patient-related complications		
Intracranial hemorrhage	3.9	1.7
Cannula site bleeding	17.2	20.9
Surgical site bleeding	16.7	25.5
Cardiac tamponade	2.6	5.7
Clinical seizures	1.1	2.1

Patient-related complications

These mostly pertain to hypoxemia and hemodynamic instability. A special mention should be made of the possibility of cerebral and coronary hypoxia associated with VA ECMO via the peripheral cannulation configuration due to the fact that the blood flow is retrograde and at times insufficient for optimal perfusion of these organs. Therefore it is recommended to measure blood gases and/or pulse oximetry from the right upper extremity as a reflection of heart and brain perfusion.

Bleeding is probably the most common complication with an incidence as high as 30–40%. Bleeding can occur anywhere in the body: surgical wounds, internally into body cavities such as abdomen, pleura, or, the most dreaded, intracranially with an incidence of 2.7%. Causes for coagulopathy include the use of the anticoagulant heparin, thrombocytopenia, heparin-induced thrombocytopenia, fibrinolysis, uremia, hepatic dysfunction, and disseminated intravascular coagulation. When bleeding occurs, the cause and source should be rapidly identified, concurrent with active management. Surgical exploration should be undertaken only if absolutely necessary, and by an experienced surgeon. Management of coagulopathy with decreasing or even temporarily stopping the administration of heparin, as well as administration of an antifibrinolytic, plasminogen inhibitor, or even factor VII have been reported. Nevertheless, the risk of fatal thrombosis is omnipresent and extreme care should be taken when such products are administered. In rare cases, cardiac thrombosis can occur in VA ECMO due to the retrograde flow towards the heart with peripheral cannulation. Of course the implications of thrombosis are more serious for VA ECMO due to the danger of clot dislocation into the systemic circulation and thus exchange of the circuitry should be performed immediately.

Infection and sepsis are common due to nosocomial pathogens, and while antibiotics are not routinely recommended, they are frequently used to prevent such occurrences. In addition, fever as a symptom of sepsis may be absent as the body temperature is controlled through the heat exchanger while on ECMO.

Neurological complications include intracranial hemorrhage, ischemic stroke, seizures, and even brain death. It is therefore imperative that sedation is kept to a minimum, so that the neurological status of the patient can be evaluated frequently and the appropriate imaging can be instigated as soon as the suspicion of a neurological complication arises. Other possible complications include renal failure, metabolic derangements, arrythmias, pneumothorax, as well as blood pressure variations.

Circuit-related complications

The most feared and potentially life-threatening circuit-related complications are massive gas embolism and blood loss due to tubing rupture or disconnection. Both require immediate clamping of the circuit and therefore loss of ECMO support.

Probably the most common complication is membrane failure due to thrombus formation, requiring immediate circuit or oxygenator exchange. Thromboembolism can be a life-threatening complication, and observation of the circuit for thrombi at the connectors as well as close monitoring of the pressure gradients is of uttermost importance.

Pump malfunction is less common in this day and age. Cannula-related complications may include vessel or right atrial/ventricular perforation, dissection, distal ischemia, or incorrect placement. Naturally, a skilled operator is essential to minimize the risk of these complications. Lower limb ischemia can be avoided by routine insertion of a shunt cannula to maintain flow distal to the ECMO cannula.

Future trends

ECMO will most likely continue to expand in the near future with surface coating of circuits that reduces the possibility of thrombi, the need for anticoagulation, and associated complications.

The use of ECMO as a bridge during and after cardiac resuscitation is still subject to intense interest, particularly as promising results are emerging.

Peri-procedural ECMO is an intervention that has not yet been fully explored. ECMO has been successfully utilized in patients who cannot tolerate any period of perioperative hemodynamic instability or hypoxia, such as patients undergoing electrophysiological ablation procedures or lung transplantation.

The use of ECMO as a bridge to organ transplantation is still a developing model and used in large centers only.

Most authors believe that ECMO patients should be cared for in larger specialized referral centers that have experience in managing these patients. Indeed the CESAR trial suggests that critically ill patients should be transferred to a tertiary care center which is equipped to provide ECMO if necessary. This might be difficult to achieve in practice since it is difficult to assess exactly who will require ECMO during the course of their illness. Some patients are transferred early, as recommended, but they do not deteriorate sufficiently to require ECMO while others will die before being transferred. In Australia, the concept of the ECMO retrieval team was successfully developed and 56% of the patients were initiated on ECMO prior to transfer to a tertiary center. The timely dispatch of a retrieval team seems to increase the chances of survival, since their expertise in assessing the need for ECMO and their experience in effectively initiating ECMO yields a lower complication rate than when ECLS is initiated by less experienced staff at non-specialist hospitals.

Self assessment

1. Which of the following statements are true?

A. ECMO should be used to support cardiac or respiratory failure when the heart or lungs are considered to have no chance of recovery

B. ECMO is a temporary means of supporting the heart or lungs, or both, to allow time for the underlying organ damage to recover

C. Patients in whom anticoagulation is contraindicated should not be put on ECMO

D. ECMO can only be used successfully in neonates

Answers: B, C

2. Which of the following statements are true?

A. Veno-arterial ECMO can only be satisfactorily conducted via centrally placed cannulae

B. Veno-arterial ECMO may be used for respiratory as well as cardiac support

C. Veno-venous ECMO cannot be used for cardiac support

D. Veno-venous ECMO can be conducted via cannulae placed in the femoral veins and/or an internal jugular vein

Answers: B, C, D

3. Which of the following are relative contraindications to the use of ECMO (select one or more)?

A. Un-witnessed cardiac arrest

B. Failure to wean from CPB during cardiac surgery

C. Aortic valve incompetence

D. Organ dysfunction such as liver cirrhosis or renal failure

Answers: A, C, D

4. Which of the following statements are false?

A. Roller pumps are commonly used in ECMO circuits

B. Bubble detectors that can stop flow if triggered and pressure sensors are usually incorporated in ECMO circuits

C. Bleeding is the least common complication associated with ECMO

D. The commonest cause of oxygenator failure is thrombus formation

Answers: A, C

Suggested Further Reading

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Chapter 15

Pediatric aspects of cardiopulmonary bypass

Davina D. L. Wong and **Craig R. Bailey**

There are important differences between pediatric and adult cardiopulmonary bypass (CPB) which will be highlighted in this chapter.

Pediatric patients are more commonly exposed to biological extremes than adults undergoing elective cardiac surgery. Such extremes include deep hypothermic circulatory arrest (DHCA), severe hemodilution, low perfusion pressures (20–40 mmHg), wide variations in pump flow rates (ranging from total circulatory arrest to highs of up to 200 ml/kg/minute), and differing blood pH management techniques (alpha-stat, pH-stat, or both sequentially).

Pediatric cardiac surgeons are increasingly undertaking more complex operations, with a shift from palliative procedures to early correction of congenital disorders. This has resulted in younger children being subjected to longer periods on bypass and its associated effects on vital organs. The neonate who requires cardiac surgery employing CPB has a unique anatomy, which means that the perfusionist must adapt and be reactive to changing circumstances during each case.

Preoperative issues

Newborns have a poorly developed immune system and an impaired response to the inflammatory effects of bypass. Newborns with genetic abnormalities such as Down's or Turner's syndrome may have associated non-cardiac abnormalities. In addition they may have undiagnosed conditions such as di George syndrome, hypogammaglobulinemia or anti-thrombin deficiency.

Preoperative poor nutritional status is associated with impaired perioperative myocardial function, poor wound healing, and an increase in postoperative infections and should therefore be addressed before surgery if there is time.

From the cardiovascular point of view patients are extensively investigated preoperatively. Matrix ultrasound probes allow detailed 3-D echocardiography images to be obtained, even in the smallest babies. Contrast-enhanced magnetic resonance imaging (CE-MRI) provides a great deal of preoperative information and has resulted in a decreased necessity for invasive procedures, such as cardiac catheterization.

Recent blood test results should be available and 2 units of fresh red cells available for transfusion. Patients should have current weight and body length recorded and should be starved of food for 6 hours, breast milk for 4 hours, and water for 2 hours.

Conduct of anesthesia before CPB

Pediatric cardiac patients arrive in the anesthetic room accompanied by at least one parent or carer and a nurse from the ward. The patient's notes should be reviewed for relevant medical issues and to confirm signed consent.

Most have no venous access, thus inhalational induction of anesthesia is performed usually with the child's carers present. Once consciousness is lost venous access is obtained, sedative drugs and a neuromuscular blocking agent administered, and an endotracheal tube, usually nasotracheal, is inserted. Central venous and arterial access is then secured and a baseline arterial blood gas analysis and ACT performed.

Drug administration by the anesthetist

A prophylactic antibiotic such as cefuroxime 30 mg/kg (unless there is documented patient or parent allergy to penicillin) is given, although the choice is determined by a locally agreed antimicrobial policy. Tranexamic acid, an antifibrinolytic which has largely replaced aprotinin, may be used to help reduce postoperative blood loss. Although the optimal dosage regimen in children has not been established, current practice is to give 10 mg/kg at the start of surgery, 10 mg/kg on bypass and 10 mg/kg after administration of protamine. Higher doses are associated with postoperative convulsions.

There is a significant inflammatory response induced in pediatric CPB due to the combination of the patient's immature immune system and the high circuit surface area to blood volume ratio compared with adults. This response may manifest as anything from mild vasodilatation to fully blown organ failure. Steroids stabilize cell membranes and may reduce ion shifts during periods of ischemia, but their prophylactic administration, using either dexamethasone or methyl-prednisolone, is controversial in cardiac surgery. Proponents claim that they reduce the inflammatory response while others believe that

they cause hyperglycemia and an increased incidence of postoperative infections. A single dose of dexamethasone, usually 0.5–1.0 mg/kg, may be given at the start of surgery and blood glucose levels maintained between 5 and 10 mmols/l using an actrapid insulin sliding scale if necessary.

Propofol and remifentanil infusions, widely used in adults, are not licensed for use in small children, thus the anesthetist will usually administer a bolus dose of opioid and sedative before institution of CPB. Isoflurane is often added to the bypass circuit by the perfusionist in order to maintain anesthesia, but the teratogenic effects are unknown and care must be taken to ensure scavenging within the operating theatre, especially if pregnant theatre staff are present.

Monitoring

Children are routinely monitored in the same way as adults; additional monitoring may include intraoperative echocardiography and intrathoracic monitoring lines, such as a left atrial line.

All pediatric patients are now monitored using NIRS, a non-invasive electrode positioned on the forehead of the patient. NIRS is able to measure changes in cerebral venous oxygen saturation (SVO_2), which is determined by cardiac output, as well as other parameters (FiO_2, hemoglobin, and oxygen uptake). It provides an early warning of potential cerebral ischemia. As with all monitors, trends are more important than actual values displayed, but cerebral venous oxygenation should generally be maintained above 40% as any reduction below this, admittedly arbitrary, value risks cerebral ischemia and postoperative neurological deficit. Treatment of low values includes either increasing oxygen supply by increasing bypass flow rate, perfusion pressure, oxygen levels, hemoglobin levels, and CO_2 levels or by reducing oxygen demand by cooling the patient and administering anesthetic agents.

Echocardiography is routinely employed in pediatric cardiac surgery. There are different sized probes available depending on the size of the patient, a microprobe being inserted in patients weighing between 2.5 and 3.5 kg and a mini-probe in patients weighing greater than 3.5 kg. If insertion of a transesophageal probe is considered too hazardous then surface echocardiography can be performed with the surgeon manipulating a sterile probe within the thoracic cavity.

Preparation for CPB

Cell salvage

It has been calculated that for cell salvage to be cost effective at least 220 ml of processed blood should be available for re-infusion. This is not always possible with small babies, but the risks associated with

transfusion of bank blood outweigh the cost consideration and cell salvage is routinely performed during pediatric cardiac surgery. The perfusionist sets up the suction at the start of surgery. Shed blood is washed, centrifuged, and filtered and red cells, re-suspended in saline, are transfused back into the patient towards the end of surgery.

The bypass circuit

Circuit integrity should be checked thoroughly before initiation of bypass. An oxygen analyzer is inserted between the gas blender and oxygenator, distal to the isoflurane vaporizer and should be calibrated prior to each case (Figure 15.1).

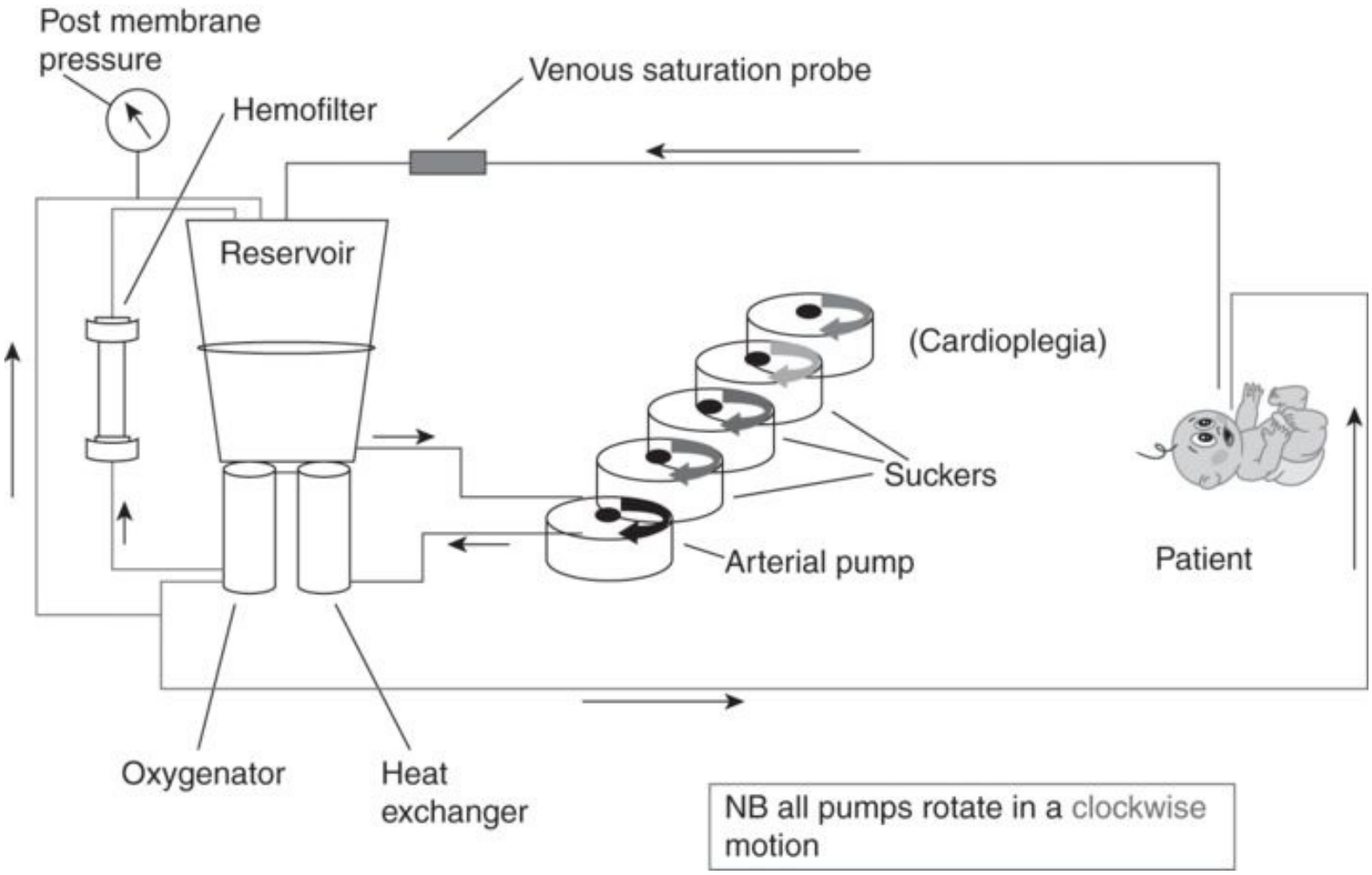

Figure 15.1 Pediatric bypass circuit.

Prime fluid calculations

First, calculate the patient's circulating blood volume (PV), which varies with weight as shown below:

Patient weight range	Calculated circulating volume (PV)

0–10 kg	weight (kg) × 85 ml
10–30 kg	weight (kg) × 80 ml
> 30 kg	weight (kg) × 70 ml

The patient's calculated circulating blood volume (PV) is added to the prime volume, making up the total circulating volume (TCV). If the calculated hematocrit (HCT) of the TCV is less than 24%, red cells need to be added to the pump prime volume.

Example 1. A 20-kg child has a calculated circulating blood volume of 20 × 80 = 1600 ml. If their hematocrit is 40% and the prime volume is 1000 ml then the total circulating volume is 2600 ml and the calculated hematocrit is 1600 divided by 2600 multiplied by 40 = 25%. Therefore bypass can be performed without the addition of red cells.

Example 2. A 5-kg child has a calculated circulating blood volume of 5 × 85 = 425 ml. If their hematocrit is 40% and the prime volume is 500 ml then the total circulating volume is 925 ml and the calculated hematocrit is 425 divided by 925 multiplied by 40 = 18.4%. Red cells must therefore be added to the prime volume to increase the hematocrit to 24% using the following formula:

(Ideal HCT – clear prime HCT) × TCV (ml)/HCT of red cells = red cells needed (ml)

Transfused red cells have a hematocrit of 70%, so in this example the amount of red cells needed is:

(24 – 18.3) × 925 / 70 = 75 ml

Typical prime fluid constituents

- Fresh red blood cells (to ensure HCT of 24% on bypass)
- 8.4% sodium bicarbonate (20 ml/l of prime volume)
- FFP/Octaplas 50 ml (if patient is 7 kg or less in weight)
- Heparin 225 IU per kg body weight
- Ringer's solution to make up the remainder volume

Most circuits require the addition of red cells in order to maintain hemoglobin (hematocrit) levels at 80 g/l (24%), which is thought to be the optimal level for enhanced rheological properties during bypass. Red cells added to the prime circuit should ideally be fresh (less than 6 days old) and in babies less than a month old they should be irradiated and cytomegalovirus (CMV) negative. Fresh frozen plasma/Octaplas is often added to maintain circulating levels of clotting factors. Octaplas is treated

pooled human plasma (derived from more than 1000 donors) that is rich in plasma proteins such as albumin, immunoglobulins, and clotting factors. It is solvent/detergent treated which reduces the levels of Protein S and alpha-2 anti-plasmin. It must be ABO group compatible and can cause adverse effects such as urticaria (in 1% of patients), thrombosis (due to reduced Protein S), excessive bleeding (due to low alpha-2 antiplasmin), and potentially transmits infection such as variant Creutzfeldt-Jakob disease (vCJD) and other, as yet unknown, viruses. The addition of any blood products will cause a much higher glucose load in the prime.

The addition of mannitol to the pump prime is carried out in some units to increase the osmolarity of the prime, and so reduce tissue edema. While mannitol certainly causes a diuresis due to its action as an osmotic diuretic, the volume of urine output *per se* is not a reliable indicator of renal function, although some anesthetists aim to maintain an hourly urine output of greater than 0.5 ml/kg/hour. As well as being an osmotic diuretic, mannitol is an oxygen free radical scavenger.

A sample from the pump prime, after addition of the red cells and Octaplas, should be run through a blood gas analyzer to ensure biochemical values, especially potassium, are acceptable before initiation of CPB.

Cardiotomy suction

Following full heparinization and confirming an ACT above the level considered safe for initiation of CPB, generally more than 400 to 480 seconds, shed blood is suctioned from the operative field and collected in the reservoir for re-circulation. The perfusionist needs to be vigilant in order to alter the pump flow rate and alert the surgeon when changes in suction occur because the degree of negative pressure that develops at the sucker tip may lead to hemolysis of red cells or occlusion. Occasionally a second reservoir is incorporated into the bypass circuit specifically to collect pump sucker blood in order to reduce the amount of foam formation within the circuit.

Cannulation

In pediatric patients blood vessels are small in caliber and the correct choice of both arterial and venous cannulae together with accurate placement are crucial in order to avoid obstructing vascular branches, misdirecting flow or impairing venous drainage.

Bi-caval cannulation is routinely performed in all but the simplest of operations as it allows more complete emptying of the heart and improves the surgeon’s view of intra-cardiac anatomy.

Ineffective venous drainage results in ventricular distension, which is poorly tolerated by neonates due to their low ventricular compliance. If drainage is inadequate, the pump flow must be reduced and the

venous cannulae repositioned.

Presence of large aorto-pulmonary collaterals or a patent ductus arteriosus (PDA) may divert blood to the pulmonary circulation from the systemic circulation thereby reducing cerebral blood flow. This can be mitigated by the surgeon gaining early control of the ductus after chest opening or the embolization of large collaterals in the cardiac catheterization laboratory prior to surgery. Patients with significant aortic arch abnormalities may require radical modifications of cannulation techniques, including formation of a temporary Gore-Tex shunt.

CPB flow rate

Full flow is calculated to be 2.6 l/minute/m^2 of body surface area (BSA). The BSA is calculated as the square root of [height (cm) × weight (kg)/3600]. For example, a 12-month-old, 10 kg in weight and length 60 cm gives a BSA of 0.41, so full flow for this child would be approximately 1 l per minute.

The infant vascular tree offers low resistance to flow so that low arterial pressures (mean = 20–40 mmHg) may be seen despite "full flow," but these are usually well tolerated.

Cardioplegia solutions

Cold crystalloid, cold blood, and tepid blood cardioplegia are all used and depend on the individual cardiac unit and surgeon preference.

Antegrade cerebral perfusion

This facilitates cerebral perfusion during long periods of deep hypothermic circulatory arrest, for example during a Norwood Stage I procedure or an extended aortic arch repair. The aortic cannula is removed from the aortic root and inserted into the right innominate artery. Perfusion is carried out at a third of the normal flow rate with cerebral oximetry and careful arterial blood pressure monitoring.

Fluid balance

There is evidence that fluid overload is an independent marker for an increase in mortality. Children are susceptible to renal impairment and many methods are employed to monitor renal perfusion and optimize fluid balance, e.g. near infrared spectroscopy using electrodes placed over the loin area is a simple non-invasive means of monitoring kidney oxygenation. Methods of renal replacement therapy include conventional hemofiltration, modified ultrafiltration, and zero balance ultrafiltration. In a recent survey of

North American units 70% of respondents utilized some form of modified ultrafiltration in a parallel circuit in order to hemoconcentrate and filter CPB fluid.

Conduct of CPB

Drug administration by the perfusionist on bypass

- Heparin to maintain an ACT of at least 400 seconds (depending on the local protocol)
- Fluids
- Potassium chloride
- 8.4% sodium bicarbonate – patient weight × base excess × 0.15
- Cardioplegia solution
- Vasodilators and vasopressors in conjunction with the anesthetist
- Isoflurane

Monitoring during bypass

Mean arterial blood pressure should generally be maintained between 30 and 45 mmHg in discussion with the surgeon and anesthetist and based on the cerebral oximetry trends.

Anticoagulation

ACT is measured 2 minutes after heparin administration, before bypass is instituted and then every 30 minutes while on bypass. A value of 400 seconds or greater, depending on the locally agreed protocol, is generally accepted as evidence of adequate anticoagulation.

Thromboelastography (TEG) / Thromboelastometry (ROTEM (R))

There have been mixed reports on the usefulness, or otherwise, of TEG or ROTEM as a near-patient testing of clot formation and fibrinolysis. Most units in the UK do not employ TEG routinely, but reserve its use for high-risk cases or when there is bleeding that is uncontrollable by surgical techniques. However, the National Institute for Health and Care Excellence (NICE) has said that the TEG and ROTEM systems are recommended to help monitor blood clotting during and after heart surgery by healthcare professionals who have had appropriate training (DG 13, August 2014).

Temperature

The patient's core temperature is routinely monitored using a nasopharyngeal probe as this approximates most closely to brain temperature. Until recently cooling of the patient was routine, but this is now less frequent apart from specific procedures requiring deep hypothermic circulatory arrest (DHCA), such as the Norwood Stage I procedure, arterial switch (Jatene), and extended aortic arch repair. In these situations the patient is cooled to 18°C, which reduces the cerebral metabolic rate sufficiently to allow a safe circulatory arrest period of up to 40 minutes. The principle holds that the patient should be cooled slowly (over a period of 20 minutes) and re-warmed slowly in order to avoid postoperative neurological complications.

Arterial blood gas analysis

Most units use an "alpha-stat" blood gas management strategy, correcting pH to values at normothermia whatever the actual patient temperature. This preserves intracellular pH neutrality and maintains enzyme function.

During procedures involving DHCA pH-stat blood gas management may be used to maintain the pH and CO_2 constant at actual core temperature during the cooling phase. CO_2 is added to the oxygenator as required. This strategy increases tissue oxygenation and cerebral blood flow during cooling and appears to result in improved patient outcome.

Lactic acid levels are routinely measured and tend to rise with prolonged bypass and aortic cross-clamp times.

Glucose control

Hyperglycemia occurs as part of the stress response. One review found that in patients undergoing the Norwood Stage I procedure hyperglycemia was associated with cerebral damage and intraventricular hemorrhage. On the contrary, hypoglycemia often occurs in neonates during the perioperative period due to reduced glycogen stores and decreased liver gluconeogenesis. This, together with reduced liver perfusion that occurs in patients with congenital heart disease, renders these patients susceptible to hypoglycemia. During DHCA the additive effect of even mild hypoglycemia may cause alterations in cerebral autoregulation and culminate in brain injury. Relatively tight glucose control is therefore recommended throughout the bypass period.

Separation from bypass

The following conditions need to be met before attempting to wean the patient off bypass:

- Intra-operative echocardiography showing acceptable cardiac function, no residual intracardiac shunts, and good flow through the coronary arteries
- Normothermia
- Normal filling pressures (left atrial/pulmonary artery/central venous)
- Normal electrolyte values, including a potassium level of 5.5 mmol/l
- Normoglycemia
- Normal arterial blood gases
- Hemoglobin level of 100 g/l
- Near infrared spectroscopy (NIRS) values above 40
- Stable cardiac rhythm at an acceptable rate for age
- Patient's lungs being ventilated by the anesthetist with visual confirmation of equal, and full, lung expansion bilaterally

Following discontinuation of bypass and administration of protamine there is a period when the child is stabilized and fluid is administered by the perfusionist via the CPB circuit as dictated by filling pressures and echocardiography. During this time most surgeons, except in the simplest of cases, will place temporary atrial and ventricular pacing wires on the surface of the heart and insert a peritoneal dialysis catheter and a left atrial line in order to monitor left-sided filling pressures. These are removed postoperatively on the pediatric intensive care unit while the mediastinal drains are still in situ.

Modified ultrafiltration (MUF) may be performed after separation from the bypass circuit and allows filtration of the patient's circulating volume and the contents of the circuit, including the venous reservoir. An ultrafilter is placed in the circuit and blood is removed from the patient via the arterial cannula and flows through the filter together with blood from the venous reservoir. The outlet of the filter is fed to the patient's right atrium. Flow through the filter is about 200 ml/minute and results in a filtration rate of 100–150 ml/minute. Constant filling pressures are maintained in order to retain hemodynamic stability during this crucial post-bypass period. The result of ultrafiltration is that the patient's total body water is reduced and the hematocrit is increased. In addition, vasoactive substances are removed, limiting the damaging effects of bypass and there is evidence that the postoperative ventilation period is reduced.

Complications following CPB

Common immediate complications following separation from bypass include:

- Hypoxemia and acidosis
- Poor cardiac function; left, right or bi-ventricular dysfunction
- Ischemia
- Arrhythmias
- Bleeding
- Pulmonary arterial hypertension

These may be inter-related and can necessitate an immediate return onto bypass and re-evaluation of the patient.

Extracorporeal membrane oxygenation (ECMO)

ECMO is discussed in detail in Chapter 14, but in summary is a technique whereby venous blood is siphoned from the patient, oxygenated, and pumped back into the patient either via a venous or arterial cannula. The National Institute for Health and Care Excellence (NICE) supports this procedure (IPG038) and indications include respiratory or cardiac failure that is unresponsive to all other measures but is considered to have a reversible or curable cause. The largest study on the efficacy of ECMO in children included 763 patients and reported a 57% survival rate. The most common complications include excessive bleeding, renal failure, infection, neurological complications, and technical problems. A perfusionist trained in ECMO must be available 24 hours a day and NHS England have specified that each patient must be looked after by two nurses. There are currently only three centers in England and one in Scotland that provide a pediatric ECMO service.

Conclusion

There are important differences between pediatric and adult CPB. Pediatric patients are exposed to biological extremes rarely seen in adults, including deep hypothermic circulatory arrest (DHCA), severe hemodilution, low perfusion pressures, wide variation in pump flow rates, and differing blood pH management techniques. The perfusionist must be vigilant at all times because pathophysiological changes occur often in children and may result in long-term disability unless treated quickly.

Self assessment

1. The following are true regarding pediatric CPB:

A. Immature physiology leads to less inflammatory response to bypass

B. Hematocrit should be kept at around 30%

C. It involves greater hemodilution compared with adults

D. Lower perfusion pressures are maintained compared with adults

E. The use of near infrared spectroscopy is routine

Answers: A False; B False; C True; D True; E True

2. Typical constituents in the pump prime for patients less than 7 kg in body weight include:

A. Fresh whole blood

B. FFP/Octaplas

C. Sodium bicarbonate

D. Platelets

E. Albumin

Answers: A False; B True; C True; D False; E False

3. Prime fluid calculations require knowledge of the following:

A. Patient weight

B. Patient height

C. Patient hematocrit

D. Patient surface area

E. Patient age

Answers: A True; B False; C True; D False; E False

4. The degree of hemodilution during CPB depends on:

A. Prime volume

B. Patient hematocrit

C. Patient blood volume

D. Prime constituents

E. Patient surface area

Answers: A True; B True; C True; D True; E False

5. The following are routinely administered during cardiac surgery in children weighing less than 7 kg in body weight:

A. Red cells

B. FFP/Octaplas

C. Platelets

D. Aprotinin

E. Dexamethasone

Answers: A True; B True; C False; D False; E True

6. Concerning alpha-stat and pH-stat management of blood gases:

A. According to the alpha-stat hypothesis, pH is kept constant at different temperatures

B. At lower temperatures, pH decreases

C. According to pH-stat hypothesis, pH remains constant at different temperatures

D. Using alpha-stat hypothesis, $PaCO_2$ is kept constant at different temperatures

E. Using pH-stat involves adding carbon dioxide to the oxygenator during deep hypothermic circulatory arrest

Answers: A False; B True; C True; D True; E True

7. The following are true regarding patients undergoing deep hypothermic circulatory arrest (DHCA):

A. They have a higher incidence of postoperative seizures

B. Cooling and re-warming should occur slowly

C. They are likely to be having complicated surgical repairs

D. Alpha-stat blood gas management may lead to improved neurodevelopmental outcomes

E. They are more likely to have long-term language and motor development problems

Answer: A True; B True; C True; D False; E True

Suggested Further Reading

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Chapter 16

Non-cardiac surgery functions of cardiopulmonary bypass

Lay Ping Ong and **Sukumaran K. Nair**

Re-warming from severe hypothermia

Every year, approximately 4 out of 1 000 000 people in the USA die as a result of hypothermia. In 2012, accidental hypothermia was an important factor in the deaths of 166 people in the United Kingdom and at least 1500 causes of death in the USA. Accidental hypothermia is defined as an unintentional decrease in core temperature below 35°C due to hypothermic exposure in individuals without intrinsic thermoregulatory dysfunction. Based on an adapted Swiss staging system, accidental hypothermia can cause various stages of dysfunction, which are summarized in Table 16.1.

Table 16.1 Stages of hypothermia

Stage I	Clearly conscious and shivering (35–32°C)
Stage II	Impaired consciousness without shivering (32–28°C)
Stage III	Unconscious (28–24°C)
Stage IV	Minimal vital signs or apparent death (24–13.7°C)
Stage V	Death from irreversible hypothermia (< 13.7°C)

Deep accidental hypothermia (DAH) usually follows accidental exposure to extreme cold, resulting in suspension of all signs of life and mimicking death, particularly if an “after drop” in temperature occurs. “After drop” is a phenomenon of conductive heat loss that is usually associated with immersion

hypothermia following accidental drowning. The most important differential diagnosis of severe hypothermia is death. Hyperkalemia may be a useful diagnostic tool to differentiate between these two states. Mair et al. in a retrospective study involving 22 hypothermic patients re-warmed with the aid of cardiopulmonary bypass (CPB), suggested that hyperkalemia exceeding 9 mmol/l, pH ≤ 6.5 or ACT > 400 s in a venous blood sample were indicative of the inability to restore spontaneous circulation due to irreversible cell death. Patients with such severely deranged metabolic parameters did not regain spontaneous circulation despite full re-warming on CPB.

Severe hypothermia is a medical emergency. Core re-warming may be required in a short space of time to prevent resistant cardiac arrhythmias and death. There are many ways of re-warming, broadly divided into invasive and non-invasive methods. In the emergency room re-warming techniques are usually limited to administration of warmed intravenous fluids, warming blankets, and gastric and bladder lavage. These methods are relatively slow and ineffective. Other non-invasive techniques for re-warming include the use of warmed inspired gases, microwave therapy, warm water immersion, and body cavity lavage. The latter involves repeated instillation of up to 2.5 l of normal saline into the peritoneal cavity, leaving it for 20 minutes before draining again. This sequence is repeated till a core temperature of 37°C is achieved.

In 1996, Kornberger et al. published their results treating 55 patients who suffered severe accidental hypothermia using three different methods of re-warming, namely:

- airway re-warming, warmed fluids, and insulation in patients in a stable hemodynamic state,
- peritoneal dialysis in patients in an unstable hemodynamic state, and
- extracorporeal circulation in patients who had circulatory arrest.

Survival rates were 100%, 72%, and 13%, respectively, in these three groups. This study concluded that the method used to re-warm a patient with severe accidental hypothermia should be adjusted to the hemodynamic status of the patient in order to achieve best results. Prognosis seemed to be excellent in patients with no hypoxic event preceding hypothermia and with non-serious underlying disease. A retrospective comparative study by Morita et al. in 2011 showed that following severe hypothermia, re-warming with CPB was far superior to conventional methods of re-warming, with mortality rates of 15.8 and 53.3%, respectively. Whenever possible, re-warming should be attempted with invasive methods. European Resuscitation Council guidelines (2010) identified extracorporeal membrane oxygenation (ECMO) and CPB as important modalities for re-warming patients with an expected survival rate of around 50%. Arrested and hemodynamically unstable patients should be treated with full CPB using a circuit incorporating an oxygenator. Formal, full dose heparinization is required. The use of

pharmacologically induced vasodilatation during the re-warming phase of CPB has been shown to improve peripheral re-warming; vasodilators enhance the distribution of blood to peripheral vessels and so help to “even out” the core–peripheral temperature difference.

Controlled studies comparing the efficacy of CPB and alternative warming techniques have not been performed so far. In a literature review published in 1994, it was shown that femoro-femoral bypass was used as a means to re-warm 72% of profoundly hypothermic patients. The overall survival was 60% in this series with 80% of the survivors suffering no long-term organ dysfunction.

Ruttman et al. compared two groups of patients resuscitated with CPB or ECMO, reporting an overall survival of 20.3%. Of the survivors, 100% returned to full neurological function. There was a significant survival benefit observed with ECMO compared to CPB, largely because it can provide continued support during acute respiratory distress syndrome, which often occurs after the return of spontaneous circulation. However, CPB may be the only option in some countries where ECMO is not widely available, and capacity may be limited.

CPB in trauma care

In complex traumatic injuries of intrathoracic organs, institution of CPB can be lifesaving. This enables the surgeon to work in a bloodless field with non-ventilated, collapsed lungs. More importantly, CPB ensures that the rest of the body is adequately perfused during the operation and allows salvaging of shed blood.

Aortic injury is the commonest and most serious intrathoracic injury. Total CPB, as mentioned earlier, or at least left heart bypass, should be resorted to before attempting repair of an aortic tear or rupture. The technique of left heart bypass may be used for repair of the descending aorta: after thoracotomy the left atrium is typically cannulated via a pulmonary vein and oxygenated blood is drained to a pump, which is used to return the oxygenated blood via a femoral arterial cannula. This provides perfusion to organs below the distal aortic cross-clamp. The left ventricle is partially decompressed and ejects the remainder of the left atrial volume into the aorta to supply coronaries as well as head and neck vessels. This allows cross-clamping of the injured aorta above and below the site requiring repair or replacement, while circulation is maintained to all vital organs. The lungs continue to function as the means of gas exchange.

CPB is also essential in the emergency repair of multiple or single chamber heart injury. In 1990, Reichman et al. published their results of using CPB for the treatment of cardiac arrest after trauma. Of the 38 patients in their series, 95% were successfully resuscitated and 50% weaned from bypass, although

the overall survival rate was only 16%. The main reason attributed to this poor outcome was the need for full heparinization, which resulted in high rates of bleeding complications. Perchinsky et al. reported far better results in 1995 using heparin-bonded circuits. They demonstrated a survival rate of 50% in six patients with severe pulmonary injuries and profuse hemorrhage.

CPB for emergency cardiopulmonary support (ECPS)

The use of a portable CPB device in the emergency room to resuscitate patients with severe hypothermia or thoracic trauma is controversial. The need for systemic anticoagulation with heparin and the subsequent bleeding complications in the setting of trauma generally result in an increased demand for transfusion. This has limited widespread application of this technique. Moreover, initial experience showed disappointing results for trauma patients. The introduction of heparin-bonded circuitry in the ECPS system has improved survival rates.

Portable ECPS devices

The development of a portable ECPS system soon followed the first successful use of CPB. In 1954, its usage was limited to the operating theatre and to the field of cardiac surgery. In the 1970s, ECPS became an evolving therapeutic option for treating medical emergencies. In 1972, Hill et al. reported the first successful application of extracorporeal membrane oxygenation in a patient with traumatic respiratory failure. Later, cardiologists started using portable ECPS for supporting patients after high-risk angioplasties and other interventional procedures following myocardial infarction.

Concept of ECPS

The system consists of a pump, an oxygenator, tubing, and percutaneous venous and arterial cannulae. Cannula sizes vary from 17 to 19 Fr for the arterial cannula and 19–21 Fr size for the venous cannula. The vessels are cannulated either percutaneously or by direct cut down. Full heparinization monitored by serial ACT measurements is required. Blood is drained from a large-bore central vein, usually the femoral vein, and perfused back, after oxygenation, via the femoral artery. A heat exchanger included in the circuit helps to control temperature. Currently portable ECPS devices are available commercially for emergency cardiopulmonary support (see Figure 16. 1).

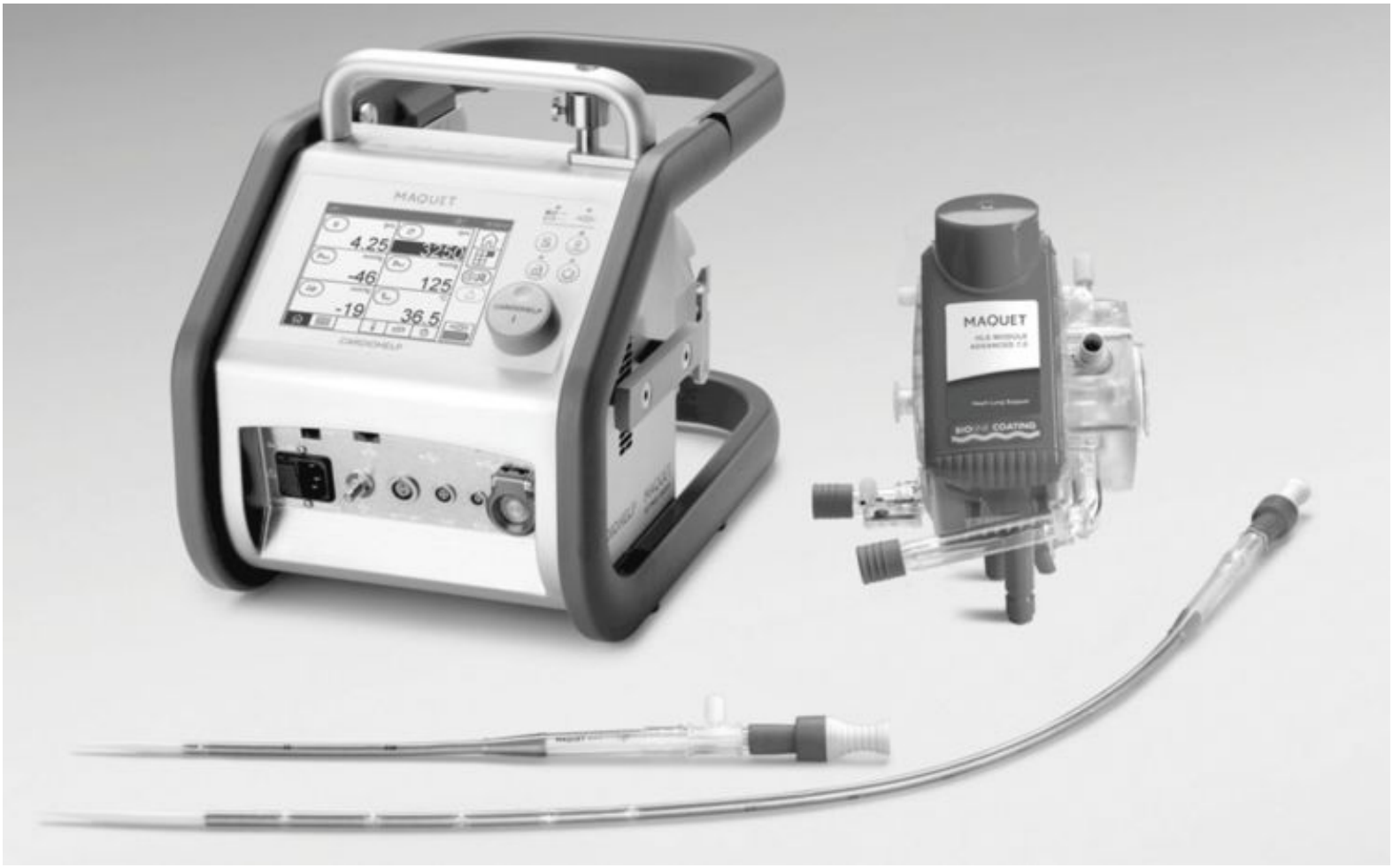

Figure 16.1 CARDIOHELP System is one of the first fully portable emergency life support systems for patients suffering cardiogenic shock. It measures 31 × 25 × 42 cm and weighs 11.5 kg with an ability to generate up to 6 l/minute flow with peripheral or central arteriovenous cannulation.

The National Registry of Cardiopulmonary Support for Emergency Applications details the main indications for ECPS (see Table 16.2). It reflects the large experience of using ECPS in the operating theatre and cardiology catheter labs. In this database, 63% of all patients died while on a ECPS system. Ten percent of patients lived for less than 30 days while 25% survived for more than 30 days. Un-witnessed cardiac arrest resulted in a high mortality even after resorting to ECPS.

Table 16.2 Main indications for ECPS (National Registry of Cardiopulmonary Support for Emergency Applications)

Indications	Percentage of patients (%)
Cardiogenic arrest post-cardiotomy	55
Cardiogenic shock	9
Cardiogenic shock post-cardiotomy	18

Hypothermia	5
Pulmonary insufficiency	6
Others	7

Though the success of survival in witnessed cardiac arrest patients supported with ECPS was better than the un-witnessed group, mortality was still over 70%. Patients who survived had more therapeutic procedures undertaken than the non-survivors, implying the importance of complete correction of precipitating medical factors for a successful outcome. Though severely compromised patients can be resuscitated effectively for a period of up to 6 hours with ECPS, further therapeutic or diagnostic steps need to be undertaken in order to save the patient's life. While ECPS is not a therapy by itself, it has been proven to buy time, potentially allowing for the correction of underlying disease processes. New heparin-bonded circuitry avoids the need for full-dose heparin, thus allowing ECPS to be used in patients with acute hemorrhage or other contraindications for extracorporeal circulation.

Definitive criteria for defining the patients who will benefit most from treatment with ECPS are still lacking, and future research should be directed to provide more information regarding this issue.

Concept of ECMO

Similar to the portable ECPS, the ECMO machine was initially developed from the concept of CPB and allows some degree of portability compared to the CPB machine. ECMO is increasingly used to provide cardiopulmonary or singular pulmonary support for patients with acute severe respiratory failure or cardiac failure. Briefly, the options are veno-arterial (VA) ECMO and veno-venous (VV) ECMO. In VA ECMO, blood is returned to the arterial system and in VV ECMO the blood is returned to the venous system. In VV ECMO, no cardiac support is provided. Figure 14.2 in Chapter 14 provides an overview of the different cannulation sites for VV and VA ECMO.

Criteria for the initiation of ECMO include acute severe cardiac or pulmonary failure that is potentially reversible and unresponsive to conventional management. The main clinical indications and contraindications for ECMO are summarized in Table 16.3.

Table 16.3 Main indications and contraindications for ECMO

Indications	• Hypoxemic respiratory failure with a ratio of arterial oxygen tension to fraction of inspired oxygen (PaO_2/FiO_2) of < 100 mmHg despite optimal ventilator settings

	• Hypercapnic respiratory failure with an arterial pH <7.20 • Refractory cardiogenic shock • Cardiac arrest • Failure to wean from CPB after cardiac surgery • Bridge to either cardiac transplantation or placement of a ventricular assist device
Contraindications	• Pre-existing conditions that affect the quality of life (CNS status, end-stage malignancy, risk of systemic bleeding with anticoagulation) • Age and size of patient • Futility

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ECMO set-up

During the initiation of peripheral ECMO, cannulae are inserted percutaneously. The largest cannulae that can be placed in the vessels are used in order to maximize flow and minimize pressures. ECMO required for complications of cardiac surgery can be placed directly into the appropriate chambers of the heart or great vessels, this constitutes “central ECMO.” Following heparinization and cannulation, the patient is connected to the ECMO circuit and the blood flow rate is increased until respiratory and hemodynamic stability has been achieved. Once the initial respiratory and hemodynamic goals have been achieved, the blood flow is maintained at that rate. Frequent assessment and adjustments are facilitated by continuous mixed venous oximetry to assess the adequacy of oxygen delivery. If needed, ultrafiltration can be added to the ECMO circuit to aid diuresis. For patients with respiratory failure, ECMO weaning can be started when there are improvements in radiographic appearance, pulmonary compliance, and arterial oxyhemoglobin saturation. For patients with cardiac failure, improving left ventricular output indicates that the patient may be weaned off ECMO support.

The institution of ECMO carries significant complications, which include neurological injury (subarachnoid hemorrhage, ischemic watershed infarctions, hypoxic-ischemic encephalopathy, unexplained coma, and brain death), fatal sepsis, bleeding (pulmonary hemorrhage, cannulation sites), systemic thrombo-embolism (including cardiac thrombosis from blood stasis when left ventricular output is not maintained), and anticoagulation-associated issues like heparin-induced thrombocytopenia (HIT).

In addition there can be cannulation-related complications, which include vessel perforation with hemorrhage, arterial dissection, distal ischemia, and incorrect location (venous cannula within the artery). At < 5% these complications are rare.

The indications for ECMO usage are definitely on the rise. In certain settings, ECMO has been shown to provide a better or equivalent alternative to CPB, such as in re-warming from accidental hypothermia or after lung transplantation.

CPB in management of acute respiratory failure

Institution of urgent CPB is of value in patients with sustained respiratory arrest or obstruction in whom endotracheal intubation is not possible. This approach can be life- saving in young patients with treatable pathology such as mediastinal lymphadenopathy due to hematological malignancies causing superior vena cava and tracheal obstruction. Mediastinal tumors can compress major airways to such an extent that the occurrence of even mild supraglottic edema can result in complete airway obstruction. This may occur following minimal handling of the airway during attempted endotracheal intubation, or following upper respiratory tract infections. Initiation of femoro-femoral CPB is the only safe interim procedure prior to controlled tracheotomy to secure an airway. This approach provides a safe solution for airway control when intubation or a surgically created airway is either unsuccessful or too hazardous to attempt.

Management of acute pulmonary embolism

In the treatment of acute pulmonary embolism (PE), medical thrombolytic therapy is often the first-line therapy as this condition can be treated effectively and safely with thrombolytic agents, delivered either intravenously or via a pulmonary artery catheter locally. In non-surgically treated PE, emergency cardiopulmonary support with CPB in massive pulmonary embolism can be helpful in increasing the efficiency of thrombolytic agents by establishing circulation. A few instances where institution of percutaneous CPB in patients with acute pulmonary embolism was lifesaving have been reported. Pulmonary embolectomy for pulmonary thromboembolism (PE) is currently rarely indicated and only reserved as a last resort for critically ill patients with hemodynamic instability, or for those who are either not candidates for or have failed thrombolysis. When emergency pulmonary embolectomy is indicated, CPB can be useful to allow immediate resuscitation and stabilization of cardiopulmonary function prior to surgery, especially when cardiogenic shock is evident. Pulmonary embolectomy can also be achieved by pulmonary arteriotomy and retrograde flushing of the pulmonary circulation via the pulmonary veins after establishment of CPB. Numerous small-sized retrospective studies have recently

reported low mortality for embolectomy when performed early and in a selected group of patients. Therefore, the criteria for surgical embolectomy could be extended from strictly rescue therapy to include hemodynamically stable patients with cardiopulmonary dysfunction.

CPB in resection of tumors

The commonest indication outside cardiac surgery to resort to CPB is the excision of a liver or renal malignancy growing into the inferior vena cava (IVC) and occasionally into the right atrium. Selective cannulation and snaring of the venae cavae, along with a generous right atriotomy after establishing CPB helps the surgeon to extract tumors extending into the inferior vena cava and right atrium under direct vision (see Figure 16.2). With tumors extending into the right atrium, or in exceptional circumstances even into the pulmonary artery, complete excision of the tumor might require deep hypothermic circulatory arrest (DHCA).

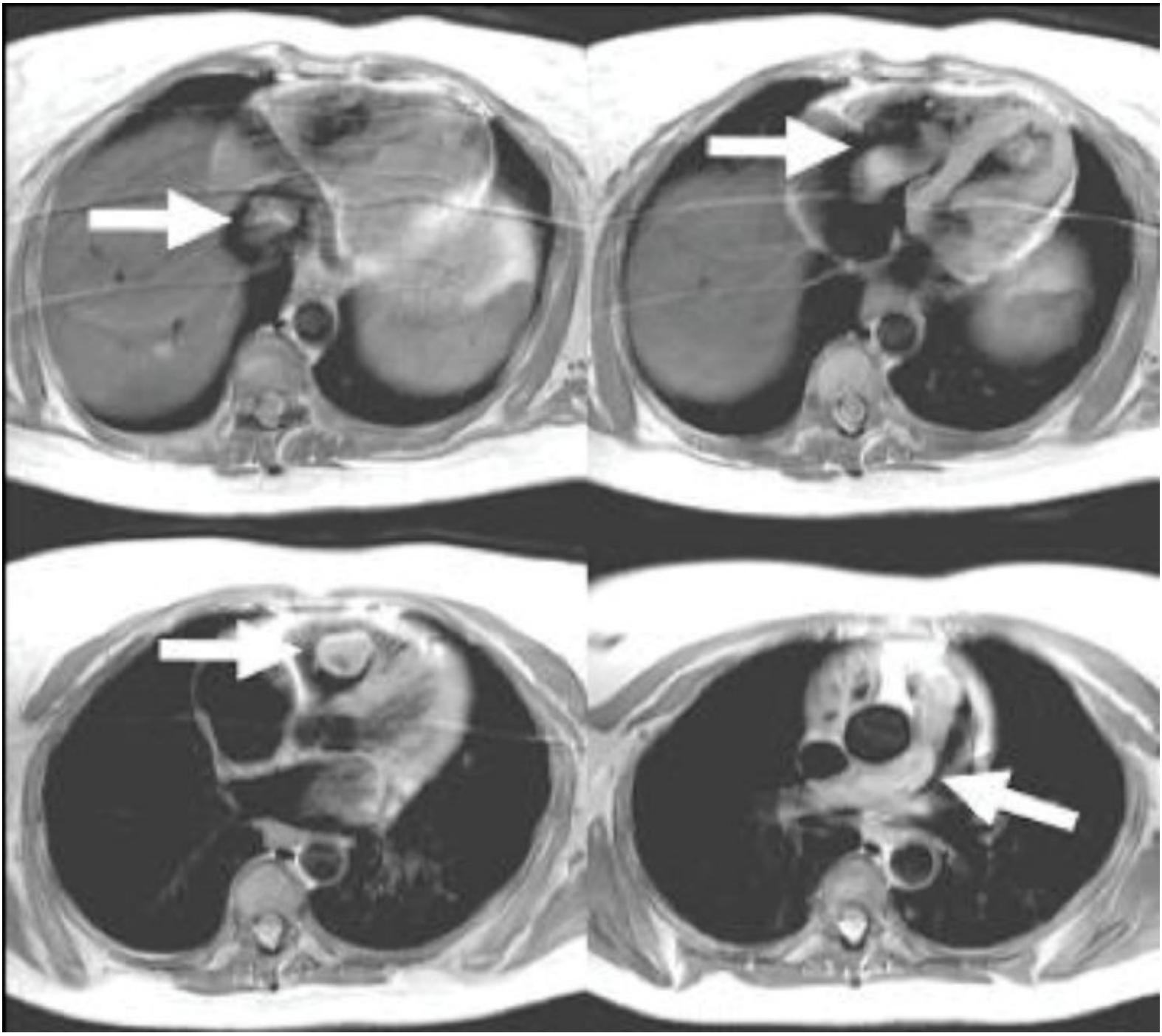

Figure 16.2 Cardiac-gated MRI scan demonstrating uterine benign leiomyoma extending from pelvis through the inferior vena cava into the right atrium, right ventricle, and subsequently into the main pulmonary artery

(Courtesy of Mr Ray George and Mr Jon Anderson, Department of Cardiothoracic Surgery, Hammersmith Hospital, London, UK.)

CPB permits maintenance of systemic perfusion at a low pressure, cessation of pulmonary artery inflow into the lungs, and, if required, drainage of the whole circulating volume into the venous reservoir, thereby allowing total circulatory arrest. The risk of stroke and other neurological complications is minimal if DHCA is employed and does not exceed 30 minutes. CPB thus enables safe resection of vascular tumors and tumors occupying anatomical locations which are difficult to access. The risk of

hemorrhage and organ damage is reduced by lowering the systemic pressure on CPB, cooling down the patient, and, if required, stopping the circulation completely for a finite period of time to allow surgical dissection in a bloodless field. A recent retrospective study of 37 patients over 16 years who underwent extended resection for tumors invading the IVC with CPB with or without DHCA had low morbidity and mortality as well as acceptable survival rates, particularly if complete resection of the tumor could be achieved. Diffuse mediastinal tumors or those infiltrating the heart and great vessels are best excised after institution of CPB. Though infiltration of major vascular structures of the mediastinum can be a contraindication for attempting curative resection of advanced lung cancer, there are studies that have shown a survival benefit when performed in selected patients with advanced T4 lung tumors assisted by CPB.

CPB in other elective procedures

Resection or decompression of complex arteriovenous malformations of the retroperitoneum, mediastinum, limbs, and brain using endovascular embolization with, or without, open surgical techniques will benefit from low flow CPB or DHCA; CPB and DHCA have been of particular value in converting otherwise inoperable tumors or vascular malformations of the brain or spinal cord to those amenable to a relatively safe surgical procedure.

Profound hypothermia, circulatory arrest, and exsanguination is a common approach in certain high-risk neurosurgical interventions to remove intracranial aneurysms, glomus jugulare tumors, and hemangioblastoma of the brain. In such instances, DHCA provides a bloodless surgical field and protection of the brain, which make precise clipping of the vascular malformation possible. The disadvantages of this technique include cardiac distension and arrhythmia during CPB, hemorrhage from systemic anticoagulation, and central nervous system injury due to inadequate cerebral protection.

CPB in non-cardiac transplantation

Single and sequential double lung transplantation

CPB has been frequently used for single and double lung transplantation. Most commonly, however, the decision to establish partial or complete CPB is made after hemodynamic assessment of the patient following occlusion of the pulmonary artery during surgery. Criteria for the establishment of CPB include a mean pulmonary artery pressure of more than 50 mmHg, hypoxia, hypercapnea, or hemodynamic instability. Prior to surgery it is also possible to get an indication of the need for CPB support by

eliminating ventilation to the operative lung. If the non-operative lung is ineffective for maintaining ventilation on its own, the patient is unlikely to tolerate the period of lung isolation during explant and implant of the operative lung and CPB will be required.

As yet, there are no reliable preoperative predictors for the need for CPB in lung transplantation. However, in a study involving 109 lung transplant recipients, preoperative right ventricular ejection fraction of < 40%, 6-minute walk test result of less than 250 m, and drop in arterial oxygen saturation on exercise to < 94% on room air were positive predictive factors for resorting to CPB.

Some transplant centers have been reluctant to use CPB during lung transplantation due to potential side effects, including hemorrhage and triggering of a systemic inflammatory response syndrome (SIRS), leading to sequestration of neutrophils and platelets in the pulmonary capillary bed, endothelial damage, increased capillary permeability, and subsequent pulmonary edema. There are numerous retrospective studies demonstrating higher short-term mortality and primary allograft dysfunction with the usage of CPB compared to without and, moreover, citing worse outcomes with unplanned CPB than planned CPB. This is contradicted by the findings of Hlozek et al. from the Cleveland Clinic, involving 74 patients over 4 years. Comparing patients who had their lung transplant with or without CPB, it failed to demonstrate any significant difference in the short- or long-term outcome between the groups. At the current time, there are numerous comparative studies assessing the benefits of CPB versus ECMO for lung transplantation which demonstrate that there are no significant differences in 30-day, 90-day or 1-year mortality, although the use of ECMO generally results in less bleeding and requires fewer blood product transfusions.

Liver transplantation

Occasionally extracorporeal circulation is used to assist liver transplantation (LTX). Cardiopulmonary bypass in LTX is indicated for hemodynamic rescue and, at some centers, serves as the hemodynamic support during liver implantation. In general terms, extracorporeal circulation provides a means of decompressing the hepato-portal circulation and reducing the risk of bleeding when operating on patients with portal hypertension. It also reduces the risk of post-transplantation renal failure and of intestinal venous congestion with subsequent hepatic dysfunction. The femoral vein is cannulated for venous return using a standard short venous cannula. The venous blood thus drained is passed through a centrifugal pump to be returned to the systemic venous circulation by cannulae inserted into the internal jugular or subclavian vein. Heparin-bonded circuits are preferred to avoid full systemic heparinization.

Systemic venous return is often impaired by surgical manipulation during both excision of the native liver and implantation of the transplant organ. Employing an extracorporeal perfusion technique allows the portal circulation to be decompressed as well as systemic venous return to be maintained at levels

adequate to maintain cardiac output. Furthermore, it allows extravasated blood to be salvaged and returned to the circulation. If portal hypertension persists despite inferior vena cava drainage via the femoral vein, an extravenous drainage cannula can be inserted directly into the portal vein. It should be noted that the circuit described here is not a CPB circuit as it does not include an oxygenator and there is no arterial cannulation because the heart maintains the cardiac output.

CPB in thoracic aortic surgery

Operations on the aorta present a particular challenge because of the unique function of the aorta as the primary conduit for blood flow to the body. Surgical procedures on the aorta can thus only be undertaken by either disrupting flow to some organs completely or by supporting organ perfusion using CPB. Of particular concern are maintenance of blood flow to the brain, kidneys, and spinal cord; if blood supply is to be necessarily compromised during the procedure then strategies to protect these organs should be adopted.

Techniques for maintaining effective blood flow to vital organs are dictated by the nature of the underlying pathology and the anatomical site requiring surgical correction.

The most commonly encountered pathologies are dissection, aneurysmal dilatation, and transection of the aorta.

Classification of thoracic aorta disease:

1. **Dissection**: intimal tear/hematoma in media creating a “false” lumen
2. **Aneurysm**: dilation, atheromatous or associated with Marfan’s syndrome
3. **Transection/tear**: following major trauma
4. **Coarctation**: congenital narrowing

Thoracic aortic dissection

Degeneration of the inner layers of the aortic wall, usually as a result of atheromatous disease, ageing or in association with hypertension, results in a sudden transverse tear of the intima; blood is forced under pressure into a false lumen created by destruction of the substance of the media and stripping of part of the media from the adventitia. Blood flow to organs and limbs may be compromised, depending on the site of the dissection, and the dissection flap may retrogradely extend to the aortic root and/or coronary ostia, giving rise to aortic regurgitation and myocardial ischemia.

Thoracic aortic dissections are classified as per the Stanford classification into:

Type A: involving the ascending aorta

Type B: involving the aorta distal to the left subclavian artery

Management is aimed at stopping progression of the dissection. Type A generally requires urgent surgery to limit progression of the dissection into the ascending aorta, prevent aortic regurgitation, intra-pericardial rupture or coronary ischemia. Type B is usually managed conservatively using vasodilators and beta blockers.

Type A dissections which do not involve the aortic arch, aortic valve or coronary ostia can be surgically corrected by interposition of a tubular Dacron graft to re-establish circulation through the true lumen; stagnation of blood in the false lumen leads to thrombosis and eventually fibrosis. If the aortic valve or coronaries are involved then additional valve replacement and/or coronary re-vascularization may be necessary. If the aortic arch is involved then more complex surgery is undertaken under deep hypothermic circulatory arrest (DHCA).

In most centers current surgical practice is to establish CPB, with core cooling, via femoral arterial and venous cannulation before attempting sternotomy. This technique provides “controlled” conditions in the event that the aorta is damaged during chest opening or exposure of the mediastinum; aortic dissections are often associated with fragility and gross anatomical distortion of the mediastinal contents leading to the potential for catastrophic hemorrhage. Commencing cooling early affords protection against neurological damage resulting from sudden, inadvertent hypotension.

Venous drainage may be poor via the femoral venous cannula; options to improve drainage include using the largest diameter venous cannula that the vein can accommodate, using vacuum-assisted venous drainage, using a long venous cannula that can be passed up the inferior vena cava into the right atrium or placing an additional venous cannula in the right atrium, once the heart has been safely exposed, and connecting the femoral and venous cannula together with a Y-connector to the CPB circuit.

Femoral arterial cannulation may be complicated by the fact that many of these patients also have peripheral vascular disease; cannulation of the vessel may lead to lower limb ischemia. An alternative approach when cannulating peripheral arteries for CPB is to first connect a prosthetic graft, using an end to side anastomosis, to the artery and then placing the cannula in this prosthetic limb rather than directly in the vessel. If the femoral arteries are grossly diseased or too small to accommodate a reasonably sized arterial cannula then the iliac artery or right axillary artery may be used instead. A further disadvantage of using the femoral artery for CPB is that perfusion is retrograde and thus, in the face of aortic dissection, may result in blood flowing up the false lumen, compromising rather than improving organ perfusion. At the onset of femoro-femoral CPB particular attention needs to be paid to line pressures, flow rates, and the monitored systemic arterial pressure to ensure adequacy of perfusion via the true aortic lumen. The

arterial cannula can be transferred to the right axillary artery following sternotomy; this has the advantage of providing antegrade perfusion and may provide better cerebral perfusion than perfusion via the femoral artery. Many surgeons will cannulate the aortic graft as soon as it is in place and use this as the route for arterial return from the CPB machine.

Operative mortality is said to be about 5–10%, with 70% surviving beyond 5 years with good control of hypertension and regular annual imaging surveillance. Mortality is higher if the arch is involved.

Thoracic aortic aneurysms

Fusiform or saccular dilatation of the aorta as a result of atherosclerosis, cystic medial necrosis or more rarely infection, give rise to an "aneurysm." The aortic wall in the region of the aneurysm is weakened and prone to rupture, with risk of rupture increasing as the diameter of the aneurysm begins to exceed 5 cm. Aortic aneurysms are classified according to their location into ascending, arch or descending.

- Location:
  - · Ascending: proximal to innominate artery
  - · Arch: between innominate and left subclavian
  - · Descending: distal to left subclavian

Ascending aneurysms may be treated with an interposition graft, sometimes also requiring aortic valve replacement and coronary ostial re-implantation or coronary artery bypass grafting. Cannulation for CPB is as described above for aortic dissection.

Arch aneurysms are more complex to correct, requiring replacement of the arch from the innominate artery to the left subclavian artery and anastomosis of the prosthesis to the great vessels. DHCA is required and in addition selective antegrade cerebral perfusion or retrograde cerebral perfusion may be used to try to protect the brain from ischemia. These techniques are discussed in more detail in Chapter 10.

Descending aneurysms require replacement of the aorta from below the left subclavian artery to the diaphragm. A particular hazard is spinal cord ischemia because of the variable origin from the posterior aspect of the aorta of the radicularis magna, the principal blood supply of the spinal cord. There are two approaches to descending aortic aneurysm surgery: the older approach is to clamp the aorta proximal to the aneurysm and sew in the graft as rapidly as possible. Alternatively partial femoro-femoral bypass can be established to maintain perfusion to the lower part of the body. The aorta is clamped proximal and distal to the lesion. Endogenous cardiac output sustains perfusion to the upper half of the body above the

proximal aortic clamp. Hypertension in the upper body commonly develops after application of the proximal cross-clamp and needs to be controlled using short-acting vasodilators, or if partial femoral bypass is used by increasing venous drainage into the bypass reservoir and so reducing circulating volume. On completion of the surgical repair, removal of the cross-clamp regularly causes hypotension and metabolic derangement. Metabolic acidosis is common following reperfusion of the lower body. Hemofiltration on bypass can be used to help with metabolic management.

Reducing spinal cord ischemia during descending aortic aneurysm surgery

As mentioned earlier the blood supply to the spinal cord is particularly vulnerable during descending aortic aneurysm surgery; up to 30% of patients sustain severe neurological injury and often end up paraplegic. The best method of protecting the spinal cord from ischemia is to keep the cross-clamp time short (< 30 minutes). Maintaining distal aortic perfusion pressure using partial femoral bypass may help in some cases, but the evidence of significant benefit in preserving neurological function is equivocal. Mild hypothermia (32°C) may have a role, but again evidence of distinct benefit is lacking. Drainage of cerebrospinal fluid (CSF) to reduce the compression of vessels supplying the spinal cord by rising CSF pressure may be beneficial in maintaining blood flow and is used as a spinal protective strategy. Using pharmacological agents such as steroids and papaverine in conjunction with CSF drainage may work synergistically to reduce spinal cord ischemia. Avoidance of hyperglycemia may reduce the damage sustained from ischemia. The role of specific pharmacological agents such as calcium channel blockers remains controversial.

Blunt thoracic aortic injury

Transection of the aorta occurs as a result of blunt thoracic injury, most commonly road traffic accidents. Eighty to ninety percent of patients die at the scene; 90% of survivors die within 10 weeks. Survivors have an intact adventitia and the most common site of injury is near the ligamentum arteriosum, distal to the left subclavian artery. Those who reach hospital alive usually have multiple injuries, which may include splenic rupture and head injury. Once the patient has been assessed and stabilized surgical repair of the transection may be appropriate and depends on the site and extent of the tear. CPB may be particularly hazardous because of the need for heparinization in the face of multiple trauma. Use of heparin-bonded circuitry with only partial heparinization has been advocated. Cannulation for CPB depends on the site of the tear and follows the principles discussed above for management of dissections or aneurysms. Use of left heart bypass for emergency aortic repair is described in the section on “CPB in trauma care” earlier in this chapter. With the recent advances made in interventional radiology,

percutaneous stenting across the transected aorta is becoming more and more common. Vascular access is achieved through the left common femoral artery and a covered stent is deployed across the transaction line under radiological guidance. Mid-term survival outcome of this percutaneous intervention is satisfactory but long-term survival outcome is still awaited.

Management of operations on the aorta requires detailed preoperative planning of the choice of initial cannulation site, core temperature management, the strategy for optimizing CPB flow, and the quality of perfusion with additional cannulation if required, adapting intra-operatively if DHCA becomes necessary. Preoperative "work up" of the patient is crucial, but there is limited time as many of these procedures are emergencies. Intra-operatively, key factors to successful outcomes are limiting ischemic times, rigorous correction of metabolic parameters, and skilled imaging using TEE, not only to define the lesion, but also to assess perfusion within the true lumen of the aorta, valvular competence, and cardiac function. Thoracic aortic surgery still carries a high rate of morbidity and mortality despite recent advances.

Self assessment

1. Which of the following statements are true with regard to accidental hypothermia (select one or more)?

A. Accidental hypothermia is defined as: "an unintentional decrease in core temperature below 35°C due to hypothermic exposure in individuals without intrinsic thermoregulatory dysfunction"

B. Invasive methods of re-warming include instillation of warm fluid in the bladder, peritoneal lavage with warm fluid, and CPB

C. Vasodilators should not be used when re-warming patients using cardiopulmonary bypass

D. Hypokalemia is a useful indicator when making the differential diagnosis between profound hypothermia and death

Answers: A, B

2. Select true or false for the following statements:

A. Left heart bypass can be used to maintain perfusion of the body above and below the proximal and distal aortic cross-clamps during repair of injury to the descending aorta

B. Heparin-bonded circuits do not reduce the risk of bleeding when using CPB

C. The most common site of transection of the aorta following blunt trauma is near the ligamentum arteriosum, distal to the left subclavian artery

D. Type B aortic dissections involve the ascending aorta

E. Type A aortic dissections are conservatively managed using antihypertensive agents

Answers: A True; B False; C True; D False; E False

3. Select true or false for the following statements:

A. ECMO can only be instituted using bypass cannulae placed in the right atrium and aorta

B. Can be either veno-venous or veno-arterial

C. Veno-venous ECMO is used to provide cardiac support

D. Mixed venous oxygen saturation monitoring is a useful guide to the adequacy of ECMO support

E. Complications of ECMO include intracranial hemorrhage, heparin-induced thrombocytopenia, and limb ischemia

Answers: A False; B True; C False; D True; E True

4. Which of the following statements are true with regard to the use of extracorporeal support in non-cardiac transplantation (select one or more)?

A. Extracorporeal support for liver transplantation is usually conducted via cannulae placed in the femoral vein and internal jugular or subclavian veins

B. The purpose of extracorporeal support in liver transplantation is to supply oxygenated blood to the abdominal organs

C. The purpose of extracorporeal support in liver transplantation is to decompress the hepato-portal circulation and so reduce blood loss in patients with portal hypertension

D. The use of cardiopulmonary bypass for lung transplantation is avoided in some centers because of the increased risk of reperfusion injury to the implanted lungs as a result of the systemic inflammatory response associated with CPB

Answers: A True; B False; C True; D True

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