Extracorporeal Membrane Oxygenation

An Interdisciplinary Problem-Based Learning Approach

Edited by

Marc O. Maybauer



OXFORD

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AN INTERDISCIPLINARY PROBLEM-BASED LEARNING APPROACH

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Marc O. Maybauer, MD, PhD, EDIC, FCCP, FACC, FASE

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To my parents

Jutta and Manfred† Maybauer

From a grateful son for their love, patience, and support

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FOREWORD

"The Times They Are a-Changin"
—Bob Dylan

This book was commissioned in 2019, long before the city of Wuhan became ground zero in what would become the largest pandemic in modern history.

Since then, the world has become a different place. No aspect of society remains untouched. Travel, education, finance, manufacturing, communication—and most importantly medicine—have changed more in the last couple of months than in the preceding 80 years. Medics and scientists have risen to the fore like never before as the world looks to clinicians and trailblazers to lead them from this dark place.

It was similar innovators who have led the rise of Extracorporeal Membrane Oxygenation (ECMO) and Mechanical Circulatory Support (MCS). This field has grown rapidly over the last 10 years. From the CESAR to the EOLIA trial, innovators have led to determine when and when not to use mechanical support. The technology improves year by year, but we still slack clarity into the optimum patient selection and timing of ECMO. As this book suggests, however, it is essential that we look beyond just "the pump and the physician" to harness the potential of MCS, as it is only when the combined power of the multidisciplinary team is brought together that we can achieve what was once impossible.

Until this composite of clinicians, scientists, rheologists, pharmacists, nurses, perfusionists, engineers, allied health, and patients are brought together—MCS programs will never achieve their full potential. Similarly, the pediatric population has led their adult brothers and sisters in MCS for many years. It is this silo-free environment combining these clinical and scientific areas that will set this book apart and provide much richer learning opportunities for the reader—regardless of which discipline they may be—and for this, the authors should be congratulated.

The editor has assembled all the key researchers and clinicians in the field, but this book achieves much more than a usual textbook through its problem-based learning approach, giving pragmatic and "real-life" tips to both the beginner and the expert. The rapid pace at which medical literature grows has made it almost impossible to keep up to date with every paper. Hence, it can be difficult for clinicians to best determine how these sometimes mutually opposing data should be used to optimize care of their patient.

The innovative approach of marrying the didactic chapters with relevant problem-based learning allows the interpretation of relevant novel data and examples of how this literature can improve outcome.

As the world learns to live with COVID, it is heartening to see the knowledgeable and pragmatic approach that this book has taken—as we recognize for our patients to achieve the best outcome, they must be treated by a multidisciplinary team.

It was British Prime Minister Winston Churchill who said, "Never let a good crisis go to waste." While there is nothing good about the current pandemic ravaging the world, it is a reminder that no matter how smart we think medicine has become, we can only continue to improve through taking all opportunity to learn and work collaboratively.

The structure and content of this book encapsulate this desire to learn for the improvement of our patients. It is hoped when the second edition is written, such improvements in our learning may have consigned COVID to a very large and sad footnote in medical history.

Professor John F. Fraser
President, Asia-Pacific-ELSO

PREFACE

The problem-based learning (PBL) approach was pioneered in the 1960s by Barrows and Tamblyn and over the years has become an integral part of medical education. My first experience with PBL occurred in 2008, when I relocated from Germany to the United States, after accepting an anesthesiology faculty position at the University of Texas Medical Branch in Galveston. Once there, I was to supervise a pulmonary physiology PBL group of medical students but as an integral part of the group, someone who could help and guide the students through the study material if needed, rather than as an educator. My own personal experience had been aligned with tuition of a classical fashion in the form of lectures and seminars, and initially I was not convinced of this approach; however, over time I learned to appreciate the beauty of it. I saw the students applying knowledge to the provided cases, making mistakes and learning from them. They built knowledge and gained experience without any harm to patients, and I was able to add questions based on my own clinical experience to enhance the learning environment. These events coincided with the CESAR trial and the following H1N1 ECMO trials, which ignited my own fascination with what ECMO technology could achieve. As a keen learner, I very often was frustrated by the limited amount of educational material and textbooks surrounding ECMO, which did not offer much guidance, as though they were scientifically correct and exhaustive; they were listings of facts and comparison of studies and outcomes, making it difficult to extract specifics on how to actually do things and why.

At this time, my best experience on how to apply knowledge to a clinical scenario came from working with senior colleagues and the ECMO course at Papworth Hospital in Cambridge, United Kingdom. Later, while working at the Manchester Royal Infirmary, I became director of the ECMO program there and in this role faced different challenges. One of which, and possibly the most challenging question, was how to educate a large body of physicians and nurses on the subject of ECMO. Of course, lectures and seminars were my first instinct, and though a relocation to the States meant I did not have the opportunity to establish PBL in Manchester, the idea for an ECMO textbook utilizing the PBL approach was born.

Extracorporeal Membrane Oxygenation—An Interdisciplinary Problem-Based Learning Approach provides an overview of the latest techniques, management strategies, and technology surrounding the clinical use of ECMO. This interdisciplinary book reviews the most common scenarios of ECMO in 62 chapters, exploring the conditions and problems arising in ECMO practice. Each chapter begins with a stem case, followed by open questions to encourage critical thinking and enable the reader to follow the management strategies of the authors, who are world leaders in their field. Following an evidence-based discussion, each chapter concludes with multiple-choice questions for self-assessment. This book is current in its knowledge of organ systems and management and keeps pace with new ECMO technology and surgical techniques coupled with current guidelines for management.

Starting with the history of ECMO and moving to technical aspects, circuit biocompatibility and interaction with blood, drugs, and flow physics, the volume then continues into pediatric and adult sections, focusing on both respiratory and cardiovascular support, followed by a section on trauma. The volume then concludes with a section on rehabilitation and ambulation of ECMO patients as well as neurologic complications, ethics, and end-of-life care. In addition, to reflect the current global health situation, this book includes a chapter on ECMO management in patients suffering with COVID-19 to cover the most urgent and pressing questions around ECMO during the ongoing pandemic.

This is the first ECMO book on the market to utilize a PBL approach and as such is an important unprecedented project on ECMO education.

I am very grateful to all the authors who kindly agreed to contribute to this book. Each has invested a considerable amount of time and energy, despite the overwhelming pressures on their profession at this present time, to write their chapters and contribute to the education of the next generation of ECMO providers during a time when it is most inspiring to see the medical community closing ranks to fight the pandemic and develop treatment and management options as well as education.

I would like to thank this group of experts from their varied interdisciplinary backgrounds for contributing to this book with the aim to guide caregivers from all disciplines in the management of ECMO and to demystify the approach to ECMO, which will be a major player in the future of resuscitation and treatment of Acute Respiratory Distress Syndrome. I would also like to thank the team from Oxford University Press for their continuous support, as well as Elham Abdelbary for kindly providing the cover photograph. Last but not least, I would like to thank my family and friends who put up with me over the past 2 years throughout this journey.

Marc O. Maybauer
Editor

CONTRIBUTORS

Mohd. H. Abdul-Aziz, BPharm (Hons), MClin Pharm, PhD
Post-doctoral Research Fellow
Faculty of Medicine
University of Queensland and Centre of Clinical Research (UQCCR)
The University of Queensland
Brisbane, Australia

Darryl Abrams, MD
Assistant Professor
Department of Medicine
Division of Pulmonary, Allergy, and Critical Care
Columbia University Medical Center
New York, NY, USA

Cara Agerstrand, MD
Assistant Professor of Medicine
Division of Pulmonary, Allergy and Critical Care Medicine
Columbia University Irving Medical Center/NewYork-Presbyterian Hospital
New York, NY, USA

Sara Jane. Allen, BHB, MBChB, FANZCA, FCICM
Cardiac Anaesthetist and Intensivist
Department of Anaesthesia and Cardiovascular Intensive Care Unit
Auckland City Hospital
Auckland, New Zealand

Othman Al-Sawaf, MD
Physician
Department I of Internal Medicine
Critical Care Medicine
University Hospital of Cologne
Cologne, Germany

Antonio Arcadipane, MD
Chair
Department of Anesthesia and Intensive Care
IRCCS-ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)
Palermo, Italy
Visiting Clinical Associate Professor of Anesthesia and Perioperative Medicine
University of Pittsburgh—School of Medicine
Pittsburgh, PA, USA

Gianluigi Li Bassi, MD, PhD
Associate Professor
Department of Clinical Medicine
School of Medicine
University of Queensland
QLD, Australia
Senior Investigator
Critical Care Research Group/The Prince Charles Hospital
Chermside
QLD, Australia
The Institut d'Investigacions Biomèdiques August Pi i Sunyer
Barcelona, Spain

Vanessa M. Bazan, BSc
University of Kentucky College of Medicine
Lexington, KY, USA

Jan Bělohlávek, MD, PhD
President of EuroELSO
President of Czech Association of Acute Cardiology
Professor of Medicine
ECMO Team Director
Director of the Coronary Care Unit
Department of Internal Medicine II, Cardiovascular Medicine
General University Hospital
Prague, Czech Republic

John T. Berger, MD
Medical Director, Cardiac ECMO
Medical Director, Pulmonary Hypertension Program
Divisions of Cardiac Critical Care Medicine and Cardiology
Children's National Health System
Associate Professor
Department of Pediatrics
George Washington University
Washington, DC, USA

Zeenia C. Billimoria, MD
Assistant Professor
Department of Pediatrics
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, WA, USA

Jean Bonnemain, MD
Senior Critical Care Fellow
Service of Adult Intensive Care Medicine
University Hospital
Lausanne, Switzerland

Daniel Brodie, MD, FELSO
ELSO President- Elect
Professor of Medicine
Section Chief for Critical Care, Milstein and Allen Hospitals
Director, Medical ICUs and Medical Critical Care Services
Director, Adult ECMO Program
Director, Center for Acute Respiratory Failure
Vice Chairman of Medicine, Special Projects
Associate Chief
Division of Pulmonary, Allergy, and Critical Care Medicine
Columbia University College of Physicians and Surgeons
Department of Medicine
Division of Pulmonary, Allergy, and Critical Care Medicine
New York, NY, USA

Thomas V. Brogan, MD, FELSO
Professor
Department of Pediatrics
University of Washington School of Medicine
Seattle Children's Hospital
Seattle, WA, USA

Lars M. Broman, MD, PhD
Senior Consultant
Associate Professor
ECMO Centre Karolinska
Pediatric Perioperative Medicine and Intensive Care
Department of Physiology and Pharmacology
Karolinska Institutet
Karolinska University Hospital
Stockholm, Sweden

Bonnie A. Brooks, MD
Pediatric Critical Care Medicine
Fellow, Pediatric Cardiology
Division of Cardiology
Children's National Hospital
Washington, DC, USA

Katherine L. Brown, MD, MPH, MRCP
Consultant, in Pediatric Cardiac Intensive Care
Associate Professor, University College London
Great Ormond Street Hospital for Children NHS Foundation Trust
London, UK

Marissa A. Brunetti, MD
Attending Intensivist
Children's Hospital of Philadelphia
Assistant Professor of Clinical Anesthesiology and Critical Care Medicine
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA, USA

Aidan Burrell, MBBS, PhD, DDU, FCICM
Intensivist and Head of General ICU
The Alfred Hospital,
Melbourne, Australia
Adjunct Senior Lecturer
School of Public Health and Preventative Medicine
Monash University
Melbourne, Australia

Hergen Buscher, MD, FCICM, EDIC, DEAA
Senior Staff Specialist
Department of Intensive Care Medicine
St. Vincent's Hospital
Sydney, Australia
Centre of Applied Medical Research
St. Vincent's Hospital
Sydney, Australia
University of New South Wales
Sydney, Australia

Gerasimos Capatos, MBBCh (WITS), FCP (SA), Cert. Crit. Care (SA)
Consultant Intensivist and Co-Director Mediclinic Parkview ECMO Unit
Adjunct Clinical Assistant Professor
Mohammed Bin Rashid University of Medicine and Health Sciences
Dubai, UAE

Massimo Capoccia, MD, MSc (Eng)
Cardiac Surgeon
Senior Fellow in Aortic Surgery
Royal Brompton and Harefield NHS Foundation Trust
Royal Brompton Hospital
London, UK

Arpan Chakraborty, MBBS, MD, FNB
President, ECMO Society of India
Senior Consultant
Cardiac Anaesthesia, Critical Care, and ECMO Services
Medica Superspecialty Hospital
Kolkata, India

Rachel L. Chapman, MD
Associate Professor
Department of Clinical Pediatrics
USC Keck School of Medicine
Medical Director
Newborn and Infant Critical Care Unit, Fetal and Neonatal Institute
Associate Chief
Division of Neonatology
Children's Hospital Los Angeles
Los Angeles, CA, USA

Dipanjan Chatterjee, MD
Senior Consultant
Cardiac Anaesthesia, Critical Care, and ECMO Services
Medica Superspecialty Hospital
Kolkata, India

Vesa Cheng, BPharm (Hons), BComm, MSHP, AdvPrac(II)
PhD Candidate
Faculty of Medicine
University of Queensland and Centre of Clinical Research (UQCCR)
The University of Queensland
Brisbane, Australia
Critical Care Research Group
Centre of Research Excellence for Advanced Cardio-respiratory Therapies Improving OrgaN Support (ACTIONS) and the University of Queensland
Brisbane, Australia
Pharmacist Educator (Advanced)
Medical Education Unit, The Princess Alexandra Hospital
Brisbane, Australia

Joshua Chew, MBBS
Senior Registrar
Department of Anaesthesia
The Prince Charles Hospital
Chermside, Australia

Matthew S. Clifton, MD
Associate Professor
Division of Pediatric Surgery
Department of Surgery
Emory University School of Medicine
Atlanta, GA, USA
Program Director
Division of Pediatric Surgery
Department of Surgery
Emory University School of Medicine
Atlanta, GA, USA
Surgical Director for ECMO
Children's Healthcare of Atlanta at Egleston
Atlanta, GA, USA

Valeria Lo Coco, MD
PhD Fellow
Cardio-Thoracic Surgery Department
Heart and Vascular Centre
Maastricht University Medical Centre
Maastricht, The Netherlands

Ryan D. Coleman, MD, FAAP
Pediatric Critical Care/Pulmonary Hypertension
Director—Right Ventricular Failure Program
Vice-Chair—Fetal Therapy and Innovation Committee
Assistant Medical Director—ECMO Program
Assistant Professor of Pediatrics and Medical Ethics
Sections of Critical Care Medicine and Pulmonary Medicine
Center for Medical Ethics and Health Policy
Baylor College of Medicine/Texas Children's Hospital
Waco, TX, USA

Sebastiano M. Colombo, MD
ICU Physician
Department of Pathophysiology and Transplantation
University of Milan
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico,
Department of Anesthesia, Critical Care, and Emergency
Milan, Italy
Research Fellow
Critical Care Research Group/The Prince Charles Hospital
Chermside, QLD, Australia

David S. Cooper, MD, MPH
Medical Director, Cardiac Intensive Care Unit
Medical Director, Cardiac Anesthesia Recovery Unit
Co-Director, Center for Acute Care Nephrology
Division of Cardiology
Cincinnati Children's Hospital Medical Center
Associate Professor
Department of Pediatrics
University of Cincinnati College of Medicine
Cincinnati, OH, USA

Julia Coull, MBBS, FCICM
Intensivist
The Alfred Hospital
Melbourne, Australia
Adjunct Senior Lecturer
School of Public Health and Preventative Medicine
Monash University
Melbourne, Australia

Mark G. Davidson, MBChB, BSc (Med Sci), MRCPCH
Pediatric Intensive Care
Royal Hospital for Children
Glasgow, Scotland

Carl Davis, MB, MCh, FRCSI, FRCPSGlas, FRCSpaed
Consultant, Paediatric and Neonatal Surgeon
Royal Hospital for Children
Glasgow, UK

Maria E. De Piero, MD
PhD Fellow
Department of Cardio-Thoracic Surgery
Department Heart and Vascular Centre
Maastricht University Medical Centre
Maastricht, The Netherlands
Consultant, Anesthesia and Intensive Care
Department S. Giovanni Bosco Hospital
Turin, Italy

Ajay Desai, DCH, DNB, MRCPCH, FRCPCH, FFICM
Consultant, in Paediatric Critical Care Medicine
Lead for Paediatric ECMO Programme
Royal Brompton Hospital NHS Foundation Trust
London, UK

Alexander Fletcher-Sandersjöö, MD
PhD Student
Department of Neurosurgery
Department of Clinical Neuroscience
Karolinska Institutet
Akademiska straket 14
Karolinska University Hospital
Stockholm, Sweden

Jo-Anne Fowles, MSc, RN
Nurse Consultant, Critical Care Area and ECMO
Royal Papworth Hospital NHS Trust Cambridge
Cambridge, UK

Guillaume Franchineau, MD
Sorbonne Université
Institute of Cardiometabolism and Nutrition
Paris, France
Service de médecine intensive-réanimation
Institut de Cardiologie
APHP Sorbonne Université Hôpital Pitié–Salpêtrière
Paris, France

John F. Fraser, MBChB, PhD, FRCP(Glas), FFARCSI, FRCA, FCICM
President, Asia-Pacific-ELSO Chapter
Professor and Pre-Eminent Specialist in Intensive Care Medicine
Director of the Critical Care Research Group
University of Queensland and The Prince Charles Hospital
Brisbane, Australia
Director of Intensive Care Unit
St Andrew's War Memorial Hospital
Brisbane, Australia
Professor of Anaesthesiology and Critical Care
School of Medicine
University of Queensland
Professor of Medicine
Bond University
Professor
School of Medicine Griffith University
Adjunct Professor
Queensland University of Technology
Adjunct Professor
Monash University
Australia

A. Reshad Garan, MD, MS, FACC
Director, Advanced Heart Failure and Mechanical Circulatory Support
Division of Cardiology
Department of Medicine
Beth Israel Deaconess Medical Center
Harvard Medical School
Cambridge, MA, USA

Iolanda Jordan Garcia, MD, PhD
Professor
Department of Pediatrics
University of Barcelona
Senior Consultant
Department of Pediatric Intensive Care
Hospital Sant Joan de Déu
Barcelona, Spain

Monica Balaguer Gargallo, MD, PhD
Consultant
Department of Pediatric Intensive Care
Hospital Sant Joan de Déu
Barcelona, Spain

Janos Geli, MD, PhD, DESA
Consultant
Department of Cardiothoracic Anaesthesia and Critical Care
Karolinska University Hospital Stockholm
Solna, Sweden

Mario Gramegna, MD
Intensive Cardiac Care Unit
Advanced Heart Failure and Mechanical Circulatory Support Program
IRCCS San Raffaele Scientific Institute
Milan, Italy

Giacomo Grasselli, MD
Associate Professor in Anesthesiology and Intensive Care Medicine
Department of Pathophysiology and Transplantation
University of Milan
Milan, Italy
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Department of Anesthesia, Critical Care, and Emergency
University of Milan
Milan, Italy

Michael D. Harper, MD, FAAEM
Department of Critical Care
MedStar Washington Hospital Center
MedStar Heart and Vascular Institute
Washington, DC, USA

Dr Emma L. Hartley, MBChB, MCEM, FFICM
Severe Respiratory Failure Fellow
Department of Intensive Care Medicine
Guy's and St. Thomas' NHS Foundation Trust
London, UK

Ibrahim F. Hassan, MD
Director of Corporate Critical Care
Chief Medicine Critical Care Division
ECMO Program Director
Deputy Medical Director Ambulance Service
Associate Professor Clinical Medicine and Genetic Medicine at Weill Cornell Medical College
Hamad Medical Corporation
Doha, Qatar

Marcus Hermann, MSc, BEng
Perfusionist, Lead for Research
Department of Clinical Perfusion
Life Systems Medizintechnik GmbH
Goethe University Hospital Frankfurt
Frankfurt, Germany

Bernhard Holzgraefe, MD, PhD
Senior Consultant
Department of Anesthesia
Surgical Services and Intensive Care Medicine
Arvika Community Hospital
Arvika, Sweden
Visiting Researcher
Hedenstierna Laboratory
Department of Surgical Sciences
Anesthesiology and Intensive Care
Uppsala University
Uppsala, Sweden

J. Andreas Hoschtitzky, MSc, FRCSEd (CTh)
Consultant Paediatric and Adult Cardiac Surgeon
Honorary Senior Lecturer
Imperial College London
Royal Brompton Hospital
London, UK

Aparna Hoskote, MD, MRCP
Consultant in Pediatric Cardiac Intensive Care
Honorary Senior Lecturer
University College London
Hospital for Children NHS Foundation Trust
London, UK

Samuel Howitt, MBChB, FRCA
Speciality Trainee in Anaesthesia and Critical Care
Honorary Lecturer, University of Manchester
Division of Cardiovascular Sciences
Academic Surgery Unit
Wythenshawe Hospital
Manchester, UK

William A. Jakobleff, Jr., MD
Assistant Professor
Albert Einstein College of Medicine
Department of Cardiothoracic and Vascular Surgery
Montefiore Medical Center
Bronx, NY, USA

Hani Jaouni, MD
Senior Consultant Intensivist
Department of Internal Medicine
Hamad General Hospital
Hamad Medical Corporation
Doha, Qatar

Federica Jiritano, MD
Cardiac Surgery Unit
Department of Experimental and Clinical Medicine
University of Magna Graecia
Catanzaro, Italy

Suzan Kakat, MD, FRCPCH
Consultant, Pediatric Cardiac Intensive Care
Honorary Senior Lecturer
University College London
Hospital for Children NHS Foundation Trust
London, UK

Håkan Kalzén, MD, PhD, EDIC
Medical Director
Department of Anaesthesiology and Intensive Care
Södertälje Hospital
Södertälje, Sweden
Senior Consultant
Department of Paediatric Anaesthesia, Intensive Care, and ECMO Services
Astrid Lindgren Children's Hospital
Karolinska Institutet
Karolinska University Hospital
Stockholm, Sweden

Harald Keller, ECCP
Chief Perfusionist
Department of Clinical Perfusion, Life Systems Medizintechnik GmbH
Goethe University Hospital Frankfurt
Frankfurt, Germany

Suresh Keshavamurthy, MD
Assistant Professor Surgery
Surgical Director Lung Transplantation
Department of Surgery
University of Kentucky College of Medicine
Lexington, KY, USA

Espeed Khoshbin, MBChB, MD, FRCS (CTh)
Consultant Cardiac and Transplant Surgeon
Department of Cardiothoracic Surgery
Freeman Hospital, High Heaton
Newcastle Upon Tyne, UK

Roxanne Kirsch, MD, MBE, FRCPC, FAAP
Pediatric Cardiac Intensivist
Bioethics Clinical Associate
Associate Chief EDI, Wellness, and Faculty Development, Perioperative Services
Assistant Professor, Pediatrics
Division of Cardiac Critical Care
Department of Critical Care
The Hospital for Sick Children and University of Toronto
Toronto, ON, Canada

Matthias Kochanek, MD
Head of Critical Care Medicine
Department I of Internal Medicine
University Hospital of Cologne
Cologne, Germany

Mariusz Kowalewski, MD
PhD Fellow
Department of Cardio-Thoracic Surgery
Heart and Vascular Centre
Maastricht University Medical Centre
Maastricht, The Netherlands, and
Clinical Department of Cardiac Surgery
Central Clinical Hospital of the Ministry of Interior and Administration
Centre of Postgraduate Medical Education
Warsaw, Poland

Petr Kuchynka, MD, PhD
Associate Professor
Second Department of Medicine—Department of Cardiovascular Medicine
First Faculty of Medicine
Charles University and General University Hospital in Prague
Prague, Czech Republic

Jan Kunstyr, MD, PhD
Associate Professor
Department of Anaesthesiology, Resuscitation, and Intensive Medicine
First Faculty of Medicine
Charles University and General University Hospital in Prague
Prague, Czech Republic

Grace van Leeuwen, MD, FSCAI
Latin-America ELSO Chair of Communication
Pediatric Cardiac Intensive Care Unit
Doha, Qatar

Juan M. Lehoux, MD
Congenital Cardiac Surgeon
Children's Heart Center Nevada
Surgical Director
Ventricular Assist Device Program
Sunrise Hospital
Las Vegas, NV, USA

Lucas Liaudet, MD
Professor and Vice Head
Service of Adult Intensive Care Medicine
University Hospital
Lausanne, Switzerland

Michal Lips, MD, PhD
Department of Anaesthesiology, Resuscitation, and Intensive Medicine
First Faculty of Medicine
Charles University and General University Hospital in Prague
Prague, Czech Republic

Roberto Lorusso, MD, PhD
Full Professor
Department of Cardio-Thoracic Surgery
Heart & Vascular Centre, Maastricht University Medical Centre (MUMC)
Cardiovascular Research Institute Maastricht (CARIM)
Maastricht, The Netherlands

Kenneth E. Mah, MD, MS
Assistant Professor of Pediatrics
Cardiac Intensive Care Unit
Department of Pediatrics
University of Cincinnati College of Medicine
The Heart Institute
Division of Cardiology
Cincinnati Children's Hospital Medical Center
Cincinnati, OH

Maximilian Malfertheiner, PD Dr. med.
Consultant
Department of Internal Medicine II
University Medical Center Regensburg
Regensburg, Germany

Gennaro Martucci, MD
Attending Physician
Department of Anesthesia and Intensive Care
IRCCS-ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)
Palermo, Italy
Clinical Assistant Professor of Anesthesia and Perioperative Medicine
School of Medicine
University of Pittsburgh
Pittsburgh, PA, USA
PhD Fellow
Maastricht University
Maastricht, The Netherlands

Christopher Mascio, MD
Alice Langdon Warner Endowed Chair of Pediatric Cardiothoracic Surgery
Children's Hospital of Philadelphia
Associate Professor
Department of Clinical Surgery
Perelman School of Medicine
University of Pennsylvania
Philadelphia, PA, USA

Dirk M. Maybauer, MD, PhD, MHBA
Professor of Anaesthesiology
Department of Anaesthesia and Intensive Care
Philipps University Marburg
Marburg, Germany

Marc O. Maybauer, MD, PhD, EDIC, FCCP, FACC, FASE
Professor
Department of Anaesthesiology
Philipps University
Marburg, Germany
Honorary Professor
University of Queensland
Brisbane, Australia
Adjunct Clinical Professor
Department of Medicine/Cardiology
Oklahoma State University Health Science Center
Tulsa, OK, USA
Integris Health
Advanced Critical Care and Acute Circulatory Support
Oklahoma City, OK, USA

Malaika Mendonca, MD
Consultant, Pediatric Critical Care
Director of ECMO Programme
Inselspital, Children University Hospital Bern
Bern, Switzerland

Jonathan E. Millar, MBBS, MCEM
Visiting Research Fellow
Roslin Institute
University of Edinburgh
Intensive Care Unit
Queen Elizabeth II University Hospital
Glasgow, UK

Lee D. Murphy, DO, MS
Assistant Professor of Clinical Pediatrics
Division of Pediatric Critical Care Medicine
Riley Hospital for Children at Indiana University Health
Indianapolis, IN, USA

Lucy W. Mwaura, MBChB, MMED, FRCA
Consultant
Department of Anaesthesia and Intensive Care Medicine
Royal Papworth Hospital NHS Trust Cambridge
Cambridge, UK

Giulia Nardi, MD
Department of Structural Interventional Cardiology
Careggi University Hospital
Florence University
Florence, Italy

Matteo Di Nardo, MD
Consultant, Neonatal and Pediatric Intensivist
Euro ELSO Chair of Communication and Education
Editor in Chief of EuroELSO website
ECMO Coordinator for Neonatal and Pediatric Respiratory Failure
Children's Hospital Bambino Gesù
Rome, Italy

Matthew J. O'Connor, MD
Medical Director of Heart Transplant Program and Attending Cardiologist
Children's Hospital of Philadelphia
Associate Professor
Department of Clinical Pediatrics
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA, USA

Matthew L. Paden, MD
President ELSO
Associate Professor
Department of Pediatric Critical Care
Emory University
Director
Pediatric ECMO and Advanced Technologies
Children's Healthcare of Atlanta
Department of Pediatric Critical Care
Atlanta, GA, USA

Federico Pappalardo, MD
Department of Anesthesia and Intensive Care
IRCCS-ISMETT (Mediterranean Institute for Transplantation and Advanced Specialized Therapies)
Palermo, Italy

Gianluca Paternoster, MD, PhD
Senior Consultant
Department of Cardiovascular Anaesthesia and Intensive Care
San Carlo Hospital
Potenza, Italy

Nicolò Patroniti, MD
Professor of Anaesthesiology
Department of Surgical Sciences and Integrated Diagnostics
University of Genoa
Genoa, Italy
Policlinico San Martino
Genoa, Italy

Giles J. Peek, MD, FRCS CTh, FFICM, FELSO
Clinical Professor
Department of Surgery and Pediatrics
University of Florida Shand's Congenital Heart Center
Gainesville, FL, USA

Antonio M. Pesenti, MD, FELSO
Professor in Anaesthesiology and Intensive Care Medicine
Department of Pathophysiology and Transplantation
University of Milan
Milan, Italy
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Department of Anesthesia, Critical Care, and Emergency
University of Milan
Milan, Italy

Renee M. Potera, MD
Assistant Professor
Department of Pediatrics
UT Southwestern Medical Center
Children's Health
Dallas, TX, USA

Amit Prasad, MD
Assistant Professor
Department of Anesthesiology and Critical Care Medicine
Heart & Vascular Institute
Adult ECMO/Mechanical Circulatory Support
Pennsylvania State University College of Medicine
Hershey, PA

Shweta Priyadarshini, MBBS, FCICM
Staff Specialist
Department of Intensive Care Medicine
St. Vincent's Hospital
Sydney, Australia
Centre of Applied Medical Research
St. Vincent's Hospital
Sydney, Australia
University of New South Wales
Sydney, Australia

Giuseppe M. Raffa, MD, PhD
Consultant
Department of Cardiac Surgery
IRCCS-ISMETT Hospital
Palermo, Italy

Dr. Lakshmi Raman, MD
Associate Professor
Medical Director of ECMO
Chair-, Protocols and Guidelines: ELSO
Department of Pediatrics
University of Texas Southwestern Medical Center
Children's Health
Dallas, TX, USA

Avideh Rashad, MD
Fellow in Neonatal-Perinatal Medicine
Department of Pediatrics
Division of Neonatology LAC + USC Medical Center
Keck School of Medicine of University of Southern California
Los Angeles, CA, USA
Fetal and Neonatal Institute
Children's Hospital Los Angeles
Los Angeles, CA, USA

Tasleem Raza, MD, MS, FCCP
Senior Consultant
Director of MICU Fellowship Program
Department of Medicine
Division of Critical Care and Pulmonary Medicine
Hamad Medical Corporation
Doha, Qatar

Daniel Rob, MD
Consultant in Cardiology
Department of Internal Medicine II, Cardiovascular Medicine
General University Hospital
Prague, Czech Republic

Peter Rodgers-Fischl, MD
Thoracic Surgery Resident, Graduateion Medical Education
Department of Surgery
Division of Cardiothoracic Surgery
University of Kentucky College of Medicine
Lexington, KY, USA

Javier Rodriguez-Fanjul, MD, PhD
Professor
Department of Pediatrics
University Rovira i Virgil
Consultant
Pediatric Intensive Care Unit
Department of Pediatrics
Tarragona, Spain

Peter P. Roeleveld, MD
Pediatric- Intensivist
Chief of PICU
ECMO Director
Leiden University Medical Center
Leiden, The Netherlands

Antonio Rubino, MD
Consultant, in Cardiothoracic Anaesthesia and Intensive Care
Clinical Lead for Organ Donation
Department of Anaesthesia and Intensive Care
Royal Papworth Hospital NHS Foundation Trust
Cambridge Biomedical Campus
Cambridge, UK

Marco Rusca, MD
Attending Physician
Service of Adult Intensive Care Medicine
University Hospital
Lausanne, Switzerland

Antonio F. Saad, MD
Assistant Professor
Department of Obstetrics and Gynecology
Division of Maternal Fetal Medicine
Department of Anesthesiology
Division of Critical Care Medicine
The University of Texas Medical Branch
Galveston, TX, USA

Michael Salna, MD
Resident
Department of Surgery
Division of Cardiothoracic Surgery
Columbia University Medical Center
New York, NY, USA

Filippo Sanfilippo, MD, PhD, EDIC
Consultant
Department of Anaesthesiology and Intensive Care
Policlinico-Vittorio Emanuele University Hospital
Catania, Italy

Fabio Sangalli, MD, FASE
Director
Department of Anaesthesiology and Intensive Care
ASST Valtellina e Alto Lario
University of Milano-Bicocca
Sondrio, Italy

Cristina Santonocito, MD
Consultant
Department of Anaesthesiology and Intensive Care
Policlinico-Vittorio Emanuele University Hospital
Catania, Italy

Kunal Sarkar, MD
Consultant Cardiac Surgeon
Medica Superspecialty Hospital
Kolkata, India

Matthieu Schmidt, MD, PhD
Assistant Professor
Sorbonne Université
Institute of Cardiometabolism and Nutrition
Paris, France
Service de médecine intensive-réanimation
Institut de Cardiologie
APHP Sorbonne Université Hôpital Pitié–Salpêtrière
Paris, France

Kiran Shekar, MBBS, PhD, FCCCM, FCICM
Adjunct Professor
Institute of Health Biomedical Innovation
Queensland University of Technology
Associate Professor
School of Medicine
University of Queensland
Associate Professor
Bond University, Gold Coast
Senior Intensive Care Specialist
Adult Intensive Care Services
The Prince Charles Hospital
Chermside, Australia
Critical Care Research Group
Centre of Research Excellence for Advanced Cardio-respiratory Therapies Improving OrgaN Support (ACTIONS) and the University of Queensland
Brisbane, Australia

Billie Lou Short, MD, FELSO
Professor of Pediatrics
The George Washington University School of Medicine
Chief, Division of Neonatology
Washington, DC

David Sidebotham, MBChB, FANZCA
Cardiac Anaesthetist and Intensivist
Director of Perioperative Transoesophageal Echocardiography
Department of Anaesthesia and the Cardiovascular Intensive Care Unit
Auckland City Hospital
Auckland, New Zealand

Kai Singbartl, MD, MPH, FCCM
Professor and Vice Chair
Department of Critical Care Medicine
Mayo Clinic
Phoenix, AZ, USA

John P. Skendelas, MD
Research Fellow
Department of Cardiothoracic and Vascular Surgery
Montefiore Medical Center and Albert Einstein College of Medicine
Bronx, NY, USA

Jana Šmalcová, MD
Consultant in Cardiology and Intensive Care
Department of Internal Medicine II
Cardiovascular Medicine
General University Hospital
Prague, Czech Republic

Justyna Swol, MD, PhD
General Hospital Nuremberg
Department of Respiratory Medicine, Allergology, and Sleep Medicine
University Hospital of Paracelsus Medical University (PMU)
Intensive Care Unit
Nuremberg, Germany

Koji Takeda, MD, PhD
Assistant Professor of Surgery
Director of Heart Transplant
Surgical Director of PTE
Surgical Director of ECMO
Division of Cardiothoracic Surgery
Department of Surgery
Columbia University
Vagelos College of Physicians and Surgeons
New York, NY, USA

Thomas A. Tribble
Mechanical Circulatory Support Coordinator
Department of Surgery
University of Kentucky College of Medicine
Lexington, KY, USA

Robert J. Vandewalle, MD, MBA
Pediatric Surgery Critical Care Fellow
Department of Surgery
Division of Pediatric Surgery
University of Tennessee Health Sciences Center
Memphis, TN, USA

Giulia Villa, MD
Fellow in Anesthesia and Intensive Care
Department of Anesthesiology and Intensive Care
San Gerardo Hospital
University of Milano-Bicocca
Monza, Italy

Akbar Vohra, MBChB, DA, FRCA, FFICM
MAHSC Professor of Anaesthesia
The University of Manchester
Manchester, UK
Visiting Professor
Nanjing Medical University
China
Consultant in Cardiac Anaesthesia and Critical Care
Department of Anaesthesia
Manchester Royal Infirmary
Manchester University NHS FT
Manchester, UK

Alain Vuylsteke, BSc, MA, MD, FRCA, FFICM
Consultant
Department of Anaesthesia and Intensive
Care Medicine
Divisional Clinical Director Surgery, Transplant, and
Anaesthetics
Associate Lecturer
University of Cambridge
Royal Papworth Hospital NHS Foundation Trust
Papworth Road, Cambridge Biomedical Campus
Cambridge, UK

Bishoy Zakhary, MD
ELSO Chair of Logistics and Education
Assistant Professor of Medicine
Department of Pulmonary and Critical Care Medicine
Oregon Health and Science University
Portland, OR, USA

Joseph B. Zwischenberger, MD, FACS, FCCP, FELSO
Johnston-Wright Professor and Chairman of Surgery
Professor
Department of Pediatrics, Bioengineering, and Diagnostic
Radiology
University of Kentucky College of Medicine
Surgeon-in-Chief, UK HealthCare
Lexington, KY, USA

HISTORY OF ECMO

1.

FROM THE FIRST ECMO PATIENT INTO THE FUTURE

Federica Jiritano and Roberto Lorusso

STEM CASE AND KEY QUESTIONS

A 24-year-old man was admitted to the hospital emergency room about 30 minutes after a car accident.[1] He had no loss of consciousness.[1] Pain was severe in the pelvis and lower extremities.[1] The systemic blood pressure was 74/30 mm Hg, the heart rate was 134 beats/min, and the respiratory rate was 32.[1] The chest x-ray showed mediastinal widening.[1] The patient was diagnosed with several right and left extremity fractures, dislocation of the right sacroiliac joint, root or peripheral nerve injury of the right lower extremity, and hypovolemia.[1]

CAN YOU DESCRIBE PAST, CURRENT, AND FUTURE PATIENT MANAGEMENT?

1971

The patient was transported to the emergency department. Respiratory support through a nasal endotracheal tube was achieved. Intravenous fluids and blood were given. A thoracic aortogram demonstrated a subadventitial traumatic aneurysm distal to the left subclavian artery.[1] After induction of general anesthesia, the aortic tear was repaired through a left thoracotomy incision, with a perfusion period of about 40 minutes.[1] No hypotension occurred during surgery. Both legs were placed in traction.[1]

2021

The patient is initially transported by air transfer to the trauma unit, where his respiratory function is supported by mechanical ventilation through an orotracheal tube. A large-bore infusion catheter is placed in the right femoral vein, and an arterial line is placed in the right femoral artery. After correction of his life-threatening injuries and multiple blood transfusions, his vital signs stabilize. A full-body computed tomographic (CT) scan shows a subadventitial traumatic disruption of the aorta distal to the left subclavian artery. In view of his multiple injuries, open surgical repair of the aorta is deemed a high-risk procedure. An endoluminal approach would be considered if a sufficient landing zone for the endoprosthesis is available. Through a cutdown in the left common femoral artery, an endoprosthesis graft is successfully deployed in the descending thoracic aorta. After balloon dilation, the control aortography shows no endoleaks.

2067

The patient will be rescued at the crash site. A radio-frequency ID chip under the patient's skin will be interrogated to read the patient's medical records. His blood chemistry will be analyzed the same way. Fluids will be given through femoral access. Respiratory function will be sustained through an endotracheal tube by a medical robot. Through a portable scanner, the patient will be diagnosed with a type B aortic dissection and immediately treated with a biocompatible and flexible stent. Then, he will be transferred to the nearest hospital.

During the third and the fourth postoperative day (POD), respiratory function progressively worsens.[1] The peak airway pressure gradually rises, and tracheal secretions are blood colored. A tracheostomy is performed, and methylprednisolone is started.[1] The pulmonary function deteriorates critically during the next 12 hours. Positive end-expiratory pressure (PEEP) is increased by 5 mm Hg and the FiO_2 (fraction of inspired oxygen) to 100%. The patient is somnolent but able to be aroused.[1]

CAN YOU DESCRIBE PAST, CURRENT, AND FUTURE TREATMENT TO IMPROVE THE PATIENT'S PULMONARY FUNCTION?

1971

Although the patient was not overloaded, massive diuresis was induced through high doses of mannitol and ethacrynic acid with the goal of improving the oxygen diffusion in the lungs.[1] A diuresis of 3500 mL urine in 9 hours was followed by an improvement in arterial oxygen tension.[1] Meanwhile, on the fifth POD a team and a membrane heart-lung machine had been flown down from the Thoracic Unit of Pacific Medical Center to Santa Barbara courtesy of the United States Navy.[1] On the sixth POD, although the maximum ventilatory support (PEEP 8 mm Hg, FiO_2 100%, tidal volume 1 L), the PaO_2 decreased to 38 mm Hg.[1] Hypoxic mental confusion, restlessness, and a reduced level of consciousness were supervening.[1] Renal dysfunction was also developing. The patient was diagnosed with "shock-lung syndrome." It was the consensus of the attending physicians and surgeons that conventional therapy had been exhausted and that the patient was dying.[1] Therefore, 18 hours after the arrival of the team from the Pacific Medical Center the decision was made to proceed with partial heart-lung bypass for respiratory insufficiency.[1]

2021

Pulmonary function and circulation of the patient deteriorate progressively. He is ventilated with the maximal settings (pressure-controlled ventilation at FiO_2 1.0 and PEEP 18 mm Hg), with poor oxygenation (SpO_2 [oxygen saturation by pulse oximetry] 55%–70%, PaO_2/FiO_2 ratio < 0.4) and hemodynamic instability (central venous pressure [CVP] 12 mm Hg, blood pressure 72/50 mm Hg with epinephrine infusion at 0.5 μg/kg/min). Urine output is less than 0.5 mL/kg/h for more than 12 hours. Transthoracic echocardiography (TTE) shows an enlarged left atrium and impaired left ventricular systolic function with ejection fraction (EF) at 35%. Epinephrine is subsequently infused at 0.18 μg/kg/min. Considering the intractable hypoxia and shock, the patient is diagnosed as having refractory acute respiratory distress syndrome (ARDS) with cardiocirculatory compromise. Veno-arterial extracorporeal membrane oxygenation (V-A ECMO) is considered the most appropriate therapeutic option.

2067

Based on gradually deteriorating respiratory function, a prophylactic, patient-tailored, and minimally invasive veno-venous (V-V) ECMO support will be timely instituted to avoid the occurrence of hemodynamic compromise. The patient will be kept sedated to allow the treatment of the concurrent traumatic lesions. In the case of severe internal lesions, suspended cardiocirculatory support (hypothermia-induced hypothermic circulatory arrest) would be used to allow bleeding control, if any, with heparinless V-A ECMO support, easily achieved from the initial V-V ECMO thanks to the ease of instituting a hybrid ECMO configuration.

CAN YOU DESCRIBE MANAGEMENT OF ECMO?

1971

The patient was connected to the Bramson membrane heart-lung machine (Figure 1.1), that oxygenated the patient's blood with use of partial V-A extracorporeal circuit.[1] The machine was assembled in 6 hours. The femoral artery and vein were cut down and cannulated after an initial dose of heparin (100 UI/kg).[1] The wound was closed around the cannulas.[1] A continuous infusion of heparin was maintained throughout the perfusion. Red blood cells and fresh frozen plasma units were transfused. The bypass flow was 3.0 to 3.6 L/min through the bypass.[1] Four hours after the start of perfusion, the urine output fell to 20 mL/h.[1] During the next 24 hours, the patient received abundant fluid to replace the dehydration.[1] On the third day of perfusion, spontaneous diuresis occurred.[1] After stabilization, FiO_2 and tidal volume were reduced to 60% and 800 mL, respectively.[1] PEEP was maintained at 8 mm Hg.[1] After 3 days with ECMO, pulmonary function improved (PaO_2 80 mm Hg with FiO_2 60%), as did the renal status.[1] The patient was weaned from the machine after 75 hours of perfusion.[1] Cannulas were removed, and the vessel was reanastomosed.[1]

2021

Veno-arterial ECMO is promptly established using the Seldinger technique. The right femoral artery (inflow) and vein (outflow) are cannulated. The distal right femoral artery is percutaneously cannulated for perfusion. The pump flow is maintained at 4.5 L/min, with a gas-blood ratio of 1:1. Careful attention is paid on the systemic blood pressure curve pulsatility, together with serial echocardiography assessments, to confirm appropriate aortic valve opening and lack



Figure 1.1 First successful extracorporeal life support patient, treated by J. Donald Hill using the Bramson oxygenator. Kind courtesy of Prof. Robert Bartlett.

of blood stasis in the left ventricle and atrium. Continuous veno-venous hemofiltration (CVVH) is used for oliguria by combining the hemofiltration device with the ECMO circuit. Anticoagulation for the ECMO and CVVH circuit is performed with an initial bolus of heparin 100 IU/kg at the time of ECMO start followed by a continuous infusion of intravenous heparin, targeting an activated partial thromboplastin time (aPTT) between 60 and 80 seconds. During ECMO, the mechanical ventilation is decreased to a mean airway pressure of 20 mm Hg and FiO_2 of 0.4 to prevent further barotrauma and oxygen toxicity. The patient improves and is weaned from ECMO after 3 days.

2067

A V-V ECMO will be applied with a minimally invasive percutaneous approach. The device will be autoregulated. The right internal jugular vein will be identified through vein scanner glasses worn by the physician. A small cannula will be advanced in the patient's right jugular vein. The circuit will be minimal and biocompatible. The membrane lungs will be round to avoid stagnation and thrombus formation in the corners. The blood flow will be 2.5–3.0 L/min with a high sweep flow. The sweep flow itself will be servo-regulated based on the exhaust gas CO_2 so that adjustments of the sweep flow will be automatic. The device will have a special surface-eluting nitric oxide membrane to inhibit platelet adhesion. No anticoagulation will be required, thus avoiding related complications. In case signs of right ventricular dysfunction are present, a double-lumen cannula positioned percutaneously in the main pulmonary artery will allow concomitant V-V and right ventricular support. In the presence of hemodynamic instability or frank cardiogenic shock also involving the left ventricle, a hybrid configuration providing right and left ventricular support will be applied. A cannula in one femoral artery predisposed to provide flow also distally to the cannulated leg will be implanted. During mechanical support, the patient will be awake and extubated. A metabolic probe will assess cellular oxygenation. The patient will be discharged to home with ECMO. The mechanical support will be removed after about 48–72 hours. At the same time, new regenerative cell therapy will be applied.

WHAT IS THE PATIENT MANAGEMENT AFTER ECMO REMOVAL?

1971

The convalescence was long, but there was sequential improvement of lung function. The tracheostomy was removed, and finally the patient was able to breath even without nasal oxygen. Together with respiratory function, the neurological status slowly improved as well. On the 15th POD, intermittent daily fever (38°C–38.5°C) occurred with sweats and increased white cell count (WCC) (from 14×10^9/L to 20×10^9/L).[1] Heavy doses of antibiotics were given, though no site of sepsis could be found.[1] Two weeks later, the fever ended, and the WCC came back to a normal value together with neurological improvement.[1] The patient was discharged after 8 weeks into an orthopedic rehabilitation unit. At 6 weeks' follow-up, his respiratory function was normal.[1]

2021

The patient remains intubated for 3 weeks. Pulmonary function gradually improves. During ECMO therapy, there was no evidence of ECMO-related bleeding. On the 15th POD, the patient experiences intermittent fever with leukocytosis. Inflammation marker levels are high (C-reactive protein 35 mg/L, erythrocyte sedimentation rate 100 mm/h). No pathogen is found in blood, urine, and sputum samples. Therefore, empiric broad-spectrum antibiotic therapy is administered. The fever disappears after 2 weeks, and the WCC value is normal again. The CVVH is weaned after 21 days. The patient is discharged 45 days after admission. A CT scan 2 months after discharge shows that the patient's lungs are almost completely recovered.

2067

As the ECMO support will be short as in the in-hospital stay, the likelihood of complications, such as infections and organ failure, will be minimum. However, in the eventuality of an infection, it will be possible to do a complete microbial scan in a couple of hours through new biochips. The process might identify mutations that make some microbes antibiotic resistant. New tablets containing genetic messengers will be easily swallowed and will modify the cell's genetic structure to achieve the patient's complete recovery.

DISCUSSION

The first successful use of prolonged life support with a heart-lung machine was conducted by John Donald Hill and his associates in 1971 in Santa Barbara (California).[1] After Hill's case, several other successful cases were reported in children and adults with severe pulmonary and cardiac failure.[2–5] In the mid-1970s, it seemed that ECMO would be the ideal treatment for an epidemic of the "new ARDS."[6] ARDS was newly named and recognized as a syndrome of severe respiratory failure complicating pneumonia, shock, trauma, or sepsis.[6] The Lung Division at the National Institutes of Health sponsored a nine-center prospective randomized trial of ECMO in ARDS.[6] The study was stopped for lack of efficacy after 90 adult patients.[6] Zapol and colleagues, indeed, reported 90% mortality with ECMO or conventional care.[7] This study of a new technology was done prematurely in inexperienced centers without standardized techniques and protocols.[6] Publication of that trial stopped the development of ECMO for adult respiratory failure for the next 20 years except in a few centers.

While the attempt to demonstrate the advantage of ECMO applied to adults was unsuccessful, neonates seemed to reap its benefits. In 1975, Robert Bartlett pioneered ECMO when treating baby girl.[2] Bartlett, who has been called the father

of modern extracorporeal support, brought ECMO into the neonatal intensive care unit to treat a newborn dying because of meconium aspiration and resultant pulmonary hypertension. After crossing the Mexican border into Orange County (California), her mother delivered her and then left.[2] The nurses named the baby girl "Esperanza," Spanish for "Hope."[2] She was on ECMO support for 72 hours.[2] She recovered successfully.[2] The results in newborn infants were encouraging, and many neonatologists and pediatric surgeons established ECMO programs for the management of newborn infants and small children with respiratory failure.[8] By 1986, 19 neonatal centers had successful ECMO teams.[9,10] With growing interest, the medical community sought randomized, controlled trial (RCT) evidence of the benefits of mechanical support over standard therapies. Bartlett and colleagues initiated an ECMO RCT at the University of Michigan.[11] During the study, the first patient receiving ECMO survived.[11] The next patient, randomized to standard care, died.[11] Increased preference went to ECMO, and the next 10 patients, all receiving ECMO, survived ($p = .0000001$).[11] The study was published in 1985, raising significant controversy and discussion, including concern that control patients did not undergo informed consent.[12] The findings, however, encouraged growing use of ECMO support in neonates.

This criticism and controversy led to the second prospective randomized trial, performed by O'Rourke and associates at Boston Children's Hospital.[13] The study design included a phase 1 approach with a traditional 50/50 randomization of patients until one arm had four deaths, followed by a phase 2 utilizing an adaptive design to favor the "winner" of the first phase.[13] Overall, 19/20 (97%) of ECMO patients survived compared to 60% of standard control patients.[13] The Boston group observed similar results (94% survival in the ECMO group).[13]

In 1985, the Michigan trial was criticized for exposing critically ill infants to the high risks of ECMO. Ironically, 4 years later, the Boston study was criticized for denying ECMO to the patients in the control group. To disperse any criticism, a multicenter RCT was performed to assess the benefit of ECMO for persistent pulmonary hypertension in neonates.[14] This trial, involving 55 centers, supported the superiority of ECMO in neonatal respiratory failure.[14] Therefore, ECMO became the standard treatment for respiratory failure unresponsive to other treatments.

There was a new proven technology, a new solution for those that, until then, were considered insuperable limits. The use of ECMO allowed the cure of patients who would have been dead without it. However, it needed to be studied and known better.

As the technology developed, it was standardized, disseminated, studied, and improved in an organized fashion. The birth of a voluntary alliance of all the investigators and clinicians using ECMO was spontaneous.[8] In 1989, the Extracorporeal Life Support Organization (ELSO) was born with the goal to pool common data on ECMO use, compare outcomes, and exchange ideas for its optimal use.[8] For the last 30 years, that group has developed guidelines and practices, published the standard textbook in the field, and maintained a registry of extracorporeal life support (ECLS) cases.

Moreover, clinicians wanted to utilize the benefits of ECMO to allow recovery in adult cardiac and respiratory failure. Since the investigation by Zapol and colleagues, enthusiasm stalled. Advances in ECMO experience, equipment, and expertise paved the way for another RCT in adult respiratory failure, the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial, under the leadership of Giles Peek.[15] It evaluated outcomes in patients with severe ARDS transferred to an ECMO referral center versus patients treated with conventional therapy.[15] Although mortality at any point was not significantly different, the study identified significantly higher 6-month survival rates in the group transferred to the ECMO referral center—of which only 75% of the patients received ECMO—versus the control group that was not transferred.[15] Thus, it may have been other aspects of care at the ECMO center, not necessarily the ECMO itself, that led to improved outcomes. The publication of the CESAR results shortly preceded the 2009 worldwide H1N1 influenza pandemic.[16,17] The acute, severe, fulminant nature of respiratory failure with H1N1 influenza made providers see ECMO as a therapeutic option.[8] The convergence helped the growth of ECMO use. Since then, indeed, ECMO support applications have exploded and continue to progress.

Today, there are more than 400 centers as members of the ELSO consortium throughout the world. The latest registry report is shown in Table 1.1[18] The survival to discharge outcomes ranged from 29% to 73%.[18] This is encouraging considering that ECMO is only used for patients with a high mortality risk, but also indicates that there is much space for improvement.

Through the decades, the gigantic heavy machine used by Hill and Bartlett has become a relatively small, portable apparatus. This rise in use of extracorporeal support was powered by several major advancements in equipment, including improvements in oxygenator components, circuit and configuration, and vascular access.

OXYGENATOR

The first ECMO circuit had a membrane oxygenator. The idea of a protective membrane between blood and air to decrease the problem of blood trauma began with observations by Kolff and Berk in 1944.[19] They noted that blood in their hemodialysis machine became oxygenated when exposed to aerated dialysates.[19] The gas contents of the blood equilibrated with that of the dialysate through the process of passive diffusion.[19] Although the potential advantage of the membrane oxygenator in decreasing the degree of blood trauma associated with direct-contact oxygenators was immediately evident, the problems were also quickly appreciated. Suitable permeable membrane biomaterials were lacking. The membrane constituted an additional barrier to gas exchange. There was not an optimal distribution of blood and gas flows. The emphasis in early membrane oxygenator development concentrated on finding suitable biomaterials, as early biomaterials had low gas

Table 1.1 OVERALL PATIENT OUTCOMES, EXTRACORPOREAL LIFE SUPPORT ORGANIZATION REGISTRY, APRIL 2021.

		SURVIVE ECLS		SURVIVE TO DC	
	TOTAL RUNS	N	%	N	%
Neonatal					
Respiratory	33,400	29,255	87	24,398	73
Cardiac	9,561	6,605	69	4,186	43
ECPR	2,244	1,574	70	953	42
Pediatric					
Respiratory	11,168	8,084	72	6,746	60
Cardiac	13,945	10,103	72	7,520	53
ECPR	5,630	3,341	59	2,388	42
Adult					
Respiratory	33,313	22,612	67	19,734	59
Cardiac	32,307	19,252	59	14,378	44
ECPR	10,115	4,213	41	3,030	29
Total	151,683	105,039	69	83,333	54

(From the Extracorporeal Life Support Organization Registry – International Registry Report)

Abbreviations: DC, discharge; ECLS, extracorporeal life support; ECPR, extracorporeal membrane oxygenation-assisted cardiopulmonary resuscitation.

exchange performance and poor mechanical properties.[20] Of the earliest available materials, ethylcellulose and polyethylene were the most permeable to oxygen and carbon dioxide.[21]

In 1958, more permeable ethylcellulose was used in multiple sandwiched layers.[22]

One disadvantage of hydrophilic membrane oxygenators is their tendency to leak plasma (Figure 1.2). This severely shortened the duration of the use of the membrane lung. To prevent this, membranes made of hydrophobic polymers were used.[20] These materials were initially derived from packaging materials used in the capacitor industry, such as polytetrafluoroethylene (Teflon™).[20] With hydrophobic membranes, Melrose realized in 1958 that it is carbon dioxide removal that was the limitation, as carbon dioxide solubility in hydrophobic solids is much less than its solubility in hydrophilic solids.[23] This problem was partly solved by the use of silicone as the hydrophobic material in membrane lungs. In 1959, the first silicone membrane lung was made using a thin continuous silicone membrane on a fabric support, which was made by dip coating a nylon mesh and the pairing of two sheets of ultrathin membranes together to decrease the risk of leakage through random pinhole defects.[24]

In 1963, Kolobow developed a coiled oxygenator utilizing a silicone rubber envelope reinforced with nylon knit wrapped around a central core.[24] Pure humidified oxygen was passed through it under a negative pressure.[24] The blood flowed across the flat tubing parallel to the axis of the cylinder.[24] The priming volume of these units averages 100 mL/m^2.[24] They could oxygenate venous blood at a rate of 1000 mL/m^2/min.[24] In 1971, Kolobow improved this disposable coil membrane oxygenator by using membrane fabricated from silicone rubber deposited on the irregular fabric structure.[25] This Kolobow oxygenator was the only oxygenator available for long-term application of ECMO for acute respiratory failure patients in the United States. Modern versions of the silicone membrane oxygenators were used for decades as long-term extracorporeal oxygenators.

Other new oxygenators are made with polymethyl pentene (PMP). Fiber PMP oxygenators are extremely efficient at gas exchange and demonstrate minimal plasma leakage.[26] They have relatively low resistance to blood flow, making them easy to prime, and are well suited for use with centrifugal blood pumps.[26] By making the oxygenators more compact and optimizing the blood flow path, it is possible to decrease the surface area of the membrane and heat exchanger, thus reducing its potential for thrombus formation and inflammatory activation.[27] The early experience with the PMP devices established them to be robust and long lasting, with limitation of the inflammatory response and decreased transfusion requirements, making them well suited for long-term use.[27] There are a number of PMP membrane oxygenators in commercial use, including the Quadrox-iD (Maquet, Hirrlingen, Germany); Hilite LT (Medos, Stolberg, Germany); Lilliput 2 (LivaNova, Mirandola Modena, Italy); and the Biocube (Nipro, Osaka, Japan). Many of these devices are marketed in both pediatric and adult sizes; however, many centers prefer to use one size



Figure 1.2 Plasma leakage in oxygenators made with hydrophobic polymers. Kind courtesy of Dr Howard T. Massey. (Massey HT, Choi JH, Maynes EJ, Tchantchaleishvili V. Temporary support strategies for cardiogenic shock: extracorporeal membrane oxygenation, percutaneous ventricular assist devices and surgically placed extracorporeal ventricular assist devices. *Ann Cardiothorac Surg*. 2019 Jan;8(1):32–43.)

of oxygenator for all patients. These new-generation oxygenators also contain an integrated heat exchange device, making it possible to precisely control body temperature without the need for additional components.

CANNULATION

The first ECMO runs were performed through the femoral vessels.[1] The cannulation was achieved through the surgical cut down of the vessels.[1] After weaning from the mechanical device, the vessels were reanastomosed.[1] A great push in the development of the cannulation procedure was the spread of the "Seldinger technique."[28] Therefore, vascular access techniques transitioned from surgical cut down and insertion to percutaneous access employing the Seldinger technique, with thin, small size, percutaneous cannulas, often characterized by nonthrombogenic surfaces.[29] Cannula design and the routine application of distal limb perfusion in case of femoral artery cannulation for a peripheral V-A approach were additional innovations for successful ECMO application with significant reduction in postprocedural complications, such as limb ischemia.[30,31] Moreover, the studies conducted throughout the years were able to identify other multiple cannulation sites and cannula designs.[29–31]

Central cannulation became an option after cardiac surgery operations.[32] Jugular vessels were employed in newborns and children.[33] Lately, a dual-lumen cannula introduced through the right internal jugular vein was applied in V-V ECMO.[34] In the last few years, a new arterial cannula for bidirectional perfusion was employed.[35] It was developed to ensure stable distal perfusion through the femoral artery, thereby reducing the risk of lower limb ischemia after femoral cannulation.[35] Moreover, the cannulation of the pulmonary artery is emerging as a valuable option for right ventricular support.[36,37]

CIRCUIT

Since the first cases in the early 1970s until 2005, ECMO circuits were assembled on site from a variety of devices.[8] Major changes in the technology occurred in 2008, with entire ECMO systems developed by the Maquet, Sorin, and Novalung companies in Europe.[38,39] The Maquet devices were available in 2009 in the United States.[12] The new devices resulted in much safer, simpler, prolonged management of extracorporeal support and have led to much wider use of ECMO. Improved devices have also resulted in a change in patient management, emphasizing minimal sedation, spontaneous breathing, and active physical therapy.[6,8,12] Coating and heparin-bonded circuit surfaces, together with the miniaturization and integration of pump systems, led to the development of more simplified, portable, and efficient mechanical support devices.[6,8,12] The most significant recent step was the development of the PMP membrane oxygenator, which allowed achieving low-priming volumes, oxygenator pressure drop, high oxygenation efficiency, and long-lasting membrane performance.[6,8,12]

ANTICOAGULATION

Not only to prevent thrombosis in the patient and in particular in the ECMO system, but also to minimize bleeding risks, adequate anticoagulation strategies are indispensable.[40] Up to the present day, unfractionated heparin (UFH) remains the main anticoagulant used for ECMO because of its rapid onset and the easy neutralization with protamine.[40] This was recently confirmed in a large survey where 96% of the responding centers reported UFH as their anticoagulant of choice.[41] Nevertheless, UFH administration for ECMO requires some caution. Besides its unpredictable clinical effect, the use of UFH could cause what is known as heparin-induced thrombocytopenia.[42] A minority of ECMO centers use parenteral direct thrombin inhibitors (DTIs) instead of UFH as their first choice.[42] Argatroban and bivalirudin are the most used anticoagulants.[42] The main advantages of DTIs is that they bind directly and reversibly to thrombin, and they do not induce antibodies against platelets.[42] In contrast to heparin's antagonist protamine, there is no antidote available for argatroban and bivalirudin.[42] The effects of both agents are mainly controlled by their short half-lives of 40 minutes and 30 minutes, respectively.[42] Balancing anticoagulation and bleeding remains a universal problem for any artificial organ in contact with blood. For five decades, many laboratories

have worked on creating nonthrombogenic surfaces, which would obviate the need for anticoagulation with extracorporeal circulation.[6] This research has led to the development of several nonthrombogenic coatings for extracorporeal devices; most of them are based on binding heparin to the surface.[6]

WHAT ABOUT THE NEXT 50 YEARS?

How can we make progress for patients of the future?

According to Darwin's *Origin of Species*, "It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change."[43] The use of ECMO, indeed, represents today and will be in the future one of the substantial changes in the management of critical patients. Improvement and development of technologies and treatment protocols will aid fast recovery. The ECMO concept will remain the same, but its structure and management will evolve. The vascular approach will continue in the future with variations of the method of placement, imaging during placement, and new cannulas. This technique will be accomplished very quickly at the bedside in an unstable patient and will not require radiographic imaging. Vessel scan glasses, indeed, will help the physician to identify the vessels for cannulation and to check the correct placement.[44] Future ECMO will be autoregulated. After implantation, the patient will be able to stay at home conducting his or her usual life. The pump, indeed, will automatically achieve flow according to the variety of conditions of patients. The doctors, however, will be able to change the settings from the hospital while the patient will be at home.[45] Membrane lungs, moreover, will be more efficient. The next generation of devices will be round to avoid stagnation and thrombosis. The blood flow required will be low, with an autoregulated sweep flow. The circuit will be very short. The next ECMO devices will not require any anticoagulant. Therefore, all the anticoagulation-related complications will not occur. The circuit surfaces will be more biocompatible and will inhibit platelet adhesion through the release of nitric oxide.[46] Genetic therapy will help provide fast recovery.[47] Therefore, the ECMO patient of the future will be awake, extubated, without systemic anticoagulation, and at his own home.

CONCLUSIONS

- In the last century, ECMO was born from the desire to overcome the limits of medicine at that time.
- Its introduction in medical care was slow.
- However, after initial obstacles, its use currently has become routine.
- Much more work remains to be done to improve ECMO technology.
- Predicting the future is always complex and rather subjective, but the current research is promising.
- It is up to today's doctors, "Hill's and Bartlett's grandchildren," to shape the medicine of tomorrow.

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REVIEW QUESTIONS

1. When was the first ECMO implanted?

   A. 1975
   B. 1971
   C. 1972
   D. 1989

2. How would you call the "shock-lung syndrome" today?

   A. Respiratory resistance syndrome
   B. Pulmonary shock syndrome
   C. Adult respiratory distress syndrome
   D. Young respiratory distress syndrome

3. How long did the ECMO support last in Bartlett's first successful ECMO?

   A. 48 hours
   B. 96 hours
   C. 24 hours
   D. 72 hours

4. In which year was ELSO born?

   A. 1971
   B. 1989
   C. 1975
   D. 1972

5. What is the disadvantage of the hydrophilic membrane oxygenators?

   A. Insufficient distribution of blood and gas flows
   B. Plasma leakage
   C. Reduced carbon dioxide removal
   D. Excessive blood trauma

6. Which are the advantages of polymethyl pentene membrane oxygenators?

   A. Low-priming volumes, oxygenator pressure drop, high oxygenation efficiency, and long-lasting membrane performance

B. Low-priming volumes, oxygenator pressure drop, low oxygenation efficiency, and short-lasting membrane performance
C. High-priming volumes, oxygenator pressure drop, low oxygenation efficiency, and long-lasting membrane performance
D. Low-priming volumes, oxygenator pressure drop, high oxygenation efficiency, and short-lasting membrane performance

7. Besides UFH, which are the alternative anticoagulants used during the ECMO run?

A. Warfarin or argatroban
B. Bivalirudin or argatroban
C. Warfarin or bivalirudin
D. There are no alternative anticoagulants besides UFH.

8. In Hill's first ECMO implantation, the cannulation was usually performed

A. Through a surgical cutdown of the femoral vessels
B. Through a percutaneous puncture of the femoral vessels
C. Through a central cannulation
D. Not described

9. The CESAR trial evaluated

A. ECMO support versus conventional therapy in ARDS patients
B. ECMO support versus conventional therapy in cardiogenic shock patients
C. ECMO support versus left ventricular assist device support in cardiogenic shock patients
D. ECMO support versus intra-aortic balloon pump support in cardiogenic shock patients

10. In 2021, the total ECMO runs for respiratory failure in adult patients were

A. 15,159
B. 33,313
C. 119,754
D. 22,193

ANSWERS

1C, 2C, 3D, 4B, 5B, 6A, 7B, 8A, 9A, 10B

TECHNICAL AND PROGRAMMATIC ASPECTS OF ECMO

2.

DEVELOPMENT AND STAFFING OF AN ECMO SERVICE

Jo-anne Fowles and Alain Vuylsteke

STEM CASE AND KEY QUESTIONS

Following potential excellent results of extracorporeal membrane oxygenation (ECMO) in the support of Covid-19 patients, your hospital management has asked you to define what resources are required to run a successful regional ECMO service.

STAFFING

Core Team

- Service leads—intensive care consultant and senior ECMO specialist
- Medical staff—intensive care consultants plus trainees
- Nursing staff—ECMO specialists, bedside ECMO trained nurses, healthcare support workers
- Perfusion scientists
- Retrieval team—ECMO consultants, ECMO retrieval nurses, and perfusion scientists

Supporting Team

- Specialist medical staff, including cardiothoracic surgeons, respiratory physicians, cardiologists, microbiologists, radiologists, hematologists, psychiatrists, and palliative and supportive care
- Allied health professionals, including physiotherapists, dieticians, radiographers, pharmacists, and speech and language therapists (SALTs)

EDUCATION AND TRAINING

- ECMO course available with curriculum based on Extracorporeal Life Support Organization (ELSO) guidelines
- Regular ECMO refresher study days
- Regular lectures for supporting team members in basics of ECMO support
- Regular practical skills sessions utilizing a primed circuit not connected to a patient
- Facilities for high-fidelity simulation team training
- Transfer training for all staff involved in both inter- and intrahospital transfers
- Annual reassessment of competencies of medical team, ECMO specialists, and ECMO trained nurses
- Time and resources to attend national and international conferences to share knowledge and expertise and maintain center practice in an up-to-date fashion

INFRASTRUCTURE

- All bed spaces in the intensive care unit (ICU) must meet minimum specification for intensive care, including sufficient supported power points and piped gas points. The patient supported on ECMO will require gas points for a ventilator, ECMO, and emergency supply.
- Specialist emergency equipment is available and maintained, including a primed circuit and specially equipped and stocked trolley.
- To ensure appropriate infection control measures, the ICU will require a number of negative-pressure isolation bed spaces.
- Consideration of potential colocation of patients should be considered to maximize efficiency.
- Round-the-clock availability of an operating room imaging facilities, including bedside ultrasounds, computed tomographic (CT) scanner, and cardiac imaging laboratories. Ideally, these facilities should be colocated (i.e., in the same building).
- Round-the-clock availability of radiology, microbiology, and hematology services.
- Appropriate secure storage areas to store equipment, including a bespoke transfer trolley and all ECMO consumables.
- Personal protective equipment immediately available and all staff trained in its use.

EQUIPMENT

- Sufficient ECMO consoles and pumps for expected number of patients.
- Backup consoles and pumps in case of failure as per manufacturer recommendation.
- Sufficient heater/cooler units, oxygen brackets, transducer plates, and bespoke trolleys.
- Bespoke trolleys for ECMO consoles and accessories. Additional equipment on the trolley should be minimized to that required in an emergency. Contents of a bedside ECMO trolley are listed in Box 2.1.
- Technical support services will need to have skills and capacity to ensure all ECMO equipment has regular and emergency servicing. Routine servicing will be programmed throughout the year to ensure availability of equipment.

REFERRAL AND RETRIEVAL

- As a regional center, the majority of cases will be referred from other centers. A robust process of managing referrals must be developed.
- ECMO coordinators must be available to receive referrals.
- Referrals may be via telephone or ideally through an online referral system.
- The ECMO coordinator will have bedside experience in ECMO management and will coordinate activation of the team and preparation for admission of the patient on ECMO.
- Round-the-clock on call ECMO consultants available to discuss and advise on management of referred patients with the referring physicians. Access to an imaging system that allows the importing images from other centers for review is required.
- Robust selection criteria based on national and international guidelines.
- An ambulance specifically set up to transfer the critically ill patient supported on ECMO with at least a three -person ECMO team. A dedicated ambulance crew and additional space for trainees should be considered.
- Ambulance specifications to include extra O_2 supplies to support ventilation and ECMO in transit and appropriate power supply as required by equipment in use.
- Bespoke transfer trolley must be able to sustain the weight of the patient, ventilator, monitors, pumps, and ECMO equipment.
- Standard operating procedures to manage the retrieval of bariatric patients should be in place.
- All equipment and consumables required to cannulate and maintain the patient during transfer should be ready in sealed transfer boxes/bags at all times. Checklists of bag/box contents should be maintained.
- Transfer documentation should be available.

FOLLOW-UP

- A clinic led by either a respiratory physician or a specialist in intensive care should be provided.
- All patients should attend clinic at a predefined time after liberation from ECMO. Six months appears a sensible choice.

QUALITY ASSURANCE

- Guidelines should be developed and regularly updated by the lead clinicians of the ECMO service and encompass all aspects of patient management. The guidelines will be available to all staff in the clinical area. Standard operating procedures are required for practices, including intrahospital transfer, handover processes, and specialist roles.
- Membership of the ELSO is necessary
- Clinical governance should be maintained through ongoing data collection and analysis, with data being input into local registries and a national or international registry such as ELSO.
- Regular mortality and morbidity meetings attended by representatives from the interdisciplinary team are required.
- The ECMO service should work with the institutional research team to ensure in-house projects are supported in addition to participation in national and international research.

Box 2.1 **CONTENTS OF ECMO TROLLEY**

5 silver clamps

Pressure bag for rapid infusion

Console and motor

Backup console and motor

Oxygen cylinder with tubing

Heater/cooler

KEY QUESTIONS

WHAT IS THE ROLE OF THE LEADS OF AN ECMO SERVICE?

An experienced and practicing ECMO clinician will have overall responsibility for the ECMO service. The lead clinician is responsible for ensuring that appropriate resources are available to ensure best possible care so that there is no need of that person being involved in the care of each individual patient. The lead clinician will work with an experienced

ECMO specialist. They will oversee all aspects of the interdisciplinary team being responsible for ensuring[1–3]

- regularly updated evidence-based guidelines and standards;
- training and assessment programs;
- involvement and engagement of multiple specialty practitioners to meet the complex needs of the patient on ECMO;
- conduct of regular performance reviews;
- maintenance of good governance processes, including regular mortality and morbidity meetings;
- submission of validated data to relevant registries.

WHAT IS AN ECMO SPECIALIST?

The ECMO specialist was defined by ELSO as "the technical specialist trained to manage the ECMO system and the clinical needs of the patient on ECMO under the direction and supervision of an ECMO trained Physician."[3] An ECMO specialist is in the ICU 24 hours a day; the role allows for timeliness of any intervention, thus improving patient care and safety.

In most ECMO centers, the ECMO specialists are nurses with at least 2 years' experience in intensive care nursing, ideally in a unit that cares for ECMO patients. The responsibilities of the ECMO specialist should be defined in clearly written guidelines and protocols and include regular circuit surveillance, accessing the circuit (e.g., for continuous renal replacement therapy), troubleshooting the ECMO circuit, ensuring the cannulas and circuit are safe during mobilization, and managing circuit emergencies.

The ECMO specialist role has expanded to encompass management of anticoagulation and weaning of ECMO support within defined guidelines.[4]

In addition to clinical and practical skills, the ECMO specialist will communicate effectively with the interdisciplinary team, the patient, and the patient's family to ensure safe and effective management while on ECMO. Integral to the role is teaching and supporting the bedside teams, and the ECMO specialist is expected to be actively involved in education programs, governance meetings, and assessment of ECMO-trained nurses.

WHAT TRAINING AND ASSESSMENT ARE REQUIRED TO QUALIFY AS AN ECMO SPECIALIST?

The ideal training course for the ECMO specialist will combine didactic, practical, and high-fidelity simulated sessions. Centers may differ in their individual approach to training and assessment but most will follow the recommendations set out by ELSO in their *ECMO Specialist Training Manual*.[5] The ECMO course is taught by experts from all specialties involved in the management of the ECMO patient, allowing the trainee ECMO specialist to benefit from the expertise of all involved in meeting the complex needs of the ECMO patient. Topics included in an ECMO specialist course are described in Box 2.2.

Box 2.2 ECMO SPECIALIST COURSE

ECMO Specialist Course

All trainees will

- identify an experienced ECMO specialist to act as mentor
- complete 3 reflective case studies
- maintain a log of clinical experience and practical skills training—minimum of 36 hours
- attend all classroom sessions

Course Content (Delivered Through Classroom, Practical Skill, and Simulation Sessions

Introduction to ECMO—history, modes and indications, complications, risks and benefits, and current research

Pathophysiology of common diseases/indications for ECMO

Contraindications for ECMO—criteria for selection

The ECMO circuit—components, configurations, and membrane physiology

Physiology of veno-venous and veno-arterial ECMO, including cannulation, indications, and complications

Day-to-day circuit and patient management, including routine circuit surveillance, monitoring, and the complex circuit

Physiology of coagulation—management of anticoagulation

Management of circuit and patient emergencies

Connection and disconnection of adjunct circuits (e.g., continuous renal replacement therapy, plasmapheresis)

Safe mobilizing of the patient on ECMO

Weaning from ECMO—assisting with decannulation

Post-ECMO complications
Ethical and social issues, including withdrawal of support

Assessment

A Viva and practical skills assessment (VIVA) practical skills assessment by lead ECMO specialist and lead ECMO perfusionist

Practical skills assessment by lead ECMO specialist and lead ECMO perfusionist

Postqualification

The qualified ECMO specialist will maintain a "passport of practice" to be completed annually. The passport will include

- evidence of reflective practice
- record of simulation and practical skills training sessions
- record of regular attendance at ECMO service meetings
- evidence of attendance at ECMO-related educational sessions, meetings, conferences

The ECMO specialist requires training in technical skills and key behavioral skills, including leadership, communication, and teamwork. Simulation-based training is well suited to the training and assessment of both technical and behavioral skills[6–9] and should be integral to the ECMO specialist training program.

Competency of the ECMO specialist is assessed on completion of the course and annually thereafter. Assessment criteria are included in each center's guidelines and provide the framework for objective assessment of the ECMO specialist. Assessment of practical skills is supported by oral exams, which utilize clinical scenarios to assess the ECMO specialist's knowledge and ability to interpret and prioritize actions.

The ECMO specialist is required to maintain skills through regular practical and simulation sessions. All ECMO specialists should be reassessed annually.

WHAT IS THE ROLE OF THE ECMO COORDINATOR IN THE RETRIEVAL OF A PATIENT?

The role of the ECMO coordinator is essential in ensuring efficiency in the referral, retrieval, and admission of the ECMO patient. The ECMO coordinator will receive the initial call/contact from the referring team, assisting the ECMO clinician by ensuring that all relevant information and imaging are available to review for suitability for ECMO.

On the decision to send a team to review a patient and potentially cannulate to commence ECMO, the ECMO coordinator's role will be to activate the team and to contact the referring hospital to ensure they are fully prepared for the arrival of the ECMO team. Preparation at the referring hospital will include, but not be limited to, availability of blood and/or blood products, an equipped theater with anesthetic support, and, where possible, asking the patient's family to be available for discussion of support with the ECMO team.

The retrieval team will be in regular contact with the ECMO coordinator during a retrieval, updating on patient status, time of departure from the referring hospital, and estimated time of arrival in the ECMO center. This information allows the ECMO coordinator to organize availability of the CT scanner for admission imaging en route from ambulance to ICU, ICU bed setup, and presence of staff ready to admit the patient.

The coordination of the retrieval of a patient on ECMO is essential in ensuring the safety of the patient.

WHAT IS THE ROLE OF THE PERFUSIONIST IN AN ECMO SERVICE?

Clinical perfusion scientists are highly skilled professionals who manage the cardiopulmonary bypass (CPB) machine and therefore the patient's physiological parameters during CPB procedures. Additional training and assessment are required to gain the knowledge and skills required to manage the ECMO circuit.[2]

The perfusionist's role in an ECMO service varies in different centers. It is usual practice for the perfusionist to be responsible for

- priming of the circuit
- changing of the circuit or any individual component of the circuit
- managing the circuit during intra- and inter-hospital transfers

The perfusionist is an integral part of the retrieval team.

WHY IS THE INVOLVEMENT OF MULTIPLE SPECIALISTS IN AN ECMO SERVICE ESSENTIAL?

The patient supported on ECMO has complex needs due to both presenting pathology and complications that may develop while supported on ECMO. Regular meetings to discuss the management of the patient need to be embedded into the team schedule. Regular discussions will ensure timely, appropriate interventions. An example of this is regular discussion with microbiologists to review infection status and ensure appropriate use of antimicrobials and antifungals. Patients awake on ECMO may benefit from the expertise of psychiatrists or palliative and supportive care specialists. Consultants from these specialties should work alongside the more traditional specialties of respiratory physicians, cardiologists, surgeons, hematologists, and radiographers as integral members of the ECMO team.

WHAT SKILLS DO BEDSIDE NURSES NEED TO CARE FOR THE PATIENT SUPPORTED ON ECMO?

The bedside nurse may be an ECMO specialist, but increasingly ECMO services function with the ECMO specialist overseeing a number of patients on ECMO supported by a bedside nurse allocated to individual patients.[4]

The bedside nurse is an intensive care nurse with experience of caring for patients with complex needs; these nurses require extra training in interpreting results of bedside monitoring of the ECMO patient and escalating concerns to the ECMO specialist. They do not have the training or skills to troubleshoot the ECMO circuit. All centers vary in their approach to developing the skills and knowledge of the bedside nurse, with some reliant on an informal experience-based approach, but increasingly centers adopt a more structured approach of didactic and practical skills learning reinforced with assessment and regular reassessment.

Regardless of approach, the bedside or ECMO-trained nurse needs

- to understand the indications for ECMO support;
- to understand and have the ability to recognize complications of ECMO;

- to know of modes of ventilation;
- to understand the indications for use and the complications of different cannulation configurations;
- to recognize the need for basic circuit surveillance;
- to master cannula site care;
- to be able to perform safe moving and handling of the patient supported on ECMO; and
- to understand the roles and responsibilities of the members of the multi disciplinary team (MDT) and the limitations of their role.

WHAT ROLE DO OTHER ALLIED HEALTH PROFESSIONALS HAVE IN AN ECMO SERVICE?

In common with all critically ill patients, ECMO patients benefit from the input of other allied health professionals.

The growth in the number of patients supported on ECMO for prolonged periods and while awake has led to an increased role in their care by physiotherapists, speech and language therapists (SALTs), and occupational therapists (OTs). Active mobilization of the patient supported on ECMO by the trained interdisciplinary team has been shown to be safe.[10,11] The benefits in reduction in ICU and hospital length of stay and improved functional abilities postdischarge are unproven, but it is recognized that they lead to a reduction in complications of bed rest, have a beneficial impact on psychological well-being, and may improve mobility status and muscle strength.[11] The physiotherapy and OT teams in an ECMO center will work closely with the ECMO specialists to provide rehabilitation sessions for ECMO patients.

The valuable contribution of SALTs as part of the ICU MDT in assisting with tracheostomy management, assessment and resolution of swallowing impairment, and use of communication aids is recognized.[12] These are all challenges frequently encountered by the awake patient supported on ECMO for a prolonged period of time.

The positive impact of the involvement of pharmacists in ICU in terms of reduction of medication errors, decrease in polypharmacy, and economic benefits has been recognized for many years[13,14] and supports their inclusion in discussions regarding the treatment of ECMO patients who have the added complexity of an extracorporeal circuit and oxygenator.

The patient supported on ECMO requires frequent, often complex, imaging, and radiographers with knowledge of the ECMO circuit and the roles of the ECMO multidisciplinary team are crucial in avoiding critical incidents, including accidental decannulation during imaging (e.g., during CT scanning).

Critical care scientist (CCSs) will add value to any ECMO team. Their specific training in the application of clinical technology, physiological monitoring, and clinical research are a valuable resource in the ECMO team. Their expertise in bedside ultrasounds, such as lung or cardiac ultrasound techniques, can provide immediate data on a deteriorating patient. Additionally, CCSs can provide invaluable support in developing and undertaking research projects.

WHAT IS THE IMPORTANCE OF RESEARCH IN AN ECMO CENTER?

All ECMO centers should support and promote research activity. ECMO still requires proof of its effectiveness as a support. Centers should encourage and support in-house interdisciplinary research. Involvement in national and international studies is recommended.

Organizations such as ELSO and the International ECMO Network promote a collaborative approach to high-quality, high-impact research.[1]

Resources in terms of staff, finance, and time need to be allocated for research.

HOW DOES AN ECMO SERVICE APPROACH ETHICAL DILEMMAS IN PATIENT MANAGEMENT?

Use of ECMO is a support rather than a treatment and as such is instituted in cardiac and/or respiratory failure as a bridge to recovery, transplantation, or long-term device. Abrams et al.[15] discussed the ethical dilemmas that may arise when a patient is unable to be bridged when ECMO effectively becomes a "bridge to nowhere." The challenges of this situation are intensified when the patient is awake and has capacity. It is not within the remit of this chapter to discuss ethical dilemmas, but this example illustrates the need for the ECMO service to allow open interdisciplinary discussions on these cases and seeking support from hospital ethics committees as appropriate.

WHY SHOULD WE FOLLOW UP PATIENTS POST-ECMO SUPPORT?

Measuring the long-term impact of ECMO on survivors can inform future practice, and ELSO includes this as a necessary element of an ECMO service.[16] Follow-up of patients is typically at 6 months post-ECMO liberation, and outcome measures include completion of a validated quality-of-life questionnaire; lung function testing, including 6-minute walk; and chest x-ray.[17]

WHY IS ONGOING EDUCATION AND TRAINING REQUIRED FOR THE ECMO TEAM?

The initial and ongoing education and training of the multidisciplinary team involved in the management of the patient supported on ECMO are essential in ensuring safe and effective practice. In addition to knowledge required for the day-to-day management of the patient, advanced troubleshooting skills and good teamwork and communication skills are essential to prevent patient morbidity and improve mortality.[18] ELSO reports common circuit emergencies, including air entrainment (0.1%), circuit changes (1.6%), pump failure

(0.7%), and oxygenator failure (2.7%) in ECMO runs. This demonstrates that potentially catastrophic events are relatively infrequent and unpredictable. Due to the rarity of potentially catastrophic events, the ECMO team's technical and nontechnical skills are not reliably maintained through clinical experience,[19] leading to a need for robust training and regular updating of technical and nontechnical skills and knowledge.[20] Successful ECMO programs are those with well-defined multidisciplinary education programs based on comprehensive guidelines. Traditional training for ECMO teams supported by ELSO recommendations is based on a combination of didactic sessions, practical sessions using saline-filled circuits, and bedside teaching complimented by supervision in the clinical area by experienced practitioners. This traditional approach is increasingly being supplemented with high-fidelity simulation-based sessions using sophisticated mannequins, which can be programmed to replicate the most common ECMO emergencies and scenarios.

HOW DOES AN ECMO SERVICE ENSURE ROBUST CLINICAL GOVERNANCE?

Clinical governance is defined as the framework through which organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.[21]

The ECMO service will achieve this through a culture of continual audit of practice against clearly defined standards. Outcome data should be submitted to ELSO and appropriate national databases with regular benchmarking of a center's outcomes completed. Regular interdisciplinary morbidity and mortality meetings should be held and adhere to a standing agenda encompassing review of activity, outcome data, review of untoward incidents, learning from incidents and best practice, audit reports, review of all patients referred to the service, and review of all patients admitted to the service.[1,2,22] Records from these meetings need to be shared within the interdisciplinary team and stored for future reference.

Openness is a crucial component of governance, and processes to gather feedback from patients and family should be in place and results used to inform and improve practice. Regular meetings with teams from referring hospitals is valuable and should be arranged at regular intervals.

WHAT ARE THE ADVANTAGES OF ECMO CENTERS WORKING COLLABORATIVELY WITH WIDER NETWORKS?

The ECMO services working within a national network meet regularly to review activity and outcomes and report on audit results on agreed standard metrics; shared governance with associated learning is one of the advantages of a cohesive national or regional service.

Regular peer reviews based on an agreed set of standards encourages a culture of continual improvement and maintenance of high standards of care.

The practice of discussing difficult or challenging cases between clinicians from different centers ensures the highest standard of care and appropriate patient selection.

Networks allow rapid, coordinated response to an increase in communicable diseases, whether caused by heightened winter pressures or pandemics.[23,24] Communication within a network allows a dynamic approach ensuring appropriate response and allocation of resources to meet demand.

DISCUSSION

Building an ECMO service is a highly complex process that requires the development of many interdependent facets. ELSO-provided guidelines describe the ideal institutional requirements needed for the development of an ECMO service.[22] The guidelines cover organizational structure, staffing requirements, physical facilities, equipment, staff training and education, patient follow-up, and program evaluation. They are intended as outline recommendations and recognize that each service will vary according to local and national influences.

Within the guidelines, ELSO noted the requirement for an ECMO service to be located in an area that can support a minimum of six patients per year, noting that to support less reduces cost-effectiveness and leads to difficulty in maintaining staff competencies and skills. The 2014 "Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients"[1] representing the consensus opinion of an international group of physicians and healthcare workers with expertise in ECMO for respiratory failure supported recommending a volume of 20 ECMO cases per year; furthermore, due to fluctuating levels of activity, ECMO centers should be organized at regional and national levels providing fewer high-volume centers. They advocated this approach to reduce costs, maintain staff competencies, and decrease individual patient risks. A multicenter observational cohort study by Warren et al.[25] of the outcomes of the National Health Service England extracorporeal membrane oxygenation service for adults with respiratory failure supported this approach, reporting survival of 74%, which is significantly higher than the 60% survival reported in 2020 by the ELSO registry. They speculated that this may in part be due to the high volume–outcome relationship related to centralizing ECMO provision in a small number of centers.[26]

STAFFING

Arguably the most important component of any ECMO service is the staff. The team needs to be available round the clock and should have resilience to meet fluctuating demand. Ramanathan et al.[16] recommend maintaining a log of all members of the interdisciplinary team trained in the management of patients supported on ECMO. Details and regular updates of staff training should be included in the log. The log fulfills the dual purpose of acting as a training register and as a resource to identify staff with the correct competencies in times of need.

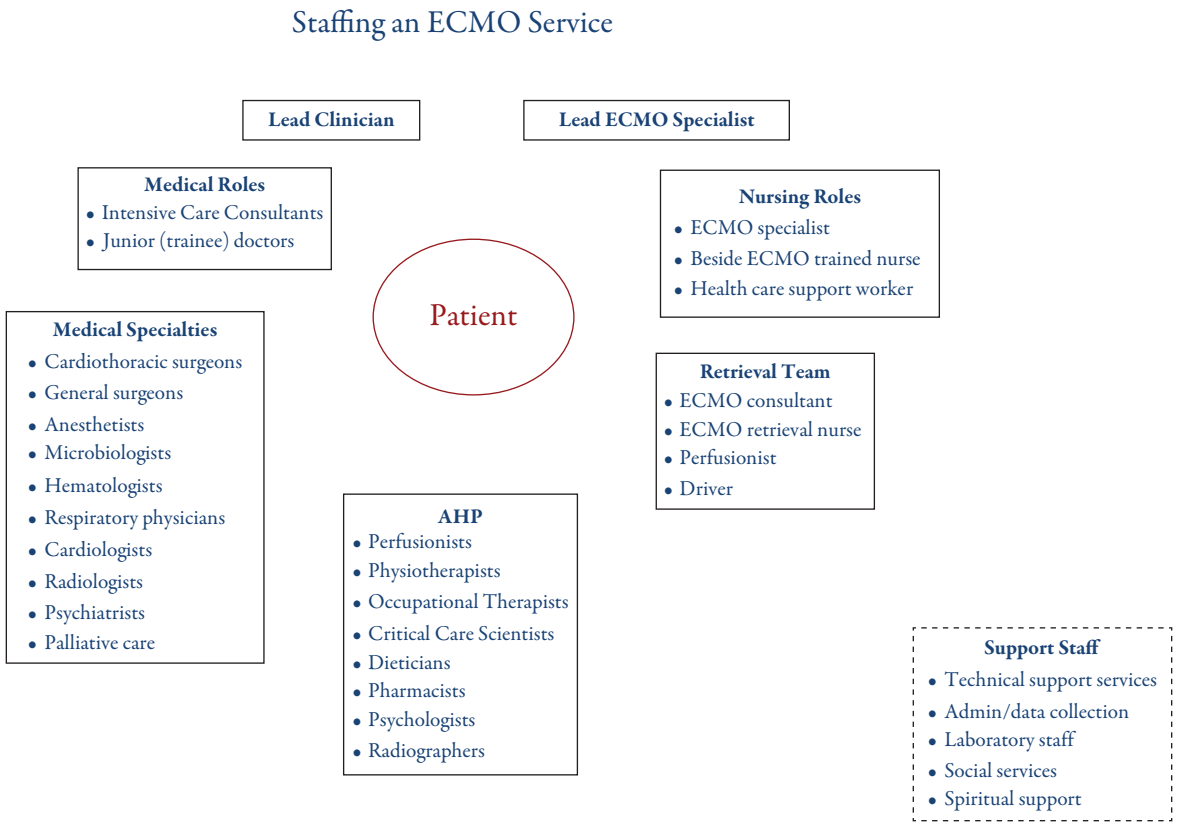


Figure 2.1 Staffing model for an ECMO center

A staffing model for an ECMO center is illustrated in Figure 2.1. It is led by a senior clinician and ECMO specialist who are responsible for developing and maintaining guidelines and protocols, education and training programs, governance, performance reviews, and valid data collection and submission to relevant registries.[22] To ensure patient and circuit safety, areas of responsibility for specific aspects of management should be clearly articulated within guidelines. Interdisciplinary meetings should be held on a regular basis and should include case discussions to share knowledge and experience ensuring the whole team continues to learn and develop.[2]

The medical staff involved in the day-to-day management of the ECMO patient are usually intensive care–trained doctors with additional training in the management of ECMO; they are supported by junior doctors in training positions.

The ECMO specialists also act as ECMO coordinators and/or retrieval nurses, with bedside nurses being ECMO trained. The qualified nursing staff are supported by healthcare support workers who are unqualified nurses who assist with basic nursing care. Although formal training is not required, the risks associated with ECMO should be discussed prior to them assisting with any care.

The perfusionist plays an important role in the ECMO service, but increasingly is not involved in the day-to-day management of the circuit. A lead perfusionist will be involved in the development of protocols and in the education, training, and assessment of the interdisciplinary team.

In a consensus agreement for best practice, Eden and colleagues,[27] representing the United Kingdom ECMO Physiotherapy Network, highlighted the importance of the role of physiotherapists in providing respiratory care and supporting rehabilitation of patients supported on ECMO. They recommended that specialist physiotherapists be involved from time of admission in the management of patients supported on ECMO. The risk of adverse incidents during treatment was acknowledged, and they advocated pre- and postprocedure checks and additional training and assessment for physiotherapists involved in the service. An interdisciplinary team working with clearly designated roles is advised when mobilizing the patient on ECMO.

Due to the demanding nature of the workload, highly technical environment, and frequent exposure to critical incidents and death, staff working in the ICUs are at higher risk of developing stress-related illnesses, including anxiety and depression.[28–30] The extra demands and complexity of the patient on ECMO compound these risks. Staff, including psychologists, chaplains, and supportive care nurses, should be available to provide psychological support to staff.[16] To minimize negative impact on staff health and well-being, regular reflective debriefing sessions should be embedded into the ECMO program, with extra sessions made available at short notice if required.

TRAINING AND EDUCATION

A robust education and training program for the interdisciplinary team is essential, and adequate resources in terms of time, personnel, and money should be allocated.[1–3] In addition

to formal courses for ECMO doctors and specialists, there should be regular updates for those specialty practitioners with only occasional input into the service.

Extracorporeal membrane oxygenation is a complex, high-risk intervention with training and education programs for the ECMO interdisciplinary team requiring equal emphasis on technical and nontechnical skills. Nontechnical skills, including poor communication and lack of corroboration, contribute to adverse incidents in healthcare.[31,32] Training that improves teamwork and communication and improves awareness of safety factors can lower these risk factors and potentially reduce the number of adverse incidents.[33] The value of high-fidelity simulation training in developing both technical and behavioral skills of ECMO teams is becoming well recognized and should be included in the ECMO service training program.[6–9]

INFRASTRUCTURE AND EQUIPMENT

Ideally, the ECMO service will be located in a tertiary medical center capable of supporting the financial impact of a high-cost service combined with the availability of the many subspecialty services and expertise the ECMO patient may require.[1,3,22] In times of high activity, as frequently seen in winter months, collocating patients in an area within the ICU allows for centralizing the highly skilled staff required to manage the ECMO patient. Plans for this should be embedded into the ECMO service guidelines.

When setting up an ECMO service, an important step is choice of ECMO pump; many centers prefer to use one standard pump for ease of training others; have different pumps for transport and long-term use. Regardless of choice of console, training will need to be ongoing for all clinical staff and for the technical staff involved in maintenance.[34]

Some ECMO pumps have a manual backup system for use in cases of pump failure, with others relying on spare backup consoles and motors. The gold standard is to provide one backup console and motor per patient, but in times of high activity, one backup console and motor may be shared between up to three patients collocated in the same area. If backup consoles are shared, clear communication must be documented to ensure the bedside team is aware of the location of backup equipment.

REFERRAL AND RETRIEVAL

A standardized form should be devised for referrers to complete when referring a patient for consideration of ECMO support. The form will include demographic details, presenting complaint, current status, known infections, and comorbidities (or frailty); completing the comprehensive form along with transfer of relevant imaging to the ECMO center team allows informed discussion between teams. Many patients referred to the service do not require ECMO, but it is the role of the ECMO center to advise on management of these patients; discussions may take place over a couple of days. When setting up a service, the time and resources required to maintain this function need to be accounted for.

Standardized criteria for consideration of ECMO support need to be published and shared with all referring centers; these will be regularly reviewed and updated in line with developing evidence.[22]

Retrospective studies into activity and outcomes showed that mobile ECMO can be safely achieved with a retrieval team of an intensive care consultant, ECMO specialist retrieval nurse, and perfusionist.[24,35]

The retrieval team needs to transport all equipment and consumables required to commence the patient on ECMO and subsequently transfer to the ECMO center. Comprehensive checklists of contents of transfer bags should be developed to assist in preparation for retrieval and use of a World Health Organization (WHO)–style surgical safety checklist are recommended. The use of checklists may reduce the number of adverse incidents associated with transfer.[36,37.] The retrieval team will be in an unfamiliar hospital with teams they may never have met before and whose individual roles are unknown; taking time out to complete the first two stages of a WHO-style checklist, sign in, and before cannulation allows the team to pause to introduce themselves and prepare for the procedure. Completing the final sign out ensures all processes are safely completed prior to leaving for the return journey.[38]

A retrieval report should be written and included in the clinical notes. The retrieval report will cover patient details, assessment, discussion with family, and procedural details. The report with the addition of a reflective section is shared with the wider team for additional learning.

GUIDELINES

Guidelines and standard operating procedures ensure all members of the team understand their role and responsibilities. It ensures patients receive the best management guided by the most recent up-to-date evidence. Local guidelines will recognize and address local idiosyncrasies to ensure members of the team do not have to reinvent new solutions on multiple occasion. Regular updating or an agile electronic format allows building on local learning and ensures practice is aligned to the best international recommendations.

CONCLUSIONS

- An ECMO service is a complex structure that goes beyond a standard ICU. ECMO should not simply be a bespoke support provided alongside many other resources, but it requires investment in people, resources, and time.
- The successful continued delivery of good outcome can only be ensured if the hospital management invests adequately in supporting all the blocks required to build a strong service.

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REVIEW QUESTIONS

1. Which statement best describes the role of the ECMO specialist?

   A. Coordinates retrieval of patients on ECMO
   B. Manages the ECMO system
   C. Manages the ECMO system and the clinical needs of the patient
   D. Provides nursing care for the patient supported on ECMO

2. Which two of the following best describe the role of the perfusionist in the ECMO service?

A. Be at the bedside 24 hours of the day
B. Prime circuits and assist in changes of circuits/oxygenators
C. Accompany the patient on any transfer outside the ICU
D. Be solely responsible for monitoring blood gases of the ECMO circuit

3. Due to the rarity of potentially catastrophic circuit complications, the ECMO teams' skills are not reliably maintained through clinical experience, leading to a need for?

A. Regular practical sessions with "wet circuits"
B. Regular assessment of skills
C. Simulation training to improve teamwork
D. All of the above

4. Which of the following is a crucial component of clinical governance?

A. Having an interprofessional team
B. Openness
C. Servicing equipment regularly
D. Robust training

5. What did the "Position Paper for the Organization of Extracorporeal Membrane Oxygenation Programs for Acute Respiratory Failure in Adult Patients" state was the recommended minimum number of ECMO patients a center should support per year?

A. 6
B. 10
C. 20
D. 30

6. Why are high–volume centers recommended?

A. Decreased individual patient risk
B. Cost efficiency
C. Maintaining staff competencies
D. All of the above

ANSWERS

1. C
2. B and C
3. D
4. B
5. C
6. D

3.

ECMO CONFIGURATIONS AND CANNULATION IN PEDIATRIC PATIENTS

Robert J. Vandewalle, Matthew S. Clifton, and Matthew L. Paden

STEM CASE 1 AND KEY QUESTIONS

A 3.5-kg female neonate at 41 weeks of gestation was born via emergent cesarean section for fetal distress and noted to have meconium-stained amniotic fluid at the time of delivery. The neonate was noted to have a poor respiratory effort with Apgar scores of 5 and 6 at 1 and 5 minutes of life, respectively. The neonate was initially supported with noninvasive positive pressure ventilation, where tracheal suctioning revealed meconium-stained fluid in the airway. Over the course of the next 48 hours, she required endotracheal intubation and had increasing oxygen requirements as well as increasing mean airway pressures to maintain adequate oxygenation. After no significant improvement with surfactant administration and inhaled nitric oxide, she was transitioned to a high-frequency oscillatory ventilator (HFOV). Serial chest x-rays revealed bilateral patchy opacities, and after optimization on HFOV, the patient's oxygen index remained greater than 40 for over 6 hours. After discussion with the institutional extracorporeal membrane oxygenation (ECMO) team, the patient was determined to be a candidate for veno-venous (V-V) ECMO and was cannulated using a dual-lumen cannula via the right internal jugular (RIJ) vein [i.e., (dl)V-V ECMO]. After 4 days on ECMO support, she was successfully decannulated to conventional ventilation and extubated 5 days later.

WHAT ARE COMMON CANNULATION OPTIONS FOR ECMO IN THE NEONATE?

The location of ECMO cannulation can be broadly categorized as either central or peripheral. In central cannulation, the catheters are placed directly in the desired cardiovascular structures utilizing a transthoracic approach via sternotomy. This typically involves placing a cannula in the right atrium (RA) and another directly in the aorta. In peripheral cannulation, a site outside of the thoracic cavity is used to gain access to the central vasculature. Central cannulation is typically reserved for pediatric patients with surgical cardiac disease and in some cases of sepsis. Therefore, peripheral cannulation techniques are the focus of this chapter. The neck (i.e., the jugular vein and/or carotid artery) and the groin (i.e., the femoral vessels) are the commonest sites for peripheral cannulation. Adequate ECMO flows cannot typically be achieved in the neonate utilizing the femoral vessels due to their small size. In addition, there is significant risk for thrombosis/ischemic events if a lower extremity is utilized in this population. Therefore, neck cannulation, also known as cervical cannulation, is the preferred site of peripheral ECMO in the neonate.

In the neonate with respiratory failure (e.g., meconium aspiration) refractory to conventional ventilation, ECMO can take the form of either veno-arterial ECMO (V-A ECMO) or V-V ECMO. V-A ECMO removes blood from the central venous circulation and returns blood to the central arterial circulation. In this manner, V-A ECMO is "heart-lung bypass" and provides not only respiratory but also cardiovascular dynamic support. V-A ECMO in the neonate requires cannulation/ligation of both a carotid artery and jugular vein and is typically completed on the right side since the cannulas are stiff and the straight path to the heart afforded by right-sided vessels is necessary. V-V ECMO utilizes individual cannulas at either two separate sites (i.e., jugular and femoral venous cannulation) or can be completed using a dual-lumen catheter through a cervical approach, with the latter evolving into the modality of choice over the last two decades for neonates and children. V-V ECMO removes blood from the central venous circulation (i.e., the superior vena cava [SVC] and/or inferior vena cava [IVC]) and returns blood to the right atrium. Thus, while physiologically serving as "lung bypass," V-V ECMO does not directly provide hemodynamic support.

WHAT ARE COMMON CANNULATION TECHNIQUES FOR ECMO IN THE NEONATE?

Cannulation techniques for ECMO in the neonate can be performed at the patient's bedside (most common), within a procedural room, or in the operative theater. Regardless of actual location, the focus should be to ensure all necessary personnel and supplies are readily available and the procedure is performed in a sterile environment. The multidisciplinary ECMO team, comprising intensivists, surgeons, surgical staff, medical staff, respiratory therapists, ECMO specialists, and others, must work in concert and have predefined roles prior to initiation of ECMO cannulation.

After a patient is determined to be a candidate for ECMO, the modality must be chosen (i.e., central vs. peripheral and V-A ECMO vs. V-V ECMO). While V-V ECMO continues to

be an increasingly used modality for neonates with respiratory distress, peripheral V-A ECMO has traditionally been used by most centers.[1,2]

In the neonate, V-A ECMO utilizes two single-lumen catheters. The arterial catheter has a single opening at the distal tip, which is ideally placed at the level of the aortic arch at the junction with the innominate artery.[3,4] The venous catheter has multiple ports on the distal end to facilitate drainage and is best positioned at the junction of the vena cava and the right atrium.[3,4] The most commonly used catheters are wire reinforced to prevent kinking while in use (Bio-Medicus NextGen Pediatric, Medtronic, Dublin, Ireland). This wire reinforcement is not present in the most distal aspect of the catheters (i.e., at the port[s]), and this must be kept in mind when using radiographs to determine catheter placement as the tip is radiolucent. This is most pronounced in venous catheters, where a significant length of the cannula contains ports and extends beyond the portion easily visualized on a chest radiograph. In some instances, there is a radiolucent marker on the tip to facilitate identification on x-ray. A blunt-tipped introducer is available for use that keeps the cannula rigid during insertion.

Preoperative chest x-ray, echocardiography, and ultrasound of the neck vasculature are essential. These imaging studies allow the surgeon to estimate the length the cannula must be advanced once placed into the corresponding vessel, evaluate for evidence of structural heart disease that may complicate or preclude successful peripheral ECMO cannulation, estimate the diameter of the carotid artery/jugular vein that will be used, and assess for any evidence of pre-existing thrombus/stenosis.[5] Even with accurate ultrasonography, it is advisable to have multiple sizes of both arterial and venous cannulas available at the time of surgery. For V-A ECMO in the neonate, the arterial catheter diameter is typically 8 French (8F), and the venous cannula is typically a 10F or 12F catheter. In all forms of ECMO, the venous flow back to the ECMO circuit will dictate maximum blood flow deliverable to the patient. While many variations on the surgical approach exist, the main technical steps for V-A ECMO in the neonate are mentioned next[3,6] (Figure 3.1).

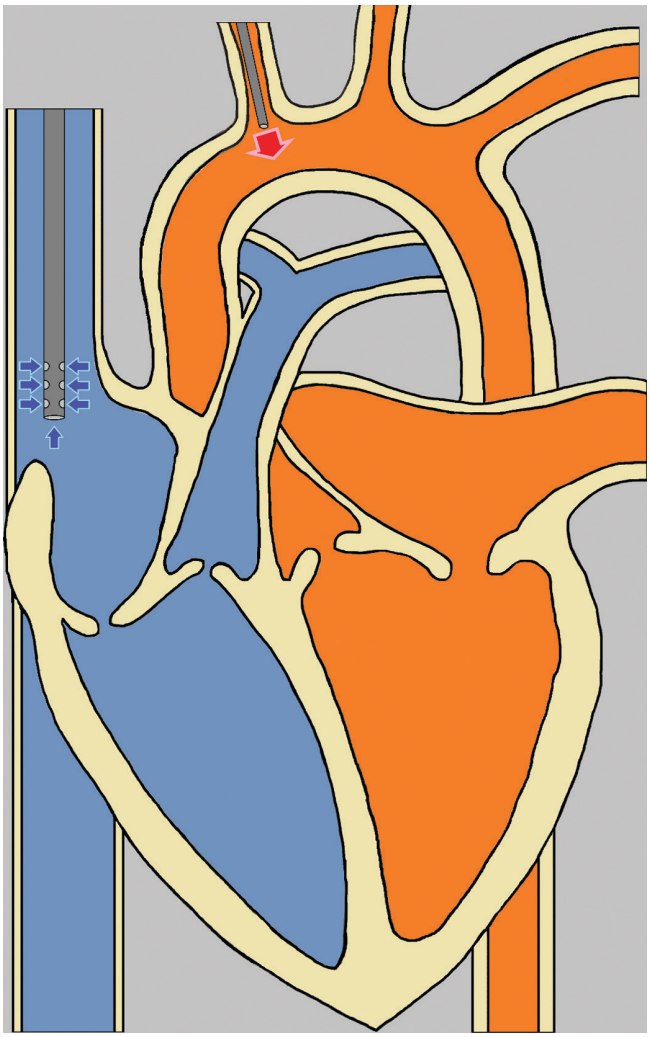


Figure 3.1 Cannula positioning for cervical V-A ECMO.

The Veno-Arterial Cannulation Technique

- With the patient in a supine position with the head at the edge of the bed/table, a shoulder roll is placed prior to sterile preparation. The neck is extended and rotated toward the patient's left to improve visualization of the right neck.
- After sterile preparation of the head, face, neck, and chest, an incision is made approximately 2 cm above the right clavicle (either transverse or oblique) overlying the split between the sternal and clavicular heads of the sternocleidomastoid muscle (SCM). Electrocautery is used to dissect through the subcutaneous tissues and the platysma. Once the SCM is encountered, dissection can be completed bluntly by mobilizing the SCM laterally or slipping between the two heads of the SCM, depending on location of the incision and surgeon preference.
- Once the carotid sheath is encountered, the sizes of the vessels should be assessed to confirm correct cannula size. Next, 2–3 cm of the right common carotid (RCC) artery is bluntly mobilized. The vagus nerve should not be manipulated during dissection to prevent bradycardia. Traction snare sutures (typically 2-0 silk) are placed on the most distal and proximal aspects of the mobilized RCC to facilitate future manipulation and control bleeding if necessary. These are left off tension after placement to prevent inadvertent injury. In neonates, the vessels are incredibly soft and pliable, making intimal injury and dissection a potential problem if delicate technique is not employed. In a similar fashion, the internal jugular vein is isolated and controlled.
- Systemic heparin is then given (50–100 units/kg) and allowed to thoroughly circulate without additional manipulation of the vasculature. The RCC is then ligated high (cranially) in the mobilized section with a heavy silk suture, and a vascular clamp or vessel loop is placed on the aortic side of the ligated vessel. The tails of the ligature are left long to facilitate traction.

- With the artery clamped, an arteriotomy is then made on the anterior half of the RCC between the clamp and the ligature with an 11-blade scalpel. With the blade pointed upward (anteriorly), the scalpel bisects the artery in a lateral-to-medial fashion. Lifting the scalpel upward completes the arteriotomy. Some surgeons prefer to bevel the arteriotomy cranially. An arteriotomy larger than half the diameter of the vessel risks complete division of the RCC with possibly retraction of the proximal section into the chest.
- The arterial cannula, with the blunt introducer, is then lubricated and gently inserted through the arteriotomy as the vascular occlusion is removed. Gentle twisting can facilitate advancement, and correct positioning should be possible without forcing the cannula. In the event cannula advancement is difficult, adjust the angle of advancement to ensure it is in line with the carotid/innominate arteries and that an inadvertent intimal dissection is not being caused.
- The arterial catheter is typically advanced 2–4 cm from the arteriotomy site in the neonate. The introducer is then removed, and back-bleeding/flushing is used to remove air from the cannula, which is then clamped until it is attached to the ECMO circuit. The silk ligature used on the RCC can then be used to help secure the cannula position as well. The caudal traction suture is also tied down to secure the cannula to the vessel; this can be done over a small portion of vessel loop to assist identification and removal at the time of decannulation, but this is at the surgeon's discretion.
- The RIJ is then cannulated in a similar fashion with some notable differences. The venous cannula is typically advanced 6–7 cm. It is important to remember during cannula advancement that back-bleeding from the side ports will not stop until all are within the lumen of the vein once the introducer is removed. Gentle manipulation is essential as the RIJ is more friable than the RCC during dissection, traction, venotomy creation, and cannulation.
- The ECMO circuit is then properly attached to both the RCC (inflow/arterial) and RIJ (outflow/venous) cannulas, and flow is initiated according to institutional protocols.
- Our institution typically places internal jugular vein cephalic drains (CDs) in neonatal and pediatric ECMO patients in order to enhance venous drainage. If the ECMO team decides to place a CD at the time of cannulation, ligation of the RIJ should be caudal enough within the mobilized section to allow enough length for both cannulas to be inserted. The CD is typically an arterial catheter one size smaller than the venous catheter used in the RIJ (e.g., an arterial 8F CD cannula if a 10F RIJ venous cannula was placed).[7] This cannula is advanced to the level of the skull base, withdrawn 0.5–1 cm, and then secured within the vein using the cephalad traction suture. In the emergent setting, the patient can be stabilized on V-A ECMO using only the RIJ and RCC cannulas while CD placement is completed. Otherwise, the tubing to both the RIJ and CD cannulas are joined with a Y connector at the time of ECMO initiation to serve as a single venous outflow. CDs typically contribute 20%–40% of venous flow to the circuit and rarely clot in our experience.
- Without compromising the sterile field, additional imaging is then obtained to confirm cannula placement. This is typically a portable chest x-ray, but echocardiography can be completed as well. A preliminary study by Thomas et al. has shown echocardiography to be better at ensuring proper arterial cannula location compared to x-ray.[4]
- Once proper position is confirmed with imaging and initiation of ECMO is satisfactory, the neck incision is closed. The cannulas are then secured to the head/neck with permanent suture in multiple places to prevent accidental migration. While securing the cannulas from migration is of the utmost importance, excess pressure on the skin from securing the cannulas can cause necrosis and complicate the ECMO course. Because the cannulation sites must be monitored frequently for both bleeding and cannula migration, dressings over these sites should be minimal.

The Veno-Venous Cannulation Technique With a Double-Lumen Catheter

If V-V ECMO is the chosen modality, a double-lumen (VVDL) catheter placed via the RIJ is the most common technique in the neonatal/pediatric population.[2] Several different types of techniques exist for VVDL placement[1,3,6,8–13]:

- In the open technique, the RIJ is dissected free in a similar fashion to the technique described for V-A ECMO while leaving the RCC relatively undisturbed; a venotomy is then made, and the catheter is advanced the appropriate length. This is typically completed with a blunt introducer and is a less commonly used technique.
- In the semiopen technique, only the anterior surface of the RIJ is dissected free. The remaining intact tissue helps provide traction for cannulation. The cannula is then placed using a Seldinger technique through either the original neck incision or a separate stab incision is made 1–2 cm cranially to serve as a subcutaneous tunnel. A large-gauge needle is then used to access the vein under direct visualization, and a 0.035-inch guidewire is advanced through the needle. The needle should enter on the anterior surface in the center of the vessel. This provides the greatest opportunity for dilation/cannulation without undue vascular injury. The length of guidewire inserted will be dependent on whether a standard dual-lumen catheter or a bicaval dual-lumen catheter is used. Once the guidewire is in proper position, dilators are used to serially expand the tract. The catheter is advanced into proper position utilizing the percutaneous introducer. This is typically completed under fluoroscopic guidance. During advancement of the catheter, it is imperative that the guidewire maintains correct position and that the introducer and

cannula move together as a single unit. Wire migration during insertion can lead to cardiac/vascular injury. Once the catheter is in correct position, the introducer is removed. Cannulas are then back-bled/flushed to remove air and finally connected to the ECMO circuit.

- Percutaneous placement of a VVDL typically starts with accessing the RIJ under ultrasound guidance. If desired, a small-gauge needle (e.g., 21 gauge), that will accommodate a 0.018-inch guidewire can be used to first access the RIJ. The wire is then advanced though this needle. Once ultrasound guidance confirms the guidewire extends to the level of the right atrium, a small access sheath can be used to exchange the 0.018-inch guidewire to a 0.035-inch guidewire. The percutaneous technique then follows the same steps as the semiopen technique once the 0.035-inch guidewire has been properly placed. Percutaneous cannulation (either V-V or rarely V-A) requires experience with ECMO cannulation, endovascular techniques, and management of their associated complications. Therefore, it should only be considered by those practitioners facile in both fields.[13–15]

The standard double-lumen catheter (e.g., OriGen Reinforced Dual Lumen VV Catheter, Origen Biomedical, Austin, TX) is designed so that the tip of the cannula is the inflow/arterial port, and side ports serve as the outflow/venous ports. Ideally, the tip of the cannula is within the right atrium and projects toward but does not cross the tricuspid valve. The venous ports should be at the junction of the SVC/IVC/atrium. The smallest standard double-lumen cannula is typically a 13F cannula (Figure 3.2).

Procedural steps unique to the standard double-lumen catheter include the following[3,6,11,13,16]:

- The 0.035-inch guidewire is advanced under fluoroscopic guidance to the right atrium.
- Serial dilators are used to dilate the tract to the size of the cannula.
- The catheter is then advanced so that the tip is within the right atrium; this is typically 1.5–2 vertebral bodies below the carina on x-ray (which can be measured preprocedure) or intraoperatively with fluoroscopy. This distance is typically 6–8 cm from the venotomy site in the neonate. The guidewire tip must stay within the atrium during placement to ensure the cannula tip does not migrate into the IVC.
- The cannula is then secured to the skin after establishing good ECMO flow, and completion imaging is typically obtained for reference. The neck incision, if a hybrid technique is used, is then closed. A completion echocardiogram is utilized at the ECMO team's discretion.

The double-lumen bicaval catheter (e.g., Avalon Elite, Getinge Group, Gothenburg, Sweden) is designed with two separate sets of ports for venous blood return; these are situated between a side port that serves as the arterial inflow. Proper

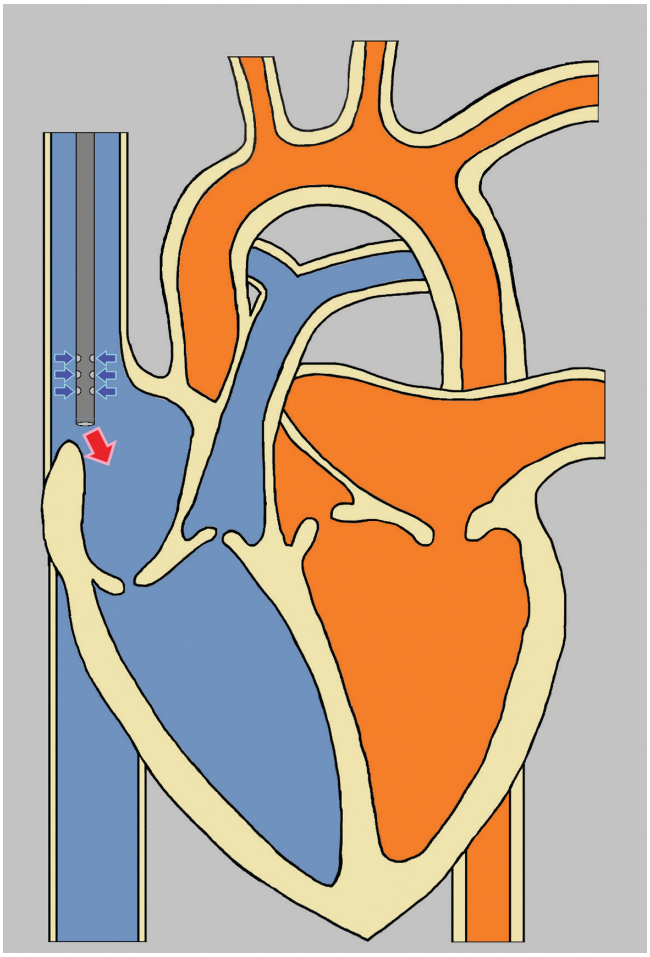


Figure 3.2 Cannula position for cervical VVDL ECMO [i.e., (ca) V-V ECMO].

cannula placement dictates that the distal end of the cannula is positioned in the suprarenal IVC, the proximal ports within the SVC, and the arterial port is oriented in the right atrium such that the outflow projects toward the tricuspid valve. Procedural steps unique to the bicaval double-lumen catheter include the following[3,6,8,9,13,15,17,18] (Figure 3.3):

- The bicaval design requires the guidewire and cannula to be placed across the junction of the right atrium and vena cava, thus placing the right heart at risk for injury/perforation during placement. The tip of the catheter must reside within the IVC and not enter the ostia of the hepatic veins. In neonates and infants, this target area is short. Therefore, most institutions complete both wire and catheter advancement under fluoroscopic guidance. Combined fluoroscopy and echocardiography has been proposed to reduce complication rates (i.e., cardiac injury) and improve positioning in percutaneously placed bicaval catheters.[13,15]
- Under fluoroscopy, the guidewire can be monitored as it passes the right atrium and is advanced below the confluence of the hepatic veins in the IVC. Ensuring the wire does not enter the hepatic veins can be enhanced with

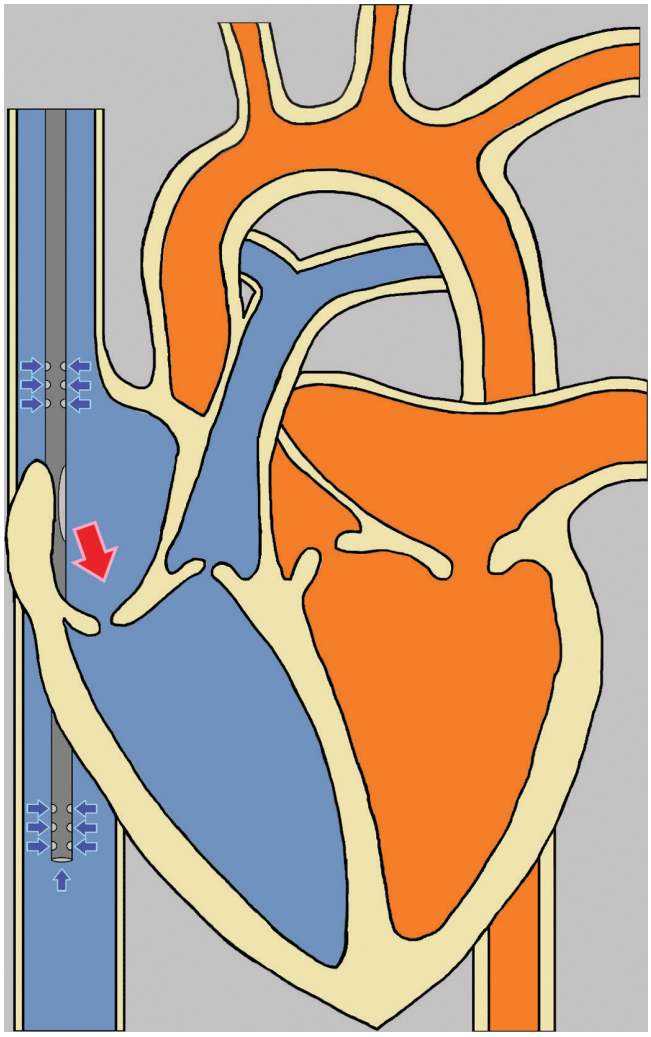


Figure 3.3 Cannula position for cervical bicaval VVDL ECMO.

concomitant echocardiography. Ideally, the tip of the guidewire is placed at least to the level of the renal veins.

- After dilating the tract, the cannula is then advanced under sonographic guidance to ensure the tip resides within the IVC and the outflow jet at the level of the atrium and oriented toward the tricuspid valve. The return (outflow/venous) limb of the catheter should be anteromedial to the outflow limb when securing it to the patient's head/neck to ensure proper orientation of the outflow jet at completion of the procedure when placed in the RIJ. Echocardiography is useful to ensure the outflow jet is oriented correctly and the tip of the catheter is not within the hepatic veins. A postprocedural chest x-ray is typically obtained for reference.

STEM CASE 2 AND KEY QUESTIONS

A previously healthy 10-year-old male presents to the emergency department with 8 days of constitutional symptoms and 1 day of progressive cough. Noting hypoxia, hypotension, and tachycardia on initial vitals, he is placed on supplemental oxygen and given an intravenous fluid bolus, which does not improve his hemodynamic status. An initial chest x-ray shows mild diffuse infiltrates in both lung fields with a significantly enlarged cardiac silhouette. After transfer to the pediatric intensive care unit, laboratory workup shows elevation in C-reactive protein, erythrocyte sedimentation rate, liver function tests, and brain natriuretic peptide. An echocardiogram reveals marked reduction in cardiac function with an ejection fraction of 40%. Viral testing proves to be positive for coxsackie virus. Despite increasing ventilatory and inotrope/vasopressor administration, the patient has worsening respiratory distress. The ECMO team then elects to urgently place him on V-A ECMO on hospital day 2. The right femoral vein and the left femoral artery are used for cannulation. A 5F distal perfusion catheter (DPC) is also placed in the left superficial femoral artery (SFA). The patient's hemodynamic status subsequently improves. Four days later, the ECMO perfusionist notices that the patient's upper extremities are showing signs of hypoxia (i.e., are pale/cyanotic), and the lower extremities are hyperemic. The patient is diagnosed with differential hypoxemia, and a repeat echocardiogram reveals improvement in cardiac function. However, the patient continues to have respiratory failure. At this time, a venous cannula is placed into the RIJ vein and is used in combination with the femoral arterial catheter to provide oxygenated blood to the patient. The differential hypoxemia resolves, and he is transitioned to V-V ECMO via the venous cannulas, at which time the arterial cannula and DPCs are removed. The patient requires an additional 4 days of V-V ECMO support, at which time he is decannulated and placed back on conventional ventilation.

WHAT ARE COMMON CANNULATION TECHNIQUES FOR FEMORAL V-A ECMO IN A PEDIATRIC PATIENT?

Both central and peripheral ECMO can be completed for cardiopulmonary support in a patient with cardiogenic shock, and ventricular assist devices have a growing role for long-term cardiac support,[6,19–21] Rajagopal et al. reported a 61% survival rate among patients undergoing ECMO reported to the Extracorporeal Life Support Organization (ELSO) Registry.[20] However, in the setting of emergent cardiopulmonary support, peripheral ECMO is typically the most feasible. In the older child, this is best completed through a femoral approach, but smaller children with cardiogenic shock can undergo V-A ECMO cannulation through the neck as previously described.[22,23] In a mixed cohort of children undergoing extracorporeal cardiopulmonary resuscitation, including those with cardiac failure as their primary pathology, Thiagarajan reported no difference in survival for central versus peripheral cannulation.[24] This would suggest that peripheral ECMO is acceptable when cannulation is completed under less dire circumstances.

Femoral ECMO cannulation can be completed in an open, semiopen, or percutaneous technique. Similar to cervical cannulation, ultrasound is useful for surgical planning and mandatory when completing the percutaneous technique. After determining candidacy for ECMO and deciding the femoral vessels will be used for ECMO, the chest, abdomen, and lower

extremities are prepped into the operative field. Most often, the arterial cannula is placed via the left common femoral artery (CFA), and the venous cannula is placed in the right common femoral vein. This configuration theoretically gives the straightest path to the central vasculature. Additionally, the left iliac vein is crossed by the right iliac artery, which may impede cannula advancement if the left femoral vein is used. Placing both cannulas in the same leg is considered by many to put the lower extremity at risk for complete vascular obstruction, but combined ipsilateral cannula placement has been used in both the pediatric and adult populations.[25,26] The open approach involves the following steps[25–30]:

- A longitudinal skin incision is made over the femoral artery just below the inguinal ligament; dissection is completed with electrocautery through the subcutaneous tissues, and then bluntly once approaching the femoral vessels. The incision must be long enough to adequately visualize the CFA as well as the origin of the SFA and the deep femoral artery (DFA).
- Once the CFA is encountered, its size is noted for proper arterial cannula size. The proximal SFA and DFA are identified. The CFA is then encircled proximally (just distal to the inguinal ligament) and distally (just proximal to the SFA/DFA), with vessel loops or heavy silk suture for vascular control. The common femoral vein is similarly isolated.
- A purse-string suture (typically 5-0 Prolene®) can be placed on the anterior surface of the CFA at the proposed arteriotomy site, but this is at the surgeon's preference. A skin stab incision is then made distal but in line with the larger skin incision to tunnel the cannula if desired.
- The patient is then systemically heparinized as previously described.
- The blunt introducer is inserted in the arterial cannula, and both are lubricated. If a subcutaneous tunnel was made, the cannula is advanced through this tunnel.
- Proximal and distal vascular clamping is completed with the vessel loops, and a longitudinal arteriotomy is made in the middle of the purse string.
- The cannula is then advanced to the appropriate length, and the purse-string suture is tied to prevent bleeding; the introducer is then removed; and the cannula is then back-bled/flushed, clamped, and prepared to be placed on circuit. Of note, care must be taken as the cannulas are advanced past the level of the pelvic brim. The curvature of the iliac vessels at this point predisposes them to injury. Preoperative placement of a bump beneath the pelvis will straighten this angle of approach and allow easier passage of the cannula.
- The groin incision is then closed in layers, and the cannulas are secured to the skin at several positions.
- The venous cannula is placed in a similar manner, but placing the purse-string suture on the femoral vein is not required.
- A technique utilizing a vascular graft to create an end-to-side anastomosis with the femoral vessels and then attaching the cannulas to the graft has also been described. This is typically completed in nonemergent settings in ECMO for postsurgical cardiac patients and precludes the need for a DPC.

If a percutaneous approach is planned, the preoperative planning remains the same. However, it should be noted that vessel caliber is determined based on sonography using this technique. Correct cannula sizing based on images can determine success of the percutaneous approach. The percutaneous technique involves the following steps[25–30]:

- The patient is prepared in a similar manner to the open technique, with a sterile ultrasound probe included in the field. A bump is placed beneath the pelvis to extend the hips and improve the angle of approach. The inguinal ligament is identified externally. Using this landmark, the CFA, SFA/DFA are identified with ultrasound.
- The cannula is then placed using a Seldinger technique, ensuring the needle accesses the CFA. If the SFA is accidently accessed, this may result in vessel rupture with dilation of the tract or cannula insertion. Conversely, if the inguinal portion of the external iliac artery is accidently accessed, this may result in unrecognized retroperitoneal bleeding. Much like percutaneous access in the neck, the needle should enter the vessel on the anterior surface in the center of the vessel. A long, 0.035-inch guidewire is advanced through the needle to ensure vessel access is maintained while the long femoral cannulas are placed. The patient is then heparinized.
- For the arterial cannula, the guidewire should be advanced to the upper abdominal aorta. For the venous cannula, the guidewire should ideally extend to the level of the SVC. Dilators are used to serially expand the tract, and a purse-string suture is place in the skin to be tied down after final cannula placement. The catheter is advanced into proper position utilizing the percutaneous introducer. Once in proper position the introducer is removed, and the purse-string suture is tied. The cannula is back-bled/flushed to remove air, clamped, and finally connected to the ECMO circuit.
- The venous cannula is placed in a similar manner.
- The semiopen technique follows the steps of the open procedure through placing the purse-string suture; afterward it follows the percutaneous technique (i.e., Seldinger technique).

Placement of the tip of the arterial cannula should be within the proximal common iliac artery to allow for retrograde flow into the aorta. Placement of the cannula into the distal aorta may obstruct the contralateral iliac artery and compromise blood supply to the pelvis and opposite extremity. The ideal location of the tip of the venous cannula is less defined.

Proposed locations have been in the IVC, at the level of the RA, and even the SVC.[25,28–30] Clinically, the ideal location is that which can be obtained/maintained and provides adequate venous return to the ECMO circuit. In our experience, the venous cannula is typically placed in the IVC.

Catheter advancement can be completed with or without image guidance. When available, real-time fluoroscopy and/or ultrasound can ensure proper location of the cannulas/guidewires and prevent complications. If real-time imaging is not available or not feasible, preprocedural x-rays can assist in measuring lengths that cannulas should be advanced. The aortic bifurcation is typically at the level of the fourth lumbar vertebra on x-ray. The sternal angle is typically 1–3 cm (depending on patient size) above the atriocaval junction both radiographically and externally. The costal margin approximates the infra-/intrahepatic IVC, and the cephalad extent of the diaphragm corresponds to the suprahepatic IVC on x-ray. At minimum, postprocedural x-rays should be obtained for conformation of location and surveillance.

Patients in cardiogenic shock/heart failure are at risk for developing left ventricular overload due to the weak heart's inability to open the aortic valve against retrograde blood flow from the ECMO circuit. This can lead to thrombus formation in the ventricle and aortic root.[31,32] In the setting of central ECMO cannulation, a venting catheter can be placed prophylactically to prevent this.[6,31] However, in peripheral ECMO cannulation, this is not easily accomplished. Surveillance for ventricular overdistention is mandatory and may require intervention in the form of a catheter-based atrial septostomy/superior pulmonary artery catheter or ventricular apex vent.[6,31]

WHAT IS THE ROLE FOR DISTAL PERFUSION CATHETERS IN THE SETTING OF FEMORAL ARTERY ECMO CANNULATION?

Cannulation of the femoral artery places the associated limb at risk for ischemic complications, including those related to low-flow states and thrombotic, and embolic phenomenon.[25,27,32–34] Rates of these complications are reported to be 10% in the adult population but have been reported as high as 52% in the pediatric patients.[27,33,34] One potential solution to these issues is placement of a DPC. These catheters are most often placed in the SFA ipsilateral to the femoral arterial cannula and supply antegrade blood flow to the extremity at risk.[25,27,34] Another common strategy is to place a catheter in the posterior tibial artery to supply blood in a retrograde manner, but this technique is not feasible in smaller pediatric patients.[27] Both strategies can be completed in an open or percutaneous technique with the catheter linked to the arterial inflow from the ECMO circuit.

While a DPC theoretically should eliminate these ischemic complications, the reality is that they still occur.[27,33,34] Previous work completed by Gander et al. was unable to identify clinical factors that predisposed patients to these complications.[33] Schad et al. subsequently reviewed their practice changes in DPC placement, with the historical group undergoing selective DPC placement when signs of ischemia developed versus the prophylactic group, where all patients underwent DPC placement.[34] All patients that had a prophylactic anterograde SFA cannula placed (4–7F sheath) preferentially underwent percutaneous placement. Among historical controls, seven of 14 patients developed limb ischemia, six had subsequent DPC placement, and the additional patient required an amputation. Three patients with selective DPC placement required fasciotomy for compartment syndrome. One required a five-toe amputation. Two of 17 patients in the prophylactic group required fasciotomy, one was associated with DPC thrombosis, and the other required an above-knee amputation. Three additional DPCs in the prophylactic group suffered from catheter thrombosis but were cleared without event. While not statistically significant, the authors reported a decreased need for intervention and improved limb salvage in the prophylactic group and recommended their use.[34] In summary, a DPC appears to reduce but does not prevent extremity-threatening complications associated with femoral artery cannulation for pediatric ECMO, especially if it is placed before ischemic complications begin.[27,34]

WHAT IS DIFFERENTIAL HYPOXEMIA (I.E., HARLEQUIN SYNDROME) AND HOW IS IT TREATED?

Harlequin syndrome is a phenomenon typically seen in femoral V-A ECMO where cardiac function improves before pulmonary function. This occurs when native blood flow from the heart is supplying relatively low-oxygenated blood to the upper portion of the body while ECMO support provides oxygenated blood to the lower body.[26,28,32] Clinically, this manifests as pale/cyanotic skin in the upper extremities with hyperemic torso/lower extremities, with the level of demarcation determined by the site in the aorta at which the two sources of blood flow mix.[28] More importantly, it signals that the cerebral vasculature and the myocardium are receiving oxygen-depleted blood.[26,28,32] This should be monitored with a physical examination and maintaining separate pulse oximeters on the right upper extremity and a lower extremity is helpful. However, harlequin syndrome should be considered when an at-risk patient begins showing signs of cardiac recovery and then develops cardiac instability.[26] Typical treatment is conversion of V-A ECMO to veno-arterial-venous ECMO (V-AV ECMO). This involves placing another venous cannula in the RIJ and using it as a secondary supply of arterial blood inflow.[26,28,32] The RIJ cannula then provides oxygenated blood to the heart and aortic arch. Blood flow from the femoral arterial cannula is then weaned, the femoral arterial cannula is removed, and the patient is converted to V-V ECMO in a two-cannula configuration. The rate of weaning from V-AV ECMO to V-V ECMO will be determined by the patient's hemodynamic status.

STEM CASE 3 AND KEY QUESTIONS

A previously healthy 2 year-old male presents to the emergency department with 4 days of fever and cough and a day of worsening work of breathing. An initial x-ray shows diffuse

infiltrates bilaterally, and the initial laboratory workup is significant for leukocytosis. After transfer to the pediatric intensive care unit, initial trials of noninvasive ventilation fail, and he requires endotracheal intubation. His viral testing subsequently has positive results for influenza A. After 5 days on the ventilator, he is noted to have worsening oxygenation, increased fevers, and increased opacity in the right lower lobe on chest x-ray. Sputum culture reveals *Staphylococcus aureus*, and he becomes hypotensive. His hypotension is minimally responsive to multiple fluid boluses, and he requires low-dose dopamine for hemodynamic support. His blood pressure then normalizes. Despite appropriate antibiotic administration, his oxygen index worsens to 45. The ECMO team then decides to place him on V-V ECMO. A VVDL cannula is then placed under fluoroscopic guidance [i.e., (dl)V-V ECMO]. He is weaned off dopamine within 12 hours of ECMO initiation and is successfully decannulated after 5 days of ECMO support.

WHAT ARE THE CONSIDERATIONS FOR ECMO CANNULATION IN A PATIENT WITH SEPSIS/SEPTIC SHOCK?

Use of ECMO for the treatment of patients with sepsis/septic shock is highly complex and requires careful consideration of the patient's condition. Ideal cannulation configuration will be based on the patient's specific needs. While historically sepsis was considered a contraindication, single-institution reviews of use of ECMO for sepsis in the 1990s revolutionized its use in the last two decades.[35,36] Consensus guidelines by the Surviving Sepsis Campaign and the American College of Critical Care Medicine recommend consideration of ECMO in experienced centers for refractory septic shock.[37,38]

Once ECMO is considered for a patient with sepsis, the patient's cardiopulmonary support requirements must be determined, specifically whether ECMO is primarily for pulmonary support or cardiac/hemodynamic support. In patients with minimal vasopressor requirements, V-V ECMO can be considered. In 2012, Smalley et al. reported a trend toward improved survival (n = 14/17 [82.4%] vs. n = 22/35 [62.9%]; p = .15) in refractory pneumonia when V-V ECMO was used compared to central V-A ECMO.[39] It was noted within this cohort that those placed on V-V ECMO had less inotropic/vasopressor requirements compared to V-A ECMO and had less bleeding/neurologic complications.[39] That same year, Skinner et al. reported a review of the ELSO Registry comparing outcome of pediatric patients undergoing V-V versus V-A ECMO for noncardiac sepsis and also reported improved survival (79% vs. 64%; p = .02) when controlling for age and vasoactive agent usage.[40] The authors recognized that the ELSO Registry does not quantify the level of vasoactive agent support, and that older pediatric patients are more likely to develop catecholamine-resistant, or "vasoplegic," shock, which cannot always be hemodynamically supported on V-V ECMO.[40-43] Thus, the V-A ECMO cohort in their study may be more critically ill. However, it is now understood that native cardiac output is often the source for coronary arterial blood flow while on ECMO.[40,44–46] Improved oxygenation of the coronary vasculature may improve cardiac function in the setting of V-V ECMO, thus reducing inotropic requirements.[40,44–46] This enhancement in cardiac support is often adequate in patients with minimal vasoactive agent needs.

In 2007, MacLaren et al. initially reported their use of V-A ECMO in refractory septic shock.[42] Patients were cannulated either peripherally or centrally (i.e., transthoracic atrioaortic cannulation) with initial target ECMO flows of 150 mL/kg/h or greater in children less than 10 kg and greater than 2.4 L/min/m^2 in children greater than 10 kg.[42] Overall survival was 47% (n = 21/45).[42] Among the 11 patients who underwent central cannulation, eight survived.[42] Central versus peripheral V-A ECMO was the only statistically significant difference in survivors versus nonsurvivors.[42] The same group then presented additional work in 2011 reviewing use of central cannulation in a nonneonatal pediatric refractory septic shock population with multisystem organ failure.[41] In both reports, more than one-third of the patients were in cardiac arrest immediately prior to ECMO cannulation.[41,42] They reported 74% (n = 17/23) survived to discharge.[41] The authors cited an ability to rapidly reverse hypoxia and correction of multisystem organ failure with high ECMO flows as a possible source of this improved survival.[41] It should be noted that among patients undergoing central V-A ECMO, 30% developed bleeding complications from the sternotomy site that required reexploration.[41]

Oberender et al. recently reported a multicenter retrospective cohort study reviewing optimal treatment of nonneonatal/noncardiac patients with severe septic shock.[43] Among the 164 patients who met inclusion criteria, 120 received conventional therapy and had a survival rate of 40%; survival was 50% for the 44 patients who underwent V-A ECMO (p = .25). Subgroup analysis revealed a survival benefit for only those patients on V-A ECMO where flows were 150 mL/kg/min or greater (n = 11) compared to lower ECMO support or conventional therapy.[41] Cannulation technique (i.e., peripheral vs. central V-A ECMO) was not specified in the study.

Similarly, Soléet al. recently reported an overall 33.3% (n = 7/21) survival rate with V-A ECMO using peripheral cannulation for septic shock in a mixed neonatal/pediatric population.[47] Patients were supported with goal flow rates of 150 mL/kg/min or greater. Neonatal survival was 50% (n = 6/12), and survival for nonstreptococcal pneumonia indications was 60%. The authors concluded that V-A ECMO is a reasonable option for hemodynamic support in this population, but streptococcal pneumonia with resultant refractory shock may portend a poor outcome.[47]

While ECMO for septic indications appears to have similar survival outcomes to other indications, it is resource/cost intensive when compared to conventional therapy.[48] The method of provided support as well the nature of cannulation must be patient specific. In the setting of primary pulmonary support, V-V ECMO appears feasible. However, when hemodynamic support is necessary, current data suggest that V-A ECMO with high-flow capacity is most beneficial. Whether or not this is achieved through central or peripheral cannulation will be based on local experience and resources.

DISCUSSION

Utilization of ECMO in the neonate with respiratory distress was first proven feasible by Dr. Robert Bartlett in 1975, and his group was the first to publish a randomized study in 1985 to prove its benefit.[49] With this success, ECMO was then proven to be beneficial in children with persistent pulmonary hypertension.[50] These initial experiences provided the foundation on which current pediatric ECMO practice is based, with survival rates for neonates with respiratory distress typically cited above 80%, not including patients with congenital diaphragmatic hernia.[7,51,52]

The main considerations in neonates center on the use of either V-A or V-V ECMO. In the setting of severe sepsis, V-A ECMO seems most appropriate. In the setting of respiratory failure, V-V ECMO may have several benefits. Utilization of V-V ECMO forgoes use of an arterial catheter, and this has several implications. The patient is not at risk for systemic arterial embolic phenomenon. Nonpulsatile blood flow from V-A ECMO may increase the risk for intracerebral hemorrhage (ICH).[46,53] As previously mentioned, V-V ECMO also increases oxygen delivery to the coronary arteries, unlike V-A ECMO. Consequences of carotid artery ligation are still a matter of debate. Teele et al. reported 23% of pediatric/neonatal patients in an ELSO Registry sample who underwent carotid cannulation suffered neurologic consequences (e.g., seizures, infarction, hemorrhage).[54] This was an independent risk factor for these complications.[54] However, Johnson et al. recently reported from the same registry that when adjusting for other factors, such as disease process, carotid cannulation did not result in higher neurologic complications.[55]

Recognizing these potential complications related to V-A ECMO, V-V ECMO has been shown to be safe and feasible in children with respiratory failure. This includes neonates with higher inotrope requirements.[7,51] Similar results in the pediatric population have also been reported by Pettignano et al.[56]

Use of CD is also a matter of debate. Once thought to protect the patient from intracerebral hemorrhage, this concept has been contested.[57] Skarsgard et al. reviewed the ELSO Registry from 1989 to 2001 and compared VVDL cannulation to VVDL with CD and found no difference in flow rates, survival, or neurologic complications.[57] However, Roberts et al. reported improved survival, reduced inotrope requirements, and improved rates of ICH when comparing their use of VVDL with CD ECMO against the ELSO Registry.[7] Of note, Pettignano et al. also used CD in their previously discussed study.[56]

When placing the nonneonate on V-A ECMO, the pros and cons of femoral versus cervical cannulation must be made. There is no consensus regarding optimal patient age or size to transition from cervical cannulation (i.e., in a "younger patient") to femoral. Garcia et al. reported a survey of the American Pediatric Surgical Association (APSA) regarding cannulation practices.[23] Of the respondents, 88.1% reported that in their institutions, pediatric general surgeons performed V-A ECMO cannulations on all children, and only 41.5% would consider femoral cannulation in children 12 years of age and younger. Further, less than half of respondents considered femoral cannulation in teenagers. Common barriers to using femoral cannulation included the need for DPC, lack of training, and the belief that the femoral vessels are too small to support ECMO flow.[23] Recognizing these barriers, it is vital to adhere to the principle of using the smallest cannula feasible to obtain the desired flow rates in any scenario as this reduces the risk for vascular injury and obstruction/thrombosis.[27]

Finally, there is wide variability in the use of imaging during cannulation. While single institutions have reported the benefit of echocardiography and/or fluoroscopy in both V-A ECMO and VVDL cannulation, these practices have not been universally adopted.[4,9,15,16] Utilization of real-time imaging is of paramount importance when using VVDL cannulas, particularly bicaval cannulas. Drucker et al. recently reported another APSA survey where 20% of respondents using VVDL did so without any image guidance. The authors concluded that given the risks of this procedure, real-time imaging should be considered the standard of care.[15,16,18,22]

CONCLUSION

- ECMO is a well-established means to provide cardiopulmonary support in the neonatal/pediatric populations with select diagnoses, including respiratory failure, acute cardiac failure, and septic shock.
- Given the variability of patient size, diagnoses, and cardiopulmonary support requirements, various ECMO cannulation/configurations exist, and each must be considered on a patient-by-patient basis. These factors along with institutional resources and physician familiarity should determine the ECMO configuration used for each individual patient.
- A patient's clinical condition is always changing; therefore, ECMO support must also be considered dynamic. Cannulas may have to be added, repositioned, or reconfigured to respond to the patient's changing needs. The configurations described above represent the most common, but not all, ways ECMO can be used in the pediatric population.

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REVIEW QUESTIONS

1. A 3.5-kg patient with congenital right-sided diaphragmatic hernia is placed on V-V ECMO via a right 13F internal jugular vein with a double lumen cannula. After changing to rest ventilator settings, the tidal volumes are less than 4 mL/kg. On 120 mL/kg/min of ECMO flow, patient saturations fall and are in the 55%–60% range, with negative venous limb pressures, a premembrane saturation of 40%, and increasing lactic acidosis. What is the next appropriate step in management?

   A. Diuretics to reduce intravascular volume and pulmonary edema
   B. Place an additional drainage cannula in the RIJ in the cephalad direction
   C. Increase ECMO flow to 170 mL/kg/min
   D. Increase ventilator settings to target a peak inspiratory pressure of 40 and a tidal volume of 10 mL/kg

2. A 10-year-old patient with myocarditis is cannulated emergently onto V-A ECMO through the left femoral artery and right femoral vein. About 36 hours after cannulation, a trend of dropping cerebral near-infrared spectroscopy is noted. The patient's premembrane saturation is 65% with pulse oximetry on his right toe of 99%. Blood pressure is normal for age in the right arm. What is the next appropriate diagnostic step?

   A. Obtain four extremity pulse oximetry values
   B. Reduce sedation to improve cerebral saturations
   C. Ultrasound of cannulas to determine position
   D. Computed tomographic scan of head to evaluate for intracranial hemorrhage

3. A 14-year-old with septic shock from meningococcus presents with widespread petechiae, metabolic acidosis, thrombocytopenia, and severe left ventricular depression on echocardiography. Extremities are cold to touch on an epinephrine infusion of 0.6 μg/kg/min. The decision is made to place him on ECMO. Which cannulation strategy would be least appropriate?

   A. Veno-venous ECMO with a RIJ drain, returning to the right femoral vein
   B. Veno-arterial ECMO with RIJ and right femoral drains, returning to the right carotid artery
   C. Veno-arterial ECMO with bilateral femoral vein drains and right femoral artery return
   D. Veno-arterial ECMO via a central approach, with direct cannulation of the right atrial appendage and the aorta

ANSWERS

1. B. Inadequate oxygen delivery is the underlying physiologic principle in this case. Placement of an additional drainage cannula, in this case, an RIJ cephalad cannula will give additional volume to the ECMO circuit of deoxygenated blood [i.e., (dl)Vcep-V ECMO]. This should help improve the negative drainage pressures, allowing you to increase flow rates to 150 mL/kg/min, which is usually considered maximum

flow for V-V ECMO. Additionally, this provides a method of reducing recirculation, and improving effective oxygen delivery, by providing a source of venous drainage that is not subject to recirculation. Both of these effects would be expected to lead to a rise in patient saturations. While placement of an additional drainage cannula in the femoral vessels or conversion to V-A ECMO would be possibilities, they involve the manipulation of additional vascular structures and likely could be avoided.

2. A. This patient likely has differential hypoxemia syndrome based on good lower body saturations but with a reduction in upper body saturations as demonstrated by the near-infrared spectroscopy. Obtaining pulse oximetry values in all four extremities provides a very rapid and simple bedside diagnostic test that can guide the need for echocardiography to confirm the improved cardiac function leading to this phenomenon. The cannulation strategy needs to be assessed based on the echocardiology results, with potential change to either V-V or V-AV ECMO.

3. A. This patient's septic shock has a large component of cardiac failure that would necessitate a V-A ECMO approach. As discussed in the text, the optimal veno-arterial cannulation strategy in this scenario has not been determined. While V-V ECMO has been used successfully in septic shock, the severity of the cardiac dysfunction described in this case argues against its use.

4.

ECMO CONFIGURATIONS AND CANNULATION IN ADULT PATIENTS

Amit Prasad and Kai Singbartl

STEM CASE AND KEY QUESTIONS

A 52-year-old, 85-kg male comes into the emergency department with a 1-week history of cough and generalized malaise. Pulse oximetry (SpO_2) on 6 L nasal cannula is 80%, and his blood pressure (BP) is 76/32 mm Hg with a heart rate (HR) 125 beats/min. He receives 2 L of isotonic saline, increasing his BP to 86/45 mm Hg and decreasing his HR to 115 beats/min, but he becomes more dyspneic. He fails noninvasive positive pressure ventilation and requires intubation. In the intensive care unit, he receives an additional 3 L of intravenous fluids and is started on norepinephrine, rapidly escalating to 0.1 μg/kg/min. His BP increases to 102/62 mm Hg, and HR continues to be elevated at 120 beats/min. His ventilator settings are pressure control at 38 cm H_2O, positive end-expiratory pressure 15 cm H_2O, and fraction of inspired oxygen (FiO_2) 1.0, obtaining a tidal volume of 300 mL. His arterial blood gas is pH 7.19, PO_2 62 mm Hg, PCO_2 48 mm Hg, HCO_3^- 19.3 mM, and lactate 7.6 mM. Chest x-ray reveals a complete whiteout of both lungs consistent with a diagnosis of acute respiratory distress syndrome (ARDS). The norepinephrine is increased to 0.4 μg/kg/min to keep his MAP greater than 65 mm Hg, and he receives an additional 2 L of intravenous fluid. The extracorporeal membrane oxygenation (ECMO) team is consulted for further management advice.

WHAT OTHER TESTS WOULD YOU WANT ON THIS PATIENT?

A transthoracic echocardiogram (TTE) is indicated as the patient's cardiac function is unknown. The patient requires a high dose of norepinephrine for presumed septic shock, but cardiac dysfunction has not been ruled out. The TTE showed reduced biventricular function with biatrial dilation.

IS THE PATIENT A CANDIDATE FOR ECLS AND WHAT IS THE BEST CANNULATION STRATEGY FOR ECLS?

After discussion with the team, it was decided to pursue extracorporeal respiratory support, that is, veno-venous (V-V) ECMO.

In general, there are two cannulation approaches for V-V ECMO: dual-lumen, single catheter placed via the internal jugular vein (IJV; discussed elsewhere in this book) or a bicaval approach with a drainage cannula placed into the inferior vena cava (IVC) via the femoral vein and a return cannula placed via the right IJV into the superior vena cava (SVC). The advantage of the bicaval approach is the greater flow rates (6–8 L/min) when compared to the single-catheter approach (around 5 L/min). Furthermore, the bicaval approach gives one the ability to quickly transition from V-V ECMO to veno-arterial (V-A) ECMO in case of hemodynamic decompensation.

Whereas the bicaval approach does not require image guidance, the single-catheter technique greatly depends on image guidance (e.g., fluoroscopy and/or transesophageal echocardiography [TEE]) for correct cannula position. Correct cannula position is critical for effective single-cannula V-V ECMO treatment as the drainage port must be in the IVC, and the return port must be directed toward the tricuspid valve.

Here, the patient is now placed on bicaval V-V ECMO (Figure 4.1). A 25 French (25F) drainage cannula is placed into the right femoral vein. A 17F return cannula is placed into the right internal jugular. Both cannulas have good blood flow. Initial V-V ECMO settings are as follows: pump flow of 4.0 L/min at 4200 RPM, FiO_2 1.0, and a sweep of 5 L/min.

However, the patient's hemodynamic status deteriorates with a mean arterial pressure (MAP) falling to less than 40 mm Hg and new onset of wide-complex ventricular tachycardia.

WHY DID THIS PATIENT BECOME HEMODYNAMICALLY UNSTABLE?

A "normal" BP in the setting of high doses of norepinephrine likely masked severe hemodynamic compromise. After commencement of V-V ECMO, the sudden increase in blood flow to the right heart can precipitate acute right ventricular failure, in particular in the setting of preexisting right heart insufficiency. The subsequent drop in cardiac output and hypotension can lead to coronary hypoperfusion with potentially lethal arrhythmias.

A stat TTE revealed a severely dilated right ventricle and collapsed left ventricle (LV) with global biventricular hypokinesis. The patient is defibrillated three times and received intravenous epinephrine. His arrhythmia resolves, but he remains hypotensive (MAP< 45 mmHg) and tachycardic (sinus tachycardia at 135/min).

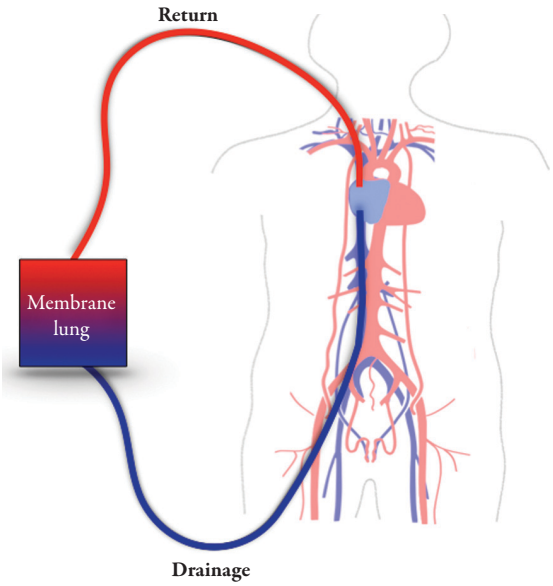


Figure 4.1 Conventional V-V ECMO configuration. A multistage cannula is placed in the right femoral vein (tip at or below IVC/RA [right atrium] junction) to drain blood into the ECMO circuit. A membrane lung provides oxygenation and CO_2 removal. The blood is then pumped and returned back to the patient through a cannula in the right internal jugular vein (IJV; tip at or above SVC/RA junction).

WHAT IS THE NEXT STEP?

As the patient remains in cardiogenic shock despite rapidly escalated pharmacological support, initiation of mechanical circulatory support is indicated. V-A ECMO can provide (emergency) hemodynamic support by replacing cardiac output and uncoupling arterial blood flow and perfusion pressure from the underlying cardiac function (Figure 4.2). Here, a 17F arterial cannula is placed into the right femoral artery, while the two venous cannulas are connected by a Y connector, draining blood into the ECMO circuit, and the patient is transitioned from peripheral V-V ECMO to peripheral veno-veno-arterial (VV-A) ECMO (Figure 4.3). After initiation of VV-A ECMO, the MAP increases to 70 mmHg.

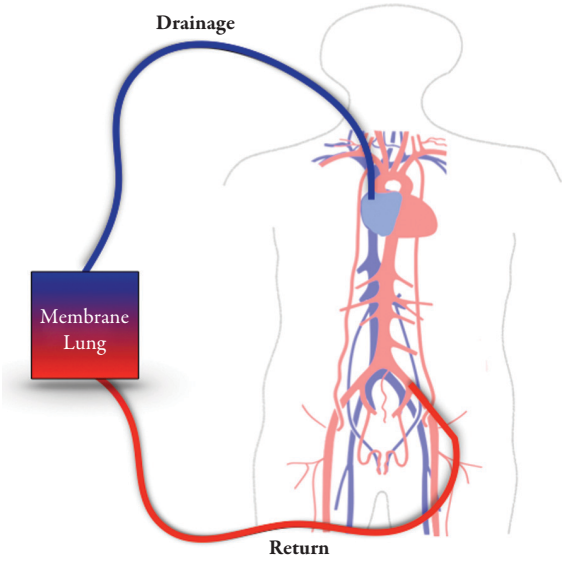


Figure 4.2 Conventional V-A ECMO configuration. A multistage cannula is placed in the right femoral vein (tip at or below IVC/RA junction) to drain blood into the ECMO circuit. A membrane lung provides oxygenation and CO_2 removal. The blood is then pumped and returned back to the patient through a cannula in the left femoral artery (tip in iliac artery).

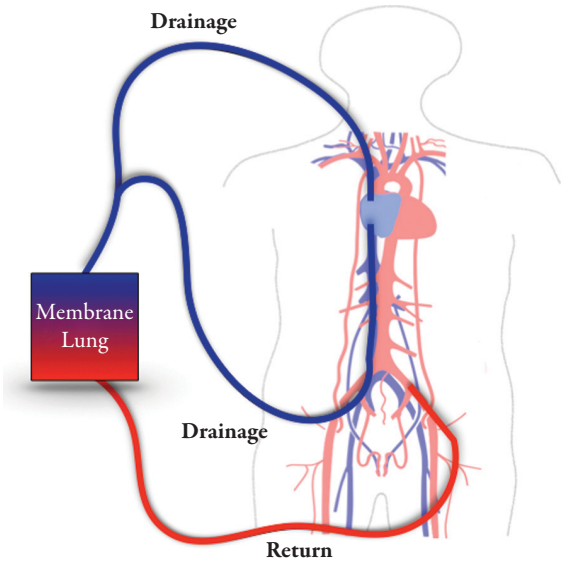


Figure 4.3 VV-A ECMO configuration.

A multistage cannula is placed in the right femoral vein (tip at or below IVC/RA junction) to drain blood into the ECMO circuit. A second cannula is placed the right IJV, also draining blood into the ECMO circuit. This configuration is usually seen in cases of pulmonary volume overload (ventricular septal defect, VSD) or after conversion of V-V ECMO into V-A ECMO for hemodynamic instability. The membrane lung provides oxygenation and CO_2 removal. The blood is then pumped and returned back to the patient through a cannula in the left femoral artery (tip in iliac artery).

NOW THAT THE PATIENT IS ON PERIPHERAL VV-A ECMO, WHAT ELSE IS NEEDED?

Following hemodynamic stabilization, a 7F limb perfusion cannula is placed into the superficial femoral artery (SFA) on the same leg and connected to the arterial cannula to provide blood flow to the distal part of the leg (Figure 4.4).

During insertion of the limb perfusion cannula, pink frothy sputum begins to fill up the endotracheal tube. The arterial line tracing now shows a flat line at 70 mm Hg. A stat TTE reveals a normal right ventricle but a dilated LV with no aortic valve opening.

WHY DID THE PATIENT DEVELOP PINK FROTHY SPUTUM COMING OUT OF THE ENDOTRACHEAL TUBE?

The patient shows signs of massive pulmonary edema because of severe LV overload, as confirmed by TTE, demonstrating a dilated, noncontractile LV. Peripheral V-A ECMO can increase LV afterload because of its retrograde flow, leading to LV distention.[1,2]

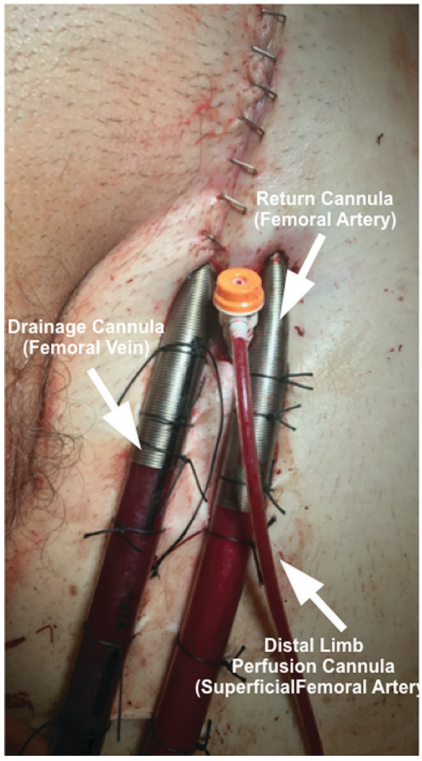


Figure 4.4 V-Aa ECMO for cardiogenic shock. To minimize the risk of leg ischemia in peripheral V-A ECMO, we recommend the placement of a distal limb perfusion cannula into the ipsilateral superficial femoral artery ("a"). Current nomenclature denotes this configuration as V-Aa ECMO. Contrary to our recommendation to cannulate femoral vein and artery on opposite sides, same-side cannulation had to be performed because of a high above-knee amputation on the patient's right side. Staple line above cannulation resulted from vascular surgery preceding the cardiogenic shock.

HOW CAN WE RESOLVE THE PULMONARY EDEMA?

Left ventricular unloading is key to promote myocardial recovery (during V-A ECMO management).[3] Treatment options involve diuretic therapy, renal replacement therapy, and titration of inotropic drugs.[4] If patients develop clinically relevant LV overload (i.e., refractory pulmonary edema) despite maximal medical management, mechanical LV decompression becomes necessary. Atrial septostomy, intra-aortic balloon pump (IABP), and insertion of an Impella® device represent generally accepted nonsurgical options.[1,2]

The patient underwent atrial septostomy with complete resolution of pulmonary edema and drastic improvement in gas exchange over the next 48 hours.[1]

DISCUSSION

OVERVIEW

In cases of cardiogenic shock and/or lung injury refractory to conventional medical treatment, extracorporeal life support (ECLS) has become increasingly valuable. ECLS entails a set of interventions to provide oxygenation, CO_2 removal, cardiac support, or a combination thereof. The first successful form of ECLS was described back in 1972 (Hill) and named extracorporeal membrane oxygenation (ECMO).

Current nomenclature for ECLS considers cannulation site, flow direction, presence of a pump, cannula hierarchy, tip position, and cannula dimension. Nomenclature symbolizes blood flow as left (drainage site) to right (return site).[5]

CENTRAL VERSUS PERIPHERAL CANNULATION

Central cannulation describes direct cannulation of the heart, aorta, or pulmonary vessels. Peripheral cannulation entails cannulations of artery or vein outside the thoracic or abdominal cavity.[5]

CANNULA HIERARCHY

Uppercase letters denote cannulas providing major blood drainage or return, whereas lowercase letters indicate minor blood flow cannulas, unloading or supplying distinct anatomical entities.[5]

A hyphen illustrates the relative position of the extracorporeal membrane lung in a particular setup.

In single-lumen cannula (SLC) applications, the drainage cannula will be left of the hyphen, and the return cannula will be right of the hyphen. Thus, V-V and V-A indicate single-lumen veno-venous and veno-arterial ECMO, respectively (Figures 4.1 and 4.2). For V-V ECMO with a double-lumen cannula (DLC), the abbreviation *dl* can be placed in parentheses before the first V, that is, (dl)V-V ECMO.[5]

If another major cannula is introduced, the additional uppercase letter is placed relative to its position to the membrane lung (hyphen) and on the outer side of the already existing cannula. In our case, the configuration was changed from V-V ECMO to VV-A ECMO. If, in cases of primary V-A ECMO, an additional return cannula is introduced into a vein to increase systemic oxygenation, a V is placed right of the "A," indicating return of blood after it has passed through the membrane lung, that is, V-AV (veno-arterial-venous) ECMO (Figure 4.5).[5]

After transition to VV-A ECMO, our patient also received a distal perfusion cannula via the SFA to provide blood flow distal to the major cannulation site of the femoral artery (Figure 4.4). The distal limb perfusion cannula represents a minor flow catheter, indicated by "a."[5] Consequently, the final configuration in our case can be expressed as VV-Aa ECMO.

CANNULA SIZE AND VESSEL DIAMETERS

Arterial and venous ECMO cannulas are available in different sizes. Sizes are usually measured on the outer diameter of the cannula and given in French. One millimeter equals 3F, that is, 7 mm = 21F. Typically, arterial cannulas range between 15F and 21F, while venous cannulas range between 21F and 25F. Identically sized cannulas, however, can vary in their inner diameter because of wall thickness used for different materials. In addition to preload, cannula resistance is another key determinant of maximum ECMO flow. Cannula resistance itself

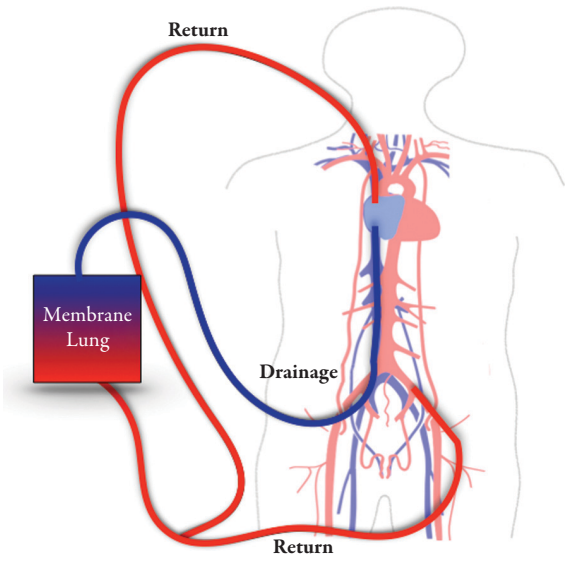


Figure 4.5 V-AV ECMO configuration

A conventional V-A ECMO configuration is expanded to V-AV ECMO by inserting an additional return cannula into the right IJV. This configuration is used in cases of differential oxygenation with upper body hypoxemia arising during V-A ECMO treatment in patients with concomitant respiratory failure who cannot be managed with ventilator adjustments alone.

is directly proportional to the length and inversely proportional to the fourth power of the luminal radius. Ultrasound-guided vessel cannulation allows for exact measurement of vessel diameter and consequently choice of appropriate size cannulas. For example, the femoral artery averages 6.6 mm in diameter in healthy adults, indicating placement of a 17F–19F cannula will fit into the vessel. However, a distal perfusion cannula will become necessary with a large arterial cannula since the flow around the cannula will be minimal.

ECMO FOR RESPIRATORY FAILURE

Background

Available evidence suggests a trend toward better survival rates for patients with ARDS and refractory hypoxemia who undergo ECMO compared to those who only receive conventional management.[6] No general consensus exists about when to initiate ECMO for respiratory failure. However, commencement of V-V ECMO under the following circumstances has shown a trend toward improved survival rates: PaO_2/FiO_2 ratio less than 50 mm Hg for more than 3 hours, PaO_2/FiO_2 ratio of less than 80 mm Hg for more than 6 hours, or an arterial blood pH of less than 7.25 with a $PaCO_2$ of at least 60 mm Hg for more than 6 hours.[6] Transfer of patients with ARDS and refractory hypoxemia to an ECMO center, even if they ultimately do not receive ECMO, also appears to confer a survival benefit.[7]

Cannulation

To commence V-V ECMO, the standard choice for ECMO in patients with isolated respiratory failure, the patient receives either two separate SLCs or a single DLC (see elsewhere in this book). Traditional cannulation sites for the SLC approach are (right) IJV and a femoral vein (Figure 4.1). However, the cannulation site is less important than the actual drainage and return sites. Draining cannulas have an end hole and several side holes at different levels. Drainage usually occurs from the most proximal side holes. Flow direction in the two-SLC approach is from the IVC via membrane lung to the right atrium (RA) or vice versa. Earlier research has shown that recirculation, that is flow of oxygenated blood from the return cannula directly into the drainage cannula, is less with the return of blood via the IJV to the RA.[8] However, more recent results allow us to question these earlier findings.[9] As the amount of recirculation inversely affects O_2 delivery, it has to be kept to a minimum to allow for efficient ECMO support. Cannula position, ECMO flow, ECMO flow direction, cardiac output, and intrathoracic/intra-abdominal pressures all can affect the extent of recirculation.[10]

Severe respiratory failure with profound, prolonged hypoxemia and/or acidosis can lead to hemodynamic compromise requiring additional mechanical circulatory support not provided by V-V ECMO. In these cases, V-A ECMO offers both hemodynamic and respiratory support.

Practical Aspects

In general, ultrasound-guided cannulation using the Seldinger technique is considered the standard approach for all cannulations. The traditional bicaval two-cannula approach involves cannulating the femoral vein (drainage) and IJV (return). A large-bore (23F–31F) cannula is used for venous drainage, and a smaller (17F–19F) cannula is used for venous return. The tip of the drainage cannula should be at the IVC/RA junction, whereas the tip of the return cannula should be at the SVC/RA junction and be far enough apart to limit recirculation (Figure 4.1). Clinical inspection of blood flowing through the drainage cannula (dark red) and the return cannula (bright red) allows for a first qualitative check for recirculation. A lack of clear color separation (i.e., dark red blood in the drainage cannula vs. bright red blood in the return cannula) (ECMO FiO_2 of 1.0) should raise immediate concerns for recirculation. Increasing the distance between the cannula tips by slowly pulling back the return cannula can resolve the issue. Final placement/position of cannulas is confirmed with either TEE or x-ray after securing the cannulas in place.

Flow through the ECMO cannula is determined by the size of the drainage cannula and by the resistance in the oxygenator. ECMO flows typically range between 5 and 6 L/min. In V-V ECMO, the flow needed is determined by the O_2 saturation targeted—typically SaO_2 greater than 88%. The amount of blood going through the lungs and bypassing the ECMO circuit is the amount of deoxygenated blood in the patient (i.e., shunt). The closer the ECMO flows are to the patient's native cardiac output (blood through lungs), the lower the shunt and the better the systemic oxygenation will be. This can be done by either increasing the ECMO flows or decreasing the patient's native cardiac output. As cardiac output equals HR multiplied by stroke volume, negative chronotropic and/or

inotropic agents can decrease cardiac output but require careful monitoring to avoid global hypoperfusion. CO_2 removal is controlled by adjusting the sweep gas flow in the ECMO circuit. The sweep is adjusted for a $PaCO_2$ of 38–42 mm Hg.

ECMO FOR HEMODYNAMIC SUPPORT

Background

V-A ECMO is not a cure for cardiogenic shock, but it allows for hemodynamic stabilization, thus limiting further end-organ damage and providing time for myocardial recovery. V-A ECMO has become the main ECLS configuration for short-term hemodynamic support in patients with critical cardiogenic shock.[11] Critical cardiogenic shock describes patients demonstrating life-threatening hypotension despite rapidly escalating inotropic support (with/without placement of an IABP) as well as critical organ hypoperfusion, as indicated by worsening acidosis and/or lactate levels.[12] Hemodynamic parameters indicating critical cardiogenic shock are cardiac index (CI) less than 2.0 L/min/m^2 with systolic BPs (SBPs) less than 90 mm Hg and pulmonary capillary wedge pressures (PCWPs) 24 mm Hg or greater, while requiring at least two vasopressors/inotropes with or without an IABP.[11]

Veno-arterial ECMO returns oxygenated blood into a major artery, in adults most commonly via a femoral artery cannula with its tip in the iliac artery (peripheral V-A ECMO; Figure 4.2). This configuration results in two opposing blood flows meeting somewhere in the aorta: retrograde flow of blood ejected from the ECMO circuit into the iliac artery versus antegrade flow of blood ejected from the LV into the ascending aorta (Figure 4.6).[13] The level of this mixing zone, or watershed, is dependent on the native cardiac output and the ECMO flow. Two potentially life-threatening complications can result from this design: (a) differential oxygenation with upper body hypoxemia and (b) LV distension with blood stasis and clot formation.[1,14]

Venous blood drained from the IVC (e.g., via a femoral vein cannula) undergoes oxygenation and CO_2 removal in the ECMO circuit and then enters the descending aorta via the iliac artery, primarily supporting the lower body (splanchnic circulation, kidneys, legs, etc.) upward until the mixing zone. In patients with combined cardiopulmonary failure, blood leaving the LV is desaturated and will predominantly support the upper part of the body (coronary, subclavian, and carotid arteries). This blood will then drain into the SVC and be pumped again through the injured lungs to the left atrium and LV without being mixed with the oxygenated blood from the ECMO circuit. This leads to low arterial and venous O_2 saturations in the upper body, increasing the risk of myocardial and cerebral ischemia.

INDICATIONS

Indications for V-A ECMO include cardiac arrest, cardiogenic shock, postcardiotomy shock, refractory ventricular tachycardia, and acute management of complications of invasive procedures.[11] In particular, critical cardiogenic shock (i.e., the "crash-and-burn patient") has become one of the main indications for V-A ECMO.[4] Critical cardiogenic shock describes SBP less than 90 mm Hg despite two or more intravenous inotropes with or without IABP and evidence of decreased organ perfusion as well as a PCWP greater than 18 mm Hg and a CI less than 2.1 L/min/m^2. Here, V-A ECMO serves as a bridge to recovery, a bridge to transplant, or a bridge to destination therapy, which involves implanting an LV assist device.

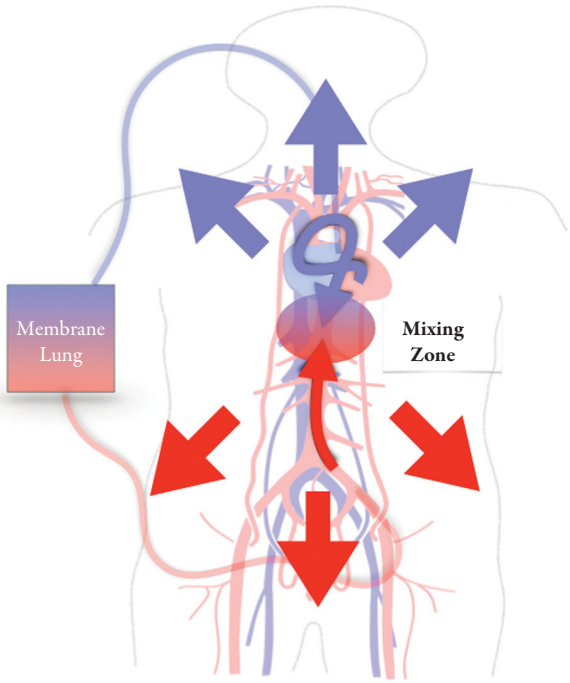


Figure 4.6 Differential oxygenation during V-A ECMO. Blood drained from the IVC via a femoral cannula undergoes oxygenation and CO_2 removal in the ECMO circuit and then enters the descending aorta via the iliac artery, primarily supporting the lower body upward until the mixing zone. In patients with concomitant cardiopulmonary failure, blood leaving the left ventricle is desaturated and will predominantly support the upper part of the body. This leads to low arterial and venous O_2 saturations in the upper body, increasing the risk of myocardial and cerebral ischemia.

CANNULATION

In adults, conventional V-A ECMO cannulation occurs via femoral vein and artery (Figure 4.2). A large-bore (21F–25F) venous cannula is placed through the femoral vein with its tip at the IVC/RA junction. We recommend the right femoral vein for anatomical reasons. The right femoral vein and common iliac veins display a relatively vertical course into the IVC. The left common iliac vein, by contrast, crosses the vertebral column and aorta to drain into the IVC, increasing the risks of complications from venous cannulation. To minimize hypoperfusion of the leg, we prefer arterial cannulation contralateral to venous cannulation. The femoral artery is cannulated with a smaller bore (15F–19F) cannula. We recommend placement of a limb perfusion catheter into the ipsilateral SFA, pointing distally, to decrease the risk of leg ischemia.[15] Placement of a limb perfusion catheter into the

SFA is more easily accomplished if done prior to cannulation of the femoral artery. The limb perfusion (5F–7F) catheter is connected to the return cannula, providing oxygenated blood to portions of the leg distal to the femoral artery cannulation site (Figure 4.4). If percutaneous placement of a distal limb perfusion catheter is not possible, we advise an open cannulation of the SFA via cutdown. A recently proposed and tested bidirectional femoral arterial cannula to prevent leg ischemia during V-A ECMO requires further studies before its risks and benefits can be fully assessed.[16]

PRACTICAL ASPECTS

Traditionally, initial goal ECMO flows are set at body surface area times 2.2. It is assumed that this allows for adequate cardiac output to other organs (liver, kidney, brain) and thus limits further secondary end-organ damage due to cardiogenic shock. After initial resuscitation, however, ECMO flow rates can be titrated to achieve/maintain physiologic levels of lactate and pH, serving as indicators of (adequate) global perfusion. We have frequently found that flow rates of 2.5–4 L/min are sufficient under these circumstances. Reducing the ECMO flow rates during peripheral V-A ECMO also reduces LV afterload, a crucial factor in limiting LV distension.

Several techniques have been proposed to treat LV distension during peripheral V-A ECMO. They comprise either surgical or percutaneous approaches.[2] Surgical approaches include placement of additional drainage cannulas for the left heart and necessitate a sternotomy or thoracotomy. Present percutaneous methods involve a pulmonary artery vent, transaortic vent, Impella pump, IABP, and atrial septostomy.[1,2] In our experience, atrial septostomy is a low risk but very efficient method to unload the LV, resolve pulmonary edema, and ultimately improve upper body oxygenation.[1] Atrial septostomy can be performed via one-time femoral vein access and does not carry the risk of (lower) extremity ischemia when compared to more invasive, percutaneous approaches like placement of an Impella pump or IABP.[2]

Monitoring for differential oxygenation during peripheral V-A ECMO, especially in patients with concomitant respiratory failure, is crucial to avoid ischemia to vital organs. Placement of a right radial arterial line with regular arterial blood gas analyses from that site and/or bilateral cerebral oximetry using near-infrared spectroscopy are the most feasible solutions under routine clinical circumstances.[17,18] If ventilator adjustments fail to improve oxygenation of the upper body, insertion of an additional return cannula into a central vein, usually the right IJV, can be beneficial (Figure 4.5).[17]

A 15F–21F venous return cannula is placed into the right IJV with the tip in the SVC, directing ECMO outflow toward the (RA) and the pulmonary vasculature to improve oxygenation of coronary arteries and upper body.[17] The amount of ECMO outflow into the venous cannula can be controlled with a clamp to balance systemic circulatory support versus upper body oxygenation. According to current nomenclature, this triple-cannula configuration is called V-AV ECMO.

CONCLUSIONS

- ECMO support can be a life-saving option for refractory cardiac and/or respiratory failure.
- V-V ECMO only provides support for respiratory failure and does not deliver any circulatory support. Initiating this type of ECMO in patients with cardiac dysfunction can be catastrophic.
- V-V ECMO support allows for lung-protective ventilation to reduce barotrauma while oxygenating and decarboxylating blood.
- V-A ECMO support is indicated in patients with critical cardiogenic shock (i.e., cardiogenic shock refractory to medical therapy).
- V-A ECMO can be used as a bridge to recovery, bridge to transplant, or bridge to destination therapy (e.g., LV assist device).
- V-A ECMO can worsen LV distention and pulmonary edema. Monitoring and treatment of LV distension are paramount.
- If medical therapy for LV distention and pulmonary edema fails, mechanical LV unloading becomes necessary (e.g., Impella, atrial septostomy, IABP, or surgical LV venting).
- Distal leg ischemia can occur with placement of an ECMO cannula into the femoral artery. Early insertion of a distal limb perfusion cannula into the ipsilateral SFA is recommended.
- In case of hemodynamic deterioration of patients undergoing V-V ECMO, insertion of a return cannula into an artery may be necessary to provide circulatory support.
- Differential oxygenation with upper body hypoxemia can occur in patients receiving peripheral V-A ECMO who also suffer from respiratory failure. Insertion of an additional return cannula into a central vein (V-AV ECMO) can improve upper body oxygenation

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REVIEW QUESTIONS

1. Indications for V-V ECMO include all the following except

   A. Dilated cardiomyopathy
   B. H1N1 pneumonia
   C. Pulmonary contusion
   D. ARDS

2. Which of the following hemodynamic parameters does NOT define critical cariogenic shock?

   A. Systolic blood pressure less than 90 mm Hg despite two or more intravenous inotropes (with or without IABP)
   B. Pulmonary capillary wedge pressure 24 mm Hg or greater
   C. Cardiac index less than 2.0 L/min/m^2
   D. Central venous pressures greater than 18 mm Hg

3. The *main* reason to consider V-V ECMO after maximum medical therapy in a patient with ARDS is

   A. Cardiac support
   B. Treatment of the underlying infection
   C. To allow for lung-protective ventilation
   D. To correct a pH of 7.35 to 7.4

4. Frequently, initial blood flow during V-A ECMO is calculated by

   A. Body surface area × cardiac output
   B. Weight in kilograms × cardiac output
   C. Weight in kilogram × body surface area
   D. Body surface area × CI, with CI = 2.2

5. Flow on V-V ECMO is mostly limited by the oxygenator and

   A. The size of the return cannula
   B. The size of the drainage cannula
   C. The distance between the two cannulas
   D. The type of motor head that is used

6. To minimize the risk of leg ischemia during undergoing peripheral V-A ECMO, patients frequently receive

   A. A reperfusion cannula in the deep femoral artery.
   B. A reperfusion cannula in the SFA.
   C. A bypass from the contralateral femoral artery.
   D. A 21F rather than 17F arterial cannula.

7. A patient is placed on V-A ECMO, and the flows are stable at 4.5 L/min. All of a sudden, the respiratory therapist informs you that there is pink frothy sputum coming from the patient's endotracheal tube. The most likely diagnosis is

   A. Pulmonary hemorrhage from the cannulation
   B. Secretions from ARDS
   C. Pulmonary edema
   D. Pulmonary air embolism from not de-airing the ECMO circuit

8. All of the following are ways to unload the LV in a patient without LV ejections on V-A ECMO except

   A. Atrial septostomy
   B. Impella placement
   C. Increasing ECMO flows
   D. Surgical LV vent

9. In V-V ECMO, the difference between the ECMO flows and the patient's native cardiac output is called

   A. Shunt
   B. Dead space
   C. Differential flow
   D. Cardiac index

10. In a single-catheter, dual-lumen V-V ECMO cannula, it is essential that the return port is located

   A. The location does not matter
   B. In the SVC
   C. In the IVC

D. In the RA/SVC junction directed across the tricuspid valve

11. A patient is placed on bicaval V-V ECMO with a 25F drainage cannula in the femoral vein and a 17F return cannula via the right IJV. When on pump, the patient's vitals are all stable except the SpO_2 increases from 75% to only 86% on full ECMO support. When looking at the drainage cannula, the blood looks bright. What is your next step?

A. Decrease ECMO flows
B. Call for cardiothoracic surgery for possible pericardial effusion
C. Pull back the drainage cannula
D. Pull back on the return cannula

12. The preferred location to place an arterial line in a patient on percutaneous V-A ECMO cannulated in the femoral artery and vein is

A. Opposite femoral artery
B. Left radial artery
C. Right radial artery
D. Right brachial artery

13. Which of the following are vascular complications from ECMO placement?

A. Vessel injury
B. Compartment syndrome
C. Bleeding
D. All of the above

14. A patient requires V-A ECMO support due to a large ventricular septal defect (VSD) from a severe myocardial infarction. At 12 hours after initiation of V-A ECMO, the patient still shows a whited out chest x-ray and is unable to be weaned from the ventilator. The next best option is

A. Placement of an Impella
B. Atrial septostomy
C. Placement of an additional drainage cannula into the pulmonary artery
D. Surgical insertion of an LV vent

15. Which of the following are indications for V-A ECMO support?

A. Patient with a ST-segment elevation myocardial infarction that shows worsening cardiogenic shock despite maximum medical therapy after stent placement
B. Patient awaiting transplant that has acute exacerbation of heart failure unresponsive to medical treatment
C. Patient after open-heart surgery who cannot be weaned from cardiopulmonary bypass
D. All of the above

ANSWERS

1 A. Dilated cardiomyopathy patients are often in low cardiac output states. Commencing V-V ECMO in a patient with a low cardiac output state be fatal. All other reasons are acceptable for V-V ECMO cannulation. Pulmonary contusion in trauma patients is one of the few indications for ECMO acceptable in trauma patients.

2D. Central venous pressure measurements do not define critical cardiogenic shock.

3C. V-V ECMO allows for lung-protective ventilation and, ultimately, lung rest. Other indications for V-V ECMO include a pH less than 7.2 due to high PaO_2 and a PaO_2/FiO_2 ratio less than 100 mm Hg. V-V ECMO does not provide any circulatory support, but it provides time to treat the underlying disease process (e.g., infection).

4D. V-A ECMO flow through the circuit is the minimum cardiac output that the body is obtaining. If the patient is ejecting over the ECMO flows, this adds to the overall cardiac output, but it is unknown how much that actual contribution is. Initially, a minimum V-A ECMO flow equaling body surface area × 2.2 is therefore set.

5 B. V-V/V-A ECMO flow is limited by two things: the size of the drainage cannula and the membrane on the oxygenator. Therefore, the drainage cannula for both V-V and V-A ECMO is a large-bore, typically 23F–25F cannula. Although the return cannula does have some effect on ECMO flows, the flow resistance between a 21F return cannula and that of a 17F return cannula is only minimal.

6 B. A common practice to minimize leg ischemia in percutaneous peripheral V-A ECMO is to place a distal limb perfusion cannula. One has to make sure that the cannula is in the SFA. The correct position can be confirmed by x-ray with bedside injection of radiocontrast through the cannula. Typically, a 5F or 7F reperfusion cannula is used. There is a risk of placing the reperfusion cannula in the deep femoral artery, in particular if done without ultrasound guidance. A bypass from the contralateral femoral artery is highly invasive and without any obvious benefits. Finally, one should always place the largest size cannulas necessary to achieve appropriate flows. Sufficient flows can be achieved with a 17F or 19F arterial return cannula in most patients.

7C. There are several reasons for increased secretions in heart failure patients. A patient can develop pink frothy sputum right after ECMO cannulation because of (almost) absent LV ejections and blood backflow into the pulmonary circulation. This is likely due to increased afterload from the opposing blood flow through the femoral arterial cannula. The failing LV in this case is not strong enough to pump against this afterload and therefore is unable to offload the blood in the LV. Most likely, the arterial wave tracing will be a flat line. LV unloading is a key component of V-A ECMO for cardiogenic shock.

8C. All of the other interventions are methods to unload the LV. Atrial septostomy allows blood to flow from the LV to the SVC, via left and RA, bypassing the pulmonary circulation. Impella is a percutaneous device with its tip placed in the LV, pumping blood into the ascending aorta. A surgical vent is also an option; however, this is rather invasive because of the need for a sternotomy/thoracotomy. Increasing ECMO flows will increase LV afterload.

9 A. V-V ECMO delivers well-oxygenated blood into the pulmonary circulation. However, the amount of blood bypassing the ECMO circuit (i.e., the difference between native

cardiac output and ECMO flows) is only poorly oxygenated in the pulmonary circulation because of the underlying lung injury. This leads to a decrease in total oxygen saturation (i.e., shunt). To minimize the shunt fraction, ECMO flows need to match a patient's cardiac output as closely as possible. If this cannot be achieved, pharmacological reduction of a patient's cardiac output might become necessary.

10D. The single-catheter, dual-lumen V-V ECMO cannulas have three ports. Two of the ports are drainage ports, and they must be in the SVC and IVC. These are the proximal and distal ports on the cannula. The middle port is the return port, and that return jet must be directed toward the tricuspid valve. Placement of this is essential because if that return jet is malpositioned, massive recirculation could occur. This is why this cannula must be placed with TEE guidance or under fluoroscopy.

11C. The reason the SpO_2 is not higher is because the patient is having recirculation of the blood in the ECMO circuit because the return and drainage cannulas are too close together. This is confirmed by seeing bright red blood in the drainage cannula. In this situation, the reasonable thing to do is to increase the distance between the two cannulas; usually, that is done by pulling back gently on the drainage cannula until there is a considerable color difference between the two cannulas. Typically, the return cannula is a shorter arterial cannula (around 20 cm), so pulling back on that increases the risk of the cannula falling out of the vessel. The drainage cannula is around 50 cm, so retracting 5 to 6 cm can be done safely. Decreasing the ECMO flows would not be advisable as this would increase your shunt. The patient has stable vital signs, so cardiac tamponade is unlikely.

12C. The location of choice for arterial line placement in a patient on percutaneous V-A ECMO cannulated in the groin is the right radial artery. This is because of the watershed phenomenon that sometimes can occur with patients that have poor pulmonary function on V-A ECMO. Here, the hyperoxygenated blood from the ECMO circuit mixes with less oxygenated blood from the patient's native cardiac function, and this mixing occurs somewhere in the descending aorta. Therefore, a PaO_2 obtained from the right radial arterial line will be the minimum oxygenation the body is receiving. Obtaining a PaO_2 from the opposite femoral artery will just give the oxygenation of blood coming from the ECMO circuit. If a right radial arterial line cannot be placed, then the next best option would be a right brachial arterial line.

13D. All answers are correct.

14C. This patient's pulmonary circulation is volume overloaded because of the VSD. Another drainage cannula is necessary. This cannula should be placed into the pulmonary artery under fluoroscopy and TEE guidance. VSD with volume overload of the pulmonary circulation is one of the main indications for VV-A ECMO. The other choices are indicated LV overload during V-A ECMO.

15D. V-A ECMO is indicated in all of the cases. V-A ECMO can be used as a bridge to recovery (A), bridge to transplant (B), and bridge to decision (choice C)

5.

THE ECMO CIRCUIT AND TROUBLESHOOTING

Marcus Hermann and Harald Keller

STEM CASE AND KEY QUESTIONS

A 56-year-old male patient underwent emergency implantation of bifemoral extracorporeal life support (ECLS) after being transferred to our institution. The dissection of the right coronary artery during a percutaneous coronary intervention resulted in hemodynamic instability and the necessity for veno-arterial (V-A) mechanical circulatory support (MCS). A 23 French (F) access and 18F return cannula were chosen based on a quick assessment of the subject's physique in conjunction with the Rotaflow blood pump system (Getinge, Rastatt, Germany) and the standard PLS 2050 (Getinge, Rastatt, Germany) circuit configuration.

With the patient stabilizing and catecholamine dependency decreasing, on-ECLS beating heart bypass surgery was performed. In the same vein, the implantation site of the return cannula was relocated to the right axillary artery, including a respective catheter for distal perfusion. The initially administered off-pump coronary artery bypass (OPCAB) dose of unfractionated heparin (UFH) (200 IU/kg body weight) was antagonized by means of protamine, and the patient arrived at the intensive care unit (ICU) with a satisfactory activated clotting time (ACT) of 160 seconds. Still, on the first postoperative day (POD), a distinctive flow reduction was observed, leading to the replacement of the extracorporeal membrane oxygenation (ECMO) circuit.

Weaning commenced without further complications and scheduled ECMO explantation was carried out on POD 5 as the patient showed signs of recovery. Unfortunately, an injury of the posterior tracheal wall during a routine procedure resulted in acute respiratory insufficiency, and ECMO was reestablished in veno-venous (V-V) bifemoral fashion, utilizing a 23F access and 21F return cannula, respectively. Heavy bleeding throughout the procedure demanded fluid transfusion via the ECMO circuit but ultimately triggered an incident of air entrapment, followed by a brief pump stop to de-air the system.

However, despite proper oxygenator function and cannula placement, the ECMO circuit proved unable to maintain adequate oxygen saturation. A second access (18F) cannula was advanced into the right internal jugular vein (IJV) on POD 6, allowing for bicaval drainage and an overall increased EMCO flow rate in the setting of triple site veno-venovenous configuration (VV-V). Given the persisting high risk of bleeding, it was decided to refrain from continuous heparin administration for the duration of VV-V ECMO therapy. The patient was successfully weaned off ECMO on POD 14 and left the institution in good health after a total of 23 days.

WHY WAS IT DECIDED TO SWITCH TO AXILLARY CANNULATION AFTER CONDUCTING THE ON-ECLS BEATING HEART BYPASS SURGERY?

Bifemoral cannulation is generally the preferred choice when conducting emergency ECLS implantation. However, due to its nature of delivering retrograde arterial flow, this configuration is prone to the development of differential hypoxemia (DH) or Harlequin syndrome. The determining factors are heart and lung function as well as the ECMO flow rate. Picturing the worst-case scenario, a well-ejecting left ventricle will pump badly oxygenated blood coming from distressed lungs to the supra-aortic vessels, while the ECMO flow mainly supplies the abdominal regions, commonly leading to cerebral hypoxia. On the other hand, increasing the ECMO blood flow rate to prevent the heart from ejecting venous blood into the aorta is possible but might jeopardize heart regeneration, as the afterload is raised considerably. It is therefore recommended to convert bifemoral ECLS to femoro-axillary configuration for antegrade flow as soon as the patient is stabilized. If a surgical team is unavailable, placing a second return cannula into the right IJV for triple-site V-AV (veno-arterial-venous) ECMO is a great alternative. Delivering arterial blood into the venous system will prevent the left heart from ejecting deoxygenated blood, thereby reducing the effect of the Harlequin syndrome.

In this particular case, symptoms of DH were yet to be discovered at the time of axillary cannulation. However, the predominantly right-sided posterior wall infarction and otherwise adequate left ventricular pump function were seen as considerable prerequisites, and the conversion was carried out as a preventive measure while still having the availability of an operating room.

WHAT CAUSED THE ACUTE FLOW REDUCTION ON POD 1?

A reduction of a liter per minute (LPM) flow while the centrifugal pump maintains constant revolutions per minute (RPM) can occur rapidly or gradually over time and should be

addressed immediately. The commonest causes include access insufficiency due to hypovolemia, inadequate cannula positioning, right atrial (RA)/ventricular thrombus formation, or flow obstruction due to kinking and oxygenator clot formation. The perfusion department was alerted the morning after bypass surgery. The flow rate had gradually decreased from 5 LPM down to less than 1.5 LPM. Nursing staff claimed a technical malfunction (false flow measurement) to be the cause while disregarding further troubleshooting as the occurrence was so sudden. The flow transducer was promptly refreshed, and a second flow probe was applied to double check, confirming that previous measurements were indeed correct.

Right heart thrombus formation and cannula migration were excluded by means of x-ray and transesophageal echocardiography (TEE), respectively. Selective fluid administration did not result in an increased LPM flow, and the postoxygenator gas analysis revealed no implication for malfunction. Furthermore, in an attempt to control the persistent bleeding, the patient had received recombinant activated factor VII (fVIIa) as well as additional doses of protamine overnight, resulting in an activated partial thromboplastin time (aPTT) of 31 seconds. The measurement of the oxygenator's pressure gradient showed an elevated value of 282 mm Hg (inlet 438 mm Hg, outlet 156 mm Hg). Specifically, the increased inlet pressure confirmed a flow obstruction within the oxygenator due to clot formation. It is important to note that clots often do not impair the circuit's capabilities to decarboxylate or oxygenate the blood, making them "invisible" when consulting postoxygenator blood gas parameters. Instead, the oxygenator merely outputs less blood volume as the flow rate adapts based on clot size and the remaining surface area available for gas exchange.

After replacing the circuit, adequate flow was reestablished without issue. Even in the event of bleeding, it is recommended to keep the aPTT in the range of 50–60 seconds to prevent circulatory thrombi. Considering the administration of protamine, antagonizing the initial OPCAB UFH dose down to an ACT of 130–160 seconds is usually well tolerated by the ECMO circuit. Additional doses of protamine are almost never a valid indication and should have been prevented. Nevertheless, the main cause for the fast clot formation was presumed to be the substitution of fVIIa. Scheduling an ECMO circuit replacement as part of a standard operating procedure is advisable in that case.

HOW WAS THE INCIDENT OF AIR ENTRAPMENT RESOLVED WITHOUT REPLACING THE CIRCUIT?

Albeit seldom, air entrapment is considered to be one of the most dangerous complications when it comes to ECMO circuits. The handling depends on the amount of entrapped air, where it accumulates, and whether oxygenator and pump head are separated (e.g., Rotaflow) or a one-unit Cardiohelp. The tubing is governed by negative pressure from the point of the access cannula until the centrifugal pump's inlet. If air were to enter at those points (e.g., accidental decannulation), circulation would quickly cease to exist. Given the lower density compared to blood, the air effectively creates a block at the pump's inlet. For that reason, it is recommended to remove all connections to the access line of the ECMO circuit after priming. However, in this case the bleeding caused by the tracheal wall injury demanded rapid fluid substitution to maintain sufficient ECMO flow. It was therefore decided to integrate an additional line (precentrifugal pump) to quickly retransfuse cell-saved blood back to the patient. In an attempt to shut off the line, the three-way stopcock loosened, allowing air to enter the circuit. Although the stopcock was fastened immediately, a 5-cm air column formed at the centrifugal pump's inlet, rendering it unable to propel blood.

The circuit was de-aired in three steps as follows:

1. The return line was clamped postoxygenator, with the access line remaining open.
2. A 20-mL syringe (piston fully inserted) with a Luer Lock connector was attached to the three-way stopcock at the oxygenator's inlet.
3. The pump's RPM was slowly reduced, and the piston was extended, drawing the entrapped air out of the circuit and into the syringe. Regarding the risk of arterial (return line) embolization, microbubbles expelled by the centrifugal pump are safely eliminated by the oxygenator's microporous, hollow-fiber membrane. In addition, the hydrostatic pressure (height difference between oxygenator outlet and return cannula tip) prevents microbubbles from advancing into the return line and instead forces them to rise within the oxygenator.

With the air eliminated, ECMO flow was successfully reestablished. The rectification of the incident took less than 120 seconds, and the downtime of ECMO support had no effect on the patient's recovery. Salvaging the circuit was critical in this case and should always be the objective to prevent unnecessary hemodilution. However, depending on the severity of the air entrapment, the replacement of the circuit might be the favorable course of action if a primed system is ready. The response time and quick decision-making after assessing the situation are crucial.

WHICH FACTORS NEED TO BE TAKEN INTO ACCOUNT WHEN FACING INSUFFICIENT OXYGEN SATURATION DURING V-V ECMO?

A decreasing oxygen saturation in spite of MCS is a direct response to insufficient oxygen delivery to the patient. The first reaction of inexperienced staff is usually the assumption of oxygenator failure. Although the partial oxygen pressure (pO_2) plays an important role, the two governing factors to ensure adequate oxygen delivery (DO_2) are the extracorporeal blood flow rate (Q_E) and hemoglobin (Hb) content (as opposed to carbon dioxide removal, which is achievable with relatively low blood flow and is more dependent on gas flow). Further, V-V ECMO is unique in that both cannulae are located in the venous system. A limiting factor regarding the delivery of oxygen is therefore the position of the cannulae with respect to each other. Close proximity will promote recirculation and

significantly impair the efficiency of ECMO, as oxygenated blood ejected by the return cannula is immediately drained into the access line of the circuit. To minimize the aforementioned cannula interaction, femoro-jugular implantation is the preferred approach. However, accessing the right IJV is not always feasible, and bifemoral cannulation has proven to be a fast alternative, especially in acute situations.

Considering the case at hand, recirculation was ruled out by the daily chest x-ray, which revealed a sufficiently distal access cannula within the inferior vena cava (IVC). Access insufficiency due to cannula obstruction (e.g., thrombi) or hypovolemia was excluded by means of TEE and the absence of chattering, respectively. Reducing pump RPM to test for excessive suction on the access site had no positive effect on the LPM. In addition, both Hb content and postoxygenator partial oxygen pressure were in normal ranges. With no apparent circuit-related malfunctions to be found, the conclusion was made that the maximum flow (4.5 LPM) provided by ECMO in bifemoral configuration simply did not meet the patient's demands for oxygen. The flow limitation stemmed from the area of drainage being confined to the IVC. Therefore, instead of switching to just femoro-jugular ECMO, a second access cannula was advanced into the right IJV, allowing for bicaval drainage. While three implantation sites are extensive, it was the only viable option to facilitate the necessary ECMO blood flow and maintain adequate oxygen saturation. Temporarily clamping the femoral access cannula before reverting to femoro-jugular ECMO (assuming signs of recovery) is advisable to guarantee that the circuit provides sufficient support in dual-site configuration. Alternatively, if the IJV proves unable to cannulate in the first place (e.g., vascular anomaly, risk of bleeding), a femoral catheter intended for bicaval access during minimally invasive tricuspid valve surgery can be utilized to increase drainage.

WHAT MEASURES WERE TAKEN TO PREVENT CLOT FORMATION WITHOUT THE USE OF HEPARIN?

Anticoagulation management on ECMO should be assessed on an individual case basis. The PLS 2050 Bioline® (Getinge, Rastatt, Germany) circuit components are inherently heparin coated to provide an initial short-term safety net. At our institution, it is therefore recommended to initiate systemic anticoagulation with heparin no earlier than 12 hours after establishing MCS, provided that an initial UFH bolus of 5000 IU was administered and the implanted cannulae are heparin/Bioline coated as well. If a patient shows no signs of coagulopathy, an aPTT of 50–60 seconds is targeted. Exceptions are, such as seen in the case at hand, the persistence of bleeding coupled with the recent subjection to surgical procedures. Heparin was set to be stopped after initiating V-V ECMO until the bleeding was controlled. The consulting specialists agreed to refrain from the use of protamine since there was no unreversed heparin left that could have implicated the bleeding. Even in Bioline-coated circuit components, though especially in membrane oxygenator (MOs), protamine highly promotes thrombosis and is only indicated to treat bleeding temporally related to heparin. Platelets, fresh frozen plasma (FFP), and fibrinogen were substituted based on the thromboelastography data instead to account for the respective deficiencies, as they are well tolerated by the ECMO circuits. Although the risk remained high, the bleeding subsided considerably. Following the conversion to triple-site ECMO, higher blood flows were achieved, which in turn reduced the need for anticoagulation as the clot formation was impaired by the increased velocities within the oxygenator. Perfusion staff therefore suggested continuing ECMO without the administration of UFH while substituting antithrombin III (ATIII) to activate the body's in vivo anticoagulation. Parameter changes implying thrombosis within the pump head or oxygenator, such as rising D-dimer, lactate dehydrogenase, free plasma hemoglobin (fHb), or falling fibrinogen levels, were monitored closely to prevent further complications.

DISCUSSION

Originally derived from the principles of cardiopulmonary bypass (CPB), ECMO circuits aim to provide prolonged MCS in a state of heart and/or lung failure. The ever-growing interest in ECMO over the recent decade[1] has led to many advancements, for example, in regard to biocompatibility and the performance of relevant artificial organs. As a result, indications, fields of application, and means to establish ECMO and meet the metabolic demands of patients have become multifold and of increasing complexity.

Modern ECMO circuits generate blood flow by means of centrifugal pumps. Large-bore catheters (cannulae) and medical-grade tubing are utilized to access the vascular system and facilitate circulation, respectively. A gas exchange device, also referred to as a membrane lung or MO, is responsible for oxygen delivery and carbon dioxide removal and commonly has an integrated heat exchanger (HE) for temperature management. These disposable core components of the ECMO circuit are complimented by a selection of hardware, including a pump console, battery pack, hand crank, heater unit, and gas blender or bottle to form a fully operational ECMO unit. Circuit function is assessed and controlled via the pump console and safety devices. Additional, more elaborate, monitoring such as pressures, arterial/venous saturation, and Hb content depend on the hardware models and the institutional philosophy. The Rotaflow system, for example, allows for basic control over pump RPM and displays the resulting LPM of blood flow with optional audible alarm settings to indicate abnormalities. On the other hand, the more contemporary Cardiohelp system provides the full range of monitoring described above, including arterial emboli detection. Furthermore, the system is unique in that pump, MO, and HE are combined into one device to open up new ways of portability. According to the Extracorporeal Life Support Organization (ELSO) report of 2016, a majority[2] of all MCS runs employed the Cardiohelp or Rotaflow systems, which are used as a reference going forward.

Technical, hardware-related incidents such as pump failure are quite rare in adult ECMO therapy.[3] More often than not, the complications encountered in clinical practice will be patient associated or due to interactions between circuit components and the human body. It is the general consensus that

ECMO circuits should follow a simplified approach, minimizing options of manipulation. Excessive tubing, stopcocks, connectors, or access sites are unnecessary sources for circuit-related complications. Further, each layer of complexity also increases the amount of comprehensive knowledge and training required to properly manage these systems. The underlying principles and interplays of all ECMO circuit components while emphasizing on the methods of troubleshooting are therefore discussed in this chapter.

GAS EXCHANGE IN MEMBRANE OXYGENATORS

Aside from establishing circulatory support, the primary objective of both V-V and V-A ECMO is the delivery of oxygen and removal of carbon dioxide. In modern ECMO circuits, gas exchange is accomplished by MOs. Blood is perfused around an intricate network of semipermeable, microporous hollow fibers. At the same time, a continuous flow of sweep gas is led through the fibers, resulting in diffusion across the membrane walls without allowing direct contact between the blood and gas phases. The fibers of modern MOs are made out of polymethyl pentene (PMP).[4] The material features a skin-like diffusion membrane and greatly reduces the previously occurring plasma leakage,[5] a phenomenon that limited both device longevity and gas exchange efficiency in the earlier ages of ECMO.[6,7] It is important to note that gas can easily penetrate the microporous membranes and enter the blood phase if no positive pressure gradient is maintained (e.g., absence of blood flow). For that reason, the PMP MOs should always be located below the patient to avoid embolization.

The governing factor regarding the diffusion of oxygen and carbon dioxide is the respective partial pressure gradients across the fiber membrane. Specifically, the DO_2 of an MO depends on the blood flow, Hb content, and pO_2. While the pO_2 gradient is considerably higher compared to carbon dioxide (pCO_2) when assuming a sweep gas oxygen content (F_GO_2) above 60%, CO_2 elimination will exceed DO_2 in any given scenario due to superior diffusivity and solubility properties. The elimination of CO_2 is therefore solely dependent on the gradient between the MO inlet and outlet and can be achieved with low extracorporeal blood flows (Q_E). As a result, a higher sweep gas flow (Q_G) will elevate CO_2 removal, whereas the demands for DO_2 are regulated via increasing the Q_E.[8] Zwischenberger et al. reported Q_E rates as low as 25% of the native cardiac output for successful CO_2 clearance.[9] With both diffusion mechanisms working independently from one another, blood flow and MO size are to be chosen based on the patient's needs for oxygen. A ratio of sweep gas to blood flow (Q_E:Q_G) of 1.0 will roughly result in equal gas exchange and represents a good initial point of reference when establishing ECMO. Further, maintaining a ratio of greater than 0.5 is advised to prevent hypoxic post-MO blood.

Membrane oxygenators are characterized by the surface area available for gas exchange relative to the device's blood volume and flow profiles, which in turn define the maximum oxygenation capacity or delivery, a concept also known as rated flow. It describes the maximum blood flow per minute at which a given MO is able to saturate venous blood from 75% at inlet to at least 95% at outlet, provided that the Hb content is adequate (12 g/dL).[10] If the MO outlet saturation falls below the threshold, abnormalities are to be assumed and investigated. That being said, modern MOs rarely experience technical malfunctions or fail to oxygenate blood when operated within rated flow. When assessing MO function, additional care must be taken when interpreting a patient's arterial oxygen saturation (SaO_2). In V-V ECMO specifically, SaO_2 ranges from 60% to 90% due to the mixing of native and extracorporeal blood flow can lead to the false assumption of MO failure. According to the ELSO guidelines of 2017, a SaO_2 of 80% and hematocrit of 40% will result in adequate systemic oxygen delivery as long as the cardiac output is able to support a delivery-to consumption-ratio DO_2:VO_2 of greater than 3.[10] In V-A ECMO, on the other hand, an SaO_2 of 95%–100% is expected when the lung is functioning normally. However, lower readings coupled with a mixed venous inlet saturation below 70% are an indication for insufficient systemic perfusion but not necessarily MO malfunction, as rated flow criteria are not applicable. In that case, inadequate Q_E or Hb content is likely the cause for hypoxemia. A reliable way to assess MO function in both V-V and V-A ECMO is therefore a blood gas analysis (BGA), drawn from the outlet at 100% F_GO_2. It is recommended to "flush" the MO prior to taking the sample by increasing and subsequently reverting the Q_G to 10 l/min for 30-60 seconds. pO_2 values in the range of 300-400 mmHg are a common BGA measurement to confirm satisfactory gas exchange. However, if the O_2 value falls below 200 mm Hg and/or the pCO_2 surpasses 45 mm Hg at a ratio of sweep gas to blood flow of greater than 4, an MO replacement needs to be considered.

A common cause for decaying MO efficiency over time is clot formation. Even in conditions of proper anticoagulation management, the prolonged exposure to artificial surfaces will trigger coagulation pathways and inflammatory responses, eventually resulting in impaired gas exchange performance.[11] Clinical parameters for MO thrombosis (secondary to reduced gas transfer) are rising D-dimer and falling fibrinogen values. Oxygenators consisting of PMP membranes inherently have a low pressure drop (50–60 mm Hg).[5] Thus, another major indication is the increasing pressure gradient between MO inlet and outlet ($\Delta P > 250$ mm Hg), which will result in a gradual or sometimes even abrupt reduction in ECMO blood flow and requires an exchange of the system. In a retrospective analysis of 265 adult patients undergoing V-V ECMO, it was found that 26 circuit replacements were indicated by acute (16) or progressive (10) clot formation within the MO that had manifested in worsening gas transfer over time. Additionally, 30% of urgently replaced circuits were due to missed routine testing.[12] It is therefore highly recommended to enforce daily monitoring of the aforementioned parameters to predict and subsequently conduct a system exchange in an elective fashion.

MANAGING EXTRACORPOREAL BLOOD FLOW

In order to provide adequate MCS, an extracorporeal circuit must facilitate 3 L/min per m^2 of body surface area

(V-A ECMO) or at least 60% of native cardiac output (V-V ECMO).[10] Aside from the patient's vascular condition and blood volume capacity, the extracorporeal blood flow is dependent on the pump, tubing, cannulae, and to some extent the MO. According to the ELSO register data[13] from 2005 to 2015, most modern ECMO circuits employ centrifugal pumps to directly drain through the MO and achieve systemic oxygen delivery. Flow is generated by a magnetically driven spinning rotor within the pump housing, creating negative pressure at the radial inlet and positive pressure at the tangential outlet. It has been shown that high flows up to 10 L/min are feasible (when coupled with 3/8-inch tubing) at a lower hemolytic index compared to roller pumps.[14,15] Nevertheless, multiple teams have reported the occurrence of hemolysis in up to 25% of cases in high-volume cohorts while using centrifugal pumps in their ECMO circuits.[16,17] Under normal circumstances, fHb is below 10 mg/dL, and values above 50 mg/dL give cause for investigation.[10] Although rare, a sudden rise in fHb is seen as a strong indication for pump head thrombosis. Lubnow et al. published a rate of 4.9% in a study analyzing the need for ECMO circuit replacements.[12] Apart from pump head thrombus formation, other underlying causes for hemolysis found more commonly in clinical practice include high MO pressure gradients, cavitation, access insufficiency, and increased negative (less than -300 mm Hg) pressure generated at the centrifugal pump's inlet.[18] The last two phenomena are closely related and manifest in a visible disruption of extracorporeal blood flow, also known as chattering of the venous access line. Excessive pump RPM, hypovolemia, and bleeding and inadequate cannula choice or placement need to be considered when facing access insufficiency. If chattering persists after reduction of RPM, careful fluid administration, and no active bleeding, then introducing an additional access cannula might be necessary to facilitate more drainage and extracorporeal blood flow. Further, thrombus formation at the return cannula and cardiac tamponade are known to cause obstruction of blood flow and should be ruled out by means of echocardiographic imaging.[19]

Choosing the appropriate cannulae and tubing length are important factors regarding the facilitation of extracorporeal blood flow while simultaneously minimizing intravascular hemolysis. Flow resistance will increase with the tubing length and induce larger surface areas prone to inflammation and possible thrombotic events.[20,21] While keeping the tubing as short as possible is clinically beneficial and also reduces the chance of kinking, the length needs to remain practical to avoid complications during transportation or mobilization. The ELSO listed the event of tubing rupture occurred at a rate of 0.3% of all registered cases in a recent report.[3]

The same principles apply to the cannula. In addition to the relation regarding the length, resistance to flow is inversely proportional to the fourth power of the radius. Short and large-bore cannula promote more efficient blood flow relative to the applied pump RPM and kinetic drainage. Consequently, the extracorporeal blood flow is limited by size of the access cannula, with the return cannula determining the systemic pressure within the circuit. Cannula sizes and lengths largely depend on the implantation site, institutional preference, and experience. Cannula designs and relevant fluid dynamics have been reviewed in detail by Kohler et al.[22] Venous access diameters in the range of 21F–27F cannulae are frequently utilized and are reportedly associated with low negative pressures.[23–25]. On the other hand, short cannulae between 15F and 25F in cannula diameter are commonly chosen for arterial return.[24,25] However, in a retrospective analysis of 101 peripherally cannulated suspects, Takayama et al. proposed that smaller size 15F return cannulae provide comparable clinical support with reduced bleeding complications as opposed to large-bore equivalents.[26] In the same vein, smaller diameter return cannulaes reduce distal limb ischemia induced by arterial vessel occlusion.[27] A meta-analysis of 1866 cases undergoing femoral cannulation for ECMO reported the incidence of leg ischemia at a rate of 11%–17%, and insertion of a distal perfusion catheter is required to establish adequate limb perfusion.[28,29]

At our institution, we follow the approach of largest cannula diameter necessary instead of largest diameter possible, and decisions are based on patient physique as well as targeted flows. Knowing the individual flow properties of available cannulae is paramount. Reimplantation due to inadequate cannula size imposes the risk of bleeding and is a preventable complication. In adult V-V, V-A, or hybrid configuration (VV-V, VV-A [veno-veno-arterial], V-AV) ECMO, we recommend 21F–23F, 50- to 55-cm, multihole cannulae (Venous HLS, Getinge Group) for femoral access; 21F, 50- to 55-cm cannulae with side-ported tips (Biomedicus, Medtronic) for femoral venous return; 15–17F, 15-cm cannulae (HLS, Getinge Group) for femoral arterial return; 17F–19F, 15- to 23-cm cannulae (HLS, Getinge Group) for internal jugular access and return; and 18F–20F, 15-cm cannulae (EOPA, Medtronic) for axillary artery return. In case of a peripheral V-A ECMO configuration, a complimentary 6F distal perfusion catheter is added to the arterial return cannula.

The various cannula sizes, lengths, and drainage port designs also play an important role in dual-site V-V ECMO. As oxygenated blood is reinfused into the venous system, a portion will inevitably be drained back into the extracorporeal circulation without entering systemic circulation and thereby limit the effectiveness of oxygen delivery (of ECMO). The resulting recirculation fraction (Rf) and its clinical relevance depend on cannula type and position, quantity, and direction of extracorporeal blood flow and native cardiac output.[30] Rich et al. have shown that access from the IVC and return to the RA reduces susceptibility to recirculation when compared to the RA-to-IVC direction approach. Specifically, the access cannula tip is best positioned near the atrial-IVC junction. With the multiholes residing within the hepatic IVC, negative pressure is less likely to cause venous collapse and drainage impairment.[30,31] Further, returning blood flow to the RA via cannulation of the IJV instead of the femoral vein (if feasible) reportedly lowers the Rf and improves oxygen delivery.[32] Techniques to quantify the Rf are complicated and potentially dangerous when dealing with critically ill patients.[33] Therefore, in clinical practice the observation of a decreasing (or nonimproving) SaO_2 (<80%) after establishing ECMO coupled with a high (mixed venous) MO inlet oxygen saturation is usually the first indication for relevant recirculation.

However, increasing the Q_E in an attempt to improve oxygen delivery when facing recirculation will instead achieve the opposite, as the Rf amplifies with the extracorporeal flow relative to the native cardiac output. The most common cause for recirculation in dual-site V-V ECMO is close proximity of the respective cannula tips and/or multiholes. Conducting daily chest radiographs to check the cannula positions is therefore advised. If necessary, retracting the access cannula (and return cannula in case of femoro-jugular configuration) is the recommended way to address recirculation. Alternatively, introducing an additional access cannula for bicaval drainage will facilitate similar extracorporeal blood flow rates at lower pump RPM, resulting in less negative pressure and recirculation.[34] Should dual-site V-V ECMO prove unable to provide sufficient oxygenation, a single-site, dual-lumen cannula is worth considering. While the Rf has been reported as low as 2%, events of cannula malposition or migration can compromise the circuit and amplify recirculation rates.[35,36]

Although recirculation is unique to V-V ECMO, a similar phenomenon known as DH or Harlequin syndrome occurs in bifemoral V-A ECMO. Returning extracorporeal blood to the femoral artery in classical fashion results in retrograde flow that competes with the native cardiac output. In the setting of cardiorespiratory failure and V-A ECMO therapy, residual left ventricular contractions eject desaturated blood into the aorta, potentially causing malperfusion of the coronary arteries and cerebral circulation.[37,38] The Q_E on the other hand merely reaches the descending aorta to ensure adequate lower body perfusion. The effect is further amplified due to the fact that peripheral V-A ECMO utilizes the IVC for venous access. Well-oxygenated blood coming from the artificially perfused lower body will reach the IVC and enter the ECMO circuit, whereas the desaturated blood from the upper body drains into the superior vena cava and right heart without being reoxygenated, effectively creating a dual-circuit circulation.[38,39] Extracorporeal blood flow representing 80% of total cardiac support will typically result in a desaturated aortic arch. To assess the development of DH, SaO_2 measurements of both upper extremities are required. Right SaO_2 less than left SaO_2 (or the respective pO_2 values) coupled with a high MO inlet saturation compared to the upper body saturation are the primary indications for DH onset. If diagnosed, delivering oxygenated blood to the upper circuit by introducing an extra return cannula into the right IJV will prevent the left heart from ejecting purely desaturated blood. Adjustable clamps are used on both return lines to regulate the relative blood flow and the emerging pre- and afterload. This triple-site hybrid V-AV configuration has been shown to improve upper body oxygenation in patients with DH and can be achieved without added risk.[40] However, MO inlet saturation might still be elevated due to recirculation and may in turn decrease oxygenation efficiency. An alternative method to completely avoid DH in peripheral V-A ECMO is antegrade blood reinfusion by means of axillary artery cannulation. In addition to being more technically demanding than femoral percutaneous cannulation, complications such as hyperperfusion (24%) and surgical site bleeding (17%) are not uncommon when employing the side-graft technique.[41,42] At our institution, direct cannulation (via arteriotomy or purse-string suture) of the axillary artery coupled with a distal perfusion catheter is therefore the method of choice. Even in post-CPB scenarios, we try to refrain from central cannulation at all cost to avoid surgical reexploration. Emergency implantations of bifemoral V-A ECMO are usually converted to femoro-axillary configuration within 24 hours of MCS establishment.

ECMO AND ANTICOAGULATION

Due to the continuous exposure of blood to the foreign surface of the ECMO circuit, anticoagulation is required to prevent hemostatic activity. UFH is the anticoagulant of choice for the majority (96%) of ECMO centers because it offers a quick onset and the option of direct antagonization by means of protamine.[43] However, balancing the inhibition of clot formation while minimizing the risk of bleeding to ensure therapeutic anticoagulation can prove challenging to achieve and maintain, as there is no clear definition of standards for clinical practice. The assessment of anticoagulation during ECMO usually revolves around the ACT and/or aPTT, with the extent of monitoring largely depending on institutional philosophy, threshold preferences, and measurement devices. Although 97% of centers seem to employ ACT,[44] it has been shown that the aPTT provides more reliable values when moderate or low doses of heparin are applied.[45] Studies analyzing target aPTT ranging from 50 to 70 and 35 to 40 seconds reported excellent survival rates without causing major complications.[46,47] Interestingly enough, Sy et al. suggested that a combination of various blood tests yielded the most favorable treatment outcome.[48] At our institution, a target aPTT between 50 and 60 seconds or ACT of 150–180 seconds is preferred. We use ACT for quick evaluation of the global coagulative state (e.g., in a post-CPB/cardiotomy scenario) but rely on aPTT for more precise UFH titration over the first 12 to 24 hours after establishing MCS in the ICU and have experienced minimal anticoagulation-related adverse events with said scheme. When conducting bedside implantation, a bolus of 5000 IU UFH prior to cannulation coupled with a heparin-coated circuit (e.g., Getinge Bioline) will warrant a sufficient time frame to assess the coagulative state of the patient and initiate anticoagulation accordingly.

However, even though circuit technology and anticoagulation management have advanced, bleeding and thrombotic events remain major sources for complications during ECMO. The ELSO and others reported all forms of clot formation at a rate as high as 40%,[49] with the MO being the most commonly affected circuit component.[12] Underlying causes include low extracorporeal blood flow (e.g., weaning), prolonged MCS, heparin-induced thrombocytopenia (HIT) and inadequate anticoagulation. For the latter, high flows (Q_E > 4 L/min) are recommended to reduce the chance of circuit-related clot formation. Considering HIT, the incidence among V-A ECMO patients is estimated to be 0.36% without a significant increase in mortality.[50] While switching to direct thrombin inhibitors such as argatroban is mandatory to prevent thrombosis, we do not see the need to conduct circuit exchanges to remove heparin-coated components in the event of HIT. Another factor that can possibly impair antithrombotic therapy in spite of

UFH administration is a deficiency of the natural anticoagulant ATIII. Colman et al. observed a higher rate of thrombosis in V-V ECMO patients with lower ATIII baseline levels.[51] Adopting an ATIII range of 80%–120% is advised and might promote in vivo anticoagulation over UFH, thus providing beneficial effects for patients with prolonged ECMO support and increased risk of bleeding.

The increased risk of bleeding in correlation with ECMO is attributed to the consumption of coagulation factors (indicated by fibrinogen levels), platelet depletion (thrombocytopenia) resulting from adhesion to circuit components and to the necessity of anti-thrombotic therapy.[52,53] Over time, said exhaustion of blood components will develop into a bleeding condition also known as disseminated intravascular coagulation.[54] In addition, multiple meta-analyses reported hemorrhagic events, predominantly found at femoral cannula sites (10%–30%) and in the postsurgical setting, and in up to 34% of their recorded cases and associated the occurrence with higher mortality.[49,53,55,56] Effects of intravascular volume loss on the ECMO circuit include access insufficiency and low Hb content, ultimately leading to reduced oxygen delivery and inadequate MCS. The respective bleeding thresholds for patients on ECMO are defined by the ELSO.[57] In accordance with our own experience, major bleeding should therefore result in cessation of anticoagulation for 12–24 hours until the source is found and controlled. Especially in the setting of prolonged CPB converting to ECMO, the onset of a pronounced coagulopathy eliminates the need for immediate anticoagulation. If necessary, rapid fluid administration via the ECMO circuit is possible but only advised in acute situations utilizing vacuum-sealed containers in the presence of a perfusionist in order to prevent or react to air entrapment. Packed red blood cells are transfused to maintain a Hb of at least 8 g/dL, depending on patient blood management protocols. Platelets, FFP, prothrombin complex (PCC), and other coagulation factors are usually well tolerated by the ECMO circuits and are safe to be substituted based on the respective institutional standards. Further, antifibrinolytics such as tranexamic acid reportedly reduce bleeding and improve impaired platelet function.[58] Nevertheless, care must be taken not to administer protamine in an attempt to achieve hemostasis, with the exception being the reversal of the initial UFH dose for CPB via central venous access. Otherwise protamine is never indicated during ECMO as it will result in MO clot formation. If bleeding persists despite the correction of platelet count and coagulation factors, substituting fVIIa has proven to be an effective alternative.[59] However, our own experiences with fVIIa show that a rapid flow reduction and MO thrombosis are not uncommon. It is therefore recommended to pay close attention to developments of extracorporeal blood flow, MO inlet pressure, D-dimers, and hemolysis markers to predict a circuit replacement within the first 24 hours after fVIIa administration.

HOW IS CONSTRUCTIVE BEDSIDE TROUBLESHOOTING PERFORMED?

When conducting CPB, the extracorporeal circuit and its components are continuously monitored for adequate function by specially trained perfusionists, and the slightest diversions in gas exchange or other vital parameters (e.g., temperatures, pressures, etc.) will immediately be addressed in conjunction with anesthesiologists and surgeons. During ECMO on the other hand, patients are transferred to (or are already situated in) the ICU postimplantation, and monitoring relies more on a point-of-care approach. As a result, successful ECMO therapy is based on an interdisciplinary effort and involves perfusionists, ECMO specialists, nursing staff, and physicians from various fields. In the same vein, the guidelines for ECMO centers composed by the ELSO encourage the development of center-specific training programs, catering toward the respective patient population, equipment, and available staff.[60]

Preventing complications is one of the most important aspects of successful ECMO therapy. Literature regarding success and complication rates of ECMO therapy is vast. However, the reporting centers rarely focus on the actual methods of troubleshooting in their publications. This is partly due to the fact that, again, institutions have developed individual approaches on how to establish and manage ECMO. In our institution, it is the responsibility of the perfusion department to establish and maintain ECMO competency. In accordance with the respective ELSO guidelines recommendation to offer lecturing courses and water drills,[61] intensive care physicians and nursing staff who are rotating to one of the ICUs are required to participate in intensive in-house, hands-on ECMO trainings. These workshops are imperative to convey and/or refresh a basic understanding of circuit design and components, clear up common misconceptions, and accustom team members to hardware handling. Every team member should possess the ability to comfortably conduct technical procedures such as ECMO initiation, console restarts, hand cranking, and clamping before being tasked to care for critically ill patients with ECMO support. Together with the underlying principles of extracorporeal blood flow, cannulae, gas exchange, and anticoagulation described in this discussion, these fundamentals lay the groundwork for good practice and will smoothen the steep learning curve that is commonly associated with ECMO. Adding to that, Anderson et al. proposed the incorporation of simulation-based methodology with real-time clinical cues into ECMO training programs and observed beneficial effects due to the increasing opportunities for active learning.[62]

Nevertheless, theoretical training and clinical practice differ. The inevitably occurring complications require timely identification and correction due to their possibly life-threatening nature. Being the first responders, nursing staff and intensive care physicians are usually confronted to carry out the initial troubleshooting process until a specialist is present. However, given the complexity of ECMO, ways of establishing blood flow, and the interaction potential between the respective circuit components, identifying the correct course of action can prove to be challenging, especially in acute situations under stress. We therefore developed a universally applicable flow chart system (Figures 5.1 and 5.2) that assists ECMO therapists of any experience level in the decision-making process when troubleshooting complications and/or initiating emergency responses.

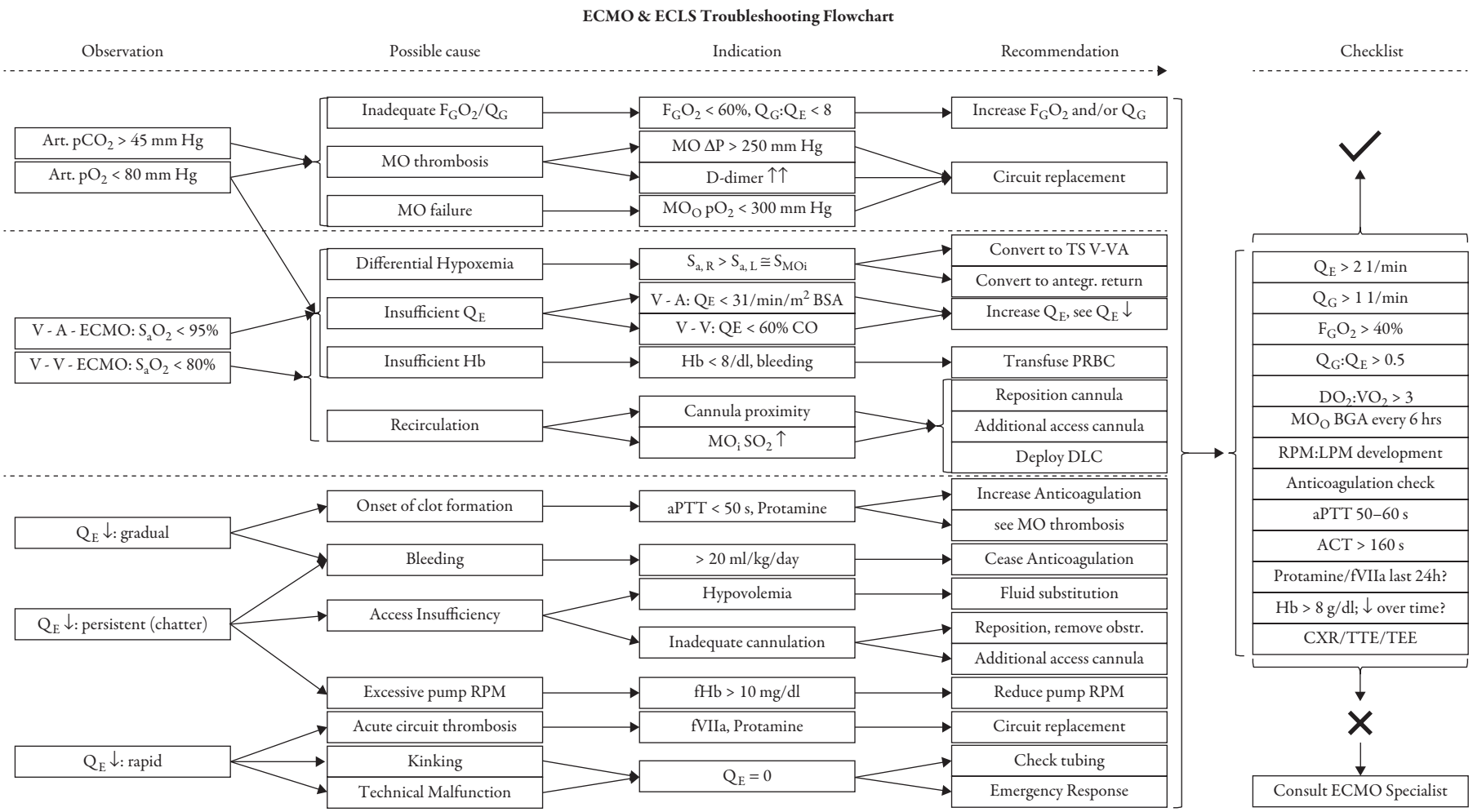


Figure 5.1 ECMO and ECLS troubleshooting flow chart for clinical practice with circuit checklist. ACT, activated clotting time; aPTT, activated partial thromboplastin time; Art., Arterial; Antegr., Antegrade; BGA, blood gas analysis; BSA, body surface area; CO, cardiac output; CXR, chest radiograph; DLC, dual-lumen cannula; DO_2, oxygen delivery; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; F_GO_2, oxygen fraction of sweep gas; fHb, free hemoglobin; fVIIa, activated factor VII; Hb, hemoglobin; LPM, liters per minute; MO, membrane oxygenator; MO_o, MO outlet; ΔP, pressure gradient; pCO_2, partial carbon dioxide pressure; pO_2, partial oxygen pressure; PRBC, packed red blood cells; Q_E, extracorporeal blood flow; Q_G, sweep gas flow; RPM, pump revolutions per minute; $S_{a,\,R/L}$, arterial oxygen saturation at right/left arm; S_{Moi}, oxygen saturation at MO inlet; TS, triple cannulation site; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; V-A, veno-arterial; VO_2, oxygen consumption; V-V, veno-venous.

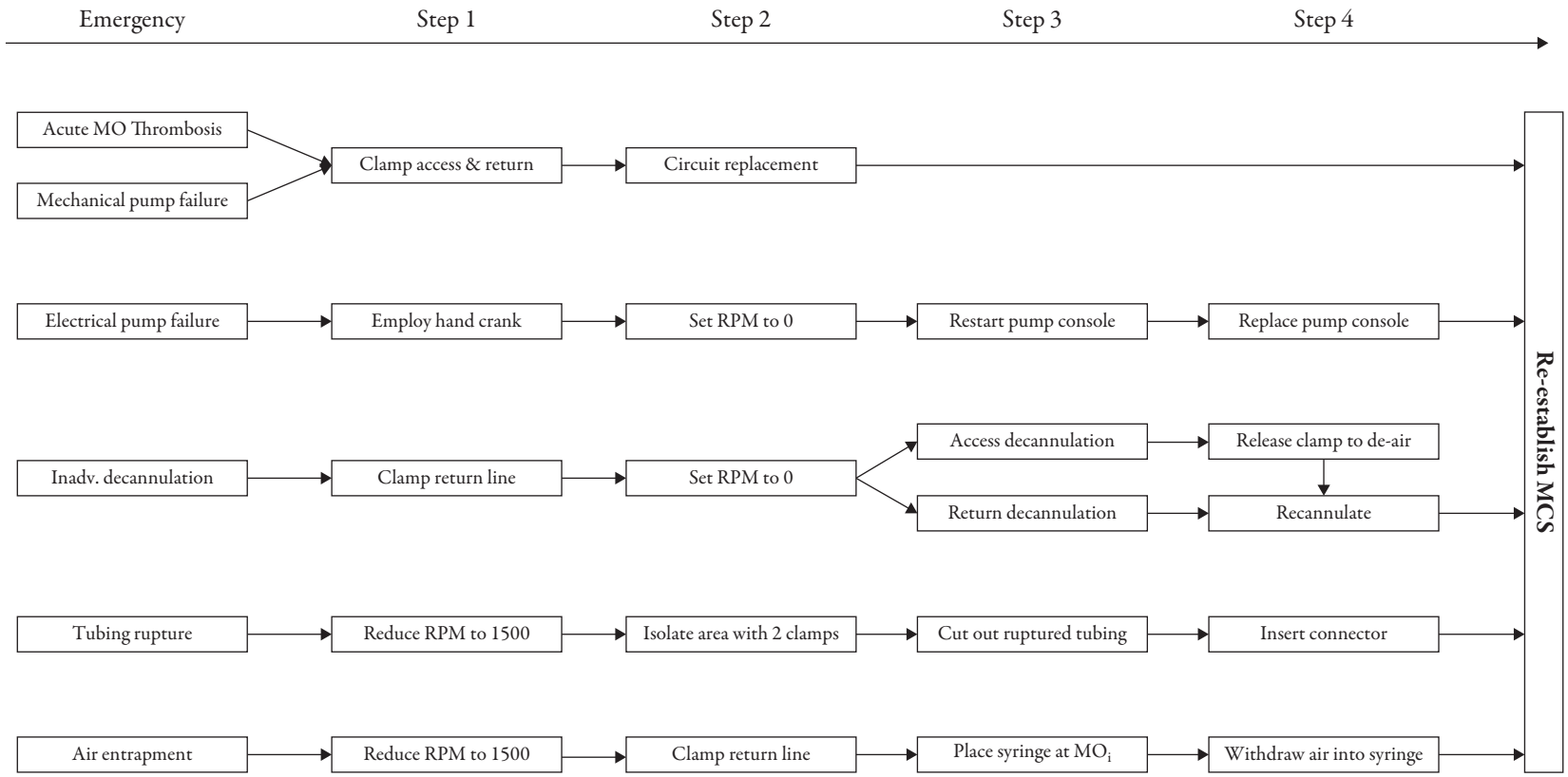


Figure 5.2 ECMO and ECLS emergency response flow chart for bedside application. ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; Inadv., Inadvertent; MCS, mechanical circulatory support; MO, membrane oxygenator; MO_i, MO inlet; RPM, pump revolutions per minute.

In our experience, complications most commonly manifest in a diversion of arterial blood gas values (e.g., SO_2, pO_2, pCO_2); extracorporeal blood flow; and the coagulative state (bleeding vs. thrombosis). If a diversion is detected, following the algorithm, Figure 5.1 will guide the user quickly toward the correct diagnosis or measure via the procedure of exclusion or step-by -step instructions in case of an emergency response (Figure 5.2). The flow chart system is complimented by a circuit and a clinical parameter checklist (Figure 5.1). The circuit checklist expands on the general consensus of ECMO care management reported in the literature,[63] focuses on the critical preconditions for preventing complications, and is to be processed before seeking consultation. Further, the clinical parameter checklist outlines the threshold values indicating, for example, hemolysis and clot formation. The checklists and flow charts are found on every ECMO unit at our institution and serve as the basis for the interactive ECMO training workshops.

Applying algorithms in the setting of ECMO troubleshooting is a promising approach. Attempts of rational algorithm-based hypoxemia management and identification of mechanical dysfunction have been reported.[64,65] By introducing the algorithm-based flow charts, the quality of troubleshooting has greatly improved at our institution. The addition of checklists reinforced our evidence-based therapy concepts and resulted in more consistent ECMO management. Especially in acute and on-call situations, communication and analysis of complications was more constructive and goal oriented and led to reassurance of inexperienced staff. Overall, intensive care physicians and nurses have accepted an even more active role in ECMO management. Due to the higher awareness of interdisciplinary staff, troubleshooting is initiated in a more timely fashion. Complications and their respective incorrect assessment are more likely to be prevented, resulting in the promotion of beneficial therapy outcomes.

CONCLUSION

- Due to their possibly fatal nature, circuit-related complications during ECMO require timely identification and correction.
- The principles of gas exchange, extracorporeal blood flow, and anticoagulation represent the foundation for constructive troubleshooting.
- Establishing checklists enforces standards, prevents complications, and results in more consistent interdisciplinary ECMO management.
- Assisting the decision-making process by means of algorithmic flow charts improves the quality of troubleshooting and promotes beneficial therapy outcomes.

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REVIEW QUESTIONS

1. Which statement regarding gas exchange in MOs is false?

   A. Higher Q_G increases the elimination of CO_2
   B. Q_E greater than 80% of native cardiac output required for decarboxylation
   C. Gas exchange depends on diffusion via pressure gradients
   D. DO_2 increases with Q_E, Hb, and pO_2 gradient

2. Which statement regarding gas exchange in MOs is correct?

   A. Diffusion of O_2 exceeds CO_2 at equal Q_E to Q_G rate
   B. Q_E determines oxygenation, Q_G determines decarboxylation
   C. A ratio of Q_G to Q_E greater than 4 indicates adequate gas exchange
   D. A MO will always output a SaO_2 greater than 95%

3. A patient with a VO_2 of 100 mL/min requires ECLS. What is the minimum required DO_2:VO_2 ratio and rated flow to ensure adequate DO_2?

   A. Ratio 2, rated flow 7 L/min
   B. Ratio 5, rated flow 4 L/min
   C. Ratio 3, rated flow 6 L/min
   D. Ratio 3, rated flow 5 L/min

4. How do you best assess the oxygenation capabilities of an MO?

   A. Mixed venous saturation at the oxygenator inlet
   B. Membrane oxygenator outlet BGA at $F_GO_2 = 1$
   C. SaO_2 drawn for the patient
   D. Membrane oxygenator pressure gradient

5. What is not a result of MO thrombosis?

   A. Access insufficiency
   B. Hemolysis
   C. Increasing D-dimer
   D. Reduction of Q_E

6. You experience a gradual, but fast, Q_E decrease from 5 to 0.7 L/min over a time span of 1 hour. The post-MO gas suggests adequate function. What is the cause for flow reduction?

   A. Device malfunction
   B. Clot formation
   C. Hypovolemia
   D. Hypoxemia

7. Which of the following factors prevents circuit-related thrombosis?

   A. Prolonged MCS
   B. High transmembrane pressure
   C. Low Q_E (<2 L/min)
   D. aPTT above 50–60 seconds

8. You are assessing anticoagulation on ECMO. Which parameter is not in adequate range?

   A. aPTT = 50 seconds
   B. AC = 180 seconds
   C. ATIII = 69%
   D. Platelet count = 100,000

9. When is a reduction of anticoagulation indicated?

   A. ATIII deficiency
   B. Weaning
   C. Surgical cannulation site bleeding
   D. aPTT > 100 seconds

10. Which of the following substitutes is not well tolerated by the ECMO circuit (long term)?

    A. Fresh frozen plasma
    B. Platelet concentrates
    C. Recombinant factor VIIa
    D. Packed red blood cells

11. When is protamine administration indicated?

    A. Bleeding due to recent surgery
    B. Bleeding due to residual heparin
    C. Disseminated intravascular coagulation
    D. Cannulation site bleeding

12. What is not an implication of hemolysis?

    A. Pump head thrombosis
    B. Oxygenator clot
    C. Excessive pump RPM
    D. Bleeding

13. Which configuration is most prone to recirculation?

    A. Single-site, dual-lumen cannula
    B. Femoral access, femoral return
    C. Femoral access, jugular return
    D. Jugular access, femoral return

14. How can the Rf be reduced?

    A. Decreasing distance between cannula
    B. Increasing Q_E
    C. Decreasing native cardiac output
    D. Adding a second access cannula

15. Which statement regarding cannulae is incorrect?

    A. Longer access cannulae facilitate more blood flow
    B. Access cannulae determine the possible Q_E
    C. Return cannulae are shorter to reduce flow resistance
    D. Larger diameter cannulae reduce hemolysis

16. Which complication is not associated with bifemoral ECLS?

    A. Peripheral ischemia
    B. Differential hypoxemia
    C. Recirculation

D. Hyperperfusion

17. You have determined access insufficiency. Which of the following causes can be ruled out?

A. Hypovolemia/bleeding
B. Excessive RPM
C. Oxygenator clot formation
D. Access cannula thrombus

18. Which observation indicates/implicates DH?

A. Low oxygenator inlet saturation
B. Nonejecting left ventricle
C. Isolated cardiac failure
D. Lower right-sided saturation compared to left

19. Rate the measures to correct DH from best to worst:

A. Adding a venous return cannula (V-AV)
B. Adding a venous access cannula (VV-A)
C. Switching to axillary access with side-graft anastomosis (V-A)
D. Switching to direct axillary access (V-A)

ANSWERS

1B, 2B, 3C, 4B, 5A, 6B, 7D, 8C, 9D, 10C, 11B, 12D, 13D, 14D, 15A, 16C, 17C, 18D, 19:D > A > B > C

6.

ECHOCARDIOGRAPHY IN THE MANAGEMENT OF ECMO PATIENTS

Sara J. Allen and David Sidebotham

STEM CASE AND KEY QUESTIONS

A 58-year-old man presented to a large tertiary hospital with a 1-day history of central chest pain and shortness of breath at rest. He had been unwell with a flu-like illness 10 days prior to his admission, from which he had fully recovered. His past medical history was significant only for hypertension, which was treated with an angiotensin-converting enzyme inhibitor.

On admission he had sinus tachycardia of 95 beats/min and was hypotensive, with a blood pressure of 94/62 mm Hg. Peripheral oxygen saturation was 94% breathing room air. The electrocardiogram (ECG) demonstrated anterolateral ST segment depression and T-wave flattening. Serum high-sensitivity troponin was elevated. His chest radiograph (CXR) was normal. A non–ST-segment elevation myocardial infarction (NSTEMI) was the presumptive diagnosis. The patient was admitted to the coronary care unit and managed with sublingual nitroglycerine spray and antiplatelet (aspirin and ticagrelor) and anticoagulant therapy (subcutaneous enoxaparin) in accordance with guidelines.[1] An angiogram was performed the following day, which demonstrated diffuse triple-vessel coronary artery disease and a normal left ventriculogram. The consensus of the cardiology team was that surgical revascularization was the optimal treatment. In view of this, enoxaparin and ticagrelor were discontinued. During the evening, the patient reported recurrent chest pain. Repeat ECG demonstrated worsening ST-segment depression in the anterolateral leads. High-sensitivity troponin was further elevated. The patient was managed with ongoing aspirin, intravenous morphine, and infusions of nitroglycerine and heparin and was referred to the cardiac surgical service. A decision was made to proceed to the operating room for emergency coronary artery bypass graft surgery.

After induction of anesthesia and placement of invasive lines, transesophageal echocardiography (TEE) was performed. This demonstrated moderate left ventricular (LV) impairment, with an ejection fraction of 40%, and regional wall motion abnormalities comprising severe hypokinesis in the mid- and apical anterior and anterolateral LV walls. Right ventricular (RV) function was normal. Valvular function was normal aside from trivial aortic regurgitation. Coronary artery bypass graft surgery was performed, using the left internal thoracic artery and three saphenous vein grafts. The aortic cross-clamp time was 91 minutes.

Initially, weaning from cardiopulmonary bypass (CPB) was attempted with moderate-dose inotrope support (infusions of dopamine and norepinephrine); however, hemodynamic instability with hypotension and low cardiac index occurred. TEE at this time demonstrated severe LV impairment with global hypokinesis and an ejection fraction of 20%. Additionally, there was akinesis of the mid- and apical segments of the anterior and anterolateral LV segments. RV function was mildly impaired. However, moderate central mitral regurgitation was now present. Aortic regurgitation remained trivial. The patient returned to CPB support, and the heart was rested. The coronary grafts were inspected and their flow checked with ultrasound and found to be satisfactory. Inotrope support was escalated (infusions of dopamine, norepinephrine, milrinone, and epinephrine), and a second weaning attempt from CPB occurred 30 minutes later. Hemodynamic parameters were acceptable, with a mean arterial pressure (MAP) greater than 65 mm Hg and a cardiac index of 2.4 L/min. TEE showed persisting regional wall motion abnormalities, but improved global LV function, with an ejection fraction of 35%.

Unfortunately, after CPB was weaned and protamine administered, excess bleeding occurred. Hemorrhage was managed with ongoing surgical hemostasis and transfusion of packed red cells and blood component therapy. After meticulous surgical hemostasis and the administration of 2 L of blood products, hemostasis was deemed acceptable, and the patient's chest was closed. At the time of chest closure, TEE demonstrated moderate-to-severe LV impairment, moderate RV dysfunction, and moderate mitral regurgitation. The patient was transferred to the cardiothoracic intensive care unit (CICU). Initially, the hemodynamic parameters were stable. However, after 2 hours in the CICU, the patient rapidly deteriorated. Repeat TEE demonstrated severe biventricular impairment and severe mitral regurgitation. Aortic regurgitation was trivial. As the patient was periarrest and no operating rooms were immediately available, a decision was made to initiate peripheral veno-arterial extracorporeal membrane oxygenation (V-A ECMO) in the CICU. Cannulation for peripheral V-A ECMO was performed with surface ultrasound and TEE guidance (see below). ECMO was initiated after a small

bolus dose of unfractionated heparin. In view of the high risk of further bleeding, an ongoing infusion of heparin was not commenced. A 29 French (F) cannula for ECMO drainage was placed in the right femoral vein and advanced so the tip was in the right atrium (RA) close to the junction of the superior vena cava (SVC) and the RA. A 17F cannula for ECMO return was placed in the left femoral artery. A 12F cannula was placed into the femoral artery and advanced distally to provide blood flow to the left leg.

At 5.5 L/min, ECMO flows were easily achieved. After initiation of ECMO, the patient's arterial line trace was noted to have minimal pulsatility, consistent with limited LV ejection. TEE now demonstrated severe LV dysfunction, with ejection fraction 10%–15%, and severe RV dysfunction. Spontaneous echo contrast was visible in the LV cavity, which was distended. No thrombus was visible. Mitral regurgitation was moderate. Aortic regurgitation had worsened to mild.

In the following hours, the patient became severely hypoxemic, and he developed frothy pulmonary edema fluid in his endotracheal tube, necessitating suctioning and increasing his positive end-expiratory pressure (PEEP) from 5 to 12 cm H_2O. Additionally, his fractional inspired oxygen (FiO_2) was increased from 0.5 to 0.8 on both the ventilator and the ECMO circuit. In an attempt to decompress the patient's left heart, it was decided to proceed to the interventional cardiology suite to perform an atrial septostomy. This procedure was successful in creating a left-to-right atrial shunt (Figure 6.1). Following this maneuver, the arterial pulse pressure increased to 15 mm Hg. However, the LV distention was not significantly reduced, and the patient's requirement for high PEEP and FiO_2 persisted.

On return to the CICU, it was noted over a period of 2 hours that the pulsatility of the arterial line trace had reduced to a minimum (<5 mm Hg). Repeat TEE was again performed, which demonstrated a large pericardial collection, with echocardiographic signs of cardiac tamponade (Figure 6.2). The patient returned to the operating room and underwent chest

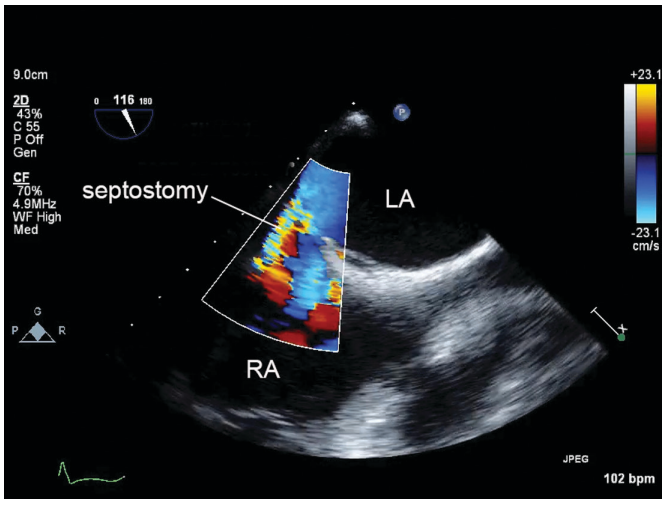


Figure 6.1 Atrial septostomy. Midesophageal bicaval view with color Doppler imaging. A color jet can be seen traversing the atrial septum, indicating blood flow from the left atrium (LA) to the right atrium (RA).

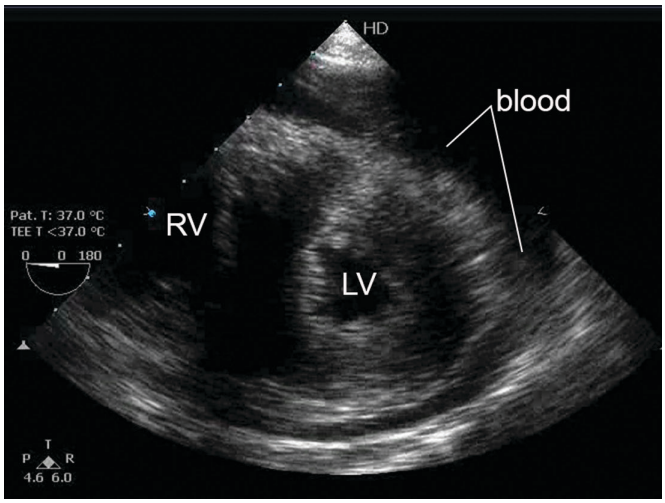


Figure 6.2 Cardiac tamponade. Transgastric mid–short-axis view. An echolucent space can be seen surrounding the left ventricle (LV) and right ventricle (RV), indicative of unclotted blood. Unclotted blood appears as an echolucent (black) space, whereas clotted blood is echo dense (gray/white).

reexploration and evacuation of blood and hematoma. He also had a surgical LV vent placed. The LV vent was tunneled under the sternum, exiting at the sternal notch, and then connected into the drainage limb of the ECMO circuit. The peripheral arterial return cannula was not changed to a central aortic cannula at this time. The patient's hemodynamics were much improved following this procedure, with 25 mm Hg of pulsatility evident on the arterial waveform. TEE demonstrated LV function had improved, with an ejection fraction of 30%. However, LV segmental wall motion abnormalities persisted. RV function improved to moderate impairment only, and mitral regurgitation now was trivial.

Over the next 48 hours, the patient's condition continued to improve. Inotropic support was weaned to a minimum (dopamine infusion alone), and increasing pulsatility was seen on the arterial waveform. ECMO flow was weaned to 3 L/min. Serial TEE studies demonstrated improving biventricular function and a reduction in the LV regional wall motion abnormalities. However, on the fourth postoperative day, the patient developed fevers with reduced lung compliance. Peripheral arterial oxygen saturation, measured at the right upper limb, dropped to 82%, despite an FiO_2 on the ventilator and ECMO circuit of 1.0. Peripheral arterial oxygen saturation measured in the left lower limb was 96%. CXR demonstrated improving pulmonary edema but new left lower lobe consolidation. Tracheal aspirates were sent and later confirmed a growth of *Klebsiella pneumoniae*. The diagnosis of ventilator-associated pneumonia and differential hypoxemia was made (Figure 6.3). Options for management of differential hypoxemia were considered and included continuing V-A ECMO with a transition to central cannulation, transition to veno-arterial-venous (V-AV) ECMO, or to change to V-V (veno-venous) ECMO. TEE was again performed to assess the patient's readiness to wean from V-A ECMO. A weaning study demonstrated suitable parameters for weaning cardiac support. However, profound arterial desaturation occurred at

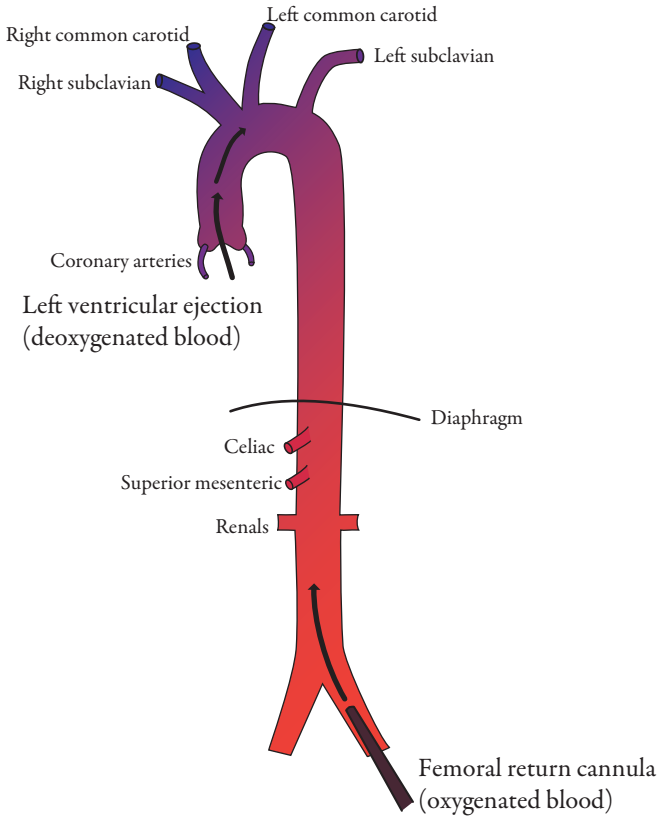


Figure 6.3 Schematic of the thoracic aorta showing differential oxygenation with peripheral V-A ECMO. Deoxygenated blood from the systemic venous return passes through the poorly functioning lungs and is ejected from the left ventricle, leading to upper body hypoxemia (affecting the coronary, cerebral, and upper limb vessels). Oxygenated blood from the ECMO return cannula preferentially perfuses the lower body.

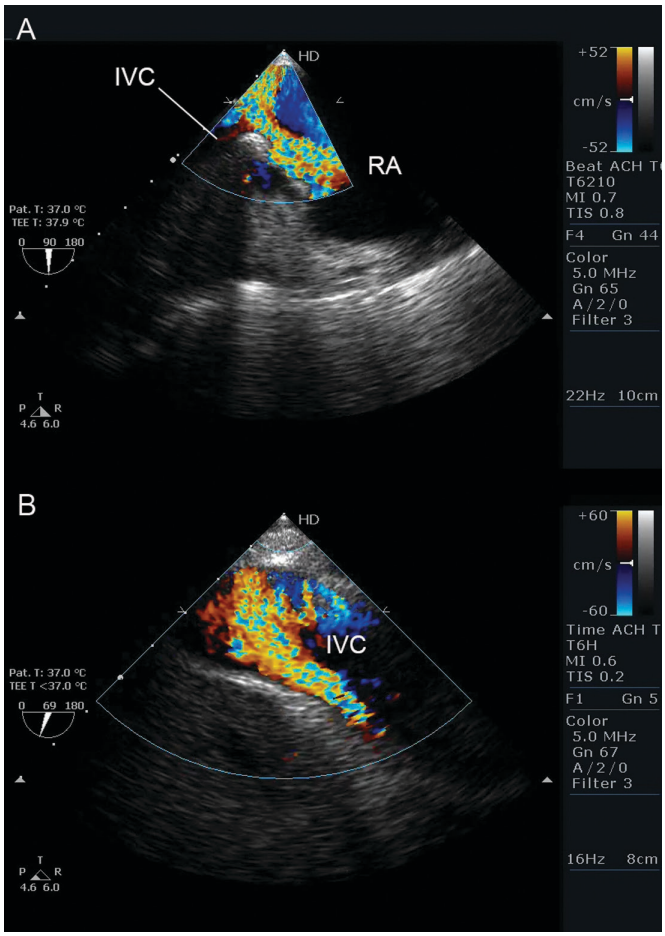


Figure 6.4 Recirculation with V-V ECMO. Panel A shows a midesophageal bicaval view. A high-velocity jet from the ECMO return cannula (which is not seen) extends into the inferior vena cava (IVC). Panel B shows a view of the IVC. The high-velocity jet from the ECMO return cannula can be seen passing down the IVC toward the ECMO drainage cannula (which is not seen). Compare with Figure 6.19, which shows the effect of manipulating the cannulae in the same patient.

ECMO flows of 1 L/min. On this basis, the patient was felt to require ongoing ECMO support for oxygenation. It was therefore decided to change to V-V ECMO.

The patient returned to the operating room and had a 19F, 18-cm long ECMO cannula inserted into the right internal jugular vein, once again guided by vascular ultrasound and TEE. This cannula was connected to the return limb of the ECMO circuit, and the femoral venous drainage cannula was withdrawn slightly. With these maneuvers, the patient's arterial oxygen saturation increased to 96%, with similar recordings obtained from the right upper limb and the lower limbs. At this point, the patient was on V-AV ECMO support.

A repeat weaning study was then performed to determine if V-A support could be discontinued. This involved progressive clamping of the femoral arterial return cannula under TEE guidance. TEE confirmed satisfactory global LV function (ejection fraction 40%, aortic valve velocity time integral 12 cm, lateral mitral annulus tissue Doppler velocity 8 cm/s). RV function was mildly impaired. Clinical parameters remained stable throughout, with a MAP greater than 65 mm Hg on moderate inotrope support (dopamine, milrinone, and low-dose norepinephrine infusions). On this basis, V-A support was discontinued. The femoral arterial return cannula was clamped and removed and the femoral artery surgically repaired. The patient returned to the CICU on V-V ECMO support at 4.5 L/min.

Overnight, the patient's arterial oxygen saturation gradually fell from 92% to 82%. V-V ECMO flow was increased to 6 L/min in an attempt to improve oxygenation, with no effect. Recirculation was suspected (Figure 6.4). A preoxygenator blood gas taken from the ECMO circuit and revealed an oxygen saturation of 90%. TEE assessment of the cannulae position and flow patterns confirmed recirculation, with the tip of the drainage cannula identified in the inferior vena cava (IVC), close to the IVC-RA junction. The drainage cannula was withdrawn under TEE guidance until the tip was in the IVC at the level of the hepatic veins (Figure 6.5). The return cannula was twisted slightly to better direct blood through the tricuspid valve and away from the IVC (Figure 6.5). With these maneuvers, the patient's arterial oxygen saturation improved to 90%.

After a further 5 days, oxygenation had improved sufficiently to allow V-V ECMO flow to be weaned to 3 L/min. A trial discontinuation of the ECMO gas sweep was well

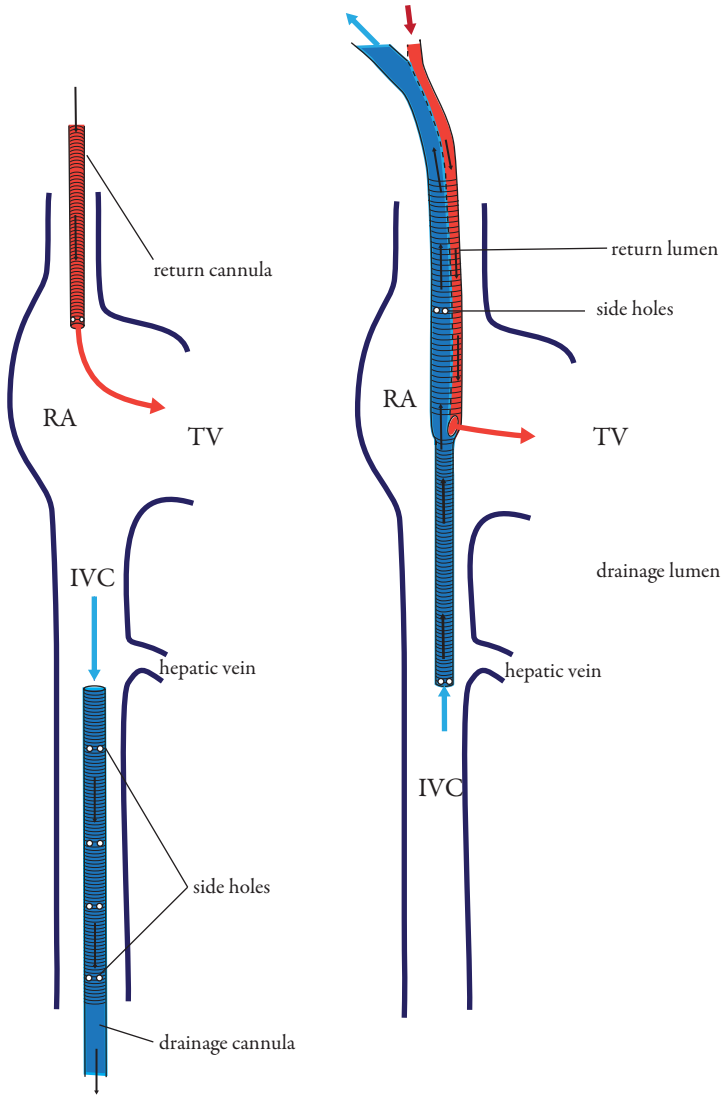


Figure 6.5 The optimal cannulae positions for V-V ECMO. The left-hand schematic shows a two-cannula technique. The tip of the return cannula is positioned at the junction of the superior vena cava and right atrium (RA). Ideally, blood from the return cannula is directed toward the tricuspid valve (TV). The tip of the drainage cannula is at the level of the hepatic veins in the inferior vena cava (IVC). The right-hand schematic shows a double-lumen cannula technique. The orifice of the return lumen is in the RA. Ideally, blood from the return lumen passes through the TV. The tip of the drainage lumen is at the level of the hepatic veins. With both techniques, ideally there should be no recirculation from the return cannula/lumen directly to the drainage cannula/lumen.

tolerated by the patient. With the ventilator set at a tidal volume of 6 mL/kg, FiO_2 0.5, PEEP 8 cm H_2O, peripheral arterial oxygen saturation was maintained above 94%. A transthoracic echocardiogram (TTE) was performed to assess RV function prior to weaning V-V ECMO. TTE demonstrated mild RV dilation and mildly impaired RV function. Tricuspid regurgitation was trivial. Subsequently, the V-V ECMO circuit was clamped and the patient successfully decannulated.

The following day, vascular ultrasound scans were performed to identify whether any arterial or venous thrombi were present at the cannulation sites. A small, nonocclusive thrombus was detected in the right internal jugular vein. No thrombus was present in the femoral artery or vein. No further action was taken.

The patient underwent percutaneous tracheostomy and was slowly weaned from mechanical ventilation and inotropic support over the next 6 days. He was discharged from the CICU to the ward on postoperative day 16 and discharged from the hospital on postoperative day 23.

HOW DOES ECHOCARDIOGRAPHY HELP DETERMINE WHICH MODE OF ECMO SUPPORT TO USE (V-A VERSUS V-V)?

Patients with severe respiratory failure and stable hemodynamics are best managed with V-V ECMO, and patients with severe cardiac failure (with or without respiratory failure) are managed best with V-A ECMO. In each of these circumstances, echocardiography is useful to confirm the indications, exclude contraindications, and guide cannula placement. However, the choice between V-A ECMO versus V-V ECMO is not always straightforward. Hemodynamic instability is

common in patients with severe respiratory failure and may be due to[2]

- RV dysfunction secondary to high intrathoracic pressures with mechanical ventilation
- RV dysfunction secondary to acutely elevated pulmonary vascular resistance due to inflammation, hypoxemia, and acidosis
- LV or RV dysfunction secondary to sepsis or underlying cardiac disease
- Vasoplegia
- Hypovolemia

Severe underlying LV or RV dysfunction necessitates V-A ECMO support, while hemodynamic instability due to correctable factors (e.g., aggressive mechanical ventilation or vasodilation) may be managed with V-V ECMO. Echocardiography is crucial for decision-making on the appropriate mode of ECMO as it allows accurate and timely assessment of LV and RV function, as well as assessment of response to therapy, such as with vasopressors or fluid.

In this patient, the initial choice of V-A ECMO was clear given the primary indication for support was severe biventricular impairment. Later, significant ventricular recovery had occurred while pulmonary function remained impaired due to resolving pulmonary edema but new ventilator-associated pneumonia. In the context of peripheral V-A ECMO, cardiac recovery with ongoing pulmonary dysfunction led to differential hypoxemia, necessitating a change from V-A to V-V ECMO. Differential hypoxemia is discussed further below.

WHAT CONTRAINDICATIONS TO ECMO ARE DETECTED WITH ECHOCARDIOGRAPHY?

Contraindications to V-A ECMO that can be diagnosed with echocardiography or vascular ultrasound include the following:

- Aortic aneurysm or dissection due to the risk of aneurysm rupture or the placement of a cannula into a false dissection lumen.
- Severe atheromatous disease of the aorta. This is a relative contraindication to ECMO due to the risk of systemic embolization of atheroma dislodged by high-pressure blood flow from the ECMO return cannula.
- Severe occlusive peripheral arterial disease (for peripheral V-A ECMO).
- Significant aortic regurgitation due to the risk of ongoing LV distention when the aortic root is pressurized via the return cannula flow. Note that mild aortic regurgitation, while not a contraindication to V-A ECMO, may worsen with aortic root pressurization, leading to LV distention and intracardiac stasis (Figures 6.6 and 6.7).[3] Therefore, the presence and severity of aortic regurgitation should be assessed both prior to and subsequent to commencing V-A ECMO.

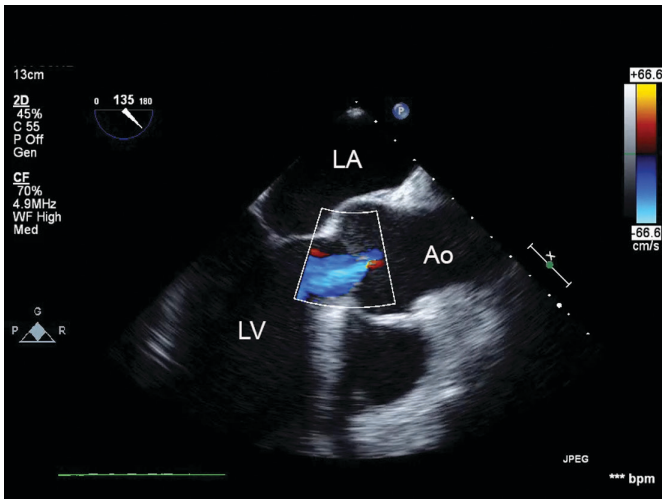


Figure 6.6 Low-velocity aortic regurgitation following the initiation of V-A ECMO in a patient with preexisting mild aortic regurgitation. Midesophageal long-axis view. The key finding is that there is no color aliasing of the regurgitant jet, which is highly atypical for a jet of aortic regurgitation. The explanation for this finding is that the left ventricle (LV) had distended following initiation of V-A ECMO, increasing LV diastolic pressure and reducing the diastolic pressure gradient across the aortic valve. This appearance is extremely concerning in a patient following initiation of V-A ECMO. Compare with Figure 6.7, which is from the same patient. LA, left atrium; Ao, aorta.

In addition, echocardiography will often aid in assessing the chronicity of LV or RV dysfunction. Features suggesting chronic dysfunction include marked dilation of the ventricular chambers and increased short-axis–to–long-axis ratio of LV or RV (i.e., the chambers become more spherical). In patients with LV remodeling due to chronic ischemia

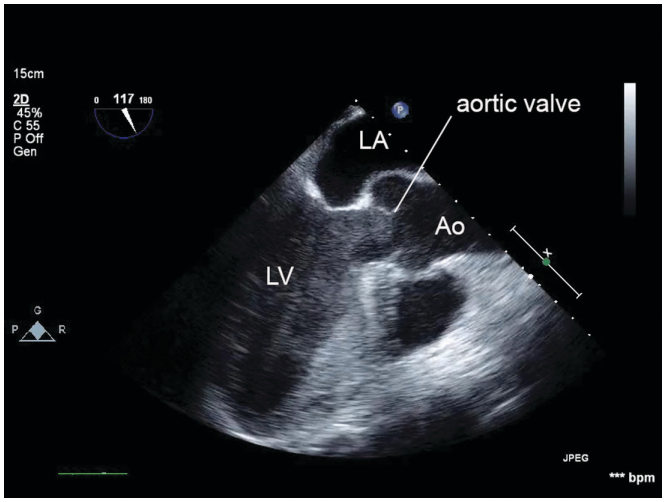


Figure 6.7 Open aortic valve with intracardiac stasis following initiation of V-A ECMO. TEE midesophageal long-axis view. This image was captured approximately 5 minutes after Figure 6.6. The aortic valve is widely open throughout the cardiac cycle; there is marked left ventricular (LV) distension (not readily apparent in this frame), and spontaneous echo contrast is present in the LV, consistent with intracardiac stasis. The pressure between the LV and aorta (Ao) has equalized throughout the cardiac cycle, which is extremely concerning. Compare with Figures 6.21 and 6.22, which are from a different patient. LA, left atrium.

or long-standing valvular regurgitation, the LV wall is typically thinned, whereas chronic RV pressure overload due to increased pulmonary vascular resistance leads to RV hypertrophy.[2] Chronic severe LV or RV dysfunction may be a contraindication to ECMO support, depending on the other clinical features and availability of other supports (e.g., bridging to ventricular assist device, bridging to transplantation).

Mitral regurgitation can also complicate the management of V-A ECMO. Severe mitral regurgitation can result in inadequate LV decompression, requiring either an atrial septostomy or an LV vent (via a surgical vent or an Impella device).[4]

Intracardiac shunts such as atrial septal defects and patent foramen ovale are not contraindications to V-A or V-V ECMO. However, intracardiac shunts may complicate V-V ECMO due to the risk of systemic embolization of gas or thrombus from the return cannula.

HOW ARE VASCULAR ULTRASOUND AND ECHOCARDIOGRAPHY USED TO GUIDE CANNULATION AND ESTABLISHING ECMO?

Vascular ultrasound and echocardiography are critical to establishing ECMO in a safe and timely fashion. Initially used to visualize and inspect the target vessels prior to cannulation (to confirm location, then guide needle tip placement, identify abnormalities such as vessel stenosis or thrombus), then to confirm correct positioning of the guidewire prior to dilation, and subsequently to confirm adequate cannulae position and function.

For peripheral arterial cannulation via the femoral artery, the presence of a guidewire in the aorta should be confirmed with two-dimensional (2-D) imaging (Figure 6.8). For femoral venous cannulation, the presence of a guidewire in the IVC and RA should be confirmed (Figure 6.9). Guidewires are seen as sharply echogenic structures on 2-D imaging. The optimal position of the drainage cannulae differs between V-A ECMO and V-V ECMO. With V-V ECMO, both the drainage and return cannulae are located in the venous system, and if they are too closely collocated, there is a risk of recirculation between the return cannula and the drainage cannula (Figure 6.4), leading to arterial hypoxemia. Thus, for V-V ECMO the optimal position for the tip of the drainage cannula is in the IVC at the level of the hepatic veins (Figures 6.5, 6.10, and 6.11). The tip of the return cannula should be positioned in the RA, close to the junction of the SVC and RA (Figures 6.12 and 6.13). Note that if a double-lumen cannula is used for V-V ECMO, the entire cannula will be

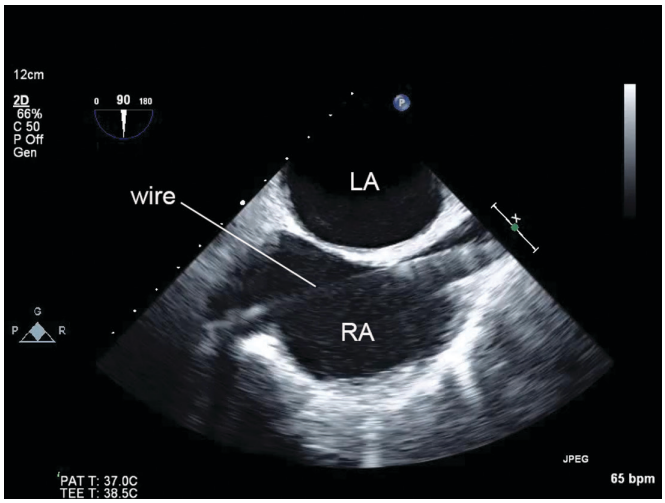


Figure 6.9 Guidewire in the right atrium (RA) prior to placement of an ECMO drainage cannula. Midesophageal bicaval view. The guidewire can be seen in the RA and superior vena cava. While not apparent in this image, the guidewire had been advanced from a femoral vein and can be seen traversing the RA and extending into the superior vena cava. LA, left atrium.

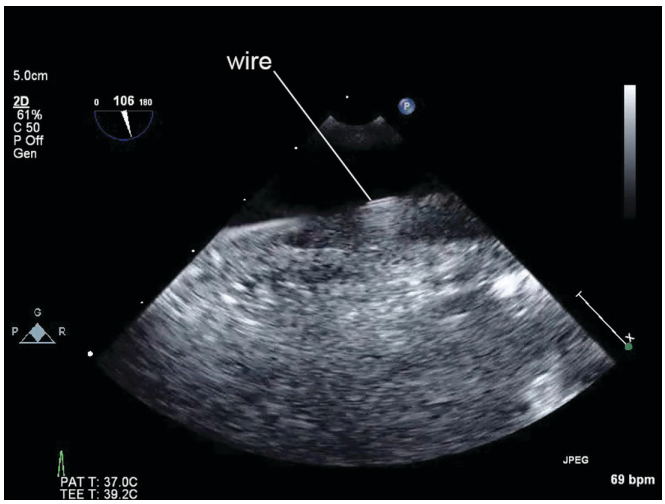


Figure 6.8 Guidewire in the thoracic aorta prior to peripheral arterial cannulation for V-A ECMO. Thoracic aortic long-axis view. A linear echogenic structure with associated reverberation artifact typical of a wire can be seen in the descending thoracic aorta. The wire has been advanced from a femoral artery.

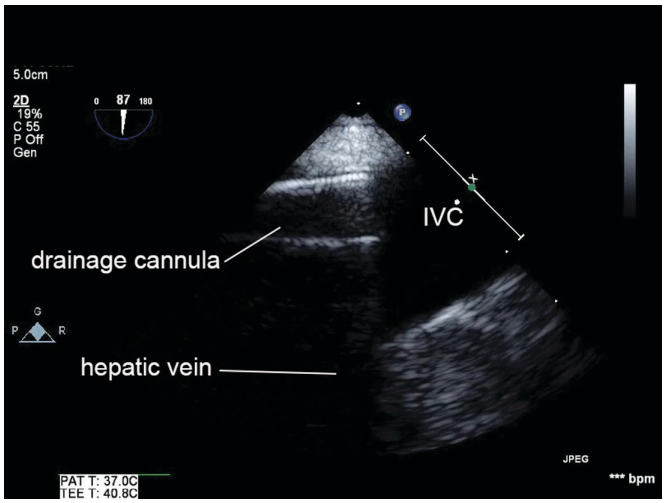


Figure 6.10 Normal position of a drainage cannula for V-V ECMO. Inferior vena cava (IVC) view. The drainage cannula has been advanced from a femoral vein into the IVC. While not readily apparent in this image, the tip of the cannula is at the level of the hepatic veins.

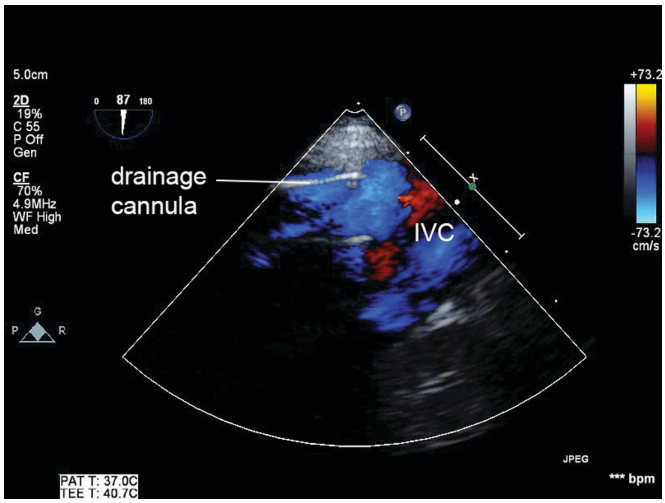


Figure 6.11 Normal position of the drainage cannula for V-V ECMO. Inferior vena cava (IVC) view with color Doppler imaging. Flow around and into the drainage cannula is of low velocity (no aliasing), which is typical of the flow pattern seen around the drainage cannula (compare with Figure 6.13).

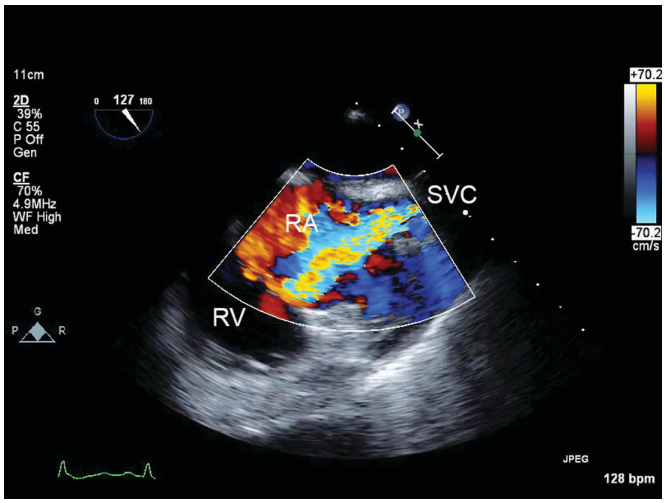


Figure 6.13 Normal flow pattern from the return cannula for V-V ECMO. Midesophageal bicaval view with color Doppler imaging. A high-velocity jet can be seen in the right atrium (RA), which originates from the return cannula in the superior vena cava (SVC), although the cannula itself cannot be seen in this image. The jet is directed toward the tricuspid valve (not seen) and right ventricle (RV), which is ideal. Compare with Figure 6.11.

inserted into the RA, and the tip (drainage lumen) should be positioned in the IVC at the level of the hepatic veins. The orifice of the return lumen is positioned within the RA, with particular attention that the flow from this lumen is directed toward the tricuspid valve (Figure 6.5). Irrespective of the cannulation strategy used for V-V ECMO, blood flow from the return cannula appears as a high-velocity jet in the RA, ideally directed toward the tricuspid valve (Figure 6.13). For V-A ECMO, there is no risk of recirculation, and the optimal position of the tip of the drainage cannula is in the mid-RA (Figures 6.14 and 6.15). This position affords the most effective drainage and therefore optimizes flow.

In this patient, surface ultrasound with a linear array vascular probe was used to identify the left femoral artery. A 12F cannula was inserted into the left femoral artery via a Seldinger technique, approximately 8 cm below the inguinal ligament, and advanced distally, to provide perfusion to the left lower limb. Following placement of the distal perfusion cannula, a 17F, 18-cm ECMO return cannula was placed into the left femoral artery and advanced to the iliac artery. As well as visualization of the needle tip puncturing the femoral artery and of the guidewire in the lumen of the femoral artery, the passage of the guidewire into the aorta was confirmed with TEE (Figure 6.8). Visualizing the guidewire in the aorta confirms arterial placement and helps avoid complications. A 29F, 50-cm ECMO drainage

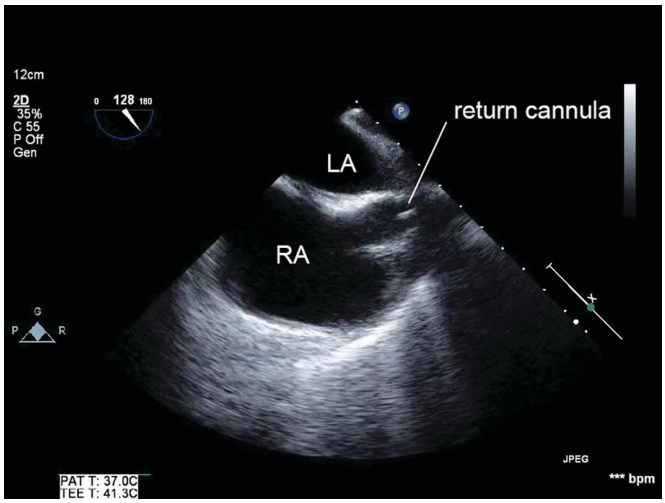


Figure 6.12 Normal position of the return cannula for V-V ECMO. Midesophageal bicaval view. The tip of the return cannula can be seen in the superior vena cava, close to the junction with the right atrium (RA). LA, left atrium. Compare with Figure 6.5.

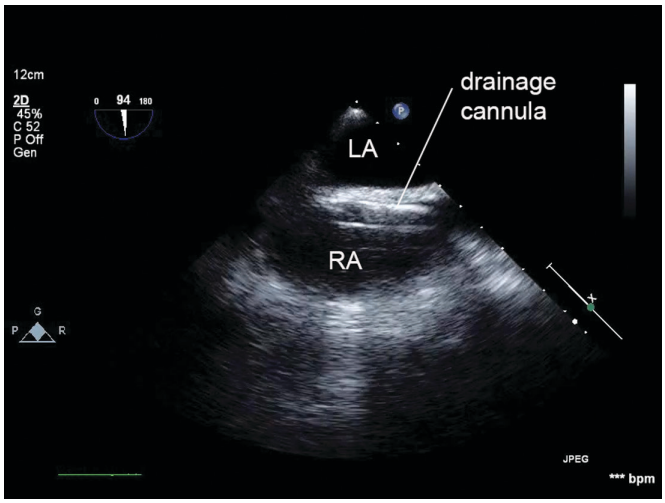


Figure 6.14 Normal position of the drainage cannula for V-A ECMO. Midesophageal bicaval view. A cannula can be seen traversing the right atrium (RA) with the tip lying close to the origin of the superior vena cava (not seen). LA, left atrium.

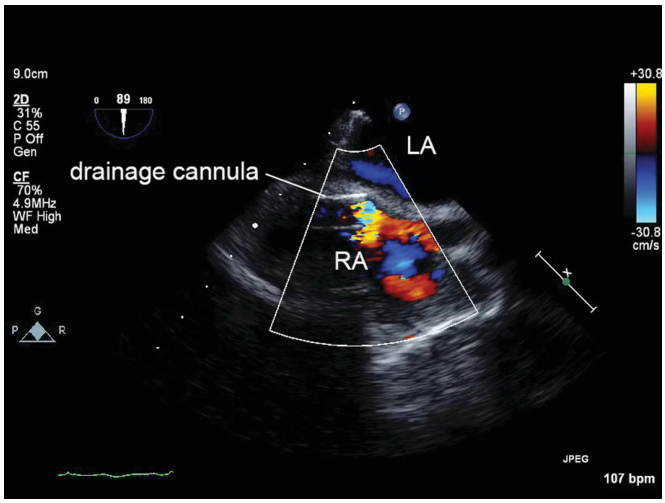


Figure 6.15 Normal position of the drainage cannula for V-A ECMO. Midesophageal bicaval view with color Doppler imaging. Blood flow can be seen around the origin of the tip of the drainage cannula, which lies in the right atrium (RA) close to the origin of the superior vena cava. Note the Nyquist limit is set to only 30.8 cm/s, which is why the blood flow demonstrates aliasing. In fact, blood flow around the origin of the drainage cannula is typically of much lower velocity (<1–2 m/s) than that from the return cannula. LA, left atrium. Compare with Figures 6.11 and 6.13.

cannula was placed into the right femoral vein. Again, surface ultrasound was used to identify the vein, confirm the needle tip position, and identify the guidewire in the lumen of the vessel. Prior to dilation of the vessel, TEE was used to confirm the guidewire in the IVC and then the RA (Figure 6.9). The tip of the drainage cannula in the RA, close to the SVC-RA junction, was confirmed with TEE (Figure 6.10).

WHAT COMPLICATIONS OF ECMO ARE DIAGNOSED WITH THE USE OF ECHOCARDIOGRAPHY?

Echocardiography is useful in the diagnosis of several complications following institution of ECMO. These include the following:

- Cannula malposition or obstruction. This may occur at the time of cannulation or subsequently during ongoing ECMO support. With 2-D imaging, the ECMO cannula may appear obstructed by cardiac structures, tissue, or thrombus (Figure 6.16), or the tip may be seen abutting a vessel wall or cardiac structure. Imaging with color Doppler demonstrates high-velocity turbulent flow that is misdirected. Repositioning of the cannula is necessary under echocardiographic guidance.
- Left ventricle distention (V-A ECMO). This may occur when ventricular function is very severely impaired, particularly if significant mitral or aortic regurgitation is present (mitral regurgitation can also occur as a *result* of LV distention).[3] Distention can impair LV recovery and cause elevated left atrial (LA) pressure and pulmonary edema. LV distension is suggested by loss of pulsatility on the arterial waveform and confirmed with echocardiography. The LV and LA appear dilated, with greatly reduced LV contractility (Figure 6.17). There is minimal or no opening of the aortic valve, and mitral regurgitation is usually at least moderate (Figure 6.18). Management of LV distention includes increasing inotrope therapy to promote LV ejection, atrial septostomy to decompress the left heart and reduce pulmonary edema, intra-aortic balloon counterpulsation, surgical venting of the LV, and use of LV microassist devices, such as the Impella.[4] Echocardiography is used to guide each of these therapies and to assess the response to treatment.
- Recirculation (V-V ECMO). This occurs when the tip of the drainage cannula is closely approximated to the tip of the return cannula, allowing oxygenated blood from the return cannula to enter the drainage cannula, which in turn prevents oxygenated blood from circulating through the lungs and reaching the systemic circulation. The result is arterial hypoxemia that is unresponsive to increasing ECMO flow. In the midesophageal bicaval view, the high-velocity jet from the return cannula can often be seen directed toward the IVC (Figure 6.4). Management involves withdrawing the drainage cannula, so the tip is at the level of the hepatic veins (Figure 6.19). Manipulation or repositioning of the return cannula is sometimes also required (Figure 6.19) to help direct blood flow toward the tricuspid valve and away from the IVC. CXR can also be used to help confirm that there is an adequate distance between cannulae tips (Figure 6.20).
- Thrombus formation (V-V or V-A ECMO). Intracardiac stasis (seen on echocardiography as spontaneous echo contrast or "smoke") predisposes to thrombus formation, which can occur in any of the cardiac chambers (Figures 6.21 and 6.22) Intracardiac thrombus is associated with high morbidity and mortality[5]; however, it is not always fatal and has been successfully managed with surgical thrombectomy in our institution.
- Cardiac tamponade (V-A ECMO). Cardiac tamponade can occur in patients receiving ECMO, most commonly in patients supported with V-A ECMO after cardiac surgery (Figure 6.2). As the patient's circulation is supported and ventricular filling and ejection usually reduced, pericardial collections may become large before causing clinical deterioration. Eventually, compression of the RA occurs, causing impaired ECMO drainage and, therefore reduced flow despite high pump speed. Central venous pressure is usually elevated. Cardiac tamponade results in blood stasis and risks intracardiac thrombus formation (Figure 6.22). Echocardiography is used to identify pericardial collections and confirm tamponade.

- Aortic dissection (V-A ECMO). Guidewire insertion and serial vessel dilation, as well as insertion of cannulae, can result in vascular injury. In particular, there is a risk of aortic dissection. Echocardiography is used to assess the thoracic aorta during and after cannulation.
- Differential hypoxemia (peripheral V-A ECMO; Figure 6.3). Differential hypoxemia (also called Harlequin syndrome) can occur during peripheral V-A ECMO when recovery of cardiac function precedes recovery of pulmonary function. In this circumstance, deoxygenated blood returning to the right heart passes through the poorly functioning lungs and is ejected from the LV. Deoxygenated blood then perfuses the proximal branches of the aorta (coronary, cerebral, upper limb circulations). Oxygenated blood from the return cannula preferentially perfuses the lower limbs and body. The diagnosis is confirmed by the finding of lower arterial oxygen saturation in the right upper limb than in the lower limbs. The diagnosis is supported by echocardiographic evidence of improved ventricular function and significant ejection through the pulmonary and aortic valves. Differential hypoxemia may be managed, as in the case discussed, by transition to V-V ECMO—assuming cardiac function has recovered sufficiently to no longer require mechanical support. However, if ongoing cardiac support is required, differential hypoxemia is managed by insertion of a second return cannula into the SVC, thus transitioning to V-AV ECMO. Alternatively, using central cannulation for V-A ECMO prevents clinically significant differential hypoxemia from developing.[6] In the case discussed, transitioning to central cannulation during the patient's return to theater for relief of tamponade may have prevented the subsequent development of differential hypoxemia.

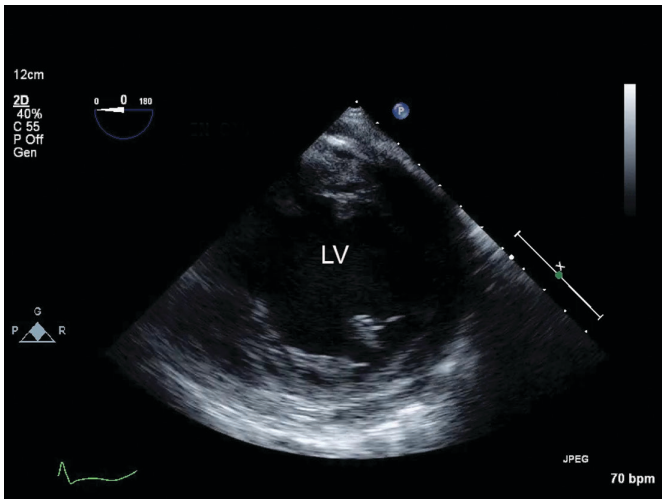


Figure 6.17 Left ventricle dilation during V-A ECMO. Transgastric short-axis view. The left ventricle (LV) is severely dilated. What is not apparent in this still frame is that the LV is akinetic, with no LV ejection and no opening of the aortic valve.

WHICH ECHOCARDIOGRAPHY PARAMETERS ARE MEASURED AND ASSESSED DURING WEANING FROM A V-A ECMO STUDY, AND WHAT ARE THE ECHOCARDIOGRAPHIC PREDICTORS OF SUCCESSFUL WEANING FROM V-A ECMO?

Weaning from V-A ECMO should be guided by echocardiography in conjunction with clinical parameters. A weaning study is usually performed with serial reductions in ECMO circuit flow to minimal levels, with assessment of cardiac function at each stepwise reduction in flow. Typically, flow is reduced by 0.5–1.0 L/min at each stage. Minimal flow is regarded as 0.5–1.0 L/min. During a weaning study, it is

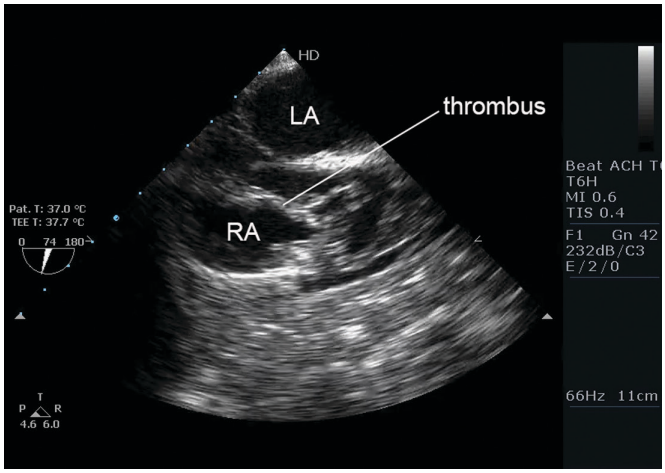


Figure 6.16 Thrombus in the right atrium (RA) during V-V ECMO. Midesophageal bicaval view. Thrombus attached to the drainage cannula (which is not seen) passed back and forth across the RA. The image shows the thrombus traversing the RA. LA, left atrium.

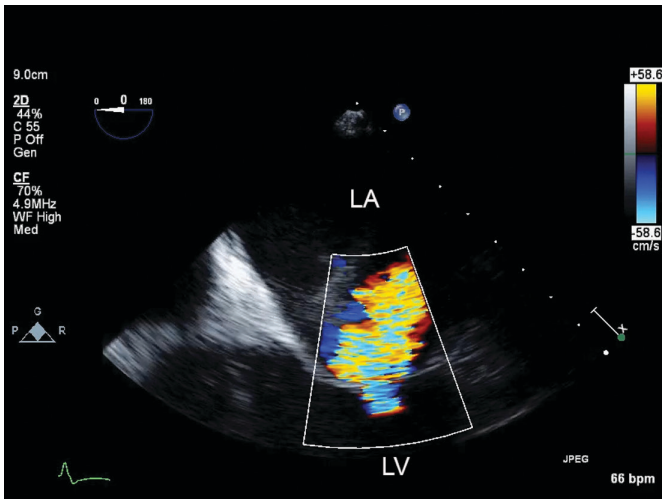


Figure 6.18 Central mitral regurgitation during V-A ECMO. Midesophageal, four-chamber view. A central jet of mitral regurgitation is seen. The vena contracta width is approximately 0.8 cm, indicating the regurgitation is probably severe. LA, left atrium. LV, left ventricle.

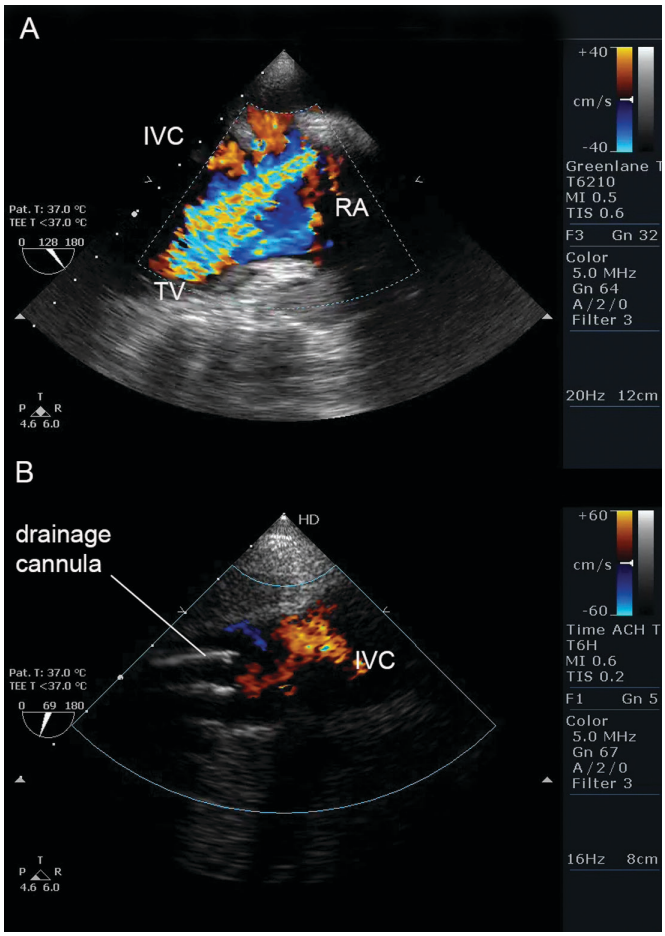


Figure 6.19 Manipulations of the cannula positions to minimize recirculation during V-V ECMO. Compare with Figure 6.4, which is from the same patient. In panel A, a modified midesophageal bicaval view is shown. The return cannula has been manipulated, and now the jet of blood is directed toward the tricuspid valve (TV) and away from the inferior vena cava (IVC). In panel B, the IVC view is shown, with the tip of the drainage cannula clearly visible. Flow around the tip of the drainage cannula has a normal appearance. Importantly, there is no evidence of a high-velocity flow around the drainage cannula, suggestive of blood flow from the return cannula.

important to ensure the patient is adequately anticoagulated, as the risk of intracardiac and circuit thrombosis is likely to be increased by low ECMO flow.

Left ventricular and RV function are assessed according to standard guidelines.[7–9] There is no single reliable echocardiographic predictor of success or failure in weaning from V-A ECMO, and it is vital to interpret echocardiographic findings in conjunction with clinical hemodynamic parameters. Echocardiographic parameters that have been associated with success include an LV ejection fraction greater than 25%, an aortic valve velocity time integral on continuous wave Doppler greater than 10 cm, and a peak systolic velocity greater than 6 cm/s on tissue Doppler imaging of the lateral mitral annulus.[10] Another study found that increases in strain and strain rate of greater than 20% compared with baseline, at minimal V-A ECMO flows, predicted successful weaning.[11] Recently, an RV ejection fraction greater than 25% on three-dimensional (3-D) imaging was found to predict successful weaning.[12]

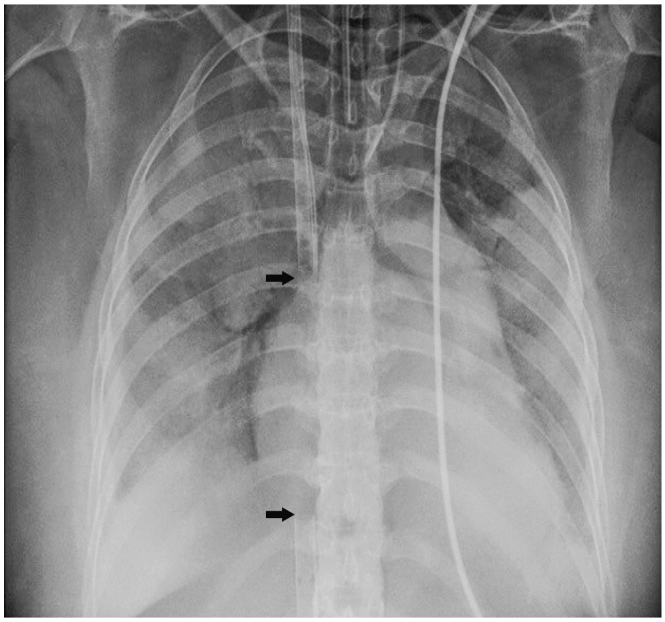


Figure 6.20 Chest radiograph showing the normal position of V-V ECMO cannulae. The tip of the return cannula can be seen at the level of the right main bronchus, and the tip of the drainage cannula can be seen at the level of the diaphragm.

IS THERE A ROLE FOR USING ECHOCARDIOGRAPHY IN WEANING FROM V-V ECMO?

For weaning from V-V ECMO, sweep gas flow rather than blood flow is reduced, and echocardiography is not required. However, echocardiography can be useful in the assessment of the RV to ensure that acute cor pulmonale is not present, particularly if moderate or high ventilation pressures are anticipated.

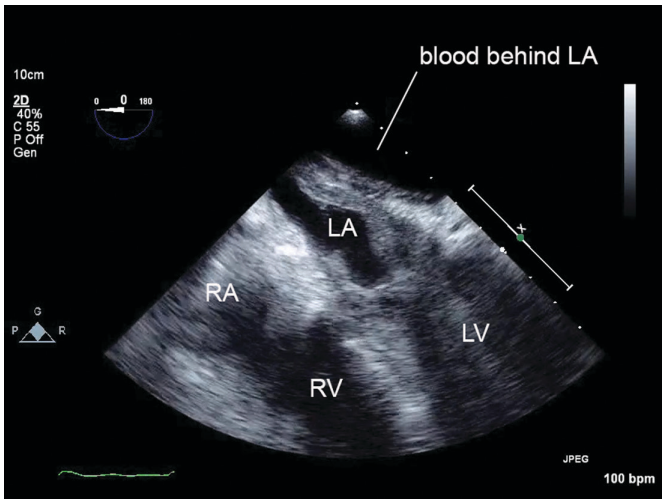


Figure 6.21 Intracardiac stasis. Midesophageal, four-chamber view. Marked spontaneous echo contrast can be seen in all four cardiac chambers, which is most obvious in the right atrium (RA). An echolucent space can be seen behind the left atrium (LA) due to blood in the pericardium. Figure 6.22 is from the same patient. Compare with Figure 6.7, which is from a different patient. LV, left ventricle. RV, right ventricle.

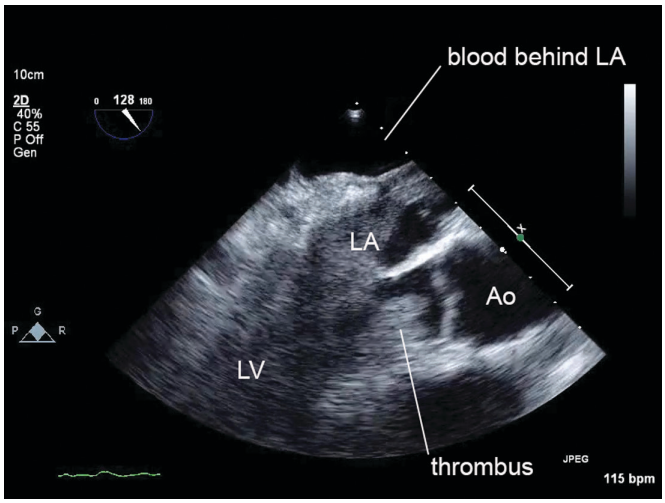


Figure 6.22 Intracardiac thrombus. Midesophageal long-axis view. This image is from the same patient as shown in Figure 6.21. As well as spontaneous echo contrast in the left atrium (LA) and left ventricle (LV), thrombus can be seen in the LV outflow tract. Compare to Figure 6.7, which is from a different patient. Ao, aorta.

IS THERE A ROLE FOR VASCULAR ULTRASOUND AFTER ECMO DECANNULATION?

The reported incidence of venous thrombosis following decannulation varies between 62% and 71% following V-V ECMO, with 28% of patients classified as having a large (>50% occlusion) thrombus and 16% having pulmonary emboli.[13,14] The incidence of arterial thrombosis after V-A ECMO is not well described. However, vessel injury or occlusion is frequent, with the requirement for vascular surgery in 10%–20% of patients.[15,16] Thus, in our institution, percutaneously placed femoral arterial cannulae are surgically removed. Follow-up arterial and venous ultrasound scanning is routinely performed 1–2 days following decannulation.

DISCUSSION

Echocardiography should be routinely used in the management of patients receiving V-V and V-A ECMO.[17] However, to date there are no established guidelines for the use of echocardiography in patients receiving ECMO therapy and few robust studies with which to make evidence-based decisions. Practice is typically guided by institutional knowledge and small single-center studies or case reports.

Prior to initiating ECMO, a comprehensive TTE or TEE study should be performed to allow treatable conditions, such as cardiac tamponade or a mechanical complication of myocardial infarction, to be excluded and to diagnose conditions that might preclude using ECMO, such as severe aortic regurgitation (for peripheral V-A ECMO) or long-standing cardiomyopathy. Careful evaluation of LV and RV function (according to standard guidelines) during the pre-ECMO study helps guide decision-making on the appropriate mode of ECMO.[7–9] If severe LV dysfunction is present, V-A ECMO is usually the appropriate mode, while if LV function is relatively normal, V-V ECMO is the modality of choice.

In the case discussed, a detailed echocardiographic examination was performed at induction of general anesthesia to provide information in the setting of high-risk coronary artery bypass graft surgery. Further echocardiographic examination was performed during weaning from CPB, to aid in the diagnosis of unexpected hemodynamic instability, and then repeated again some hours later in the CICU when ECMO was being considered. Repeating the echocardiographic examination at critical time periods ensured the most accurate information was available and that treatable conditions, such as cardiac tamponade and recirculation, were excluded or confirmed. There are no studies examining the frequency with which a comprehensive echocardiographic assessment allows the diagnosis of an alternative treatable problem or contraindication to be identified in patients being considered for ECMO. However, there are case reports of morbidity and mortality during ECMO when used in the presence of relative contraindications.[3]

In the case discussed, the initial mode of ECMO support required was clear, with TEE clearly demonstrating severe biventricular dysfunction. In a young patient with possible stunning or perioperative myocardial infarction, the use of V-A ECMO for postcardiotomy support is not controversial. However, the choice of *peripheral* V-A ECMO in a patient who has just undergone cardiac surgery is controversial due to the potential issues associated with peripheral, rather than central, cannulation. These issues include difficulty accessing the femoral artery in a shocked patient, the risk of peripheral vascular injury, the potential for lower limb ischemia necessitating a distal perfusion cannula, the increased risk of ongoing LV distention (central V-A ECMO allows direct surgical placement of an LV vent to minimize this problem), and, later, the problem of differential hypoxemia.

Regarding LV distention and cardiac tamponade, early recognition of the clinical signs, and subsequent diagnosis, with TEE or TTE is critical—allowing timely intervention to prevent intracardiac stasis and the development of intracardiac (and possibly intracircuit) thrombosis. Cardiac tamponade is treated by timely surgical exploration and evacuation of hematoma. LV distention is managed with increased inotrope therapy; atrial septostomy; intra-aortic balloon counterpulsation; microaxial ventricular assist devices, such as the Impella; or direct surgical placement of an LV vent.[4,18,19] Currently, the optimal strategy for decompression of the LV is unknown, although unloading of the LV during V-A ECMO with an Impella device has been reported to improve outcomes in a single-center retrospective study.[19] Importantly, if thrombus is identified, treatment is still possible—while associated with a high mortality,[20] survival is also reported.[21] Experience in our institution is that early thrombectomy via cardiac surgery can be life-saving.

In the case presented, the emergent clinical situation and the nonavailability of cardiac operating rooms dictated that peripheral V-A ECMO was commenced in the CICU. One advantage of peripheral V-A ECMO is that it can be instituted at the bedside. Later, though, when the patient returned

to the operating room for bleeding, a transition to central V-A ECMO would have likely avoided the problem of differential hypoxemia. Differential hypoxemia can be difficult to manage, as not all patients are ready to transition from V-A to V-V support. Patients may have recovered sufficient cardiac function to allow deoxygenated blood to circulate through the lungs and into the systemic circulation, causing differential hypoxemia, but insufficient cardiac function to facilitate safe weaning of V-A support. Patients in this circumstance are best managed with V-AV ECMO. Echocardiography is crucial in judging whether cardiac function has recovered sufficiently to wean from V-A ECMO or whether V-AV ECMO will be required.

As previously described, the evidence regarding the echocardiographic parameters for weaning from V-A ECMO is limited. A study by Aissaoui and colleagues in 2011 found three predictors of successful V-A ECMO weaning: an LV ejection fraction greater than 25%, an aortic velocity time integral greater than 10 cm, and a lateral mitral annulus peak systolic velocity greater than 6 cm/s.[10] Markers of LV filling pressures were not predictive of successful weaning. In 2012, the same group found that increasing strain and strain rate (by > 20%) as V-A ECMO flows were reduced was predictive of success in weaning.[11] Increasing LV function during reduction of ECMO flows—in the absence of any other intervention—occurs due to the Frank-Starling effect and represents LV contractile reserve (Figure 6.23).[22]

Recent studies have examined the role of the RV in weaning success. Huang and colleagues used 3-D imaging to assess RV function and found that an RV ejection fraction greater than 24.6% was predictive of successful weaning from V-A ECMO, while smaller RV dimensions and improved RV strain parameters at reduced flows were also predictive.[12] Interestingly, a predictor of *failure* to wean may be ventricular interdependence, suggested on TEE by decreasing LV dimensions with concurrently increasing RV dimensions during progressive weaning of ECMO flow.[23] What is clear from these limited studies on weaning from V-A ECMO is that assessment at progressively lower ECMO flows is essential to allow examination of the LV and RV under preload and afterload conditions that are closer to those present when ECMO is weaned.[22] In our institution, TEE-guided weaning studies are performed for all patients on V-A ECMO and involve serial reductions in ECMO flows to a minimum of 0.5–1.5 L/min, with assessment at each reduction of clinical indices, and echocardiographic parameters.

Overall, there is limited evidence for the optimal protocols and parameters to use in the echocardiographic assessment of patients receiving ECMO. Consensus guidelines and further studies are needed so that problems unique to the management of ECMO are more readily identified, and so that parameters indicating likely successful weaning from V-A ECMO can be more confidently established.

Notwithstanding the limited data, echocardiography has an integral role in the management of ECMO, and should be used prior to establishing ECMO, for diagnosing critical events and guiding ongoing treatment during ECMO support, to facilitate weaning from V-A ECMO, and to assess ongoing recovery in the post-ECMO period.

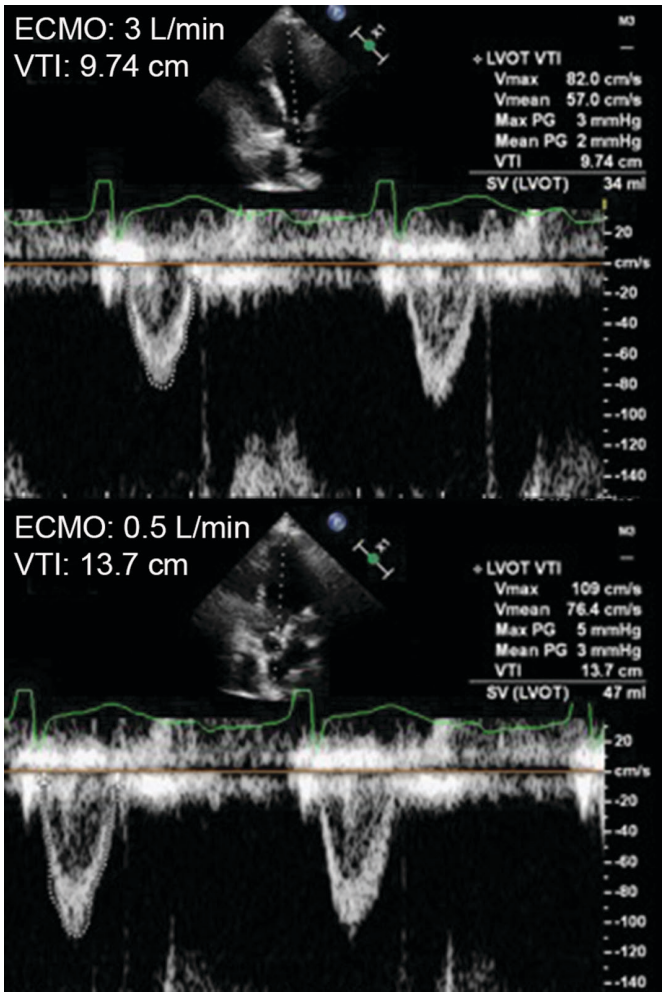


Figure 6.23. Pulsed Wave Doppler imaging from the left ventricular outflow tract (LVOT) during V-A ECMO weaning. The images were obtained from the deep transgastric view. In the top frame, ECMO flow is 3 L/min, and the LVOT velocity time integral (VTI) is 9.74 cm. In the bottom frame, ECMO flow has been weaned to 0.5 L, with no other changes to the patient's therapy. The LVOT VTI has increased to 13.7 cm. The change in VTI from the top to the bottom panel represents contractile reserve due to the Frank-Starling mechanism as a consequence of increasing preload due to reduced V-A ECMO flow.

CONCLUSIONS

- Echocardiography and ultrasound are essential tools in the management of ECMO.
- Echocardiography has a critical role in decision-making when choosing the appropriate mode of ECMO support.
- Vascular ultrasound allows rapid and accurate location and examination of access vessels and minimizes the risks of vascular injury and misplaced cannula.
- In the ongoing management of patients receiving ECMO, echocardiography is vital to diagnose complications and to assess recovery.
- No single echocardiographic measurement is reliable in predicting successful weaning from V-A ECMO. However, the combination of several echocardiographic parameters

in association with clinical indices is likely to best indicate a patient's readiness to wean.

- Following ECMO weaning, echocardiography can be used to assess ongoing cardiac recovery.
- Vascular ultrasound is useful to screen previously cannulated vessels for post-ECMO thromboses.

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REVIEW QUESTIONS

1. Which of the following findings on echocardiography is a contraindication to peripheral V-A ECMO?

   A. Mild aortic regurgitation
   B. Severe arterial occlusive disease
   C. Previous abdominal aortic aneurysm repair
   D. Atrial septal defect

2. Which of the following parameters is associated with successful weaning from V-A ECMO?

   A. Aortic valve velocity time integral 8cm
   B. Tissue Doppler imaging lateral mitral annulus peak systolic velocity 5 cm/s
   C. LV ejection fraction 30%
   D. Fractional area change (short axis mid papillary view) left ventricle 20%

3. Which of the following lesions may complicate V-V ECMO?

   A. Severe aortic regurgitation
   B. Aortic aneurysm
   C. Severe tricuspid regurgitation
   D. Atrial septal defect

4. Which of the following is correct for central V-A ECMO?

   A. Return cannula tip at junction of superior vena cava and right atrium
   B. Drainage cannula tip in mid right atrium
   C. Drainage cannula tip in inferior vena cava at level of hepatic veins
   D. Return cannula tip in mid-right atrium

5. For V-A ECMO, which of the following is not used to manage LV distention?

A. Atrial septostomy
B. Increased inotrope therapy
C. Reduced ECMO flows
D. Intra-aortic balloon counterpulsation

6. Which of the following is not a potential cause of low circuit flows during V-A ECMO?

A. Recirculation
B. Hypovolemia
C. Cardiac tamponade
D. Drainage cannula thrombosis

7. During V-V ECMO, which of the following is not a potential cause of hypoxemia?

A. Recirculation
B. Cannula thrombus
C. Oxygenator thrombus
D. Differential hypoxemia (Harlequin syndrome)

ANSWERS

1B, 2C, 3D, 4B, 5C, 6A, 7D.

7.

AIRWAY MANAGEMENT IN ECMO PATIENTS

Samuel Howitt and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 50-year old woman presents following a large anterior myocardial infarction. Revascularization via stenting or coronary artery bypass grafting is not possible, and the patient is being considered for mechanical circulatory support (MCS) for management of impending cardiogenic shock. During assessment, the patient's condition deteriorates. She becomes tachypneic, tachycardic, and hypotensive. Oxygen saturations drop to 88% on 15 L oxygen via a nonrebreather mask, and a transthoracic echocardiogram shows left ventricular systolic dysfunction due to anteroseptal, anterior, and anterolateral hypokinesis. Despite initial heart failure treatment, including diuretics and noninvasive continuous positive airway pressure ventilation, she starts to tire and the decision is made to anesthetize her and start mechanical ventilation. The attending anesthesiologist conducts a preoperative assessment of the airway and notes that the patient ate a sandwich around 2 hours ago. Consequently, a rapid sequence induction is performed. After a relatively straightforward induction of anesthesia and endotracheal intubation, the patient is transferred to the operating theater for initiation of MCS in the form of a biventricular assist device (BiVAD). The configuration of the BiVAD is shown in Figure 7.1. After 3 days in the intensive care unit, the patient is considered stable enough to undergo tracheostomy to allow sedation to be lightened. The tracheostomy is inserted percutaneously, and the procedure is uneventful.

The following day, bleeding is noted from the patient's pharynx after nasogastric tube insertion. The otorhinolaryngology team reviews the patient, identifies a mucosal tear, and packs the mouth with gauze in an attempt to promote hemostasis. Six hours later, ventilation via the tracheostomy becomes difficult, with obstruction of the expiratory phase of the respiratory cycle. A fiber-optic bronchoscope is passed into the tracheostomy tube, and a clot is identified at the end of the tube. The clot cannot be cleared by suction or with a grasper passed through the bronchoscope, and the patient's oxygenation begins to fall.

The decision is made to insert an oxygenator into the BiVAD circuit to perform extracorporeal membrane oxygenation (ECMO). The procedure is uneventful and the otorhinolaryngology team reviews the patient and is able to identify and treat a bleeding point in the posterior pharyngeal wall related to the nasogastric tube insertion. Two days later, the oxygenator is removed from the circuit, and oxygenation is maintained via the tracheostomy until the patient receives a heart transplant.

HOW WAS THE PATIENT INTUBATED AND WHAT ANESTHETIC DRUGS WERE USED?

The patient was intubated and ventilated following intravenous induction of anesthesia. Drugs were chosen to minimize cardiovascular instability in the setting of cardiogenic shock. Etomidate and a small dose of fentanyl were used to induce anesthesia, and rocuronium was used to provide rapid muscle relaxation. Cricoid pressure was applied when the drugs were administered and released after intubation. The patient was

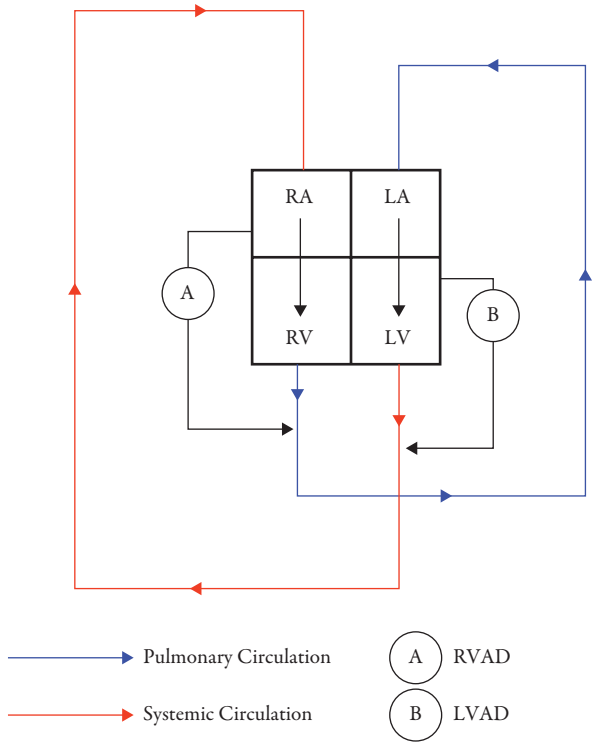


Figure 7.1 Setup of the biventricular assist device. LA, left atrium; LV, left ventricle; LVAD, left ventricular assist device; RA, right atrium; RV, right ventricle; RVAD, right ventricular assist device. (Reprinted with permission from Howitt SH, Stirling S, Krysiak P, Pate B, Maybauer MO. Oxygenation via a biventricular assist device for emergency airway management. *A & A Case Reports.* May 1 2016;6(9):288–290.)

intubated at the first attempt via direct laryngoscopy with a cuffed endotracheal tube and ventilated according to lung-protective ventilation protocols.[1]

HOW WAS THE TRACHEAL TUBE POSITION CONFIRMED?

Adequate positioning of the tracheal tube after intubation must be confirmed using criteria such as auscultation of bilateral breath sounds and observation of symmetrical chest expansion. Capnography waveform detection should be performed in any patient in the critical care setting to confirm tracheal positioning. However, it cannot be used to confirm the correct location within the trachea. After intubation of the airway, a chest radiograph should be obtained to document proper tube position. Incorrect positioning of the tracheal tube within the airway after intubation can result in serious complications. Accidental mainstem bronchus intubation is associated with contralateral atelectasis, ipsilateral pneumothorax, hypotension, and increased morbidity. Conversely, failure to place the tube several centimeters beyond the vocal cords may result in inadvertent extubation, aspiration pneumonia, or laryngeal spasm. Ideally, the tip of the tube is located between the clavicles and about 2–3 cm above the carina.[2,3]

WHAT GUIDELINES FOR DIFFICULT AIRWAY MANAGEMENT SHOULD BE CONSIDERED?

Traditionally, the term *difficult airway* has been used to describe the scenario in which a conventionally trained anesthesiologist experiences difficulty in ensuring oxygenation through face mask ventilation and/or endotracheal intubation.[4] Published guidelines from the American Society of Anesthesiologists[4] and the Difficult Airway Society[5,6] proposed an organized structure for interventions to be attempted when a difficult airway is encountered and detailed the equipment that should be available in these scenarios. Planning is an important factor in the safe management of the intubation process, and formal preintubation checklists should be used in all cases where a difficult airway is anticipated.[6]

WHAT ARE PHYSIOLOGICALLY DIFFICULT AIRWAYS?

Recently, it has been acknowledged that aside from this traditional definition of an "anatomically" difficult airway, patients who are exhibiting cardiovascular or cardiorespiratory instability also constitute "physiologically" difficult airways.[6,7] In such patients, even where endotracheal intubation is relatively straightforward, induction of anesthesia can lead to hypoxemia, profound hypotension, and cardiorespiratory collapse. In cases where tracheal intubation proves to be technically difficult, delays in securing the airway lead to increased risk of these adverse events occurring around the time of induction.

Recommendations made by the guidelines referenced above, such as careful preoxygenation and the insufflation of oxygen during intubation, are particularly pertinent to the management of patients who are showing signs of cardiorespiratory compromise during induction. Similarly, careful consideration of the choice of anesthetic agents and vasoactive medication is also recommended.

WHAT ALTERNATIVE AIRWAYS SHOULD BE AVAILABLE?

In addition to standard face masks, laryngoscopes, and endotracheal tubes, airway adjuncts including oro- and nasopharyngeal airways, bougies, supraglottic airway devices (SADs), and video laryngoscopes should be available. A front-of-neck airway (FONA) kit should also be available to be used if all attempts at endotracheal intubation through the mouth fail and oxygenation is not possible using face masks or supraglottic devices. The choice of supraglottic devices is relatively large, and the choice of technique for gaining FONA control includes scalpel cricothyroidotomy[6] and jet ventilation or retrograde intubation via a needle cricothyroidotomy.[7]

HOW WAS THE BIVAD CONFIGURED?

The BiVAD contained two circuits—a right ventricular assist device (RVAD) circuit and a left ventricular assist device (LVAD) circuit—connected in series. Blood was taken from the right atrium by the RVAD circuit and passed via a pump to the pulmonary trunk. The blood passed through the lungs, and oxygenated blood was then taken from the left ventricle through a pump in the LVAD circuit and delivered into the ascending aorta (Figure 7.1).

WHICH TECHNIQUE WAS USED FOR THE TRACHEOSTOMY?

The tracheostomy was inserted percutaneously on the critical care unit by two trained cardiac anesthesiologists. One anesthesiologist controlled ventilation via the endotracheal tube and visualized the tracheal lumen using a flexible fiberoptic bronchoscope. The second anesthesiologist first used ultrasound imaging to ensure no major vessels lay over the anterior aspect of the trachea and then prepared an aseptic field over the front of the neck and infiltrated local anesthetic with adrenaline to improve hemostasis. The tracheostomy tube was inserted using Seldinger technique in which a cannula was inserted between the second and third tracheal rings under bronchoscopic vision. A guidewire was then passed through this cannula and a dilator passed over the wire before the tracheostomy tube was inserted and the wire removed.

HOW WAS COAGULATION FOR THE TRACHEOSTOMY MANAGED?

In order to balance the risk of airway bleeding with the need to provide anticoagulation for the extracorporeal circuit, the heparin infusion was paused for 2 hours before insertion of the tracheostomy tube and not resumed until 6 hours after the

procedure was completed. At this time, the platelet count had dropped to 42 × 10^9/L, fibrinogen concentration was noted to be 1.14 g/L, and hemoglobin concentration was 95 g/L. Therefore, two pools of platelets and two bags of cryoprecipitate were transfused. At this point, the prothrombin time was 14.3 seconds, and the activated partial thromboplastin ratio was 1.0 (off heparin).

HOW DID THE OTORHINOLARYNGOLOGY TEAM MANAGE THE INITIAL BLEEDING?

When bleeding was noted in the pharynx 18 hours after tracheostomy insertion, the otorhinolaryngologist examined the patient and identified a mucosal tear in the posterior pharyngeal wall. The tear was likely to have been caused during nasogastric tube reinsertion that morning. Due to the friability of the tissues, attempts were made to achieve hemostasis by packing the pharynx. At this time, the platelet count had risen to 70 × 10^9/L following the transfusion the previous day, while the hemoglobin concentration had dropped to 66 g/L so 2 units of packed red cells were administered. No further bleeding was noted from the oropharynx, and aspiration of the nasogastric tube revealed no blood. Heparin was therefore continued to prevent thrombosis in the extracorporeal circuit. Heparin was administered with the aim of achieving an activated clotting time (ACT) of 180 seconds.

HOW WAS THE DECREASE IN TIDAL VOLUMES MANAGED?

The patient was ventilated using pressure-controlled ventilation. Later that day, tidal volumes dropped from around 500 to 100 mL, while peak inspiratory pressure remained set at 24 cm H_2O. At this point, the packs in the oropharynx had become bloodstained, and on clinical examination the thorax was noted to be hyperexpanded with quiet air entry bilaterally. Expiratory flow measured by the ventilator was markedly reduced. As bleeding was suspected in the packed pharynx, it was considered that visualizing the glottis through the upper airway would be difficult. In addition, the upper airway mucosa was known to be friable and consequently further instrumentation was to be avoided, so direct laryngoscopy was not attempted. A Mapleson C circuit was attached to the tracheostomy tube, and oxygenation improved with manual ventilation, but exhalation was still markedly reduced. A flexible fiber-optic bronchoscope was passed through the tracheostomy tube and revealed a large clot on the end of the tracheostomy tube, which was acting as a ball valve. The inner tube was removed, but the clot remained in situ over the end of the tracheostomy tube. The clot was moving distally on inspiration, allowing flow of inspired gases but was closing over the end of the endotracheal tube during exhalation and obstructing gas flow. The scope was passed around the clot, holding the clot away from the end of the tracheostomy tube, and exhalation improved. Distal to the clot, the airway was normal with no evidence of bleeding from within the bronchial tree.

HOW WERE VENTILATION AND OXYGENATION SECURED?

Initial attempts to clear the clot using suction through the bronchoscope channel and using wider suction catheters failed. Using grasper devices, the clot was partially cleared but quickly re-formed. A size 6.0 endotracheal tube was passed through the tracheostomy tube and past the clot to provide a more secure airway, but with ongoing bleeding, this tube was also at risk of clotting, so a more permanent solution was required. The decision was made to insert an oxygenator into the BiVAD circuit, and a perfusionist was called to the critical care unit. The perfusionist briefly paused flow in the BiVAD, applied two clamps to the tubing of the LVAD, divided the tubing between the two clamps and inserted a primed oxygenator into the circuit resulting in a de facto V-A ECMO configuration as shown in Figures 7.2 and 7.3. Flow was restarted within 30 seconds. The oxygenator provided reliable means of gas exchange even if flow through the tracheostomy tube was lost. It also allowed the otorhinolaryngologist to temporarily remove the tracheostomy tube during their subsequent reexamination to ensure all sources of bleeding were identified.

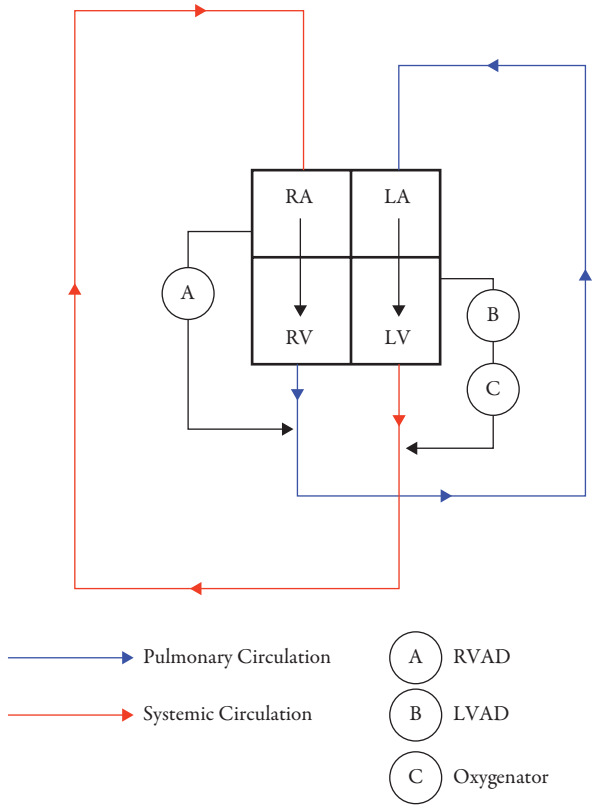


Figure 7.2 Setup of the biventricular assist device after insertion of the oxygenator. LA, left atrium; LV, left ventricle; LVAD, left ventricular assist device; RA, right atrium; RV, right ventricle; RVAD, right ventricular assist device. (Reprinted with permission from Howitt SH, Stirling S, Krysiak P, Pate B, Maybauer MO. Oxygenation via a biventricular assist device for emergency airway management. *A & A case reports.* May 1 2016;6(9):288–290.)



Figure 7.3 Biventricular assist device (BiVAD).

HOW WAS THE BLEEDING CONTROLLED?

Once gas exchange had been secured using the oxygenator, the otorhinolaryngology team was called back to review the patient. Additional bleeding points were identified on the right palatoglossal fold. Surgical hemostasis was achieved using bipolar diathermy, and large volumes of clot were aspirated from the pharynx, larynx, and subglottis above the tracheostomy tube cuff. The tracheostomy tube and the endotracheal tube that was inserted through it were both removed, revealing a further bleeding point at the tracheostomy site, which was also treated using diathermy, and a new size 8.0 tracheostomy tube was inserted. Throughout this procedure, gas exchange was maintained using the oxygenator in the BiVAD circuit in a V-A ECMO (veno-arterial ECMO) configuration.

HOW WAS THE PATIENT SWITCHED FROM V-A ECMO TO A BIVAD?

A heparin infusion was restarted 6 hours after the surgical intervention and targeted an ACT of 180 seconds. The following day, once it had been confirmed that bleeding had not recurred and that ventilation was adequate with low ventilator pressures, a trial off ECMO was performed. When fresh gas flow was removed from the oxygenator, arterial oxygen and carbon dioxide concentrations remained adequate, so it was decided to remove the oxygenator from the circuit. The perfusionist paused flow in the circuit for 30 seconds, divided the circuit either side of the oxygenator, and reattached each end of tubing to restore the original BiVAD circuit.

DISCUSSION

AIRWAY ASSESSMENT

Preoperative identification of the difficult airway is often challenging. Numerous risk factors for difficult bag-mask ventilation and difficult intubation have been elucidated, but no tool proposed gives reliability when used to identify difficult airways preoperatively.[8]

Various studies have identified risk factors for difficult bag mask ventilation[9–11]:

- Facial hair (poor mask seal)
- Increasing body mass index (BMI) greater than 30 kg/m^2
- Increasing age (>57 years)
- Snoring/obstructive sleep apnea
- History of radiation therapy to the neck
- Lack of teeth

Similarly, various screening tools have described how to identify patients for whom endotracheal intubation is likely to be difficult. Studies have shown that the following risk factors are associated with difficult intubation[12–14]:

- Mouth opening less than 5 cm
- Thyromental distance less than 6 cm
- Mallampati class III or IV
- Poor neck mobility
- Inability to protrude the jaw

However, even when used in combination, these risk factors do not predict all incidences of difficult intubation. This has led to the development of guidelines specifically for use when the anesthesiologist encounters an unanticipated difficult airway.[5]

AIRWAY MANAGEMENT GUIDELINES

Key to all difficult airway guidelines is the idea that oxygenation remains paramount. The number of attempts at endotracheal intubation should be limited to three, and after each failed attempt, oxygenation should be maintained by face mask ventilation and consideration of techniques that might optimize intubating conditions. In particular, profound neuromuscular blockade should be ensured, patient position should be optimized, external manipulation of the larynx should be attempted, and the use of adjuncts such as bougies should be considered. Different laryngoscope blades, such as the McCoy

blade,[15] which has a hinged section that when positioned in the vallecula is used to lift the epiglottis anteriorly to reveal the glottis, may be considered. Video laryngoscopes such as the Bonfils rigid scope,[16,17] the GlideScope,[18] and the McGrath MAC video laryngoscope[19] may also be useful in these settings as they allow vision of the glottis without the need of a clear line of sight through the mouth to the glottis.

Where another, more experienced operator is available, one further attempt at tracheal intubation may be attempted. However, after three attempts by the first intubator (or a fourth if a more experienced colleague is available), failed intubation should be declared and insertion of a SAD or a blind insertion airway device is recommended.

Supraglottic airway devices are not designed to pass the vocal cords and can be inserted without direct vision, although the use of a laryngoscope during insertion may be helpful. A range of such devices are available, including the laryngeal mask,[20] LMA ProSeal,[21] and iGel.[22] All of these devices consist of an elliptical mask on the distal end of a tube. These masks are positioned above the vocal cords, where they form a seal against the supraglottic walls.

While these devices can maintain gas exchange via the lungs, they do not protect the glottis or the lower respiratory tract from upper airway secretions or bleeding or from the aspiration of gastric contents.

Alternative blind insertion airway devices such as the Esophageal Tracheal Combitube[23] and the EasyTube[24] are available. These devices consist of two joined tubes, one with a proximal opening and one with a more distal opening, each with its own cuff. If the distal lumen enters the trachea, the cuff just above this opening is inflated, and ventilation occurs down this lumen. If the distal tube passes into the esophagus, the upper cuff (at the level of the pharynx) and the lower cuff (in the esophagus) are both inflated, and ventilation of the lungs then occurs through the proximal lumen to the trachea. In this scenario, the cuff in the esophagus prevents air entering the stomach and gastric contents entering the pharynx.

All of these devices can potentially be used in the emergency setting in which endotracheal intubation under direct or indirect vision is not possible. The devices allow positive pressure ventilation, although high-pressure ventilation through the mask-type supraglottic airways is often prevented by the leaking of airway gasses through the seal between the device and the walls of the laryngeal inlet.[24–27]

If oxygenation is secured via a SAD, the anesthesiologist and surgical team must then decide whether to

- Wake the patient up and abandon the procedure,
- Proceed without endotracheal intubation,
- Attempt endotracheal intubation through the SAD, or
- Gain surgical access to the trachea through a tracheostomy or cricothyroidotomy.

If oxygenation cannot be achieved due to inability to insert an endotracheal tube, inability to ventilate via a SAD or another blind insertion airway device and inability to ventilate via a face mask, a "can't intubate, can't ventilate" emergency should be declared, and surgical access to the airway must be gained through the front of the neck.

In patients with severe cardiovascular and/or respiratory compromise requiring anesthesia for MCS/ECMO, the induction of anesthesia should be swift, but cardiovascularly stable and optimal intubating conditions should be achieved as quickly as possible because any delay in mechanical ventilation may result in hypoxia. Where there is elevated risk of aspiration of gastric contents due to inadequate fasting, delayed gastric emptying, or significant gastroesophageal reflux, this necessitates rapid endotracheal intubation. In such cases, bag-mask ventilation is generally avoided as it may lead to insufflation of the stomach and subsequent aspiration of gastric contents. As bag-mask ventilation is to be avoided, intubation of the trachea should be achieved as quickly as possible because hypoxemia is likely to occur rapidly following the apnea caused by induction of anesthesia and muscle relaxation in this patient group.

When preparing to intubate the patient who requires ECMO or MCS, there are a number of logistical considerations to be taken into account. First, the appropriate healthcare professionals should be present. The intubator should be someone who is experienced in airway management, and there should be a trained assistant present who is competent in the setup and use of specialist airway equipment. In addition, a third member of staff should be present to act as a runner, and often it is useful to have a second anesthesiologist present to administer the anesthetic drugs. Airway suction equipment should be available, and the patient should be on a tilting table. Difficult airway equipment (see below) should be locally available in case an unanticipated difficult airway is encountered. Preinduction checklists ensure that all foreseeable complications are discussed and contingency plans are in place before induction of anesthesia begins.

If a rapid sequence induction is required, precalculated doses of hypnotic agents and muscle relaxants are administered. Muscle relaxation occurs within 60–90 seconds and no positive pressure ventilation is performed until the trachea is intubated.[28] In some regions, it is common for cricoid pressure to be applied as described by Sellick[29] at the point of induction. This maneuver consists of the application of 30–40 N force posteriorly on the cricoid cartilage with the aim of compression of the esophagus against the cervical vertebral bodies and decreasing reflux of gastric contents into the oropharynx.[30] The use of cricoid pressure is controversial because it has not been shown to reduce aspiration risk in randomized clinical trials[31] and may make laryngoscopy more difficult.[32] Currently, there is a lack of clear evidence that cricoid pressure provides a clear benefit in outcomes during rapid sequence induction,[33] and its use therefore often depends on local airway management policies. However, the release of any applied cricoid pressure is one of the first steps in the management of a difficult intubation.[5]

One risk associated with rapid sequence induction is that having anesthetized and paralyzed the patient, the clinician is unable to intubate the trachea and then discovers that the patient also cannot be manually ventilated. A true rapid

sequence induction is therefore performed using short-acting or reversible drugs so that in theory the patient could be woken up, and spontaneous respiration could restart and prevent hypoxia. In compromised patients undergoing initiation of MCS or ECMO, a successful return to spontaneous ventilation is unlikely to occur given the premorbid state, so this consideration is less important.

CHOICE OF ANESTHETIC DRUGS

Etomidate

Etomidate induces anesthesia within one arm-brain circulation time when given in a bolus dose of 0.15–0.3 mg/kg. This rapid onset of anesthesia is associated with a stable cardiovascular profile.[34] Historically, there have been concerns that the direct adrenal suppression caused by etomidate[35] could lead to poor outcomes, especially in the critically ill.[36] However, the association with increased mortality is not clear, particularly if only given as a single induction bolus,[37] and no effect on mortality has been observed in cardiac surgery patients.[36] From our experience in adults, a single dose of 5 mg is very often sufficient in patients with cardiogenic shock.

Ketamine

Particularly for patients who require ECMO for acute respiratory distress syndrome, a combination of ketamine (1–2 mg/kg) and a small dose of midazolam (0.05–0.1 mg/kg) may be a suitable alternative to the drugs used in this scenario. Ketamine provides analgesia and hypnosis with relative hemodynamic stability while maintaining airway reflexes. The ability to increase blood pressure and cardiac output through indirect effects, including protection of sympathetic drive,[38] adds to the favorable profile of this agent, especially in noncardiac patients for veno-venous ECMO (V-V ECMO) who are not at risk for coronary ischemia as compared to patients who require V-A ECMO for cardiocirculatory support. Ketamine in higher doses causes undesired side effects, such as hallucinations or delirium; therefore, it is recommended to use it in combination with a short-acting benzodiazepine, such as midazolam.[39]

Propofol

Propofol is widely used to induce anesthesia and maintain sedation in the critical care unit. When given as a bolus dose (1–2.5 mg/kg) to induce anesthesia, propofol may decrease systemic blood pressure by decreasing systemic vascular resistance and cardiac output. While the decrease in systemic vascular resistance is caused by a direct effect on arterial tone, the decrease in cardiac output is chiefly driven by decreasing venous return due to venodilation[40] rather than a direct effect on contractility.[41] These effects make propofol relatively difficult to use as a sole induction agent in patients with cardiovascular compromise who require emergent induction of anesthesia. However, the combination of smaller doses of propofol and other agents may be used or vasopressors may be coadministered to offset propofol's vasodilatory effect.

Thiopentone

Thiopentone reliably induces anesthesia within one arm-brain circulation time when given as a bolus dose of 5–7 mg/kg. However, in such doses thiopentone is known to decrease blood pressure through reductions in both myocardial contractility and systemic vascular resistance.[42,43] Thiopentone is therefore rarely used in patients with severe cardiovascular compromise.

Benzodiazepines

Benzodiazepines can be used in combination with other induction doses or as the sole induction agent. When used in isolation at lower doses, benzodiazepines such as midazolam 0.1 mg/kg have minimal effect on the cardiovascular system.[44] However, when given in such doses the onset of anesthesia is relatively slow, which may be problematic in critically ill patients, where deoxygenation prior to tracheal intubation may be swift. While larger doses of up to 0.3 mg/kg will induce anesthesia within 60 seconds, at such doses hypotension is likely to occur due to vasodilation.[45,46]

Muscle Relaxants

The speed of onset of action is also a key consideration when selecting a muscle relaxant during rapid sequence induction. Succinylcholine (1–2 mg/kg), a short-acting depolarizing muscle relaxant, and rocuronium, a longer acting nondepolarizing muscle relaxant (used in higher doses of 1.2 mg/kg to ensure rapid onset of action), are both commonly used for rapid sequence induction.[28] The effect of succinylcholine is short-lived in all but a very small proportion of the population who lack the functional plasma cholinesterase required to metabolize the drug.[47] As a depolarizing muscle relaxant, succinylcholine causes muscle contraction prior to paralysis. This may be associated with release of potassium from the myocytes and can exacerbate hyperkalemia. The release of potassium will be exaggerated in patients who have suffered upper or lower motor denervation, major trauma, or severe burns. Succinylcholine use is therefore contraindicated in such patients.[48]

The muscle relaxation induced by rocuronium can be swiftly reversed by the administration of sugammadex, a reversal agent that sequesters the rocuronium molecules, rendering them inactive.[49]

In practice, for patients requiring anesthesia for ECMO or MCS, successful return to spontaneous ventilation in the event of failure to intubate is unlikely due to the preexisting cardiorespiratory compromise exhibited by such patients before induction. Therefore, it is sensible to choose technique and medication with the goal of optimizing the chances of successful intubation rather than prioritizing reversibility of sedation and muscle relaxation.

COAGULATION AND HEMORRHAGE

Mechanical circulatory support and ECMO are both associated with coagulopathy.[50] The risk of bleeding is increased by the therapeutic anticoagulation required to prevent thrombosis within the extracorporeal circuit.[51] Guidelines from the Extra-Corporeal Life Support Organization[52] (ELSO) recommend managing anticoagulation using unfractionated heparin with a bolus dose of 50–100 units/kg, followed by an intravenous infusion aiming to achieve an ACT of 180–220 seconds. The therapeutic coagulation achieved through the administration of heparin may be potentiated by pathological disorders of coagulation. These disorders may include acquired von Willebrand disease, thrombocytopenia, and hyperfibrinolysis.[50,51,53,54]

Consequently, up to 30% of patients receiving these treatments experience hemorrhagic complications.[51,55] The commonest sites of bleeding in patients receiving MCS or ECMO are the sites of cannulation or surgical access.[50,56] Less frequent but often more clinically deleterious bleeding complications include intracranial, gastrointestinal, and pulmonary hemorrhage.[50,57]

Bleeding into the supraglottic airway has been found to make up 15% of all hemorrhagic complications of ECMO.[57]

Rates of coagulopathy in patients with oxygenated circuits (ECMO) have been shown to be higher than those in MCS without membrane oxygenation.[58] Possible explanations for the increase in coagulopathy seen with ECMO include increased platelet damage during flow through the oxygenator, hyperfibrinolysis secondary to thrombosis in the oxygenator, and development of a consumptive coagulopathy secondary to contact activation as the blood passes the membrane.[50,59]

Patients receiving ECMO or MCS on the critical care unit are likely to require instrumentation of their upper airway during airway management, oral hygiene procedures, and the insertion of orogastric or nasogastric feeding tubes. Therapeutic anticoagulation and pathological dysfunction of coagulation both increase the risk of these procedures causing bleeding from the airway mucosa.

The management of airway hemorrhage in patients receiving ECMO or MCS is complicated by the need to ensure systemic anticoagulation that is adequate to prevent thrombosis within the circuit and the patient's vasculature. Surgical attempts to stop the bleeding often cause further damage to tissues, and in the setting of a required hypocoagulable state may result in exacerbation of the hemorrhage.[50] Consequently, initial treatment often centers on applying pressure to the bleeding source through packing the site with gauze or hemostatic dressings.

In this case, oropharyngeal packing did not achieve hemostasis, and blood collected on top of the cuff of the endotracheal tube. It is well recognized that endotracheal cuffs do not perfectly protect the lower respiratory tract. Secretions or blood may leak past the cuff due to pressure variation within the cuff, movement of the endotracheal tube during patient care, and the presence of folds within incompletely inflated cuffs.[60]

Blood from the mucosal tear in the pharynx bypassed the cuff and formed a clot at the end of the endotracheal tube. The phenomenon of thrombi partially blocking oral endotracheal or tracheostomy tubes and acting as ball valves has been previously described, and in some cases this has resulted in death.[61]

Removal of the inner tube from a blocked tracheostomy and oxygenation via the upper airway are both important rescue techniques in the blocked tracheostomy scenario.[62] However, in this scenario removal of the inner tracheostomy tube did not improve ventilation, and oxygenation via the oropharynx was not possible due to the packed oropharynx and likely ongoing bleeding. Case reports describing similar situations in which oxygenation via the upper airway was impossible detailed the bronchoscopically guided use of forceps, graspers, topical thrombolytics, and suction to remove clots from the blocked airway.[61,63–68]

In this setting, the use of fiber-optic bronchoscopes and suction catheters to hold the ball valve open provides a temporary solution to the problem. However, removal of the clot may prove difficult, or worse still, the clot may become dislodged and pass lower down the airway, causing complete obstruction at the level of the carina.[63]

The use of ECMO in the emergency management of airway obstruction has been described previously.[69] However, often the unexpected onset and rapid progression of the emergency precludes the instigation of ECMO as an emergency treatment. In the presence of existing MCS, the addition of an oxygenator to allow ECMO is a relatively straightforward and potential life-saving technique.

CONCLUSIONS

- Airway management in patients requiring ECMO can be difficult due to cardiorespiratory compromise.
- Guidelines and checklists have been proposed to reduce morbidity and mortality associated with airway management.
- Hemorrhagic complications are common during ECMO/MCS therapy.
- Airway bleeding is a recognized complication.
- ECMO may be useful in the emergency setting where oxygenation via the lungs is not possible.
- Guidelines for the management of the physiologically difficult airway and management of blocked tracheostomy tubes are available.

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REVIEW QUESTIONS

1. Which of the following characteristics is not a risk factor for difficult bag-mask ventilation?

A. Lack of teeth
B. Facial hair
C. BMI greater than 30 kg/m^2
D. Mouth opening less than 5 cm

2. Which of the following drugs would be least likely to result in hypotension when used as the sole hypnotic agent to induce anesthesia in a patient requiring a rapid sequence induction for institution of ECMO following an acute myocardial infarction?

A. Propofol
B. Thiopentone
C. Midazolam
D. Etomidate

3. Which of the following is not a supraglottic airway device?

A. Laryngeal Mask
B. iGel
C. LMA ProSeal
D. GlideScope

4. How many cuffs are present on the EasyTube device?

A. 1
B. 2
C. 3
D. 4

5. If cricoid pressure is applied, which of the following is an appropriate force to apply (once the patient is asleep) to the cricoid cartilage?

A: 10 N
B: 15 N
C: 30 N
D: 45 N

6. Which muscle relaxant should be avoided in a patient who is paraplegic following spinal cord injury?

A. Succinylcholine
B. Rocuronium
C. Atracurium
D. Vecuronium

7. Which of the following is the most reliable method of verifying ideal endotracheal tube position?

A. Capnography
B. Observation of chest expansion
C. Chest radiography
D. Misting of the endotracheal tube

8. According to the ELSO anticoagulation guideline, what should be the target for ACT monitoring during anticoagulation therapy using unfractionated heparin in patients receiving ECMO?

A. 110–150 seconds
B. 180–220 seconds
C. 240–280 seconds
D. 280–400 seconds

9. What is the approximate frequency of hemorrhagic complications in patients receiving MCS or ECMO?

A. 10%
B. 30%

C. 50%
D. 70%

10. Supraglottic airway bleeding accounts for what proportion of hemorrhagic complications for those receiving ECMO/MCS?

A. 5%
B. 15%
C. 30%
D. 60%

11. Which is the commonest site of bleeding in patients undergoing ECMO or MCS?

A. Airway
B. Gastrointestinal tract
C. Surgical wound or cannulation site
D. Intracranial

ANSWERS

1D. Limited mouth opening is a risk factor for difficult intubation but not bag-mask ventilation.

2D. When used as the sole induction agent at a dose that would reliably cause the rapid onset of anesthesia required for a rapid sequence induction, propofol, thiopentone, and midazolam are all likely to cause hypotension. Etomidate would be the most cardiostable induction agent.

3D. The GlideScope is a video laryngoscope. All other options are supraglottic airway devices.

4 B. The EasyTube is a blind insertion airway device with two cuffs. Whether the distal lumen of the device enters the esophagus or the trachea, the cuffs can be inflated in a manner that allows ventilation and protection of the respiratory tract from gastric secretions.[24]

5C. A force of 30–40 N should be applied to the anterior aspect of the cricoid cartilage to compress the esophagus, which sits posterior to the trachea and larynx.

6 A. Succinylcholine administration is associated with marked potassium release from myocytes in patients with denervated muscles. Resulting hyperkalemia could result in cardiac arrhythmias or arrest.

7C. Capnography is an essential tool to exclude esophageal intubation. Observing chest expansion is also an important and easy-to-perform test to detect bronchial intubation. However, the most reliable method of confirming ideal endotracheal tube positioning among the options is chest radiography.

8 B. The ELSO anticoagulation guideline states that for patients being anticoagulated with unfractionated heparin an ACT between 180 and 220 seconds should be targeted.

9 B. Systematic reviews have identified frequency of hemorrhagic complications for patients receiving ECMO/MCS of around 30%.[51,55]

10 B. Supraglottic airway bleeding accounts for 15% of hemorrhagic complications for patients receiving ECMO/MCS.[57]

11C. The commonest sites of bleeding in patients receiving ECMO/MCS are the surgical site or the site of cannulation.[50,56]

8.

ACUTE RENAL FAILURE AND RENAL REPLACEMENT THERAPY IN ECMO PATIENTS

Julia Coull and Aidan Burrell

STEM CASE AND KEY QUESTIONS

A 44-year-old, previously healthy, female presents to hospital with a 5-day history of viral symptoms, including fever, rhinorrhea, arthralgia, cough, and shortness of breath. On examination she had a respiratory rate of 28, oxygen saturation (SpO_2) 86% on room air, and bibasal crepitations on chest auscultation. Her chest radiograph revealed extensive bilateral lower and middle zone consolidation. She was initially managed with high-flow nasal cannulae with 60 L/min flow and a fraction of inspired oxygen (FiO_2) of 0.5 and treated with oseltamivir, ceftriaxone, and azithromycin. Her condition deteriorated, necessitating invasive ventilation, muscle relaxation, and high positive end-expiratory pressure. She had a trial of prone ventilation and inhaled nitric oxide with minimal improvement in oxygenation. She had a normal creatinine of 50 μmol/L on admission; by day 3, her creatinine had increased to 94 μmol/L. At this time, her urine output remained greater than 0.5 mL/kg/h with the assistance of furosemide 20 mg every 6 hours, and her fluid balance was positive 4 L since admission.

Despite the above respiratory support measures, she was unable to be ventilated safely and was commenced on veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) with femoral (inferior f) drainage and jugular (inferior j) return cannulae (V_f-V_j ECMO) on day 4 of her admission. Post-ECMO commencement, her oxygenation improved, increasing from a PaO_2 of 65 mm Hg to 123 mm Hg. In the 24 hours following ECMO initiation she became increasingly hypotensive and shocked with a hyperdynamic ventricular function consistent with septic/vasodilatory shock. Norepinephrine and vasopressin were commenced, with vasopressin at 0.03 units/min and maximal noradrenaline dose of 0.45 μg/kg/min. Her antibiotic coverage was broadened to piperacillin-tazobactam and vancomycin. She continued on oseltamivir and azithromycin. This change in hemodynamic status was associated with a further rise in creatinine to 129 mmol/L and progressive anuria despite high-dose furosemide.

The following morning her creatinine had reached 154 μmol/L, with a urea of 7.3 mmol/L and an estimated glomerular filtration rate (eGFR) of 34 mL/min/1.72 m^2. An arterial blood gas showed pH 7.31, Base Excess (BE) -6, bicarbonate 19, potassium 4.5 mmol/L, and lactate 1.6 mmol/L. Her recorded fluid balance was now 8 L positive since admission, and her FiO_2 had risen from 0.6 to 1.0. A renal ultrasound was performed, which showed normal-size kidneys with no evidence of hydronephrosis.

The patient was commenced on continuous veno-venous hemodiafiltration (CVVHDF) connected to the pre- and postoxygenator ports of the ECMO circuit. A bicarbonate replacement solution was used; systemic anticoagulation with a heparin infusion was already in effect due to the ECMO circuit. There was appropriate reduction in her creatinine and urea, correction of acid-base disturbance, and control of serum potassium.

The patient's hemodynamic status improved over the next 3 days, and she was weaned from all vasopressor support. Her lung injury resolved to the point where she could be oxygenated and ventilated safely, and she was liberated from ECMO after 7 days. The patient was trialed off renal replacement therapy (RRT) when the ECMO circuit was removed. Furosemide was given to assist diuresis, but at 36 hours post-decannulation the patient remained oliguric with an increasing fluid balance. A short-term dialysis catheter was inserted in her left femoral vein, avoiding the previous right femoral ECMO cannulation site, and CVVHDF was recommenced. The nephrology team was consulted, and after a further 48 hours the patient had a trial of intermittent hemodialysis (IHD) in the intensive care unit. There was no hemodynamic instability associated with this trial, and she proceeded on second daily IHD. At this stage, the patient was no longer requiring intensive care support and was transferred to the ward for ongoing management.

A technetium-99m mercaptoacetyltriglycine (MAG3) scan was performed. It showed well-preserved renal perfusion, progressive uptake of the radiotracer in the parenchyma, and lack of excretion—features consistent with a diagnosis of renal tubular necrosis. A tunneled jugular central venous dialysis catheter was inserted, and the patient continued IHD three times a week. Over the next 4 weeks her renal function gradually improved, and she was able to cease dialysis. Three months after hospital discharge, she could walk at a slow pace for 30 minutes and complete activities of daily living independently. Her renal function had returned to baseline.

HOW IS ACUTE KIDNEY INJURY DEFINED AND DIAGNOSED?

Acute kidney injury (AKI) is a syndrome characterized by a rapid decline in renal excretory function, leading to a constellation of clinical features, including retention of nitrogenous waste products, extracellular volume imbalance and accumulation of metabolic acids and electrolytes.[1] AKI is a common complication of critical illness and often begins well before a patient is admitted to a critical care environment. The definition or classification of AKI is based on changes in the serum creatinine (SCr) level and volume of urine output. There are three validated classification systems for AKI: the Acute Dialysis Quality Initiative's (ADQI's) risk, injury, failure, loss, end stage (RIFLE) criteria[2]; the Acute Kidney Injury Network's (AKIN's) criteria[3]; and the Kidney Disease Improving Global Outcomes' (KDIGO) guidelines.[4] A summary of these classification systems can be found in Table 8.1.

Changes in urine output and SCr values used for diagnosis of AKI in the above classification systems are limited in their ability to detect early AKI and focus only on the excretory functions. In clinical practice, there are many pitfalls in using the above classification systems for AKI diagnosis, and there are certainly patients who have evidence of renal injury who do not meet the urine or SCr criteria.[5] The glomerular filtration rate (GFR) needs to decline significantly before the SCr rises; therefore, the SCr may take up to 72 hours to rise. The SCr may be falsely lowered in critical illness due to a fall in production and hemodilution resulting from fluid resuscitation.[5,6] Urinalysis and microscopy can be helpful in identifying features consistent with glomerulopathies and acute tubular necrosis or differing prerenal failure from tubular injury.[7]

Progress has been made in the discovery of reliable biomarkers for AKI, but their incorporation into clinical use has been hindered by the complicated and heterogenous pathophysiological processes of AKI. Some biomarkers have been shown to perform well in certain patient populations, but poorly in others. The evaluation of biomarkers is challenging as they are usually compared to SCr, which is imperfect. The novel biomarkers for AKI can be stratified according to anatomical location of physiological function. There have been more than 25 biomarkers studied; examples are presented in Figure 8.1.[5] A single biomarker that performs well for the early diagnosis of EAKI is unlikely to be found given the broad range of causes, with a combination of biomarkers more likely to yield reliable results.[8]

Renal ultrasound with or without Doppler is the most commonly used imaging modality and is useful for evaluating preexisting structural renal disease or obstruction of the renal collecting system but is unable to provide information pertaining to the renal microcirculation. There has been renewed interest in the use of contrast-enhanced ultrasonography (CEUS) in sepsis-associated AKI (S-AKI) and bypass-associated AKI because of its ability to provide data relating to the microvascular flow. CEUS uses microbubbles as contrast media to provide real-time information on both the anatomic and functional characteristics of the microvascular flow.[9] There is little evidence on the use of this technique in the ECMO population, but given the pathophysiological nature of EAKI, it may warrant further exploration.

There are other imaging techniques that have shown promise in determining the status of the microcirculation but are incompatible with ECMO. These include arterial spin

Table 8.1 SUMMARY OF AKI AND STAGING[a]

		CREATININE (SCR) OR GFR DEFINITION	URINE OUTPUT
RIFLE	**Risk**	**Increased SCr × 1.5 or GFR decrease > 25%**	**<0.5 mL/kg/h for 6 hours**
	Injury	**Increased SCr × 2.0 or GFR decrease > 50%**	**<0.5 mL/kg/h for 12 hours**
	Failure	**Increased SCr × 3.0 or GFR decrease > 75% *or* SCr ≥ 4.0 mg/dL *or* acute increase ≥ 0.5 mg/dL**	**<0.3 mL/kg/h for 24 hours *or* anuria for 12 hours**
AKIN	**Stage 1**	**Increase in SCr ≥ 0.3 mg/dL (≥ 26.4 μmol/L) *or* ≥ 150% to 200%**	**<0.5 mL/kg/h for 6 hours**
	Stage 2	**Increase in SCr to 200%–300% (>2- to 3-fold) from baseline**	**<0.5 mL/kg/h for 12 hours**
	Stage 3	**Increase in SCr to > 300% (>3-fold) from baseline *or* SCr ≥ 4.0 mg/dL (354 μmol/L) with an acute increase of ≥ 0.5 mg/dl (44 μmol/L)**	**<0.3 mL/kg/h for 24 hours *or* anuria for 12 hours**
KDIGO	**Stage 1**	**Increase in SCr 1.5 to 1.9 times baseline *or* increase in SCr by ≥ 0.3 mg/dL (26.5 μmol/L)**	**<0.5 mL/kg/h for 6–12 hours**
	Stage 2	**Increase in SCr to 2.0 to 2.9 times baseline**	**<0.5 mL/kg/h for ≥ 12 hours**
	Stage 3	**Increase in SCr to 3.0 times baseline *or* increase in SCr to ≥ 4.0 mg/dL (353.6 μmol/L) *or* initiation of RRT**	**<0.3 mL/kg/h for ≥ 24 hours *or* anuria for ≥ 12 hours**

[a]Modified from Bellomo et al.,[2] Mehta et al.,[3] and Khwaja et al.[4]

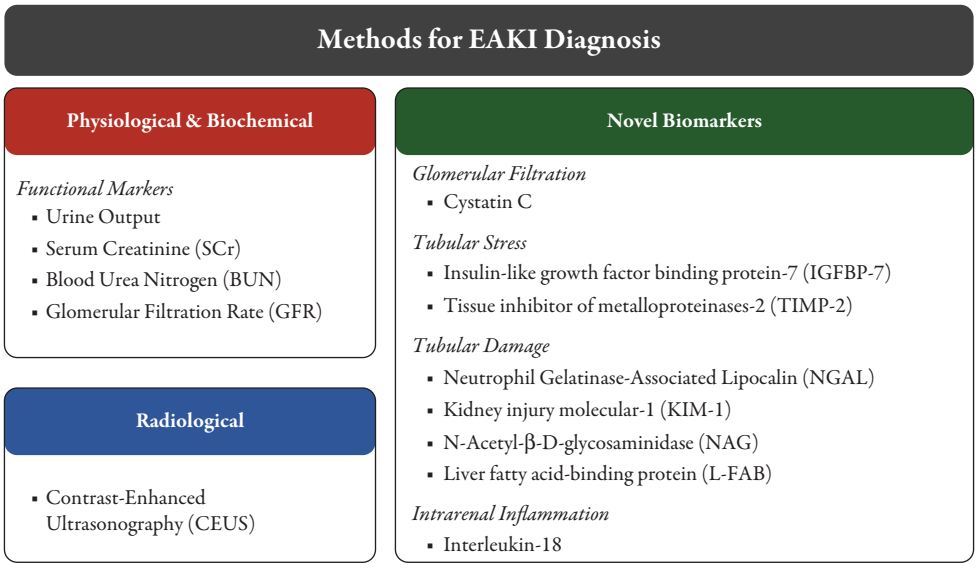


Figure 8.1 Summary of methods for EAKI diagnosis.

labeling, blood oxygen level dependent, and sodium magnetic resonance imaging.[7]

WHAT ARE THE RISK FACTORS FOR ECMO-ASSOCIATED ACUTE KIDNEY INJURY?

There are several important risk factors for development of EAKI. These include baseline patient characteristics such as advanced age, preexisting renal dysfunction, and cirrhosis.[10] Illness-related sequelae that are associated with EAKI include elevated lactate prior to ECMO initiation, severely reduced left ventricular ejection fraction, high-dose inotropic drug requirement, increased transfusion requirement, and shock state post cardiotomy.[11,12] ECMO-related factors associated with an increased probability of EAKI include veno-arterial (V-A) configuration, higher ECMO pump speed, and duration of ECMO support.[13]

WHAT ARE THE PATHOPHYSIOLOGICAL MECHANISMS FOR EAKI PATIENTS?

The pathophysiology of EAKI and renal failure is complex and not well understood. Much of the current understanding has been extrapolated from animal models and in vitro studies investigating entities such as S-AKI and AKI associated with cardiopulmonary bypass. The pathophysiology of AKI can be subdivided into factors that affect

- renal perfusion pressure,
- the renal microcirculation, and
- secondary renal parenchymal cell death.

However, there is significant overlap between the causative mechanisms and their pathophysiological outcomes. An outline of these processes and expanded notes on factors specifically associated with critical illness and ECMO can be found in the Discussion section of this chapter.

WHAT PREVENTIVE MEASURES MAY BE BENEFICIAL?

Acute kidney injury has an incidence of up to 50% in critically ill patients and is associated with increased morbidity and mortality; therefore, attention should be afforded to potential mitigating factors.[14,15] Sepsis, hypovolemia, and administration of nephrotoxic agents are the most common causes of AKI; therefore, these form the target for most preventive interventions.[15] Given the multifactorial nature of the pathophysiology of AKI and the complex organ crosstalk that occurs in critically ill patients, care must be taken as interventions to prevent the progress of AKI may adversely affect other organ systems.

Reduced renal perfusion pressure due to hypovolemia is a significant risk factor for the development of AKI; therefore, early correction of volume depletion is important. Overresuscitation with fluid leading to hypervolemia may also cause reduced renal perfusion pressure by increasing renal and pulmonary interstitial edema and central venous pressure (CVP).[15] Large-volume resuscitation with isotonic crystalloids may result in hyperchloremia and decreased renal perfusion pressure via renal vasoconstriction.[15]

The administration of loop diuretics to assist in prevention of AKI development or progression is not beneficial, although they do have a role in the maintenance of appropriate fluid balance and to this end may prevent ECMO patients from requiring RRT.[15]

There are also important considerations regarding mean arterial pressure (MAP) targets in ECMO patients with AKI. The accepted MAP target of 65–70 mm Hg, or higher in patients with preexisting hypertension, may not be appropriate for the V-A ECMO patient with severe cardiac failure

where afterload reduction is required to maintain forward flow and aortic valve opening.

Higher ECMO pump speed is also associated with the development of EAKI,[13] possibly via hemolysis-related heme pigment AKI[16–18] and oxidative/nitrosative stress.[19] Therefore, using the lowest pump speed that achieves adequate oxygenation or perfusion may prevent this.

WHAT ARE THE INDICATIONS FOR RENAL REPLACEMENT THERAPY?

Indications for RRT in EAKI are congruent with the standard RRT indications for other critically ill patients and include acidosis, electrolyte derangement, intoxicants, fluid balance management, and uremia. In a survey conducted across participating Extracorporeal Life Support Organization (ELSO) centers, fluid balance management was the most common indication for RRT, followed by defined AKI and then electrolyte disturbances.[20]

The initiation of RRT may allow maintenance of a neutral fluid balance during the administration of large fluid volumes for nutrition, medications, and blood products. It also avoids the prolonged use of potentially ototoxic diuretics to assist in maintaining fluid balance.[17]

WHEN IS THE OPTIMAL TIME TO COMMENCE RRT IN AKI?

In the absence of life-threatening indications mentioned above, the optimal timing for the commencement of RRT in critically ill patients is not conclusively known.[21] In practice, it is a decision made on a case-by-case basis by balancing the many competing clinical priorities. In patients with AKI and preserved urine output, high-dose loop diuretics may lead to rapid fluid shifts and intermittent access insufficiency in the ECMO circuit. In contrast, for patients with established AKI and low urine output, high-dose loop diuretics are unlikely to allow maintenance of an appropriate fluid balance and have the risk of ototoxicity. Early continuous RRT (CRRT) may also need to be established to facilitate renal protection after administration of contrast agents related to angiography or computed tomography.

Studies have shown that in critically ill patients, a positive fluid balance is independently associated with worse oxygenation; longer lengths of mechanical ventilation, length of stay, and ECMO duration; as well as increased mortality.[17,22,23] There is also evidence that reduction in positive fluid balance leads to improved pulmonary compliance and shorter ECMO duration.[17,24] Given the above, we feel that early identification of AKI and initiation of CRRT in ECMO patients may play a role in improving ECMO patients' outcomes and therefore have a low threshold for commencement.[10,25]

WHAT ARE THE DIFFERENT MODALITIES AVAILABLE FOR RENAL REPLACEMENT IN ECMO PATIENTS?

Several modes and configurations can be used to provide RRT in ECMO patients; these include peritoneal dialysis (PD), IHD, and CRRT. They each have their own advantages and disadvantages.

Peritoneal dialysis is widely used in neonatal and infant critical care and has been successfully used in this population in conjunction with ECMO and CRRT to augment fluid balance control.[26,27] In adults its use is limited by inefficient solute clearance, especially in highly catabolic patients; interference with ventilation; and propensity for peritonitis. There are no reports of successful use in the adult ECMO population.

Conventional IHD uses high dialysate and blood flows, allowing it to achieve therapeutic effect in 3–4 hours. The swiftness of this option causes rapid fluid shifts, often resulting in hemodynamic instability, making IHD prohibitive in the setting of ECMO.

Sustained low-efficiency daily dialysis (SLEDD) is a hybrid RRT, combining features of intermittent IRRT and CRRT. It is not continuous, but each session runs for longer than a conventional IHD session. It utilizes reduced dialysate and blood flow rates, which may ameliorate the hemodynamic instability usually associated with traditional IHD. To date there are no trials that compared the utilization of SLEDD and CRRT in ECMO patients.

Continuous modes include continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), CVVHDF, and slow continuous ultrafiltration (SCUF). All these continuous modes confer the following advantages: reduced hemodynamic impact, controlled acid-base status and electrolyte balance, and continuous control of fluid balance. CVVHDF is most commonly utilized as it optimizes both electrolyte and acid-base control. There are no clinical trials comparing the safety, efficacy, or outcomes of all of the various modes or configurations.[28]

WHAT ARE THE OPTIONS FOR CONNECTING CRRT TO AN ECMO CIRCUIT?

There are two methods available to connect CRRT to the ECMO circuit: incorporation of an external CRRT device into the ECMO circuit and the "in-line techniques."

Incorporation of an External CRRT Device Into the ECMO Circuit

The incorporation of an external CRRT device into the ECMO circuit method for performing RRT allows the precise control of blood flow, accurate measurement of fluid balance, and monitoring of RRT circuit pressures.[29,30] The major limiting factor in this method is overcoming the pressure alarms inbuilt into commercial CRRT machines.

Location of the inflow and outflow lines for the CRRT machine vary with the ECMO console and pump type. In consoles fitted with roller pumps, the inflow and outflow lines may both be connected before the roller pump, whereas in machines with a centrifugal pump, the CRRT inflow and outflow lines can be placed in a variety of configurations (Figures 8.2 and 8.3). With a centrifugal pump, due to the high risk of air entrainment on the (negative) prepump side, the CRRT inflow line is best positioned distal to the ECMO pump, but

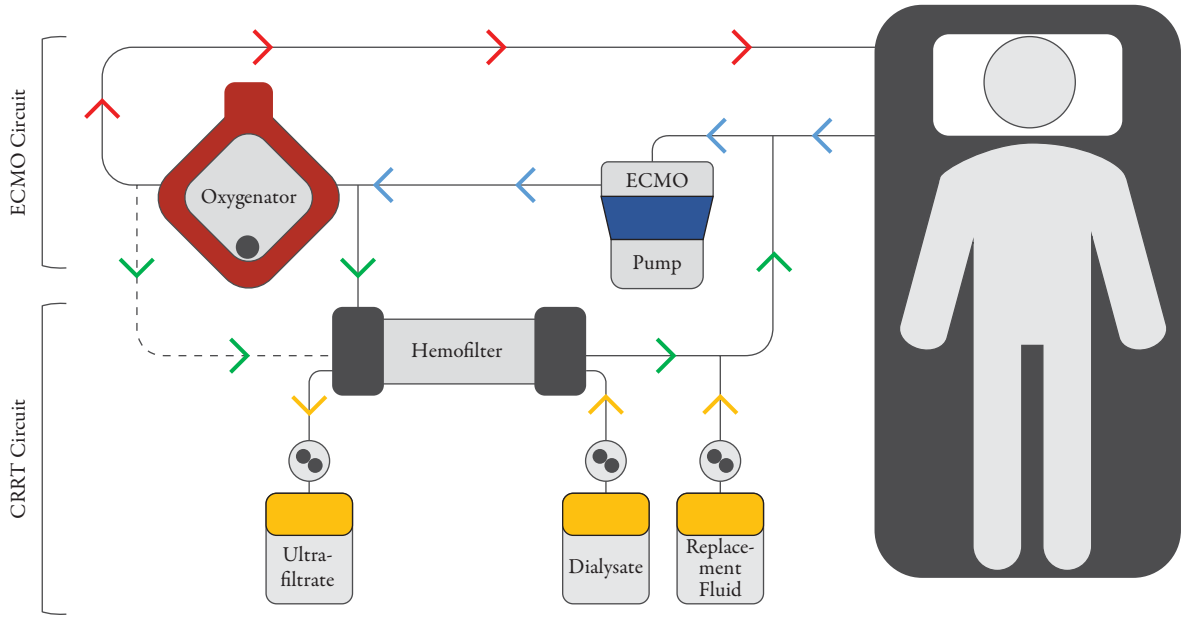


Figure 8.2 Renal replacement therapy during ECMO using an in-line hemodiafilter. Flow is diverted to the hemofilter after the ECMO pump and either pre- or postoxygenator. Blood returns to the ECMO circuit from the hemofilter before the ECMO pump. Dialysate, ultrafiltrate, and replacement fluid rates are controlled using an intravenous pump. Replacement fluid can be given as pre- or postdilution (only postdilution shown).

may lie before or after the oxygenator (Figure 8.2).[17] The CRRT outflow line location can be either prepump or preoxygenator; once again the former will increase the risk of air entrainment (Figure 8.3). In many of these configurations, the CRRT inflow and outflow lines necessitate addition of a connection line to the ECMO circuit; these can lead to areas of increased turbulence and increased risk of thombus formation.[31] The simplest and safest configuration is one that minimizes additional connections, diminishes the risk of air entrainment, uses the oxygenator as a safety barrier to trap embolized air or thrombus, and still allows pre- and postoxygenator pressure readings and blood sampling. The optimal configuration to achieve the above will differ depending on ECMO console and circuit type.

Commercial CRRT machines have default inbuilt pressure alarms to detect unsafe access and return pressures. The access pressure alarm is typically a negative pressure alarm due to the normal requirement of a negative access pressure to remove blood from the patient. When operating within an ECMO circuit, the post-ECMO pump access pressure will be positive. The CRRT outflow pressure required to return blood back into the ECMO circuit is typically higher that returning in

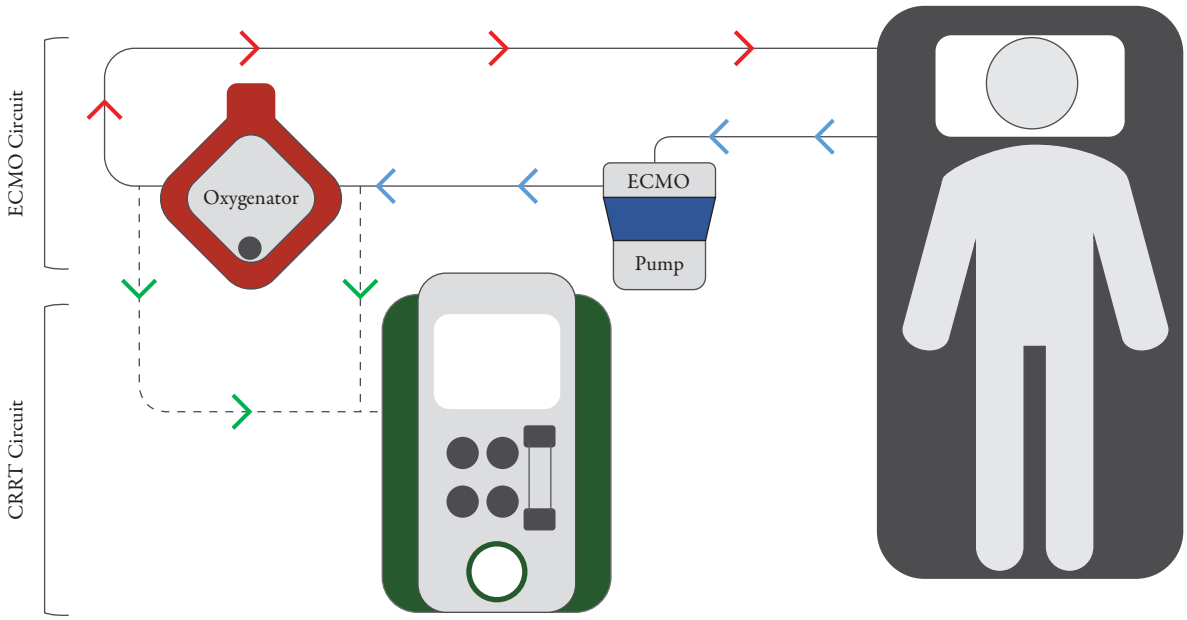


Figure 8.3 Incorporation of an external CRRT device into the ECMO circuit (centrifugal pump): inflow line location options.

a normal circuit; therefore, a high return pressure alarm may also obstruct optimal CRRT function. Consequently, some manufacturers have allowed the clinician to change the pressure settings when used in conjunction with ECMO.

In machines that do not allow adjustment of the pressure alarm settings, flow restrictor devices have been used to maintain pressure within the alarm limits.[17] As previously discussed, these devices are known to cause an area of altered flow with increased risk of thrombosis and hemolysis. A wide-bore intravenous cannula can also be utilized as a return site to overcome high return pressure alarms; vigilance is required to avoid high-volume extravasation into the subcutaneous tissues.

Introduction of a Hemodiafiltration Filter Into the ECMO Circuit—The "In-Line Technique"

The introduction of a hemodiafiltration filter into the ECMO circuit in the inline method utilizes the positive pressure generated by the ECMO pump to drive blood through a hemodiafilter placed within the circuit. SCUF is the most commonly used RRT therapy for the in-line technique.[29] The connections and placement of the hemodiafilter within the circuit are crucial for minimizing risk. The inflow or access limb for the hemofilter is typically placed after the ECMO pump but before the oxygenator. There are multiple options for the location of the outflow or return line, each with their own advantages and disadvantages. Blood from the hemofilter can be returned to the ECMO circuit on the prepump (negative pressure) side; this has the benefit of a pressure gradient. However, connections to the negative pressure side of the ECMO circuit can predispose to air entrainment (Figure 8.4). In this case, the oxygenator is used to minimize the risk of thrombus or air returning to the patient. This configuration will lead to a degree of recirculation through the hemofilter, reducing its efficiency to a small degree. Alternatives are to connect the hemofilter return line to the positive pressure postoxygenator site; this avoids the risk of air entrainment but provides no barrier to air embolism. Another option is to return hemofilter blood to the patient via a separate central venous line. This method will result in a shunt if the blood is acquired preoxygenator.[31]

The hemofilter blood flow rate is largely determined by the ECMO pump speed, but adjustments can be made via a flow-restricting device, such as a stopcock.[17] Use of a flow-restricting device can result in an area of high turbulence and further complications, such as thrombus formation and hemolysis. An ultrasonic flow probe can be used to determine the flow through the hemofilter, but there is no method of measuring pressure within the additional circuit and may result in delayed recognition of thrombi within the circuit.[30]

Standard infusion pumps are used for countercurrent dialysate fluid, replacement fluids, and ultrafiltrate (Figure 8.4). The use of external intravenous infusion pumps for this purpose can lead to inaccuracies, with an error rate of about 12.5% reported, resulting in greater than an 800-mL/d discrepancy in ultrafiltrate volume.[30,32] Ultrafiltrate volume is measured via a standard urine volume measurement kit.[17]

ARE ANY OTHER OPTIONS AVAILABLE FOR PERFORMING CRRT?

Continuous RRT may be performed via an independent vascular access and an external RRT device. This is the simplest method for achieving access for RRT and has the advantage of not having to interfere with the ECMO circuit. The disadvantages to this method include the requirement for an additional central vein (which may be limited in ECMO patients) and increased bleeding at the catheter site if inserted post-ECMO cannulation and anticoagulation has been instituted.[29]

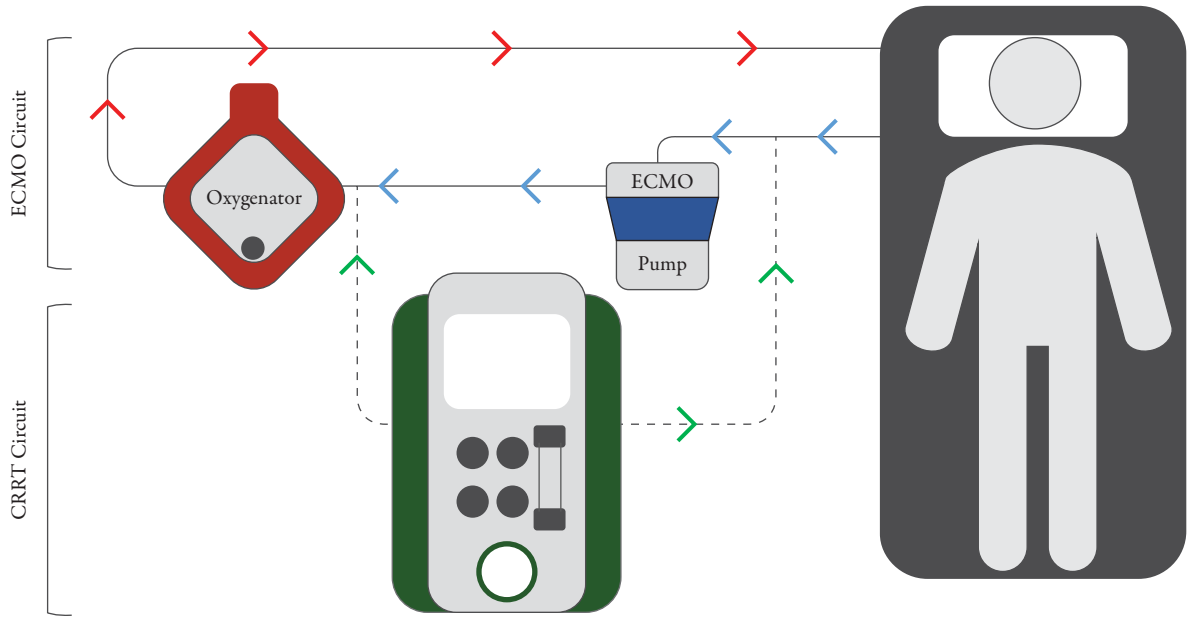


Figure 8.4 Incorporation of an external CRRT device into the ECMO circuit (centrifugal pump): outflow line location options.

HOW DO YOU ANTICOAGULATE THE CRRT CIRCUIT?

A systemic infusion of unfractionated heparin is the standard technique for anticoagulation and prevention of thrombus within the ECMO circuit. Additional anticoagulation to prevent thrombus formation in the CRRT circuit is not routinely required. Two, small retrospective studies investigated the use of regional citrate anticoagulation for the CRRT when used in conjunction with an ECMO circuit. These studies established that the technique is feasible and safe, but given their retrospective nature and small sample size, were unable to conclude that using regional citrate anticoagulation improved CRRT circuit life span.[33,34]

HOW DO YOU PREVENT HEAT LOSS THROUGH THE RRT CIRCUIT?

Under usual circumstances, there is a proportion of heat lost from blood passing through any CRRT circuit, and a warming device is advantageous in restoring this loss. In the circumstance of combined ECMO and CRRT, an additional warming device on the CRRT machine may not be required.[17] If the blood from the CRRT circuit is being returned preoxygenator, it may be sufficiently warmed by the ECMO water heater.

WHAT FACTORS DETERMINE THE RRT FLUID REMOVAL RATE?

A positive fluid balance in critically ill patients is associated with prolonged duration of mechanical ventilation, ECMO duration, intensive care unit stay, and increased mortality.[17,22,23] Modern CRRT machines are able to accurately measure and maintain a preset fluid status, but how this translates to the patient and their management is the challenge that faces the critical care clinician.

Fluid removal via RRT occurs primarily from the intravascular compartment; however, it is fluid accumulation in the interstitial space that results in adverse outcomes. A patient's ability to withstand the hemodynamic effects of fluid removal via RRT is dependent on the total intravascular volume, the total interstitial volume, and the rate of movement of fluid between these compartments. The rate of movement of fluid from the interstitial space to the intravascular compartment is variable between person, space, and time and is impossible to predict. One of the advantages of CRRT in the critically ill patient is that fluid removal can occur gradually over a 24-hour period and be titrated within that period to match clinical status.

As a wider group, patients requiring V-V ECMO for respiratory failure benefit from strict control of fluid balance. A negative cumulative daily fluid balance often improves pulmonary compliance.[24] The goal of negative fluid balance needs to be balanced with the tendency for intermittent access insufficiency in the patient who has high intrathoracic pressure and pulmonary sepsis and is intravascular depleted, leading to hypotension due to capillary leakage and vasodilation. Despite efforts, a daily negative fluid balance may not be achievable until after the initial resuscitation phase.

The clinical indications for V-A ECMO are varied, and each has their own requirements with regard to fluid management. Postoperative cardiothoracic patients may incur massive blood loss, while post–myocardial infarction and cardiac arrest patients experience an inflammatory response leading to systemic capillary leak and vasodilation.[35] In both these cases, substantial fluid loading may be required in the early phase to maintain effective ECMO flows. On the other hand, the patient with acutely decompensated chronic cardiomyopathy may present with features of fluid overload and pulmonary edema. Early, aggressive fluid removal in this group results in left ventricular unloading and improved myocardial performance.

WHAT COMPLICATIONS CAN BE ENCOUNTERED WITH RRT IN ECMO PATIENTS?

There are several complications related directly to the addition of an RRT circuit to the management of an ECMO patient, and they differ depending on the configuration adopted. If RRT run via an independent vascular access is the chosen configuration, then there is increased risk of bleeding and infection at the vascular access site.[29]

Connection of the RRT circuit to the ECMO circuit may lead to an increased risk of air embolism if the inflow or outflow lines are connected proximal to the ECMO pump, where there is negative access pressure. This risk can be mitigated by placing the line connections distal to the ECMO pump, where there is positive pressure.[17] Examples of inflow and outflow line placement can be seen in Figures 8.2 and 8.3.

The additional line connections required to incorporate an RRT circuit into the ECMO circuit create areas of increased turbulence and thrombus formation.[30] Additional thrombus formation may lead to increased hemolysis, and it has been demonstrated that patients receiving CRRT while on ECMO, compared to those on ECMO alone, have higher peak plasma free hemoglobin levels, indicating increased rates of hemolysis.[36,37]

DISCUSSION

The estimated incidence of AKI in patients requiring ECMO is 52.1%–72.4%, and 40.8%–49.0% will require RRT.[10] Patients on V-A ECMO had a higher incidence of AKI (60.8%) than those on V-V ECMO (45.7%) The combination of ECMO and AKI is associated with a high mortality rate of 54.7%–68.8%, and this increases further to 62.6%–73.6% if RRT is necessary.[10]

As discussed previously in the chapter, the pathophysiology of EAKI and renal failure is complex. The contributing factors can be subdivided into those that affect

1. Renal perfusion pressure
2. Renal microcirculation
3. Secondary renal parenchymal cell death

ALTERATIONS IN RENAL PERFUSION

A reduction in renal arterial pressure (MAP) or an increase in renal venous pressure (CVP) will result in reduced renal perfusion pressure, according to the formula MAP - CVP = Renal perfusion pressure. Biventricular heart failure may both reduce MAP and increase CVP such that renal perfusion and function are compromised. Large-bore venous access cannulae may further impair renal venous drainage. The initiation of ECMO may reverse this by increasing renal artery pressure and reducing venous pressure resulting from inferior vena cava drainage cannulae.[19]

In V-A ECMO, cardiac output is a mixture of native pulsatile and nonpulsatile ECMO pump flow. In contrast, pulsatile renal blood flow (RBF) is preserved in V-V ECMO. There is some evidence from the cardiopulmonary bypass population that maintaining pulsatile arterial blood flow provided superior renal protection,[38,39] but this has not been definitively proven in ECMO.

The ECMO initiation period is often marked by rapid alterations in hemodynamic status, with fluctuating vasopressor/inotrope dosages; this leads to altered RBF with recruitment and washout of hypoxic renal microcirculation.[17,19] Intravenous fluid therapy use is often significant both the pre-ECMO and throughout the early ECMO course; in response, diuretic therapy may be used to reduce extravascular lung water, achieve a negative fluid balance, and improve pulmonary compliance. The combination of a positive fluid balance and diuretic use can further add to the development of EAKI.[22,40]

There is a substantial interaction between the lungs and the kidneys related to the development of AKI; these factors are especially relevant in the V-V ECMO patient population, who may have received high ventilatory pressures prior to ECMO initiation. Positive pressure ventilation results in decreased RBF due to its effect on hemodynamics via alterations in venous return, pulmonary vascular resistance, and cardiac preload and afterload.[41] Mechanical ventilation alters neurohormonal systems such as the renin-angiotensin system and atrial natriuretic peptide, resulting in lowered RBF and increased fluid retention.[42] Animal models have also shown that mechanical ventilation can lead to an increase in Bowman's space, collapse of the glomerular capillaries, and perivascular edema.[41,43]

Severe hypoxemia results in increased release of vasoactive factors such as angiotensin II, endothelin, and decreased nitric oxide (NO), increasing renal vascular resistance, and ultimately decreasing RBF.[41] In vitro, severe hypoxemia and hypercapnia can induce apoptosis of renal tubular cells.[44]

CHANGES TO THE RENAL MICROCIRCULATION

Normal healthy renal function depends on an adequate oxygen supply to the microcirculation, which enables the generation of ATP (adenosine triphosphate), reactive oxygen species (ROS), and NO.[45] The kidney is particularly vulnerable to ischemia because of its complex microvasculature,[46] high energy demand, and the borderline hypoxemic state of the renal medulla at baseline.[47] In pathological states such as sepsis or shock or ischemia of the renal microvasculature, disruption of the NO and ROS homeostasis is common.[45] Nitric oxide has a direct vasodilatory effect and is thought to inhibit platelet aggregation and leukocyte activation, functions essential for effective renal microcirculations. Its production by endothelial nitric oxide synthase (eNOS) is diminished during reperfusion injury and sepsis due to depletion of cofactors and uncoupling of eNOS.[45,48]

In the pre-ECMO setting, multiple management strategies implemented with the aim of maximizing cardiorespiratory function are often detrimental in preserving renal function. Examples include intravenous fluids administration, diuretic use, high inotrope/vasopressor use, and positive pressure ventilation. Although there is improvement in oxygenation, increased MAP, and diminished oxygen consumption after the initiation of ECMO, the period of pre-ECMO hypoxia or low cardiac output syndrome can lead to an ischemia-reperfusion injury. Restoration of blood flow to previously hypoxic cells results in production of reactive oxygen/nitrogen species (RNOS) and oxidative stress-mediated injury.[19,49] Furthermore, the supraphysiological blood oxygen content resulting from ECMO may result in the formation of superoxide and increased RNOS production.[50,51]

The activation of pro-inflammatory mediators and systemic inflammatory response by an underlying disease process, such as sepsis, may be amplified by the interaction between blood and the nonbiological and nonendothelialized ECMO circuit. Tumor necrosis factor-alpha, pro-inflammatory cytokine, and interleukin (IL) 1β, IL-6, and IL-8 are implicated in this process, but their precise role is not clear.[19,52,53] The activation of these inflammatory cascades can also alter hemodynamics, resulting in a hyperdynamic vasodilated hypotensive circulation, causing reduction in renal perfusion pressure.[10]

Hemolysis occurs in between 5% and 18% of ECMO patients.[54–57] Hemolysis can contribute to EAKI via heme pigment–induced AKI[16-18] and oxidative/nitrosative stress.[19] Plasma-free hemoglobin reacts with hydrogen peroxide and is implicated in EAKI by promoting free radical production via scavenging of NO.[19,58] Free iron is also known to contribute to nephrotoxicity via the increase in production of RNOS.[58,59]

SECONDARY RENAL PARENCHYMAL CELL DEATH

Secondary renal parenchymal cell death is most commonly the consequence of altered renal perfusion and acute tubular necrosis but may result from administration of nephrotoxic agents, such as contrast agents, antibiotics, and anti-inflammatories. EAKI can also result from renal ischemia due to microemboli and microthrombi formation within the renal vasculature, particularly during V-A ECMO. Interaction between blood and the nonendothelialized ECMO circuit and destruction of the glycocalyx are thought to be the provoking factors for microthrombi formation.[19,50,60–62]

MORTALITY AND OUTCOMES

A 2019 meta-analysis estimated the hospital and/or 90-day mortality rates of patients on ECMO complicated by AKI.[10] The mortality rate for those with AKI was 62.0%, increasing to 68.4% if severe AKI requiring CRRT was present. This analysis included studies spanning 18 years; despite the significant advances in technology over this time, there was no correlation between year of the study and the incidence of AKI. Severity of illness and presence of multiple organ dysfunction syndrome is proposed to be a large contributor to the high mortality in these patients, with AKI being the independent risk factor, not the requirement, for CRRT.[63]

Data regarding the recovery of renal function in this cohort of patients are limited. There are some data to show that 93%–96% of pediatric patients who survive ECMO and CRRT go on to have renal recovery.[64,65] In adults, patients with stage 3 KDIGO AKI prior to commencement of ECMO were less likely to have renal recovery, and those on CRRT for more than 7 days had a higher risk of end-stage renal failure.[66,67]

CONCLUSIONS

- ECMO-associated acute kidney injury occurs in over half of ECMO patients.
- The pathophysiology can be subdivided into factors that affect
  - renal perfusion pressure,
  - renal microcirculation, and
  - secondary renal parenchymal cell death.
- Urine output and SCr remain the most utilized modalities for diagnosis and classification of AKI in ECMO patients.
- The risk factors for development of EAKI include underlying patient characteristics, illness-related sequelae, and the impact of ECMO.
- The management of fluid balance is the most common indication for RRT in ECMO patients.

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REVIEW QUESTIONS

1. A 35-year-old, 70-kg, normally fit, and well male patient is admitted to the Intensive Care Department after initiation of V-V ECMO for influenza pneumonitis. He has a creatinine level of 186 μmol/L and a urine output of 340 mL over the last 12 hours. Which KDIGO classification stage applies?

   A. Stage 1
   B. Stage 2
   C. Stage 3
   D. There is not enough information to determine the stage.

2. Which of the following is not a risk factor for the development of EAKI?

   A. Advanced age
   B. Cirrhosis
   C. Pneumococcal pneumonia
   D. Severely reduced left ventricular dysfunction

3. Which of the following is not a pathophysiological cause of development of EAKI?

   A. Corticosteroid administration
   B. Reduced renal perfusion pressure
   C. Injudicious fluid resuscitation
   D. Hemolysis

4. Which of the following is not an indication for urgent RRT?

   A. Hyperkalemia
   B. Low urine output
   C. Acute poisoning
   D. Pulmonary edema

5. When using an external CRRT device, which of the following is not a potential location for the CRRT outflow line?

   A. Proximal to the ECMO pump
   B. Via a wide-bore intravenous cannula
   C. Distal to the ECMO pump, preoxygenator
   D. Distal to the ECMO pump, postoxygenator

6. Which of the following RRT modes has insufficient solute clearance to be used in the adult ECMO patient?

   A. Intermittent hemodialysis
   B. Sustained low-efficiency daily dialysis
   C. Continuous veno-venous hemodialysis
   D. Peritoneal dialysis

7. Which of the following is not a complication encountered when combining CRRT and ECMO circuits?

   A. Hemolysis
   B. Hypothermia
   C. Air embolus
   D. Thrombus formation

8. What is the estimated mortality rate of ECMO patients with severe AKI who require RRT?

   A. 36%
   B. 54%
   C. 68%
   D. 83%

ANSWERS

1. B. Given the patient is young, usually well, and male, it can be assumed that they have a normal baseline creatinine of about 80 μmol/L. A value of 186 μmol/L would be between 2.0 and 2.9 times this baseline. A urine output of 630 mL over 12 hours would equate to less than 0.5 mL/kg/h.

2. D. There is no known association between pneumococcal pneumonia and increased risk of EAKI. Answers A, B, and C are correct.

3. A. There is no known association between corticosteroid administration and development of EAKI. Answers B, C, and D are correct.

4. B. In the absence of acid-base disturbance, hyperkalemia, pulmonary edema, or uremia, low urine output itself is not an indication for urgent RRT. Answers A, C, and D are correct.

5. D. Distal to the ECMO pump, postoxygenator, is not a safe option for the outflow line as the risk of thrombus or air embolization to the patient is high. Answers A, B, and C are correct.

6. D. Peritoneal dialysis has been successfully utilized in the pediatric ECMO population but is unable to achieve sufficient solute clearance in adults. Answers A, B, and C are correct.

7. B. Hypothermia is usually not problematic in ECMO patients because of the efficient blood warming device. Answers A, C, and D are correct.

8. C. The rate is 68%; the mortality of those with AKI but not requiring RRT is 62%. Answers A, B, and D are correct.

9.

AMBULANCE GROUND TRANSPORTATION OF ECMO PATIENTS

Grace van Leeuwen, Matteo Di Nardo, and Nicolò Patroniti

STEM CASE AND KEY QUESTIONS

A 35-year-old gentleman presented in a secondary hospital with fever, cough, and shortness of breath. He was diagnosed with H1N1 pulmonary infection and sepsis. The respiratory distress progressed quickly, and after 12 hours he developed severe acute respiratory distress syndrome (ARDS). The patient was intubated, ventilated, sedated, and paralyzed. High ventilator settings and prone position were attempted with poor clinical response. He also required norepinephrine infusion at 0.15 μg/kg/min for hemodynamic impairment. Despite the best medical therapy, his vital signs were still worrisome: heart rate (HR) 103 beats per minute (beats/min), blood pressure (BP) 95/65 mm Hg with mean arterial pressure 75 mmHg, SpO_2 (oxygen saturation by pulse oximetry) 83%, mixed venous saturation 58%, lactate 1.8 mmol/L with a PaO_2/FiO_2 (fraction of inspired oxygen) ratio of 68 mm Hg.

The closest extracorporeal membrane oxygenation (ECMO) center was called since the patient met ECMO criteria.

HOW SHOULD PRETRANSPORT EVALUATION AND TRANSPORT BE ORGANIZED?

The nearest ECMO center (200 km away) was contacted through the referral center by the intensivist in charge, and the patient's condition was discussed with the ECMO team of the receiving hospital. Both agreed that the patient was an ECMO candidate. The communication with the referral hospital included assistance in the patient's stabilization; solicitation of several preparation procedures, such as central and arterial lines and indwelling urinary catheter; availability of blood bank products; and some laboratory tests. Also, it was requested to have some personnel such as intensive care unit (ICU) and scrub nurses available and the presence of an ultrasound/ ECHO physician to assist in case of difficult cannulation.

WHICH VEHICLE IS THE BEST OPTION FOR THIS PATIENT TRANSPORT?

The ECMO team was activated following institutional guidelines, and it was decided that for such transference the best option would be a ground transport ambulance because of the relatively short distance. Furthermore, the team should be composed by the two ECMO consultants with cannulation skills, the ECMO specialist, the transport nurse, and the ambulance paramedics.

WHICH ECMO MODALITY SHOULD BE USED?

The team discussed that the best ECMO modality would be veno-venous (V-V) ECMO, as the patient had stable hemodynamics with acceptable vasopressor support. The cannulation of choice would be a double-lumen 31 French (31F) single cannula in the right internal jugular vein (RIJV). An alternative plan was made for dual-site cannulation with femoro-femoral configuration in case of any issues, including the possibility of veno-arterial (V-A) ECMO in case of hemodynamic instability on arrival and patient assessment.

A pretransport checklist was applied, including the equipment and disposables to be taken, including multiple cannula options.

After completion of the pretransport checklist, the ECMO team was sent to the referral hospital, maintaining close communication with the in-house intensivist regarding estimated arrival time and obtaining updates on the patient's condition.

The team arrived at the referral hospital, introduced themselves to the local team, and evaluated the patient, confirming the V-V ECMO indication.

The availability at the bedside of all the necessary medication, blood products, and equipment was confirmed. The circuit was primed, and V-V ECMO was initiated with a double-lumen cannula placed in the RIJV without concerns, achieving good blood flows, with arterial saturation of 90%. The ventilator settings were slowly decreased to "rest settings". Norepinephirne could be decreased to 0.05 μg/kg/min. When the patient was stabilized and the procedure was finished, he was moved onto the ECMO stretcher and then to the ambulance.

WHAT COMPLICATIONS COULD BE EXPECTED DURING THE TRANSPORT?

Before leaving, a checklist was reviewed; all major possible complications were anticipated, and a plan was made to deal

with each possible complitation. The patient's family was seen before and after the procedure. Before, informed consent was obtained, and afterward the family was informed about the procedure and the patient's outcome. They received a written pamphlet explaining about ECMO and describing the receiving hospital and the ICU, including the location.

During the trip, the patient started to desaturate as low as 70%. It was noted that the color of the cannulae was similar and red, consistent with recirculation. The major causes of recirculation were discussed by the team: hypovolemia, pneumothorax, cardiac tamponade, displacement of the cannula, low cardiac output syndrome, and excessive blood flow on ECMO. The team decided to give two fluid boluses after their assessment; the arterial saturation reached 84%, and the venous saturation dropped to 70%. The remainder of the transport was uneventful, and the patient arrived safely at the ECMO center.

After handover, the receiving ICU team at the ECMO center took charge of the patient. The transport team had a brief debrief and filled out the necessary paperwork.

DISCUSSION

Extracorporeal membrane oxygenation is a life-saving procedure for patients with severe refractory respiratory and/or circulatory failure. Patients eligible for ECMO are, in general, in an unstable condition maintained by maximal ventilator support and other intensive care salvage therapies. A conventional transport may be hazardous, and deaths have been described.[1,2] Cannulating the patient at the referring hospital and transporting the patient on ECMO was first described by Bartlett et al.[3] The concept of traveling to the referring hospital with a portable ECMO system, cannulating the patient, and transporting the patient to the nearest ECMO center was then further described by Cornish.[4] Since then, the number of centers providing transports on ECMO has increased, but this practice became widely accepted and utilized just in the late 2000s.[5]

When the transport team is required to perform cannulation for ECMO support at the referring facility and then provide transport with the patient on ECMO to the receiving hospital, it is defined as *primary transport*; *secondary transport* refers to patients already on ECMO at the referring hospital needing transfer to another institution.[6]

INDICATION FOR PRIMARY ECMO TRANSPORTATION

A primary ECMO transport should be considered when a patient is clinically deteriorating and meeting predefined criteria for ECMO while being located in a hospital that is not an ECMO center.

According to the Extracorporeal Life Support Organization (ELSO) guidelines,[6] the main indications to pursue primary ECMO transportation are discussed next.

Refractory Hypoxemia/Hypercapnia (Failure of Conventional Mechanical Ventilatory Support)

- As per the best clinical judgment of the attending physician and the local team, there is an unacceptable risk of deterioration during conventional transport.
- There is an inability to maintain acceptable oxygenation/ventilation in adult patients using the ARDSnet protocol.
- There is an inability to maintain acceptable oxygenation/ventilation in pediatric patients without utilizing high-frequency oscillatory ventilation (HFOV) (although high-frequency modes of ventilation during transport are possible in select patient populations, HFOV transport is not currently feasible).
- The presence of air leak syndrome is likely to worsen with continued high levels of positive airway pressure and altitude.

Refractory Septic/Cardiogenic Shock Despite Aggressive Inotropic/Vasopressor Support

- ECMO support for refractory septic shock may be considered as an indication for ECMO transport in all age groups of patients.

SOME CLINICAL SCENARIOS MAY NEED SECONDARY ECMO TRANSPORT

- ECMO support initiated at a referring center for primary cardiac failure and evaluation for orthotopic heart transplantation or other cardiac intervention
- Patient who is a possible candidate for lung transplantation requires ECMO for safe transfer to a lung transplant center
- Patient placed emergently and unexpectedly on ECMO support at a center without resources to maintain patient on long-term ECMO support
- ECMO center which exceeded its capacity to look after the patient due to bed space or staffing or both

INDICATION, ADVANTAGES, AND DISADVANTAGES OF GROUND TRANSPORTATION

Interhospital transport of critically ill patients is a complex and high-risk procedure due to the extreme instability of certain patients. A way to facilitate this is the use of ECMO.[7] Nevertheless, adding an ECMO system to an already deteriorating patient requires expertise and significant human resources. The most common form of ECMO transportation is the ground ambulance; however, this transport modality depends on several factors, including the distance between the referral hospital and the tertiary care institution, the local geography (street roughness, traffic, etc.), and specific patient issues contraindicating air transportation.[8]

When planning for a transport, the choice of transport modality is the first step. Several factors need to be assessed to provide fast and safe transportation. Generally, ground transportation is used for short distances (<100 km); however, many centers use this mode of transport also for longer distances (300–500 km).[9,10] This generally happens when the local geography contraindicates air transportation (bad weather conditions, inability to use fixed-wing aircraft due to the lack of an airport in the surrounding area, inability to provide night landing and departure, lack of helipad for helicopter, etc.) or because of the lack of a trained flight team.

Ground transportation has the disadvantage that is slow, but it has the great advantage of allowing transportation of a bigger team and is generally not influenced by weather conditions.[11]

Air transportation can be done both with fixed-wing or rotating-wing (helicopter) aircraft. Generally, air transportation is preferred when it can save at least 2 hours compared with ground transportation. Fixed-wing flights constitute a significant portion of the medical transport and have the advantage that they can be performed in relatively bad weather conditions and during the night.[12] ECMO transport using the fixed-wing aircraft is limited by the fact that it requires a nearby airport to collect and deliver the patient and another ambulance to move the patient to/from the airport, requiring more stretcher mobilizations. Helicopter transportation, instead, can operate from a wide range of surfaces since helipads are more widespread than airports; however, helicopter internal space, weather conditions, and patient clinical issues can contraindicate the use of this modality. Alternatively, an ambulance can be loaded into a large fixed-wing aircraft (Hercules army aircraft), avoiding the time-consuming and risky procedure of loading the patient on and off.[13,14]

HISTORY AND EPIDEMIOLOGY OF ECMO TRANSPORTATION

Boedy et al.[15] first described the hidden mortality associated with conventional transportation of patients to an ECMO center. They reported an overall 11% mortality in infants who were referred to an ECMO center but died before leaving the referring center, during transport, and just before receiving ECMO support. The impressive results of ECMO in the neonatal and pediatric population, and the need to refer the patients to specialized centers while ensuring safe transfer, pushed the development of ECMO programs that included specialized teams able to connect the patients in the referring hospital and providing the transport while already on ECMO.[4] As mobile ambulances were not yet equipped with power and monitoring equipment adequate for transportation of ECMO patients,[16] most ECMO transfer experiences were by aircraft or helicopter.[3,4,16] The preference for air transportation also derived from the need to reduce the transit time after reports on trauma patients showing a 25% reduction in expected mortality with helicopter compared to ambulance transport.[17]

In the following years, an increasing number of ECMO centers developed ECMO transport programs, extending the indications also to adult patients and implementing ECMO ground transportation for shorter distances. One of the earliest reports on ground or mixed air/ground transportation with ECMO was in 1994 by Bennet et al.[18] In 1997, Rossaint et al.[9] reported their experience with ground transportation with ECMO in eight ARDS patients. They equipped a large bus as a mobile ICU. The bus contained a bed, ICU ventilator, a monitor system, infusion pumps, and a blood gas, hemoglobin, and electrolyte analyzer, thus providing most routine ICU equipment. This allowed the team to switch from the minimized transit time paradigm in favor of space for treatment and full ICU equipment availability. Transport distance was 495 ± 135 km with a duration of transport of 341 ± 151 minutes; no significant complications were reported. Six of the eight patients survived. In 2002 Foley et al.[19] reported the first 100 patients (68 adults and 32 children) transported with ECMO from the team of the University of Michigan Medical Center. ARDS was the most frequent indication (78 patients), followed by cardiac failure (7 patients), sepsis (7 patients), and asthma (5 patients). Overall survival to discharge was 66%. The authors also reported a total of 17 complication episodes during transport. Temporary electrical failure was the most frequent (10 cases). However, all patients were transported to the hospital safely. Covering a time period of almost 10 years (from 1990 to 1999), this review also gave important information on how the choice of the transportation mode and the ECMO configuration changed over the years. Ground transportation by ambulance accounted for 80% of all cases and was the most frequent mode of transportation since 1990. ECMO cannula configuration was V-A in 47 and V-V in 53 patients. V-A ECMO was the configuration of choice in the first period, even in patients without hemodynamic instability, as it was thought that additional cardiac support should have provided better hemodynamic stability and safer transportation. However, after some experience, there was a progressive shift toward V-V ECMO, limiting V-A ECMO only to patients needing cardiac support.

In the following years, most of the few centers in the world providing ECMO also developed a retrieval ECMO program.[7,20–22] However, in most of the cases the ECMO program was not part of a regional network recognized and funded by regional or national institutions. In 2009, the publication of the results from the Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial on one side and the H1N1 influenza outbreak on the other led to the worldwide spread of the use of ECMO and the development of new ECMO centers able to provide ECMO transportation.[2] The CESAR trial enrolled 180 adult patients with severe acute respiratory failure who were randomized to receive ECMO after being transferred to the Leicester ECMO center or conventional treatment remaining in the designated treatment centers. Patients allocated to the ECMO group (independently of effectively receiving ECMO or not) had significantly better survival, and the authors concluded that referral of ARDS

patients to an ECMO center may increase survival. Besides several criticisms, the results of the study encouraged the use of ECMO and the development of ECMO networks with a hub-and-spoke model. However, the study also highlighted the weakness of an ECMO referral program not providing safe transportation with ECMO. In fact, though the transfer of patients from referral hospitals to conventional treatment centers was provided by the ECMO team, patients were not transferred on ECMO, and the patients were not moved until conventional transport was considered safe. This resulted in three deaths before the transfer to the ECMO center and two deaths during transportation. These data clearly indicated the opportunity to provide ECMO transportation for a safe and effective transfer to the ECMO center.

This need became manifest during the H1N1 influenza outbreak. Following the Australian experience,[23] many countries organized regional networks to centralize ARDS patients to a few ECMO centers. ECMO transportation was an integral part of the network activity, and the number of patients transported with ECMO accounted in some reports for almost half the patients.[13,24–26] Importantly, survival of patients transferred by ECMO was no different from ECMO patients who were not transferred.[13,24,26] In the more recent EOLIA trial,[27] ECMO retrieval was a crucial part of the protocol, and 40% of patients in the ECMO group started ECMO in the referring hospital before being transferred to the ECMO centers.

In the last 10 years, ECMO transportation activity has increased and consolidated in both old and new ECMO centers, and several case series reporting local experience have been published.[5,10,14,28–42] The largest case series, published in 2019, is from Karolinska University hospital in Stockholm.[41] This review includes 908 neonatal (n = 284, 31%), pediatric (n = 150, 17%), and adult (n = 474, 52%) patients transported with ECMO between 1996 and 2017. V-A ECMO accounted for 55% of all transports. However, data on ECMO indications were not reported, and independently from the indications, sicker patients were preferably treated with V-A ECMO. V-A ECMO was more common in neonatal (66%) and pediatric (58%) compared to the adult (47%) population. ICU survival was 76%, with neonatal and pediatric patients showing better survival (respectively 85% and 78%) compared to adult patients (69%). Considering that 33% were long-distance international transports, ground ambulance represented 38% of all transports. With the limitations of the retrospective nature of the study (which is shared by all published data on the topic), the Karolinska's report is, at the moment, the most specific study on complications during ECMO transportation. Of note, V-A ECMO and transport with fixed-wing aircraft were associated with higher incidence of severe complications.

The increasing worldwide rush to ECMO treatment, especially for respiratory indications, along with costs, resources, and expertise involved, imposes a discussion on which organizational model is best to balance costs, safety, and efficacy. As for most high-risk and resource-intensive techniques requiring specialized expertise and proper resource allocation, a direct relation between volume of procedures and outcome has been shown also for ECMO.[43–45] Thus, it seems reasonable to centralize ECMO activity in a few high-volume centers, with expertise not only in ECMO, but also in the management of all respiratory and cardiovascular clinical conditions representing current indications for ECMO treatment. However, to be effective, such a centralization model must also provide a safe transfer of patients from the spoke to the hub centers. Available data, though mostly retrospective and all from single-center experiences, show that cannulation and initiation of ECMO at the referring hospital, and following transfer to the referral centers, is a safe procedure. In a systematic review from Bryner et al.[5] including 27 case series with a total of 643 patients, both pediatric and adults, overall survival was 64%. When stratified by age and primary indications for ECMO, survival of transported patients was not significantly different from that of ECMO patients in the ELSO Registry. Survival rates were confirmed in a more recent systematic review,[46] including 38 studies for a total of 1481 patients. Survival for adult and pediatric patients was, respectively, 62% and 68%. Only two deaths occurred during transportation, and no major complication was associated with outcome consequences. Ground transportation by ambulance accounted for 53% of all transportations.

In summary, available data show that transportation with ECMO performed by an experienced team is safe, and the data support a hub-and-spoke organization model to centralize ECMO activity to a few experienced ECMO centers.

SAFETY AND COMPLICATIONS

Despite the ELSO transport guidelines,[6] definitions on adverse events and follow-up are lacking.[47] The most frequent reported adverse events may be grouped into equipment-/vehicle-related technical failures or patients' complications.

The most common problem reported is due to the acute loss of power supply due to battery or electrical power.[20,48] Other frequent complications are membrane lung failure, circuit tubing leakage and pump-circuit uncoupling. Cannula dislocation and tube kinking are also frequent complications, as well as accidental extubation or thoracic drainage dislocation; however, despite the frequency of all these complications, they have not been associated with death.[14,42,47] The incidence of transport adverse events are unknown; in published series, it varies from none to more than 30%.[5,19,41] In neonates, transport complications may reach as high as 40%, as reported by Burgos et al.[49] This high number may be related to the case mix as well as a high frequency of V-A ECMO patients and the use of fixed-wing transport, both associated with an increased risk for transport complications.[41] In a mixed group of both neonatal and pediatric patients, five adverse events were reported in 20 ECMO transports[14] Death during transport is reported to be rare, less than 0.5%,[47] and ECMO ground ECMO transport has been considered safe and effective. With no international registry and low published numbers, robust data on

mortality is lacking. However, ECMO transport seems to be safe overall, at least in the hands of experienced teams.

AMBULANCE CHARACTERISTICS AND EQUIPMENT

Independently from the vehicle used, it must provide adequate electrical power for all equipment (ventilator, monitors, infusion pumps, ECMO power console, oxygenator, heater, etc.). For ground transportation, most centers use specially equipped ambulances.[47] While all centers utilize power provided by the internal battery of the ambulance, an extra power inverter is mounted in most ambulance in case of failure of the primary generator. Most centers furnish the ambulance with an extra oxygen supply. Oxygen capability must account for distance, oxygen consumption with 100% of oxygen delivery for both ventilator and ECMO oxygenator (considering high flow rate), plus extra supply for possible delays, leaks, and other unexpected events. Most centers report using the same equipment used for in-hospital ECMO applications.[47] For ambulance transport, this is also true for other equipment, such as the ICU ventilator and hemodynamic monitoring. Commercially available stretchers and scoops are equipped with additional custom racks and bridges to position and compact all equipment together (Figure 9.1).

ORGANIZATION

Only a few data are available on specific organization issues. Most ECMO programs have been funded and developed within hospital or regional administrations. Few nations have tried to integrate and organize ECMO center activity to cover all national territorial ECMO needs,[13,45] avoiding spreading of ECMO application without control.[50,51]

Organizations should aim to ensure human, equipment, and economical resources to provide a 24/7 ECMO retrieval service. Economical coverage, administrative, and legal issues are commonly managed according to national and regional rules.[47] Team composition is variable according to transportation vehicle and specific ECMO indications (cardiac or respiratory support, neonatal/pediatric or adult). For ambulance transportation, which allows more space, the team is composed of at least four people (two doctors, intensivists, or surgeons; one perfusionist; one nurse). Independently from the type of transport and the type of ECMO, the team must have expertise in not only ECMO technology, but also all clinical aspects of cardiac and respiratory management. Team members in training are often included, which requires extra space, and it is not rare to use two vehicles to reach the referring hospital.[14]



Figure 9.1

NEONATAL AND PEDIATRIC ECMO TRANSPORT

The transport of severely ill neonates and children on ECMO support requires understanding of the distinct pediatric/neonatal physiology and the consequent transport challenges of such patients on ECMO, on top of being able to troubleshoot the circuit/device and deal with ECMO emergencies. Some of the most important challenges are the temperature control of small children and newborns, the difficulties securing intravenous access, and the possibility of cannulae dislodging due to their size and insertion distance.[1,14,42]

TEAM COMPOSITION

The team members must have ECMO and pediatric/neonatal transport expertise. Usually, the ECMO attending/consultant is not the person who will cannulate the patient. In neonates and babies, the surgical cutdown is the most common cannulation technique, especially for V-A ECMO when the carotid artery is used. For that, a physician with surgical skills or more frequently a surgeon should be part of the team whenever ECMO initiation is planned in the referring facility.

EXTRA EQUIPMENT

A surgical cutdown tray and a variation of different cannula sizes and designs are needed as extra equipment.

CANNULATION PARTICULARITIES

Peripheral percutaneous cannulation is almost universal for adults. In the pediatric population, cannulation setup and technique can vary extensively; however, surgical cannulation is the most frequently used, especially in neonates.[36]

SIZE OF THE CIRCUIT

Especially for neonates, the circuit extension is always kept as short as possible to decrease the priming size. The ideal is to have the stretcher and the ECMO components assembled in one unit, making it possible to have shorter tubing and also minimizing the risk for tubing kinking during loading and unloading the patient into/out of the ambulance[1] (Figure 9.2).



Figure 9.2

BLOOD PRODUCTS

Most centers use blood prime for small children. They are also more prone to have hematological and coagulation disturbances, requiring frequent blood product transfusion for ECMO initiation and during transport. It is important to request these products from the referral facility beforehand.

TEMPERATURE CONTROL

Neonates and infants are at high risk of hypothermia, and heaters should always be used.

Unfortunately, during the transport of the patient from and to the ambulance, the available heaters do not operate.[1] All other means of passive or active protection against hypothermia should be applied, and the ECMO heater should be plugged in and turned on as soon as the patient gets to the ambulance or the ICU.

HYPOGLYCEMIA

Glucose requirements are high in neonates and small children, and they are more susceptible to hypoglycemia as a response to stress and infection. As the patient will not be receiving anything by mouth for transport, a glucose intravenous infusion should be started and glucose levels checked frequently.

LINES AND CANNULA DISPLACEMENT

Small changes in cannula position can impair ECMO flow and even lead to accidental decannulation. It is mandatory to have good fixation of the cannulae and good position of the child's neck to avoid kinking the cannulae during transport. Different positions can be tested before departing from the referring center to achieve the maximum flow. Deep sedation and paralysis can be required during transport to avoid displacement of devices, such as the endotracheal tube, cannulae, and thoracic drains, to name a few.

PHASES OF TRANSPORTATION

The ground transportation of ECMO patients can be divided into five phases:

1. Pretransport patient evaluation between referring and receiving center; transport organization and recommendations to the referral center prior to departure;
2. On-site stabilization of the patient and pre-ECMO preparation (including obtaining written and informed procedural consent);
3. Cannulation and initiation of ECMO, pretransport stabilization, and debriefing with local team;
4. ECMO ambulance ground transportation;
5. Handover and debriefing (stabilization of the patient at the receiving facility).

Phase 1

The process begins with the request for ECMO by the referring hospital. The attending physician at the referring facility generally contacts by phone the ECMO attending physician of the hub center. The ECMO attending physicians, after confirming that ECMO criteria are met, start planning the best transport options as well as the best ECMO cannulation and configuration strategies. Recommendations for patient stabilization are also generally given in this phase from the receiving to the referring center.

Each ECMO center should have an operative algorithm, including the phone numbers or other contacts of the ECMO team staff. The composition of the team is generally variable and depends on the type of transport (ground vs. air transport) and the type of patient (adult vs. pediatric). Collaboration with the staff of the referring center can be arranged in this phase (availability of a cardiologist for echocardiography, operating theater lights, scrubs, etc.). Also, some disposables and other materials for the cannulation procedure can be requested from the referring hospital. Every request should be arranged in advance and sent by email/fax to the referral facility as described in Box 9.1 (checklist). Such lists should be accessed before the team leaves the ECMO center to be sure that everything needed will be available or an alternative plan will be necessary regarding what is missing.

Box 9.1 **CHECKLIST (TO BE SENT TO THE REFERRAL HOSPITAL)**

Patient Tests and Procedures

- Blood typing and crossmatch
- Laboratory tests: arterial blood gas analysis, chemistry, coagulation (international normalized ratio [INR], activated partial thromboplastin time [aPTT], fibrinogen)
- Chest x-ray, head ultrasound (for babies), echocardiogram
- Arterial line for invasive blood pressure (preferred right radial)
- Central venous pressure monitoring
- Central line (location depending on ECMO cannulation site)
- Indwelling urinary catheter
- Rectal/esophageal thermometer (if not included in urinary catheter)
- Nasogastric tube (open)
- Skin protection

Medication and Blood Products Available at Bedside

- Fluid bolus (normal saline, PlasmaLyte, Ringer's lactate)
- Epinephrine
- Propofol
- Hydralazine
- Midazolan
- Ketamine
- Morphine
- Rocuronium
- Heparin
- Prophylactic antibiotic as per institution protocol

Material, Equipment, and Disposables

- _____
- _____

Crossmatched blood products and some specific medications should be requested and should be ready when the ECMO team arrives on site. Each ECMO center should decide how much collaboration can be expected from the referral facility.

When the ambulance for the ground transportation is prepared, all the equipment must be secured and plugged into the power source by the ambulance paramedic. A pretrip briefing about the patient's status is done before leaving so that the entire team has the complete information. The referral hospital is generally informed when the ECMO team is leaving and estimated time of arrival (ETA) must be communicated as well.

Meanwhile, the ECMO center's ICU team assembles the room to receive the patient after transport (ECMO bed, ventilator, chest-opening kit, etc.).

Phase 2

On arrival, the ECMO team introduces themselves to the referral hospital's team, and the definition of roles is communicated. Then, part of the team checks the material and medication provided by the referral hospital while the other members assess the patient and confirm/refuse the ECMO indication and explain the next steps to the staff working on the patient. The ECMO configuration and cannulation strategy are reviewed. If possible, the patient and/or his or her surrogate are included in the discussion and consent is obtained.

All equipment will be assembled and the materials will be brought with the mobile ECMO to the bedside.

Phase 3

The cannulation and initiation of ECMO are undertaken as discussed elsewhere in this book.

Before ECMO cannulation, it is very important to have a portable x-ray and an ultrasound machine at bedside to guide and confirm correct cannulation and screen for complications such as a pneumothorax or pericardial effusion.

The optimal ECMO blood flow is achieved and adjusted according to clinical and hemodynamic parameters and laboratory values. FiO_2 and sweep flow are adjusted according to arterial blood gas results, and mechanical ventilation settings are slowly decreased to achieve resting ventilation per the institutional protocol. After this initial patient stabilization, the pretransport checklist is completed again, and all possible issues that could occur during transport are raised and discussed. A quick debriefing is performed and includes the ECMO and the local teams. The family is updated. The materials/equipment transported are checked, and medications and blood products are prepared for transportation.

Phase 4

As soon as the patient is stabilized, procedures for transportation to the ECMO center will be initiated. The ambulance crew is consulted regarding transit (traffic, inclement weather, etc.), and a plan is made accordingly. Safety of the crew is paramount; traveling in suboptimal conditions is not acceptable; sometimes waiting in the referral center with a stable ECMO patient is better than getting stuck in traffic or putting the crew and the patient at risk. The patient is loaded on the stretcher, and all equipment (circuit, console, heater/cooler, hand crank or spare pump motor, and all monitoring and infusion pumps) are accommodated on it. The circuit is organized in the stretcher, making sure that the bridge (if present) and sample ports are accessible and clearly visible. After that, the

sweep gas is transferred to the oxygen cylinder, and the patient is placed on the transport ventilator. It is ensured that volume is spiked and ready to give, and the power bar/power cords are secured. Power availability is checked by the ambulance crew. Before transferring the patient from the site to the ambulance, the intrahospital ECMO transport checklist is applied.

Next step is to accommodate the stretcher with the patient, equipment, and staff in the ambulance (Figure 9.2). The ECMO center is informed that the transport will dispatch, and the patient status and the ETA are communicated. When arriving at the ECMO center, the intrahospital ECMO transport checklist is applied, and the patient is transported from the ambulance to the ICU. On special occasions, the patient can be transported directly to other locations at the ECMO center (computed tomographic scan, catheter laboratory) if indicated and the patient is stable.

Phase 5

When the patient has securely reached the ECMO center (hub), a comprehensive and structured handover is performed. After the handover, the receiving ICU team at the ECMO center takes charge of the patient. The family is updated and introduced to the ICU team. A debriefing is performed with all the team involved in the ECMO transport, and documentation is completed.

CONCLUSION

- ECMO is a life-saving modality when applied in specific clinical conditions.
- ECMO requires a high level of expertise and thus can be managed only in well-trained centers.
- Many patients requiring ECMO are treated in hospitals without ECMO facilities and require transfer.
- Transport of ECMO patients is associated with low risk and accounts for only a few complications if performed by an experienced center.
- The most frequent vehicle used to transport ECMO patients is the ambulance.
- The ability to transport depends on the local geography, patient issues, and distance between the hub and spoke center.
- Neonatal and pediatric transport requires dedicated staff trained to manage this particular population.

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REVIEW QUESTIONS

1. Which of the following situations indicates ground transportation over any other type?

   A. Distance 800 km with bad weather conditions
   B. Distance 100 km, good weather conditions
   C. Distance 100 km, but only if bad weather conditions
   D. Distance 100 km independently from the weather

2. What is the most frequent technical complication during ground transportation?

   A. Loss of electrical power supply
   B. Loss of tidal volume
   C. Arterial hypotension
   D. Cannula dislocation

3. Compared to ECMO patients not transferred on ECMO, patients undergoing ECMO transportations show

   A. Better survival rate
   B. Same survival rate
   C. Worse survival rate
   D. Fewer ECMO complications

4. Compared to standard ambulance, which additional equipment is recommended for ECMO transportation?

   A. A tertiary ECMO console
   B. Extra space for teamwork

C. None; most centers use a standard ambulance
D. A secondary power inverter

5. Which of the following are important challenges during neonatal/pediatric ECMO compared to adult ECMO?

A. Temperature control of small children and newborns
B. Difficulties securing intravenous access
C. Possibility of cannula dislodging
D. All of the above

ANSWERS

1. D. For distances as short as 100 km, ambulance transportation is always the first choice. Though ground transportation for distances close to 800 km have been reported, air transportation is recommended for such long distances.

2. A. Loss of electrical power is the most frequent reported technical complication.

3. B. Patients transported on ECMO show similar survival compared to in-hospital ECMO patients.

4. D. Given that loss of power supply is the most frequent complication, an additional power inverter is recommended.

5. D. Temperature control can be very challenging in small children and newborns. For this reason, the oxygenator heater is mandatory during neonatal/pediatric transportation. Securing intravenous lines and ECMO cannulae is difficult, and loss of the central line position and ECMO cannula dislodgment are frequently reported.

10.

FIXED-WING AND HELICOPTER AIR TRANSPORT OF ECMO PATIENTS

Antonio Arcadipane and Gennaro Martucci

STEM CASE AND KEY QUESTIONS

Your extracorporeal membrane oxygenation (ECMO) center has been contacted concerning a 48-year-old male (height 180 cm and weight 85 kg) metalworker with a passion for performing as a house music deejay in his free time, who was admitted for respiratory failure. The referring hospital is located in another region, 480 km from your ECMO center. The patient is affected with influenza A H1N1, with a bacterial pneumonia due to multidrug-resistant *Acinetobacter baumannii*. He was admitted to the hospital 10 days prior and ventilated on pressure control ventilation (PCV) with 35 cm H_2O plateau pressure and positive end-expiratory pressure (PEEP) 15 cm H_2O until yesterday, when a spontaneous pneumothorax occurred, and two chest drains were placed. At that time, PEEP was reduced to 12 and plateau pressure to 30 cm H_2O (tidal volume 310 mL, respiratory rate [RR] 24 breaths/min). The center asks for a second opinion and, eventually, veno-venous (V-V) ECMO because the patient is hypoxic on inspired fraction of O_2 100% and hypercapnic (PaO_2 54 mm Hg and $PaCO_2$ 74 mm Hg), and the pneumothorax poses a considerable risk in ventilating patients in these conditions in order to achieve acceptable gas exchange.

WHAT DATA ARE NEEDED TO UNDERSTAND THE CLINICAL PICTURE DURING A PHONE CONSULT?

The decision to place ECMO in a patient should be carefully considered, taking into account the benefit in the clinical case, as well as the possible complications due to ECMO, and the start of the procedure when there is a critical determination that the patient will be later weaned from ECMO and also discharged from the intensive care unit (ICU). Futility of treatment should be avoided even more when the procedure involves a distant referral, far away from the patient and the family. This should be based on a thorough exploration of the current and past status.

Past medical history of the patient is almost unremarkable: asthma at a young age, light smoker in adulthood (fewer than five cigarettes per day), no documented use of drugs, no admission to the emergency room or general practitioner in the last months, and with constant medical checkups for work exposure to metal powder; therefore, chronic lung disease can be excluded. The patient is sedated; hemodynamic support is given through a low dose of noradrenaline 0.03 μg/kg/min and urine is passing with an output of 1900 mL in the last 24 hours, but creatinine is 3.5 mg/dL (high since admission, 1.9 mg/dL).

A computed tomographic scan is not available since the patient is unstable from a respiratory standpoint, and the chest x-ray shows consolidations in the four quadrants, without pneumothorax, while the drains are on aspiration.

Hematocrit was 32%, hemoglobin was 9.9 g/dL, and there was no bilirubin increase; the white blood cell count was 16,000/dL.

Looking at the therapy for pneumonia, the patient was on colistin, ceftazidime, and amikacin, as well as oseltamivir 100 mg daily, because his primary admission was due to influenza A (H1N1), as proven by a positive molecular assay from a rhinopharyngeal swab.

WHAT IS YOUR FIRST IMPRESSION BASED ON CLINICAL DATA, AND IS AN ECMO MISSION FEASIBLE?

The clinical picture is of a severe case of acute respiratory distress syndrome (ARDS), with a Murray score of 3.8, without potential contraindications to ECMO treatment. The presence of a pneumothorax is a risk in air transportation, but this is a relative risk considering that aspiration is available on medical air transportation devices, the mechanical ventilation can be reduced to minimal levels or even stopped in the presence of a full-flow ECMO support, and the effect of altitude on gas is limited below 2000 feet.

At that time, the components of the ECMO team and the members of the aeromedical transportation should be alerted that there is a potential ECMO mission in the coming hours. At the referral center, intensive care bed availability should be checked and finally confirmed when the transportation is decided.

WHAT CAN BE ASKED OF THE REFERRING CENTER TO UNDERSTAND DEFINITIVELY THAT THE PATIENT IS REFRACTORY TO THE ARDS TREATMENT?

The first consult request to the referring center is to start neuromuscular blockade and to lay the patient prone as soon as

possible. PEEP should be left at the current value (no new increase) since the recent pneumothorax is a continuous threat. If the center achieves a saturation of 90% and a PaO_2 higher than 60 mm Hg, with hemoglobin higher than 10 mg/dL, the plateau pressure could be slightly reduced, as well as the PEEP, according to the saturation to avoid the risk of further barotrauma.

Meanwhile, you ask to start furosemide as a continuous infusion to achieve a negative fluid balance.

Moreover, echocardiography is requested of the referring center; it would be useful to rule out relevant cardiac complications or concomitant preexistent diseases potentially contributing to the clinical picture.

You ask the center for an update after 1 hour: The prone position did not improve the hypoxia, so the dose of noradrenaline was increased to 0.1 μg/kg/min to keep the mean arterial pressure greater than 65 mm Hg in the hope of obtaining better tissue perfusion. Given the patient's condition, ECMO transportation is confirmed by the referral center, the team is assembled, and the ICU bed is confirmed at the referral center. As salvage therapy, while waiting for the ECMO team's arrival, we suggest starting nitric oxide at 20 ppm. Nitric oxide is not currently considered an evidence-based support for severe ARDS, but it can increase oxygenation and decrease the pulmonary shunt for a few hours because a component of pulmonary hypertension is always present in severe ARDS; this strategy can contribute to a temporary increase in PaO_2. The referring center is requested to provide at least 4 units of packed red blood cells for the procedure, as well as large sterile drapes to allow a full sterile field during ultrasound-guided cannulation with a linear probe and all disposables needed for central cannulation.

WHAT DO YOU BRING AS EQUIPMENT?

The team brings the equipment for starting ECMO considering minimum need. Several cannulae should be brought: two pairs for each femoral venous cannula, long and short (38 and 55 cm, 19 French (F), 21F, 23F, 25F), as well as arterial cannulae (17F, 19F, 21F). Single-lumen introducers (7F and 9F) or reinforced pediatric bypass cannulae for eventual distal leg reperfusion in case of emergency need for veno-arterial (V-A) cannulation. A surgical kit is available for potential surgical cannulation. Two ECMO circuits are present (since a sudden oxygenator failure must be anticipated) and the emergency hand drive. All the ECMO equipment complies with the Airworthiness Directive.

WHAT HAPPENS WHEN THE TEAM ARRIVES AT THE REFERRING HOSPITAL?

On arrival at the referring hospital, the case is reevaluated in order to confirm the ECMO need. The echocardiogram showed no impaired cardiac contractility or valvular diseases. After resupination of the patient, peripheral veins are explored on ultrasound to decide the best cannulation site and avoid the presence of preexisting thrombosis. A central line is present in the left jugular vein; no thrombosis is recognized. Given the patient's characteristics, a femoro-jugular dual-site cannulation can be achieved since this configuration is considered the best to reduce the rate of recirculation. Vascular access is considered as well because if a new central line needs to be placed this is the best time before heparinization. In this case, the central line was placed 24 hours before.

Once the procedure is confirmed, thorough information should be communicated to the family about the disease, ECMO cannulation, and transportation. The wife of the patient understands the need for the long transportation and consequently agrees to the ECMO placement and transfer. According to the local laws and protocols, an informed consent for cannulation, transfer, and transportation can be requested.

Finally, a full sterile V-V ECMO cannulation is done with a femoro-jugular configuration using a 25F/39-cm femoral drainage cannula and a 19F/15-cm return cannula in the right internal jugular vein under ultrasound guidance.

WHAT TO DO AND HOW TO STABILIZE THE PATIENT AFTER ECMO INITIATION?

After ECMO is initiated, mechanical ventilation is progressively reduced in plateau pressure and RR, while the ECMO flow is increased to ensure adequate oxygenation. After 30 minutes, the ECMO blood flow is 3.9 L/min on 3200 revolutions per minute (RPM) with an oxygen sweep flow of 2 L/min and ECMO fraction of inspired air (FiO_2) of 1.0. Mechanical ventilation is still on PCV with a plateau pressure of 25 cm H_2O, PEEP 10 cm H_2O, and ventilator FiO_2 0.5. On blood gas analysis, pH was 7.35, PaO_2 65 mm Hg, $PaCO_2$ 51 mm Hg, SpO_2 88%, hematocrit 30%, and hemoglobin 9.7 g/dL. Hemodynamics are still stable, with noradrenaline 0.07 μg/kg/min, with a urine output of 2 mL/kg/h. The patient is considered stable from a respiratory standpoint since oxygenation is in a safe range while CO_2 was being reduced, even though still out of normal range. CO_2 should be reduced slowly because hypocapnia can lead to alkalosis, and a slow reduction is considered safer than rapidly achieving normal range, especially considering that hypocapnia may also lead to cerebral vasoconstriction and hypoperfusion.

But, the increase of RPM does not actually easily achieve the desired flow of higher than 4 L/min, so the intravascular volume is optimized with 1 unit packed red blood cells reaching a blood flow of 4.9 L/min on 3900 RPM, while the rest of the blood is kept for transportation in case of need. You should be sure you are able to reach the maximum theoretical flow according to the cannulae and the patient size before starting the journey and also whether the current clinical condition would require just partial support. Intravascular volume and hemoglobin have to be adjusted according to the need of the patient and the machine.

WHAT DO YOU DO BEFORE STARTING THE JOURNEY?

Cannulae should be fixed in at least two sites. Currently there are several commercial devices able to help in fixing the cannula

at its puncture site, but for the cannula in the neck a tight bend should be placed on the head to fix it inbuilt with the neck movements. The cannula insertion (on the skin and on the cannula) should be marked to ensure that the cannula is not migrating in or out during travel, or at least these movements should be recognized early. The femoral cannula is fixed at the skin insertion with a dedicated device able to accommodate the connector of the cannula and in the distal part of the thigh.

Following ECMO initiation and before starting the travel, you again meet the family of the patient if possible to reassure them of the successful cannulation and ECMO initiation and to give them information on the transport and destination.

To avoid any redundant movement of the patient, your protocol established that the helicopter stretcher is brought into the hospital, so the patient is carefully moved onto it and checked for ECMO function and clinical parameters. Before leaving, the team leader proceeds with the checks as per the "time out" procedure and reminds the other crew members to check the parameters during travel to guarantee continuous monitoring.

Before landing, a final check is made to ensure that the patient's stretcher belt and all the components and circuits are in place and safe.

DO YOU HAVE ANY CONCERN ABOUT A LONG AEROMEDICAL TRANSPORT WITH CHEST DRAINS?

While the presence of a pneumothorax is a concern under ECMO, air travel is considered to be relatively safe. Having in place adequate cannulae and with adequate volemia (packed red blood cells are also available), the ECMO blood flow is sufficient to provide oxygenation and complete relief of the strain on respiratory function; therefore, mechanical ventilation can be reduced or interrupted in order to avoid the risk of pneumothorax air refilling. Moreover, the equipment provided in the helicopter includes a functioning aspiration that can be connected to both thoracic drainages. Despite this, you ask the pilot to avoid too high altitude (up to 2000 feet) and keep the drainage on suction.

HOW DO YOU CALCULATE THE AVAILABILITY OF OXYGEN DURING AN ECMO TRANSPORT?

Before medical transportation you should calculate approximately how much time there is of oxygen availability at the current oxygen flow settings. To calculate the remaining time of oxygen availability you can use the following formula:

- Remaining time (min) = (Cylinder Volume × Pressure) ÷ Consumption
  - Cylinder tank capacity (liters)
  - Pressure available (atmosphere)
  - Oxygen consumption (ECMO gas flow [L/min] and minute ventilation [L/min] if ventilated)

Considering an oxygen flow of 2 L/min, the consumption will be at least 120 L/h, so for a journey of about 2.5 hours you will need an availability of at least 600 L.

Always consider for safety reasons at least twice the calculated O_2 consumption and do not forget to calculate the oxygen needed for the ventilator as well.

For long-distance travel with a helicopter, intermediate stops for fuel and oxygen refilling may be necessary based on the captain's decision.

HAVING THE HIGH ADVANCED SUPPORT AND MONITOR ON ECMO, DO YOU NEED ANY OTHER MONITORING DURING TRAVEL?

The parameters monitored by your crew are electrocardiogram (ECG), heart rate, SpO_2 (oxygen saturation by pulse oximetry), invasive arterial pressure, and end-tidal CO_2. Make sure the transducer cables are compatible with the helicopter monitoring before the journey. The patient is also monitored during travel for adequate color difference between the drainage and return circuit, temperature, skin color and mottling, urine output, as well as drainage status in cases of long-distance travel.

WHAT ARE LOGISTICAL ISSUES OF THE JOURNEY, AND WHO DECIDES THE RIGHT TIME TO LEAVE?

After stabilization of the patient in the helicopter, the pilot recognizes that the weather conditions are permissive during the route, so they can proceed with the flight. The pilot restates the safety rules on the helicopter, explains the route and the forecast during the travel, and accepts the request to avoid, if possible, too high an altitude. The journey lasts 2.5 hours without complications. Following the advanced crew resource management, with correct team dynamics, the patient arrives safely and is fully supported at the ECMO center to continue the treatment and finally be discharged and rehabilitated.

DISCUSSION

THE NEED FOR SPECIALIZED SUPPORT

Extracorporeal membrane oxygenation is only available in highly specialized cardiac or tertiary centers. Without mobile support, it might be impossible to transport a patient requiring ECMO. On the other hand, it is now evident that ECMO offers a survival advantage in severe respiratory failure; therefore, an advanced healthcare system should find a way to guarantee access to this high level of support, even in remote and peripheral areas.[1,2] To manage this challenge, the tool is specialized medical transportation through ambulance or aeromedical travel, which has the goal of bringing the patient to a referral hospital and starting treatment.[3]

The increasing cooperation among medical institutions and specialists, broader indications for extracorporeal life support (ECLS), and progressive miniaturization of ECLS

equipment, as well as the increasing recognition that high-volume centers achieve better outcomes, are likely to increase the need for patient transfer in the near future. While in past years the transportation of patients under ECMO was considered a relative contraindication and a dangerous undertaking, today, in the modern ECMO era with less cumbersome and miniaturized easier-to-use devices, ECMO transportation is safe, and several single-center experiences have highlighted that the outcomes of transported patients are the same as those of patients cannulated and treated on arrival at the referral center.[4–7]

To transport an ECMO patient is to carry out an ECMO mission, which is radically different from the simple or complex transportation of a critically ill patient.[8]

The goal when transporting ECMO patients is to start treatment outside the in situ facilities of the referral center, continue ICU treatment as safely as possible throughout the journey, and be in a position to provide additional emergency treatment if necessary.[9,10] This goal must be achieved in the minimal and unfriendly space of aircraft, helicopters, and ambulances in various weather or road conditions, with often poor or reduced visibility.[11,12]

During the initial contacts, a list of all the needed equipment should be sent, including a request for 2 to 4 units of packed red blood cells and an ultrasound machine with linear and convex probe.

GENERAL CHARACTERISTICS OF AEROMEDICAL TRANSPORT AND ITS RELATION TO ECMO

Aeromedical transport is preferred for transferring critically ill patients over large distances or in areas with inadequate road networks or geographical and infrastructural barriers. It comprises fixed-wing aircraft and rotary wing aircraft (helicopter). By definition, ECMO transport is principally a secondary transport from a referring hospital to a referral hospital, namely, the ECMO center.

The air ambulances, from their use in the military, were introduced into the civilian environment, where they are now used for primary scene retrieval and secondary interfacility transport in modern health systems.[13] Their principal advantage is the shorter journey time, and it is generally considered one of the preferred modes of secondary transfer. Air transport should be considered for journeys longer than approximately 100 km. A useful benchmark is to use air transport when it would save at least roughly 2 hours compared with ground transport.

Fixed-wing flights constitute a significant portion of aeromedical transport and are preferred when distances are more than 350–400 km, with the considerable advantage of being able to travel in inclement weather. The biggest disadvantages of conventional aircraft are that they require airports to collect and deliver their human cargo, and hospitals are rarely near airports, so this invariably requires ground transfers. Takeoff and landing times should also be taken into account. Medium-range aircraft provide adequate working space for patient care, can fly within a range of 500 to 1500 km, and can reach speeds of up to 250 knots. Small jets have the longest range (up to 5000 km) and the fastest speed (up to 450 knots). However, their streamlined shape severely limits cabin space, interfering with the care of the critically ill patient.

Helicopters typically cruise at 120–150 knots (220–280 km/h), with a useful radius of 50–500 km. The advantage over fixed-wing aircraft is the ability to operate from a range of surfaces, and helipads are more diffuse than airports. The maximum advantage is found in areas with underdeveloped roadway systems. As demonstrated during the H1N1 pandemic, delivery of advanced medical technology can be achieved even in remote and underserved areas that present a variety of geographical barriers. Major concerns in helicopter transportation are related to safety for the medical team, relative influence from the weather conditions, and the poor visibility at night.

The choice between rotary-wing aircraft (helicopters) or fixed-wing aircraft should be made following a cost-versus-benefit analysis, using criteria such as travel distance, landing infrastructure, weather conditions, and clinical emergency.

TO SET UP AN ECMO MISSION IS ALL ABOUT PREPARATION AND ANTICIPATION

Transferring a patient on ECMO support from one facility to another should not be viewed as an extraordinary event, but as an integral part of a medium-large ECMO program, which is composed of a number of actions implying a complex interplay between the referring hospital, the transport team, and the receiving ECMO center.

The triage and first contacts are fundamental to ensure proper treatment allocation. In fact, it should be clear in the mind of the ECMO specialist accepting the transfer of the patient that ECMO is indicated only if the severe respiratory or cardiorespiratory failure is potentially reversible or if the plan for ECMO as a bridge to transplantation is already considered. These considerations should be discussed to avoid futile application of ECMO at a distant hospital.[14]

After the first contact, a coordinated discussion between the referring physician and the ECMO specialist should occur to guide medical optimization, request further laboratory tests or diagnostic examinations, ask for locally available equipment or blood products, and finally to discuss logistics for ECMO transportation.[15]

During initial communication between the hospitals, the ECMO team leader must confirm the availability, at the referring hospital, of some required equipment and supplies: 2–4 units of packed red blood cells, an ultrasound machine, a large sterile surgical drape to completely cover the patient, and a small surgical light for possible surgical isolation of vessels in case of impossible percutaneous cannulation. These requests are part of our protocol of ECMO placement. As far as requesting blood products is concerned, some centers ask for a large quantity of packed red blood cells to be available, while our protocol calls for only a safely adequate supply because we operate in an area with a limited availability of blood.[16]

WHAT TO BRING FOR AN ECMO TRANSPORT: NOT TOO MUCH, NOT TOO LITTLE

ECMO devices have become increasingly smaller thanks to centrifugal pump–based systems, shorter circuits, and miniaturized monitors. The technological precision and biocompatibility are increasing, but there is still the risk of oxygenator failure; consequently, a safety rule is to always bring two complete ECMO circuits.

It is important to bring a limited set of disposables instead of storing all possible items in a bulky emergency kit. Take into account that if stabilization prior to transfer is adequate, this equipment is seldom used. The kit should be inspected prior to each departure. Clear labeling increases awareness of the site of the material and avoids time-consuming searches.

The number of oxygen cylinders to be transported depends on the duration of transfer and the size/capacity of the cylinders. Ensure that all cylinders are full before transport, in both ambulance and aircraft. Make sure that the patient monitor is compatible with the arterial pressure transducer connection cable.

All the ECMO equipment must be certified by the national or international flight safety agency for airworthiness or the pilot will not allow you to bring it onboard. The use of a dedicated checklist just before departure is part of a systematic safety check of equipment and drugs.

All these instances easily suggest that the transportation of a patient on ECMO should not be undertaken suddenly. To achieve the best and constant safety for the patient, it should be performed solely in the framework of a detailed program where all human resources are properly trained and the equipment tested appropriately.

Surgical instrument kits should be available to cover the possibility of surgical vessel exposure in case of difficult cannulation or vessel repair in case of damage (the latter is a rare complication when a complete echo-guided puncture is adopted and cannulation is in experienced hands, but it is still to be considered).

START THE TRANSPORT OF A PATIENT ON ECMO

The minimum ideal team should be composed of at least one medical ECMO specialist, one surgical ECMO specialist (for eventual open technique approach to the vessels), and a perfusionist.[15]

Principles for avoiding critical events during transport are based on extensive anticipation, effective communication, and patient assessment/stabilization. Though stabilizing the patient before transport is mandatory, it can be time consuming, so the degree of stabilization should be dictated by the estimated time of arrival at the referral hospital.[17] Knowing all the data, the general rule is easily dictated: The patient should be transferred only when the team is convinced he or she is stable and will be effectively stable for the planned travel.[18]

Before starting operations at the referring center, the transport team should always meet with the patient's family to describe the nature of the support and the type of transport. The potential complications and stabilization of the ECMO patient involve optimization of oxygen delivery (DO_2), though hemodynamics should be carefully assessed.

The ECMO circuit function has to be tested, and whenever possible a chest x-ray should be done to exclude a pneumothorax and to check the cannula positions. Any necessary intervention and/or pharmacologic treatment needs to be done prior to leaving the referring hospital. Since the ECMO circuit is a modified cardiopulmonary bypass circuit without an external reservoir (the reservoir is represented by the patient), the main parameter to be adjusted before starting the journey is the intravascular volume, which has to be adjusted according to the need of the patient and the needs of the machine. Before moving the patient, in fact, the ability to reach the maximum theoretical flow according to the cannulae and the body surface should be checked, and, eventually, if the volume is inadequate it is usually preferable to keep the hematocrit higher through transfusion as a safety profile of the transportation. Moreover, the urine output should also be monitored since, even if not on board, the effect of previous diuretics may still be active, and forced diuresis, even if somewhat therapeutic, should be replaced in selected cases.

Finally, during the transport, to ensure comfort for the patient, avoid unnecessary moving of the patient. To reduce ventilator efforts that may impair the ability of the drainage cannula, it is better to ensure an adequate sedation level, compatible with the hemodynamic status. Several centers also suggest complete paralysis during the transportation of an ECMO patient.

Spare intravenous access is mandatory, and all unnecessary medication must be discontinued before the transfer. Particular attention must be given to monitoring the ECMO cannula positions and to preventing any kinking within the ECMO circuit, along with a careful and tight connection of the membrane lung to the oxygen supply.

The following are items to be checked:

- whether there are enough drugs (catecholamines, sedatives, neuromuscular blockers, and spare syringes) to cover the patient's needs during transport;
- which medications are indispensable, and which can be interrupted temporarily;
- whether there is special and adequate tubing, depending on the type of pump; and
- battery power and the number of wall sockets available.

Preparation of medications and syringe pumps will be easier in the secure environment of an ICU than in the close confines of a shaky helicopter or a small aircraft, with possibly poor lighting. In many helicopters, and certainly in small airplanes, the ceiling is not high enough to guarantee a sufficient spontaneous flow (because of gravity) of intravenous fluids. Therefore, pressure bags or additional infusion pumps may be needed. Glass bottles should be avoided. Beware of air embolism from pressurized intravenous lines.

A so-called time out for the transport team before departure is now successfully being used as a security check. Items on a checklist should include the following:

- Patient's name and diagnosis.
- Comprehensive documentation, including angiography, radiography, and laboratory examinations.
- The patient's medical chart is a legal obligation and an integral part of patient care.
- Destination unit, shortest route from the landing pad/ambulance point of departure.
- Final check of weather conditions.
- Names and phone numbers of physicians responsible for the transfer.
- Duration of the transfer and subsequent calculation of required quantities of medical gases, medications, and other equipment.
- Possible plan B for transfer.

During the transport, it is preferable to avoid moving the patient unnecessarily; consequently, if possible you can bring the helicopter or airplane stretcher with you to avoid extra movements since every time the patient is moved from one surface to another there is the danger of decannulation or circuit complications, such as kinking of tubes and cannulae. This occurrence is clearly rare, even more so for experienced ECMO specialists, but when it happens it can have severe consequences; therefore, it should be always avoided.

The ECMO blood flow should be checked several times because kinking of tubes and links can indicate early flow reduction and pressure changes. All aspects of monitoring should be checked by all components of the ECMO team several times per hour to increase the probability of detecting, again early, every (even minimal) change in the quality of the support and patient conditions.

DURING TRANSPORT

In helicopters, internal noise levels are frequently greater than 95 dB, so that normal conversation is impossible. Auscultation is impracticable, as is reliance on audible monitor alarms. Earplugs have to be used for all patients, regardless of conscious state, to prevent hearing damage. Cabin lighting may be poor because strong lighting can distract the aircrew and adversely affect pilot night vision. All this can make monitors, cyanosis, veins, and patient movement difficult to see. Vibration is greatest at takeoff and landing and may induce pain in unstable fractures; it also makes accurate adjustment of fluid infusion rates difficult.

Often, fixed-wing aircraft suffer less from noise but are characterized by stronger acceleration/deceleration forces during landing/takeoff.

Incidents related to transport are principally associated with equipment-related problems, vascular line management, inadequate monitoring, and inadequate communication among staff.

The following should be monitored: A safety procedure in an unfriendly environment is to always check all the monitored parameters without losing any of them during loading from one means of transport to another. The only rule to bear in mind is not to force any step of the safety checks during transport, and it is fundamental that the patient is stable and adequately supported by ECMO; therefore, some additional minutes can be added to check any alarm of out-of-range monitoring.

- Three-lead (or more) ECG with heart rhythm and ST segment monitoring.
- Invasive pressures (if too time consuming or not available, noninvasive blood pressure is acceptable in case of emergency cannulation in life-threatening conditions, but before transport the patient should be fully monitored, and it is worthwhile to wait for invasive arterial pressure monitoring).
- Hemoglobin oxygen saturation. For very long-distance transport, SvO_2 (mixed venous oxygen saturation) is mandatory. Regarding end-tidal capnography, in case of V-V ECMO end-tidal CO_2 is an effective monitoring measure since it gives complete information about the mixed pulmonary flow that comprises ECMO and patient blood flow, mainly giving information about CO_2 removal (it is not rare that when shifting the oxygen source from the portable tank to the central oxygen of the means of transport, in a limited space and poor visibility, the airflow may be accidentally changed).
- Temperature: Airplanes that reach higher altitudes have greater temperature drops, with risk of hypothermia for a critically ill patient. Prevention of hypothermia, or restoration of normothermia, must be ensured using so-called space blankets, and the circuit tubing should be wrapped with aluminum foil. In cases of long-distance transport, a dedicated heat exchanger device is necessary. For longer transport, you should consider some additional monitors, such as portable point-of-care arterial blood gas monitors.[19]

Complete assessment of the patient and equipment is mandatory throughout the transport.[20] In addition, there are some particularly crucial things to consider:

- patient movement to and from the transport vehicle, including to/from the stretchers and helicopter;
- securing of the patient, the circuit, and oxygen supply during takeoff and landing;
- effects of altitude on membrane gas exchanges; and
- recognition and management of in-transport emergencies.

It is to be kept in mind that ECMO is a very resource-consuming technique in terms of human and economic resources.

Therefore, during transport every effort should be made to avoid any complication that may impact the patient's life and significantly impact the health system.

EFFECTS OF ALTITUDE

With an increase in altitude, temperature, and a decrease in barometric pressure, the partial pressure of oxygen drops. This effect also influences the gas exchange capacity of the membrane.

Furthermore, according to Boyle's law, as the atmospheric pressure falls, gas volume increases. At a typical helicopter altitude of 2000 feet, this increase is about 8%. In the case of pressurized fixed-wing transport, the problem is less central, but still present. A pneumothorax, pneumoencephalus, bubble emboli, or air trapped in the abdominal cavity will all expand in proportion to the drop in cabin pressure. All surgical drains should be unclamped and patent. Air in the endotracheal cuff also expands, with possible tracheal injury. Endotracheal tube cuffs should be filled with saline or have their pressure rigorously checked and adjusted inflight. If the pulmonary artery catheter is in place, make sure that the balloon is fully deflated.

These are just some of the considerations that dictate complete stabilization and assessment of the potential ECMO patient before transport, though this should be done for all transported patients.

In any event, you should reduce to the minimum the mechanical ventilation since you are on ECMO full flow. During travel you may also reach no ventilation.

ACCELERATION AND DECELERATION FORCES

When a supine patient is exposed to the force of sustained acceleration or deceleration in the longitudinal plane, blood flow is diverted to either the feet or the head depending on the patient's orientation. Theoretically, this blood flow diversion can cause cerebral underperfusion or excess perfusion (if the force exceeds cerebral autoregulation), with a risk of deterioration in patients with an intracranial pathology. Cardiac preload and afterload can also be influenced by such forces, which can cause further deterioration in hemodynamically compromised patients.

The main problem is related to circuit problems. During air transport, the circuit and patient must be well secured to the aircraft and watched carefully during takeoff and landing to avoid shifting in the position of the cannula or kinking and accidental dislodgment of the circuit. Movement of the patient is recognized as one of the more dangerous practices in critical care.[21]

SAFETY

Safety of the patient and aeromedical team is paramount and should be based on specific training in aeromedical transport. For interhospital helicopter transport, additional training is required so the physician can adequately provide critical care support outside the ICU.[22]

To achieve complete safety for the medical crew and the transported patient, no pressure must be put on the aircrew to alter their normal safety procedures. The captain has the final say on whether the conditions are suitable for flight, independent of the patient's condition. The strength of the team should be dictated by just one rule: A patient just put on ECMO has to be considered stable enough to wait until easier and safer transport can be carried out.

CONCLUSIONS

- Transportation on ECMO is currently increasing because this means of support should be available to all citizens in advanced healthcare systems.
- Recent studies have highlighted that the outcomes of patients transported on ECMO by a specialized ECMO team are the same as those of patients cannulated at an ECMO center.
- Air transport on ECMO allows patients to a reach peripheral hospital at a very long distance or with infrastructural barriers.
- Air transport should be considered after a thorough evaluation of the clinical picture to exclude that the ECMO treatment is futile, and that there is a strong probability that it would constitute a bridge-to-recovery treatment or, in particular cases, a bridge-to-transplantation.
- An ECMO mission begins with an initial consultation with the referring center, during which the ECMO center can suggest treatments or procedures to definitively understand that the patient is refractory to all the available standard and rescue treatments.
- ECMO transportation is safe when the ECMO team is composed of experienced members and they cooperate actively in a continuous check and treatment of the patient during the journey.
- Complete monitoring should be available and applied during transportation: ECG, heart rate, SpO_2, invasive or noninvasive blood pressure monitoring, and end-tidal CO_2.
- Transportation from the referring center should be started only when the patient is considered effectively stable from respiratory and hemodynamic standpoints, potential complications after cannulation are resolved, and the ECMO flow easily reaches the maximal theoretical value for the patient, even when a partial support is needed.

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REVIEW QUESTIONS

1. Which of the following sentences is incorrect concerning the setting up of an ECMO mission?

A. When discussing with the referring hospital, the results of thorough examinations and laboratory tests should be requested.
B. During the evaluation you may ask for further examinations, such as echocardiography.
C. When you receive a call for ECMO you should deliver cannulation within 1 hour.
D. Before starting the ECMO run, the referring center should have available compatible red blood cells for the patient.

2. In case of acute respiratory failure, you should request all but one of the following actions and wait to see if they lead to an improvement.

A. Add neuromuscular blockade.
B. Perform tracheostomy.
C. Place the patient in a prone position.
D. Add nitric oxide.

3. Which is not necessarily considered routine equipment onboard an ECMO transport unit?

A. End-tidal CO_2
B. Intravenous infusion pump
C. Stock oxygen tank
D. Portable arterial blood gas machine

4. Which of the following statements is incorrect regarding cannulation for ECMO transportation?

A. Both cannulae should be double fixed and periodically checked by all the components of the team during the journey.
B. The transport should be carried out with a femoro-femoral configuration.
C. In case of peripheral V-A ECMO transportation, when a distal perfusion cannula is in place, it should be checked, and special attention should be focused on not placing equipment on the cannula or stopcocks to avoid malpositioning.
D. Cannulae and circuits should be fully checked after every change of position: bed > stretcher > helicopter/ambulance/aircraft.

5. A patient with previous polytrauma in acute respiratory failure should be started on ECMO. He has several fractures in the spine and face, with open wounds on the neck and on thorax. Which would be the best option for cannulation?

A. Femoro-jugular configuration to reduce the risk of recirculation.
B. Double-lumen cannula to have just one cannula to manage.
C. Femoro-femoral configuration to avoid unsafe mobilization of the neck and allow appropriate care of the wounds.

D. This patient has a contraindication to ECMO.

6. You are going to transfer a patient on V-A ECMO with peripheral access. A cardiac surgeon has placed a 7F distal perfusion cannula homolateral to the femoral artery open cannulation. Before you move the patient, you recognize there is bleeding from the skin cut. What do you do?

A. Change the distal perfusion cannula.
B. Put a compressive dressing on the skin incision.
C. Ask the surgeon to revise the cannula placement and check the presence of dorsalis pedis artery pulse.
D. Correct the coagulation imbalance with protamine.

7. What do you suggest to your colleagues to bring for an ECMO transfer?

A. Bring one newly arrived circuit because it ensures the best oxygenation performance.
B. Bring two complete ECMO circuits and a pair of each cannula from the well-known and used type.
C. Bring as many drugs as possible to face every possible emergency.
D. Ask the treating physician of the referring hospital to come with you since he better knows the patient's clinical history.

8. Which of the following sentences on the effect of altitude on gas exchanges and gas volume is correct?

A. When altitude increases, the temperature and barometric pressure increase.
B. According to Boyle's law, when the atmospheric pressure falls, gas volume increases.
C. When altitude decreases, the partial pressure of oxygen drops.
D. Pneumothoraces always increase in volume when the altitude is higher.

9. Which one of the following does not cause sudden reduction in blood flow during transportation of an ECMO patient?

A. Metabolism of neuromuscular blockade and inadequate dosage
B. Reduction of volemia due to increased urine output after administration of diuretics
C. Kinking of the tubes or compression under the stretcher
D. Hypothermia

10. Who is the person ultimately responsible for starting travel when the patient is stable?

A. The director of the referring hospital when a new admission is requested
B. The ECMO specialist leader of the mission when it is determined that no other treatment can be performed in the referring hospital where the patient has been cannulated
C. The pilot of the aircraft or helicopter after checking the weather conditions and safety of the journey
D. The administrator of the ECMO center when there is a bed available

ANSWERS

1C, 2B, 3D, 4B, 5C, 6C, 7B, 8B, 9D, 10D

11.

IMPLICATIONS AND EXPERIENCES WITH LONG-RUN ECMO

Hani Jaouni, Marc O. Maybauer, and Tasleem Raza

STEM CASE AND KEY QUESTIONS

A 37-year-old Filipino female, who was working as a housemaid in Doha, Qatar, for 2 years, presented with shortness of breath, cough, fever, and weight loss of 4-week duration. She was thin (body mass index 18), using accessory muscles when breathing, and with mild cyanosis and SpO_2 (oxygen saturation by pulse oximetry) of 88% breathing ambient air.

Her chest x-ray showed bilateral pulmonary infiltrates with bilateral cavitary lesions, more in the right upper lung zone. She was intubated for severe acute hypoxemic and hypercapnic respiratory failure. She was diagnosed with severe acute respiratory distress syndrome (ARDS) secondary to possible underlying pulmonary tuberculosis (TB) and started on standard ARDS care. She failed lung-protective ventilation and prone positioning, prompting initiation of veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) for severe hypoxemia.

Her bronchoalveolar lavage smear and culture were positive for *Mycobacterium tuberculosis*, for which she received antituberculous therapy. Although she developed hepatotoxicity from first-line antituberculous medications, a prolonged course of second-line therapy led to a negative respiratory culture for TB. After about 6 weeks of ECMO support and TB therapy, her lung infiltrates improved but left behind multiple large cavities in both lungs. Although her ECMO support could be weaned to minimum levels at times, she could not sustain a trial off ECMO for a long enough period to be liberated from ECMO support. She was tried on various ventilatory strategies and diet manipulations (to reduce CO_2 production) to try to get her off ECMO, but none of these strategies worked, and she remained ECMO dependent throughout her hospital course.

For most of her treatment period, she was anticoagulated with intravenous heparin but later was changed to bivalirudin due to possible heparin-induced thrombocytopenia (HIT). During her ECMO course, she had four circuit changes. The shortest time of oxygenator membrane failure was 12 days and longest was 73 days. One membrane failure episode was while she was off heparin due to hemoptysis and had a brief hypoxemic cardiac arrest requiring emergent circuit change. Two other membrane failure episodes were due to oxygenation failure and severe disseminated intravascular coagulation and coagulopathy.

During her course, she developed multiple pulmonary bacterial infections, urinary tract infections, and one central venous catheter–related bloodstream infection. All of her infections were treated appropriately and responded well to therapy. She remained with the same V-V ECMO cannulae, which were inserted at the time of initial cannulation, without any infectious or thrombotic complications.

A structured physical therapy program was initiated early in her course. She was routinely sitting up in a wheelchair and taken out of the unit for short tours, even out to the hospital garden and to the vending machine. She was able to swallow in the presence of a tracheostomy. She was encouraged to walk a few steps as tolerated, but her muscle wasting was severe enough to make this task very hard to continue.

Psychologically, she was well supported by the MICU staff, many of which spoke her language. A chaplain of her faith visited her along with her aunt, who stayed in Qatar for a good part of the patient's stay in the hospital. The patient was offered to arrange for her son to be brought from the Philippines, however, she refused as she did not want him to see her in her ill status. In general, she became so familiar with the medical intensive care unit (MICU) routine to the point of asking the staff on many times to adjust the sweep gas flow for her comfort.

After several months of no further improvement in her pulmonary function, it was obvious that the only outcome for her was lung transplantation, which is still not available in Qatar. Efforts were made to find a nearby center that would accept her; however, due to financial and logistical issues, this could not be done. Discussions with the patient, her relative, the MICU physician and nursing staff and with the ethics committee resulted in the decision to continue with full support, hoping she would eventually have enough recovery of her pulmonary function that she would at least not need ECMO support and would continue to be ventilator dependent. If that state could be reached, then it would be easier to transport her back to her country, as per her wishes.

She also developed some unique complications from her disease. She developed a large bulla in the left lower lobe, which was causing compression of adjacent lung. After multidisciplinary team discussion, this bulla was drained percutaneously,

hoping for some expansion of relatively less diseased surrounding lung and better lung function. Although she did not develop any procedure-related complication, lung recovery from drainage was minimal. She also developed intermittent episodes of severe hypoglycemia associated with severe lactic acidosis in later stages of her disease, which were most likely due to hyperadrenergic response associated with hepatic glycogen store depletion and hepatic congestion. These episodes were managed conservatively with good response.

She developed progressively increasing right ventricular (RV) dysfunction with development of resistant severe RV failure, which prompted her death after being on ECMO support for more than 300 days.

WHAT ARE ECMO-RELATED ISSUES DURING PROLONGED ECMO RUNS?

Extracorporeal membrane oxygenation runs for more than 2–3 weeks are considered prolonged runs.[1,2] Long ECMO runs are becoming more common after the realization that some patients may recover their lung function weeks or even months after the initial insult.[3,4] Issues due to prolonged ECMO runs include membrane failure; coagulation and hematological disturbances; and metabolic, pulmonary, musculoskeletal, psychiatric, and ethical issues.

WHAT ARE THE MEMBRANE-RELATED ISSUES?

The longer the ECMO run, the higher the chance will be for the oxygenator to fail in its ability to transfer gases across its membrane thickness.

This failure could be a sudden event and considered a medical emergency. It usually occurs secondary to acute clot formation inside the membrane itself or the interface between the membrane and the rotator base. If the lung recovery is not enough to provide significant gas exchange and oxygenation for the patient during the period required to change to a new membrane, severe hypoxemia will lead quickly to hypoxemic cardiac arrest with grave consequences of sudden death or severe neurological sequelae of ischemic hypoxemic encephalopathy.

A more common scenario is that of the gradual signs of membrane failure, like increasing transmembrane pressure (TMP; ΔP), gradual decrease in CO_2 removal capacity, gradual decrease in the postoxygenator PO_2, and the formation of fibrin deposits and/or visible clots on the surface of the membrane. As a general rule, if the ΔP doubles compared to the starting value of the ECMO run or if the ΔP is greater than 50 mm Hg, then the membrane should be changed preemptively. The same applies if the postoxygenator PO_2 is less than 200 mm Hg or calculated oxygen transfer is too low for the amount of blood flow through the oxygenator.

Another membrane-related issue is consumptive coagulopathy. Our patient had one emergent membrane change secondary to acute large clot formation in a period when she was off anticoagulation to minimize her hemoptysis. The two other membrane changes were done electively as there was evidence of decreased membrane efficiency.

WHAT WERE ANTICOAGULATION-RELATED ISSUES?

Fibrin deposition, thrombosis, and bleeding are not uncommon with ECMO runs. The longer the ECMO run, the higher the rates of such complications. Activation of the coagulation system is initiated from exposure of blood to synthetic material of the surface and from shear stresses of the circuit.[5]

Initial fibrinogen deposition and subsequent activation of coagulation factors and complement lead to platelets and leukocyte adherence to the oxygenator surfaces and enhancement of thrombin generation. Thrombosis happens at a higher rate in these patients.

Furthermore, bleeding rates are higher. Homeostasis is altered secondary to platelet dysfunction and loss of their key adhesive molecules.[6] The shear effect of the circuit leads to acquired von Willebrand defect. In addition, there is altered fibrinolysis and anticoagulation administration for the maintenance of the circuit flow.

Prolonged heparin therapy may lead to a decreased volume of cancellous bone osteoporosis.[7] Most of the studies of these adverse effects are from pregnant patients requiring heparin. This effect is much more pronounced with unfractionated heparin (UFH) as compared to low-molecular-weight heparin (LMWH). Both can cause a dose-dependent decrease in the level of serum alkaline phosphatase (Figure 11.1). Both UFH and LMWH can lead to enhanced osteoclast activity and lead to dose-dependent decrease in osteoblast differentiation and proliferation.

Another issue is the development of HIT. Our patient had a positive HIT study and was managed with prolonged bivalirudin therapy.

WHAT IS THE IMPACT OF NOSOCOMIAL INFECTIONS DURING LONG-RUN ECMO?

Catheter duration is a well-known risk factor for catheter colonization or catheter-related bloodstream infection. Moreover, the prevalence of nosocomial infection increases with ECMO duration.[8] ECMO device infection rate (cannula infections or ECMO device–related bloodstream infections) was reported at 9.7%, and the ECMO device colonization rate was reported at 32%.

Throughout her stay on V-V ECMO, from June 2015 until April 2016, our patient had only one positive peripheral blood culture of *Enterobacter cloacae*. However, she had several endotracheal tube aspirate and bronchoalveolar lavage positive cultures, including infection with *Mycobacterium tuberculosis* complex (first positive culture was June 11, 2015, and first negative culture was August 17, 2015); *Candida albicans* (respiratory and urinary); *Candida tropicalis*, E. *cloacae*, *Escherichia coli*, *Candida parapsilosis*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, and *Klebsiella pneumoniae* (Figure 11.2). She also

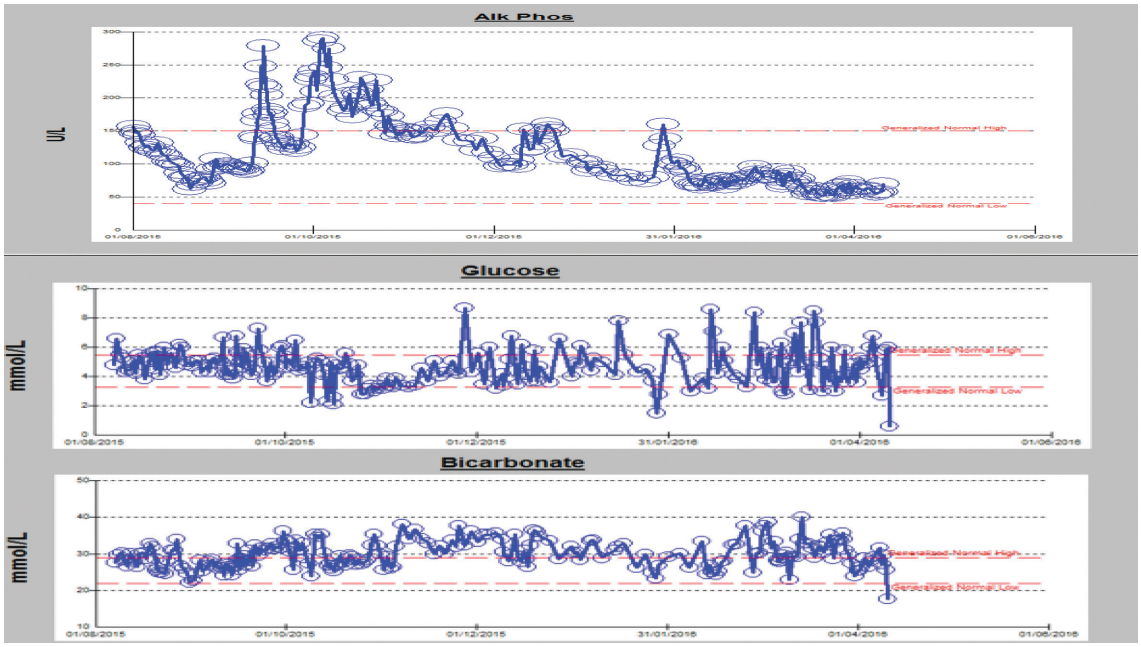


Figure 11.1 Serum alkaline phosphatase (Alk Phos), serum glucose, and bicarbonate levels while on long-run ECMO. Serum alkaline phosphatase levels on ECMO and long-term unfractionated intravenous heparin and bivalirudin treatment. U/L, units per liter. The relationship between serum glucose and bicarbonate levels over an 8-month period of the patient's stay on V-V ECMO. Toward the later stages of her stay, she developed repeated episodes of severe hypoglycemia associated with decreased bicarbonate levels secondary to lactic acidosis believed to be secondary to depleted glycogen stores. The patient responded well to glucose replacement.

had a positive skin wound culture of coliforms and one-time positive screen for *Clostridium difficile* toxin in the stool.

WHICH CARDIAC CHANGES CAN BE EXPECTED DURING LONG-RUN ECMO?

Prolonged ECMO runs can lead to acute cor pulmonale (ACP) with severe RV dysfunction leading to cardiac arrest. Generally, this may occur after 4–6 weeks of ECMO run.[9] The proposed mechanism includes hypoxemic and hypercapnic pulmonary vasoconstriction; macro- and microvascular thrombi; progressive structural parenchymal and vascular injury and fibrosis from ARDS; and high nonpulsatile flow into the right heart. Long duration of nonpulsatile flow may lead to inhibition of ventricular recoil and progressive RV dysfunction. If detected early, RV dysfunction may be managed with medical therapy with pulmonary vasodilator therapy and inotropic support, in addition to prevention of hypoxemia, hypercapnia with

	26/6/15	17/7	11/9	20/10	12/11	6/12	2/1/16	11/1	28/1	28/2	26/3
Resp	1	2,3	4,5	3,6	6	6	2, 6	7,8	8	8	
Urine	1	3									1
Blood				2							
Skin							1				
Stool											9

1. Candida Albicans and Parapsilosis
2. Enterobacter Cloacae
3. E. Coli
4. Pseudomonas aeruginosa
5. Serratia marcescens
6. Stenotrophomonoas maltophila
7. Klebsiella pneumonia
8. Achromobacter xylosoxidans
9. C. Difficile toxin

Figure 11.2 Table of the different cultures for this patient while on long-run ECMO. Different nosocomial infections throughout the patient's stay for more than 300 days on V-V ECMO.

TTE	01/07/15	17/01/16	23/03/16
LV	EF 50%, grade 1 diastolic dysfx	EF 55–60%, grade 1 diastolic dysfx	–
LA	N	N	–
RV	N	Moderately enlarged, Moderately impaired systolic fx	Severely enlarged, Moderately impaired systolic fx
RA	N	Mildly enlarged	Moderately enlarged
RVSPest	33	56	62

Figure 11.3 Transthoracic echocardiographic findings during the patient's stay on V-V ECMO for more than 300 days. Progressive enlargement of the right ventricle with impaired function and progressively increasing estimated right ventricular systolic pressure. dysfx, dysfunction; EF, ejection fraction; fx, function; LA, left atrium; LV, left ventricle; N, normal; RA, right atrium; RV, right ventricle; RVSPest, right ventricular systolic pressure estimation.

acidosis, and anticoagulation for any potential microthrombi. Failure of medical therapy may require the need to change ECMO configuration from V-V to V-AV (veno-arterial-venous) to provide both pulmonary and RV cardiac support since our patient developed terminal RV failure and cardiac arrest, leading to her death (Figure 11.3). Alternatively, a percutaneous ProtekDuo RV assist device (RVAD) with oxygenator could have been considered but was not available at the time.

WHICH CHANGES CAN BE EXPECTED IN FIBROCAVITARY LUNG DISEASE?

Patients with extensive fibrocavitary lung disease can develop large lung cavities with positive-pressure ventilation, which can further impair gas exchange. Percutaneous pleuropulmonary procedures are at high risk during ECMO due to severe bleeding complications and risk of chronic bronchopleural fistula with intended risks of infection. Drainage of large pneumatoceles and cavities to improve gas exchange remain controversial but has been successfully performed in non-ECMO patients and should be considered on an individualized basis.[10,11] We performed percutaneous drainage of a large bullous lesion without any untoward event. Unfortunately, there was no significant improvement in gas exchange (Figure 11.4).

WHICH METABOLIC CHANGES CAN BE EXPECTED DURING LONG-RUN ECMO?

Severe hypoglycemia with type 2 lactic acidosis has many causes, including sepsis; medication induced (biguanides, linezolid,

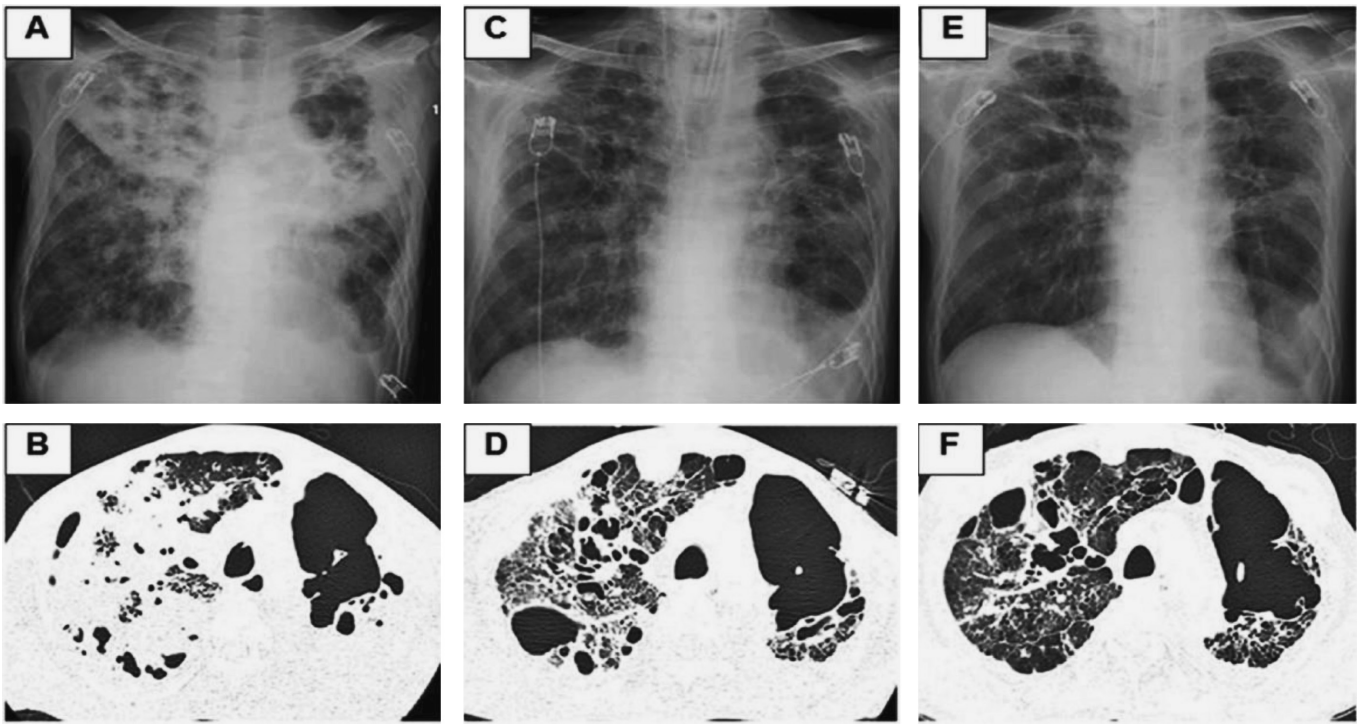


Figure 11.4 Chest x-ray and concomitant chest computed tomographic findings at different stages of long-term ECMO. Cavitary lesions of both lungs at different stages of the patient's stay on V-V ECMO for longer than 300 days. A and B were in the early days of her admission, C and D were around 150 days of her stay, and E and F were in the last 30 days of her stay. Her left lung large bulla continuously increased its size.

propofol); Warburg effect of malignancy; diabetes with hypoglycemic agents; poor nutritional intake; hepatic dysfunction with reduced glycogen stores; impaired glycogenolysis and gluconeogenesis; and impaired lactate clearance.[12,13]

Prolonged ECMO runs with their antecedent complications, hypercatabolism, frequent tube feeding interruptions, congestive hepatopathy with poor glycogen stores, and impaired glycogenolysis and gluconeogenesis may lead to hypoglycemic episodes. This induced hypoglycemia may lead to a hyperadrenergic response with increased lactate production. Lactate clearance may be impaired due to congestive hepatopathy. This leads to a vicious cycle of hypoglycemia, leading to hyperadrenergic response and hyperlactatemia. Adequate glucose replenishment generally breaks the vicious cycle and leads to relatively quick resolution of lactic acidosis. This has significant implications as failure to recognize this rare cause of hyperlactatemia may lead to extensive sepsis workup and evaluation for bowel ischemia. These episodes of hypoglycemia and hyperlactatemia can generally be prevented by adequate glucose intake and avoiding any episodes of hypoglycemia. Our patient developed the episodes of hypoglycemia and increased lactate with lactate level greater than 10 mmol/L at times. With the realization of the above mechanism as the underlying etiology, glucose supplementation rapidly led to resolution of these episodes, eliminating the need for extensive workup for sepsis or bowel ischemia.

HOW IS SKIN INTEGRITY AND MUSCULOSKELETAL FUNCTION MANAGED DURING LONG-RUN ECMO?

Besides adequate nutrition, mobility and muscle exercises are extremely important to maintain musculoskeletal functional status.[14] The physical therapy team should be involved with a comprehensive program of exercises, including passive and active movements of the upper and lower extremities, in-bed paddling, sitting up in bed and in a bedside chair, mobilizing in a wheelchair, and even walking as much as tolerated. All of these activities need collaborative teamwork, including an ECMO physician, an ECMO nurse, a bedside nurse, and respiratory and physical therapists. It is extremely important that all activities are coordinated to minimize the chance of complications, including inadvertent ECMO line, central venous line, or mechanical complication; ventilator circuit disconnections; and inadvertent hemodynamic and respiratory compromise. A well-coordinated team with clear role assignment for each member is crucial during all physical therapy sessions, particularly while mobilizing the patient out of bed and while ambulating. We utilized all these strategies and managed to mobilize our patient not only inside the intensive care unit (ICU) but also with trips out of ICU, including brief out-of-hospital trips and trips to different areas of the hospital.

WHAT WAS THE PSYCHOLOGICAL IMPACT ON THE PATIENT?

Long-run V-V ECMO survivors have persistently impaired physical, functional, and psychological components of health-related quality of life, despite optimal supportive care provided during their ICU stays. A long-term ECMO run with prolonged ICU stay with limited mobility, limited family connections, and lack of significant progress provides a rich recipe for depression and other psychosocial issues.[15]

Understanding this concept, ICU team members should strive to keep the patient in good spirits throughout their stay. Psychological evaluation and support during a prolonged ECMO run are extremely important. Innovative solutions with family involvement via social media to interact with the patient; video calling; participation in local culture events by visits from local community; and relaxing the visitation rules, including visits by favorite pets or the like, may be helpful to avoid a severe downhill course of depression, leading to lack of active participation in multimodality therapies. With our patient, nurses from the patient's own country would have casual conversations with her, conducted a birthday party for her, and observed other religious celebrations like Christmas and Easter with her. When the patient was at a stage where she could eat and drink, nurses from her community would cook her traditional dishes. At times when she was strong enough, she would be escorted to the vending machine in the hospital so she could choose her snacks. We also encouraged involvement of her country's embassy staff and made it possible for her to use social media to communicate with her family in the Philippines in the hope that this might help in mitigating some of her depression and loneliness.

WHAT IMPACT DOES A PROLONGED ECMO RUN HAVE ON TEAM MORALE?

Patients who have a long-term stay in the ICU pose a unique challenge for the ICU staff, especially the nurses, being the firsthand caregivers. This may become extremely stressful when caring for a patient on prolonged ECMO with the realization that the patient will not be able to wean off ECMO and destination therapy like lung transplant is not available. Ethical conflicts of personal autonomy with societal justice to provide care for other patients may be extremely distressing for the staff. Therefore, it is important that staff have easy access to psychological evaluation and support. It is important that this process is proactive, with early recognition of signs of depression and burnout leading to lack of empathy in the staff. It is extremely important that the institutional culture is of openness and not one where any signs of psychological stress in staff is considered a professional weakness. With our patient, the staff stress risk was particularly high as the patient was awake with full mental capacity, interacting with staff like family, and staff inherent realization that she was likely going to die on ECMO due to an "ECMO-to-nowhere" scenario. To deal with this challenge and to help keep the decisions of patient care as insightful as possible and in the best interest for the patient, the team had frequent debriefing sessions detailing the latest challenges in the patient's daily care followed by a clear management plan. In these debriefing sessions, all the team members were encouraged to voice their concerns and to share their views and feelings.

WHAT ETHICAL CONSIDERATIONS DEVELOP WITH THE ROAD TO NOWHERE?

Extracorporeal membrane oxygenation to nowhere creates tension among the team members due to different views about the ongoing care of these patients. The principle of patient autonomy may conflict with other ethical principles. Continued ECMO support may be perceived by some as violating the principle of nonmaleficence and of beneficence if there are no destination therapies, while others may perceive withdrawal of ECMO as violating the same principles.[16] The crucial principle of justice may be considered violated if some patients cannot be admitted to the ICU for life-saving therapies due to ICU bed shortage. Consideration of withdrawal of care is a major moral and ethical issue and needs to be resolved by involvement of all team members, the local ethics committee, religious scholars' input, consideration of local policies, and input from the patient and any available family members. Our patient was counseled multiple times with involvement of the local ethical committee, and she always chose to continue with full support. Hence, based on the principle of autonomy, it was felt that she should continue with full support, including ECMO care.

The change from ECMO from "nowhere" to "somewhere" should always be considered and may need nonconventional means to achieve that goal. Exploration for nonregional transplant centers and resolution of financial constraints by support from the local embassy, social services, hospital administration, charitable organizations, and conducting fundraising activities should be explored if local policies allow for these options.

In our patient, ethical principles of beneficence, nonmaleficence, justice, and autonomy were considered and debated. Most of the team members felt that she was deriving benefit from ongoing ECMO support as she was fully awake and interactive and seemed to have some enjoyment by celebrating her birthday and other religious activities and crucially interacting with her young son via video chat in the Philippines. Most of the team felt that ongoing ECMO was not violating the principle of nonmaleficence as she was in no pain or distress due to ECMO continuation. As healthcare in Qatar is state funded and our ICU philosophy of "ICU without borders," where our team takes care of patients in the emergency department and on medical floors, it was felt that no other patient was denied ICU care due to her utilizing an ICU bed during this prolonged ECMO run. Therefore, the principle of justice was not violated. Ultimately and crucially, the principle of autonomy superseded all the ethical principles, and according to her wishes she was provided full ICU and ECMO care until the end of her life. Palliation and comfort care were discussed with her, and she chose to continue full care; therefore, her wishes were respected to preserve the principle of autonomy.

RETROSPECTIVELY, WAS PLACING THE PATIENT ON V-V ECMO APPROPRIATE?

We believe that placing the patient on V-V ECMO was the right decision for the treatment of her underlying ARDS with active, cavitary tuberculous pneumonia. To date, there are case reports of similar patients with prolonged courses and long runs on V-V ECMO who eventually had enough recovery to become free from ECMO and even the ventilator.[17,18] At one point of time during her course, around the third month on V-V ECMO, she was on minimal ventilatory support with sweep gas flow of zero. Unfortunately, that did not last long as she developed many infection-related ventilator events, which increased her ventilatory requirements and precluded taking her off ECMO support.

State-funded healthcare was also a factor in facilitating her prolonged care. She or her family were not burdened financially due to her ECMO care, although loss of earning due to prolonged ECMO run led to possible hardship for her family back in the Philippines.

It is our belief that the providing physicians should not base their decisions of limitation of care of any patient based on financial considerations of high cost of care. However, local policies and healthcare pay structure may be a constraint to provide continued high-cost prolonged care. Innovative solutions to deal with the financial constraint of care should be explored. We believe that regional transplant centers should be able to provide free-of-cost care in highly selected patients with a potentially good outcome. This kind of service may have led to a better outcome in our patient, with possible overall financial cost saving considering the cost of long-term ECMO care provided, with much better long-term functional outcomes.

DISCUSSION

Long-run ECMO support is becoming more accepted and practiced. Although challenging in many aspects, with good multidisciplinary care it can lead to favorable outcomes. Keys of success include a team of providers who are well trained and updated in their knowledge, dedicated staff members of ECMO-specialized nurses, physical therapists, respiratory technicians, pharmacists, dieticians, and of course physicians.

Other factors of success are the anticipation of common and unusual complications and issues that might arise throughout the long ECMO run. Many of the common complications will probably happen more often, such as clotting, coagulopathy, and bleeding or acquired von Willebrand syndrome and impaired platelet function.[19]

Anticoagulation management in the ECMO patient is complex due to the risk of both thrombosis and bleeding. With advancement in circuit technology, the risk of circuit thrombosis is much reduced. There are multiple case reports of patients successfully managed on V-V ECMO without anticoagulation, when risk of bleeding is very high. Heparin is commonly used for ECMO anticoagulation management, with the potential risk of development of HIT.[20,21] If the HIT diagnosis is confirmed, the patient needs to be on alternative anticoagulation in view of the risk of thrombosis associated with HIT. All heparin therapy needs to be discontinued. Although ECMO circuits may have heparin coating, discontinuation of ECMO cannulae is not recommended due to

significant risks involved.[22] Different agents may be used for anticoagulation management in patients with HIT. Direct thrombin inhibitors (DTIs) such as argatroban, bivalirudin, and lepirudin have been described (see anticoagulation chapters in this book). Argatroban is primarily hepatically metabolized, excreted through the fecal route, and does not need renal adjustment. Among the DTIs, bivalirudin has the shortest half-life of 25 minutes and potentially the best pharmacological profile for use during V-V ECMO, especially given the broad experience with bivalirudin in patients undergoing coronary interventions and cardiac surgery. The short half-life of bivalirudin may also be advantageous compared to other DTIs such as argatroban (39–51 minutes) and lepirudin (78 minutes) for titration of anticoagulation. However, the short half-life of bivalirudin has major implications for patients on V-A (veno-arterial) ECMO as any region of stasis of blood in the system/patient, or areas of blood being disconnected from the systemic blood flow, may lead to a critical decrease in the regional bivalirudin concentrations and may cause thrombus formation. Therefore, cardiac contractility and ejection must be maintained during V-A ECMO.[23]

Another possible issue with anticoagulation for extracorporeal circuits is represented by the occurrence of heparin resistance, commonly caused by low antithrombin III (ATIII) levels. This challenge is often managed with supplementary heparin and fresh frozen plasma or ATIII concentrate.[24]

Case reports have shown that V-V ECMO support, in combination with anti-TB drugs, may be a useful tool in the management of ARDS with refractory hypoxemia. While some patients may recover, extensive pulmonary parenchymal damage can be expected in most patients with pulmonary TB, and those may need a bridge to lung transplant.[25–27]. Nosocomial infections of the respiratory system are expected to be more frequent, while catheter-related infections would occur at the usual rate of other ICU patients.

Depression and anxiety, muscle wasting, and ICU neuropathy/myopathy are all well-known complications of a long stay in the ICU, whether on ECMO or not. Early mobilization and neuromuscular electrical stimulation have only a little evidence for benefit. ICU-acquired weakness predisposes to adverse short- and long-term outcomes. Unfortunately, only a few preventive but no therapeutic strategies exist to mitigate these complications.[28]

Unusual problems should be kept in mind and dealt with in advance. Right heart failure, hepatic congestion, hyperlactatemia, and hypoglycemia are not common but serious conditions that providers should anticipate and prepare to deal with. Right heart failure was certainly the main complication in this case and led to the death of the patient. A switch from V-V to V-AV ECMO could have been an option to provide cardiocirculatory support. However, placement of a femoral arterial cannula would have contributed to further immobilization. Recently, the ProtekDuo double-lumen cannula has been introduced and would have been a good alternative to V-AV ECMO, especially in light of mobilization. It is composed by one lumen working as drainage from the right atrium and second lumen delivering blood into the pulmonary artery through a multifenestrated tip. This allows achieving RV support through a single percutaneous access site without cannulae in the groin. In addition to the right heart support, an oxygenator can be cut into the system and provide oxygenation similar to a double-lumen V-V ECMO cannula.[29]

If the patient would have benefitted from ProtekDuo placement or if it would just have prolonged the road to nowhere remains unclear because the patient had died. It would, however, been a feasible solution for a patient awaiting lung transplant.

A long ECMO run is a treatment for patients who are candidates for recovery or destination therapy. In general, such patients are awake and interactive. Hence, psychological concerns of the patient and the family should be taken care of.

Finally, one of the main keys is the morale of the providers. Keeping the cohesiveness of the team intact and their morale high throughout the ECMO run is paramount for the success of such cases, especially in borderline cases with ethical dilemmas that involve decision-making and the autonomy of patients.[30–33]

CONCLUSIONS

- Long ECMO runs are technically and medically feasible. However, they can be prohibitively expensive.
- This treatment modality requires access to a variety of medical services, including cardiothoracic surgery and organ transplant capability, namely, heart/lung(s) transplant.
- Other important services are access to the patient's family, psychological support, and ethics and spiritual support.
- Understanding the interaction between the patient, ECMO machine, and the circuit is essential whether the run is short or long. However, managing the unique conditions arising from long runs, such as physiological, metabolic, and right heart complications, requires anticipation, continued learning, and alternative devices.

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REVIEW QUESTIONS

1. You are evaluating a patient with ARDS secondary to H1N1 influenza pneumonitis who has been on V-V ECMO for the last 3 weeks using a CardioHelp pump and circuit (Macquet). He started to have a decrease in his SpO_2 over the last 4 days. His initial ECMO flow was 3.2 L/min; however, it has been gradually increased to 4.8 L/min to improve the patient's oxygenation. The patient continues to be deeply sedated with no spontaneous efforts of breathing, continues to be on the same ventilator settings with no change in his tidal volume, and his temperature is controlled. The TMP on initiation of ECMO flow was 19 mm Hg. You temporarily decrease the flow to 3.2 L/min and find out that his TMP is 40 mm Hg. You correctly diagnose oxygenator membrane failure and perform a bedside circuit change with prompt improvement in the patient's oxygenation and TMP. All of the following are indications for circuit/oxygenator membrane change, except

   A. Decreased oxygenator membrane efficiency for gas exchange
   B. Presence of blood clots in the 3′ and 9′ positions of the CardioHelp Quadrox membrane
   C. Grinding sound coming from the oxygenator
   D. Oozing of blood from the cannulation sites with decreased fibrinogen and platelets

2. A 48-year-old patient is started on emergency rescue V-V ECMO for severe hypoxemia after no improvement with optimized ventilation, inhaled nitric oxide (NO), and prone positioning. His family could not be contacted at time of cannulation, but his son visits after 24 hours and informs the ECMO physician that the patient is a Jehovah Witness and will not agree to blood product transfusions, even if he has severe anemia and/or bleeding that would lead to his death. He also brings a durable power of attorney for healthcare,

which confirms patient's wishes. During his third week of V-V ECMO run, he starts having severe acute duodenal ulcer bleeding. Despite endoscopic and interventional radiology treatments, he continues to bleed. The patient's wife is asking the ECMO physician to transfuse blood for her husband; however, the physician confirms with the patient's son that no blood transfusion should be given. The patient eventually dies. The hospital Ethics Committee was asked to review the case. How would you rule in this case?

A. Peptic ulcer disease bleeding is a reversible disease process, and death could have been easily avoided if blood transfusion was done. Saving the patient's life with blood transfusion should have been a priority regardless of his wishes.
B. As the patient was unable to make decisions at the time of severe bleeding, his wife would be the next of kin to make decisions for him. The treating physician should have followed her wishes against the son's wishes and should have transfused the patient with blood.
C. Having the patient on ECMO would forfeit, by default, the patient's wishes of "no blood transfusion" since practically blood is being continuously drawn from the patient and transfused back to him through the ECMO circuit. This would have put the treating physician at no fault if transfusion was done.
D. The ethics principle of autonomy should be upheld. The patient clearly expressed his wishes at the beginning and refused all blood and blood products transfusions even if it would have saved his life. The treating physician's decision was correct.

3. During the Covid-19 pandemic, you are taking care of many V-V ECMO cases. The number of cases has increased significantly and has placed the ECMO team under significant pressure. As the pandemic was expected to continue for several more weeks, you decided with your team to be more selective of any new cases. However, you have just used your last pump for a new ARDS case, and now you have a new referral for a 22-year-old woman with single-organ failure who failed all conservative measures to improve her oxygenation. Among your old ECMO patients, you have a 63-year-old man with no appreciable lung function improvement since initiating ECMO support more than 4 weeks ago. His Glasgow Coma Scale is 4 without sedation. He currently requires renal replacement therapy and has had several sepsis episodes from repeated respiratory infections. His chance of survival and to be liberated from ECMO support is less than 5%. What should you do next?

A. Nothing different. You should continue with the current management for all old patients and continue maximal support of the new patient and hope for the best. You believe in "first come, first served" rule.
B. As the patient is unconscious and this is an emergency situation, you decide to start the old ECMO patient on intravenous morphine infusion, set the ventilator on maximum possible settings, and decannulate him so you can start the new patient on V-V ECMO.
C. You quickly review the hospital bylaws and as there are no clear instructions for such a situation, you call for an emergency ethics consultation to advise on withdrawing the ECMO support from the unconscious patient (after informing his family) to be used for the new patient.
D. You decide to call the unconscious patient's family and explain to them the situation and inform them that their relative has had his chance, and it would be unethical if they refuse to withdraw ECMO care from their relative to benefit a younger patient.

4. A 32-year-old Nepalese gentleman is admitted with a 4-week history of cough, night sweats, and weight loss of 4 kg. Over the last week, his cough worsened associated with progressively worsening dyspnea. On the day of presentation, he was tachycardic at 115 beats/min, tachypneic with RR of 30, room air SpO_2 of 87%, diffuse crepitations on chest examination, and chest x-ray showing diffuse lung infiltrates. He deteriorates rapidly, requiring intubation, and fulfills criteria for ARDS. His tracheal aspirate smear is positive for acid-fast bacteria, and he is started on anti-TB therapy. Despite optimization of ventilation, positive end-expiratory pressure, inhaled NO, and prone position, his P/F ratio remains less than 80 on FiO_2 (fraction of inspired oxygen) of 0.8. The primary team requests initiation of V-V ECMO support. Which of the following is the correct statement?

A. Veno-venous ECMO should not be initiated as it is well established that prognosis of TB-related ARDS is dismal.
B. It will be impossible to achieve mycobacterial culture negativity while the patient is on ECMO due to suboptimal and unpredictable drug levels while on ECMO.
C. The high risk of bleeding in pulmonary TB will preclude use of anticoagulation while the patient is on ECMO support.
D. If ECMO is initiated in this patient, duration of ECMO should be limited to 6 weeks as chances of recovery beyond that period are extremely low.
E. Extracorporeal membrane oxygenation should be initiated after thoughtful discussion and team consensus, with anticipation that the patient may require a prolonged ECMO run for weeks to months.

5. A 50-year-old male is admitted with severe acute respiratory failure secondary to viral pneumonia. He develops severe ARDS and fails ventilatory optimization, inhaled NO, and prone ventilation to improve oxygenation, prompting V-V ECMO initiation. A transthoracic echocardiogram 2 days after ECMO was unremarkable. After 8 weeks on ECMO, the patient developed mild hypotension. A repeat echo evaluation showed normal left ventricular ejection fraction, mild RV dilation and dysfunction, right ventricular systolic pressure (RVSP) of 58, and Tricuspid Annular Plane Systolic Excursion (TAPSE) of 1.7. All the following are correct, except which of the following:

A. Acute cor pulmonale can occur in 20%–30% of ARDS patients, despite utilizing protective lung ventilation.
B. Acute cor pulmonale related to ARDS requiring ventilator support usually occurs in the first week, while ECMO-related ACP generally develops 6 weeks after ECMO support.
C. Treatment strategies for ACP may include pulmonary vasodilator therapies; correction of hypoxemia, hypercapnia, and acidosis; inotropic support; and change of ECMO configuration to V-VA.
D. Prognosis of ACP on ECMO is excellent with specific pulmonary vasodilator therapy.
E. Nonpulsatile blood flow and chronic ECMO-related microthrombi are likely contributors to ACP in addition to chronic lung injury and fibrosis.

6. A 65-year-old male is receiving V-V ECMO support for severe ARDS after severe bacterial pneumonia for the last 10 days. He is receiving UFH therapy to keep the activated partial thromboplastin time (aPTT) 1.5–2 times the baseline aPTT. His course was complicated by nonoliguric acute kidney injury, requiring intermittent sustained low-efficiency dialysis. Initial platelet count after ECMO initiation was variable from 120 to 130 × 10^3 per μ, from baseline of 220 × 10^3 per μL. However, over the last 1 day, the platelet count has dropped to 65 × 10^3 per μL. His 4T score is 4; HIT screen and confirmatory testing are positive. What is the most appropriate next step in the management of thrombocytopenia in this patient?

A. Discontinue all heparin therapy, and there is no need for any other anticoagulation therapy as the platelet count is less than 70 × 10^3 per μL.
B. Discontinue heparin therapy and initiate argatroban to maintain anticoagulation targets.
C. Discontinue heparin therapy, initiate argatroban to maintain anticoagulation targets, and remove ECMO cannulae as heparin-coated cannulae are the precipitant for HIT.
D. Discontinue heparin therapy and initiate lepuridin for anticoagulation targets.
E. Discontinue heparin therapy, monitor platelet count, and once platelet count is more than 70 × 10^3 per μL, start fondaparinux.

ANSWERS

1. B.

The presence of small clots visible in the corners of the membrane is not an indication on its own for membrane/circuit change. This has to be associated with other signs of membrane failure, such as decreased membrane gas exchange efficiency (low PaO_2 in the patient's arterial blood gas, decreased postoxygenator PaO_2, decreased calculated oxygen transfer) or a grinding sound indicating the presence of a large blood clot between the oxygenator and the rotating plate of the pump.

Another reason is consumptive coagulopathy evidenced by bleeding tendency along with low platelets and low fibrinogen. This could be an indication of the presence of clotting in the membrane with resultant fibrinolysis, which would improve with changing the membrane.

2. D.

The patient's autonomy should be respected and upheld. As the patient was able to make his own decisions before the acute bleeding, he made a clear statement about his wishes regarding blood and blood product transfusions based on his personal belief system. He made it very clear that no transfusion should be given even if it would save his life. The wife or the treating physician has no right to reverse this decision even though the patient became unable to decide for himself since he knew the consequences of his decision. Autonomy of the patient should always be respected.

3. C.

This is not an easy situation to face. To start with, there is no consensus on the definition of futility of care. This makes it difficult to argue for withdrawing life-sustaining care when dealing with similar situations. Although it might seem that we are prolonging the pain and suffering of the patient, the family might think otherwise and might want to continue full care, including ECMO support, even with the very insignificant chance of survival. With the high probability of litigation if the care is withheld against the family's wishes, it is highly advisable that the treating physician consult the hospital's ethics committee and even the administration of the hospital. In extreme cases, a court order might be needed to deal with such cases.

Some might argue that it is not for the treating physician to decide who lives and who dies, and the care of the unconscious patient should continue as it is. However, based on the principle of justice, others will argue that it is unjust to continue with a highly specialized treatment modality for a patient with a very low chance of survival and withholding it from someone who has a much higher chance of survival if applied early.

Fin ally, it is advisable that the hospital would develop guidelines to deal with such cases in the future and not leave it for emergency situations, which might lead to an increase in litigation cases.

4. E.

Although TB-related ARDS prognosis is poor, with reported mortality from 60% to 90%, multiple case reports have been published regarding successful TB-related ARDS management with V-V ECMO. The ECMO circuit and membrane can affect drug levels of anti-TB therapy, but patients have been successfully managed with mycobacterial cure while on ECMO. Although TB cavitary disease can lead to hemoptysis, which may complicate anticoagulation management on ECMO, routine anticoagulation should not be withheld if there is no active bleeding. TB-related ARDS requiring ECMO generally requires prolonged ECMO runs lasting from weeks to months. This should be anticipated at the time of V-V ECMO start, and ECMO support should not be prematurely terminated in these patients.

5. D.

Acute cor pulmonale is relatively common in ARDS patients. Prior to a volume-limited lung protective strategy, ACP was reported in up to 50%–60% of patients. With lung-protective ventilation, ACP develops in about 20%–30% of patients, usually in the first week after ARDS. Hypoxemia, hypercapnia, acidosis, and structural lung changes are the possible underlying mechanisms for ACP development. In ECMO patients, ACP may develop at a later stage of about 6 weeks after ECMO. The additional mechanisms for development of ACP in ECMO include pulmonary microthrombi related to ECMO, as well as nonpulsatile blood flow into the RV during V-V ECMO. Management strategies for ACP include specific pulmonary vasodilator therapies with inotropic support in addition to correction of hypoxemia, hypercapnia, and acidosis. If there is poor response to these therapies, ECMO configuration change to V-VA or the use of a ProtekDuo RVAD may provide RV support for a failing RV and oxygenation to the failing lung.

6. B.

Direct thrombin inhibitors like argatroban or bivalirudin are the alternative anticoagulants of choice for ECMO patients who have developed HIT (see discussion).

ECMO BLOOD INTERACTION

12.

THE UNHOLY BLOOD–BIOMATERIAL INTERACTION IN EXTRACORPOREAL CIRCULATION

Emma L. Hartley, Jonathan Millar, and John F. Fraser

STEM CASE AND KEY QUESTIONS

A 40-year-old, previously healthy, female developed severe acute respiratory distress syndrome (ARDS) secondary to influenza A complicated by Panton-Valentine leukociden (PVL) *Staphylococcus aureus* infection. Despite low tidal volume mechanical ventilation, neuromuscular blockade, and prone positioning, she developed progressive hypoxemia requiring extracorporeal life support (ECLS). On day 4 of ECLS there was a rise in d-dimer and lactate dehydrogenase (LDH) concentrations. Following transfusion of cryoprecipitate and platelets, platelet and fibrinogen levels began to fall. Plasma free hemoglobin (pfHb) was elevated. The circuit, previously functioning well, now needed increased pump revolutions to achieve the same flow rate, with an associated rise in transmembrane pressure. The diagnosis of circuit-induced hematological failure was made.

WHAT IS CIRCUIT-INDUCED HEMATOLOGICAL FAILURE, AND WHAT IS THE ETIOLOGY?

Initially, the extracorporeal circuit continued to achieve adequate flow rates, albeit with an increased but stable pump speed and transmembrane pressure. The following day, the pump head emitted an unusual noise. This sign of thrombosis resulted from the foreign material of the circuit stimulating several inflammatory and coagulative processes, ultimately leading to pump head thrombosis and hemolysis.

WHAT ARE THE EFFECTS OF BIOMATERIAL INTERACTION IN THE CIRCUIT, AND HOW IS IT DIAGNOSED?

Blood testing revealed a further rise in d-dimer and LDH concentrations, which were felt not to be related to the underlying *S. aureus* sepsis. Platelet count fell to below 50×10^9/L and fibrinogen less than 150 mg/dL, despite repeated transfusion. This picture, not dissimilar to disseminated intravascular coagulation (DIC), occurs as a result of the complex interplay of hyperfibrinolysis and other hypercoagulative effects of the circuit. This includes platelet aggregation and contact activation. A repeat pfHb was 1000 mg/L, a sign of hemolysis resulting from mechanical shear stress on red blood cells.

HOW IS IT TREATED?

The patient was reliant on extracorporeal support for oxygenation, with minimal native ventilation. However, due to circuit-induced hematological failure, an emergency circuit exchange had to be performed. Although not without risk, the circuit change was performed swiftly without sustained desaturation. Afterward, the ratio of pump revolutions to flow rate improved, the pfHb fell, and there was a reduced requirement for product replacement. The patient's condition slowly improved with lung rest, and she was successfully removed from extracorporeal support on day 11 and extubated on day 12.

DISCUSSION

The term *biomaterial interaction* is used to describe several inflammatory and coagulative processes that occur when the patient's blood meets the foreign surface of the extracorporeal circuit.[1] In the last decade, the indications for, and use of, extracorporeal support have expanded. Heparin-bonded circuits have reduced the need for systemic anticoagulation,[2] and there is increased portability with smaller devices.[3] However, several limitations associated with the foreign material of current extracorporeal membrane oxygenation (ECMO) circuitry remain. This chapter explores the underlying inflammatory and coagulative responses associated with the institution of extracorporeal circulation (Figure 12.1).

PATHOGENESIS

Difference Between ECMO and Cardiopulmonary Bypass

Exposure of the patient's blood to the extracorporeal circuit results in immediate release of inflammatory mediators. This can result in a systemic inflammatory response syndrome (SIRS), leading to endothelial injury and organ dysfunction.

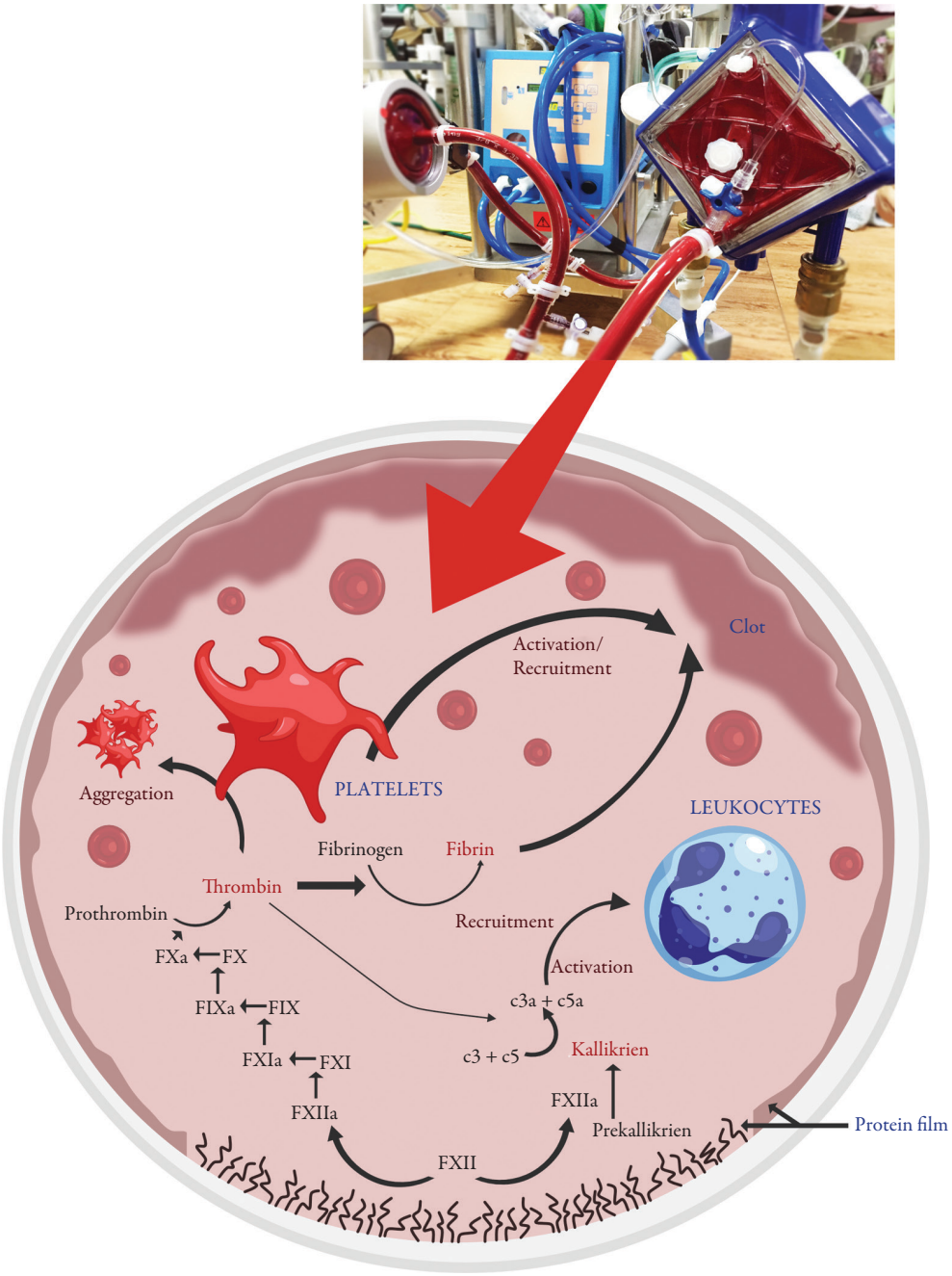


Figure 12.1 The inflammatory and coagulative response to extracorporeal circulation. FXII, factor XII; FXIIa, activated factor XII; c3,5, complement proteins; c3a,5a, anaphylatoxins.

The cascade of events is well described in cardiopulmonary bypass (CPB) but has been less frequently studied during ECMO.[4,5] While ECMO shares some similarities with CPB, there are several important distinctions one must be aware of when inferring data from one support to another. Both use a nonendothelialized surface; however, CPB is commonly employed for a short duration to facilitate a surgical procedure, whereas ECMO support may be prolonged, especially in those with multiorgan failure.

Heparin doses are higher with CPB and reversed with protamine at the end of the procedure. This practice is not employed with extracorporeal support due to the inherent risk of circuit thrombosis and failure. Protamine forms complexes with heparin and can result in complement activation, exacerbating the inflammatory response.[6]

Patients undergoing CPB are cooled; however, in ECMO this is not frequently undertaken. There are conflicting data regarding the effect of hypothermia on inflammation[5]; however, it is associated with platelet dysfunction and coagulopathy.[7] ECMO may be associated with less inflammation due to the lack of blood-air interface present in CPB (cardiotomy suctioning, venting of blood, and venous reservoirs). Studies have demonstrated higher levels of pro-inflammatory cytokines present within cardiotomy suction blood.[8–10]

Pulsatility, present in varying degrees in veno-arterial (V-A) extracorporeal support, may further reduce the inflammatory response compared with CPB, which commonly involves nonpulsatile flow.[11] After unclamping of the aorta, CPB is associated with an ischemia-reperfusion injury, resulting in an inflammatory picture that can, if severe, cause lung injury.[12] This reperfusion injury is not seen in extracorporeal support but may be present in cases after cardiac arrest.[13]

Finally, patient differences also occur, which may alter the underlying inflammatory response. In ECMO, there is often multiorgan failure with associated inflammation from the underlying disease process, in contrast to CPB with chronic disease.

Coagulation Cascade

Activation of factor XII (FXII) occurs when blood meets the artificial surface splitting into α and β FXIIa fragments, initiating the contact activation system. Prekallikrein is rapidly converted into its active form kallikrein and splits bradykinin from high-molecular-weight kininogen, activating neutrophils and promoting inflammation and coagulation.[14] There are limited data on bradykinin and its role in ECMO, but elevated levels are noted in CPB, which may be associated with a vasodilation.[15] Given that the predominant site of bradykinin catabolism is within the pulmonary circulation (bypassed during CPB), it is unclear how applicable these data are to extracorporeal support.

The contact pathway activates further factors, in association with the tissue factor (TF) pathway, resulting in the final common step in which FX is converted to FXa. The extracorporeal circuit also activates TF and the extrinsic pathway, possibly through expression on circulating monocytes[16] or inflammatory cytokines.[17] The end result is generation of thrombin from prothrombin and finally fibrin from fibrinogen. Thrombin generation results in endothelial cell activation and neutrophil adherence and increases the release of inflammatory cytokines.[18]

Complement

Complement, a system of proteins, plays a key role in innate immunity. Through proteolytic cascades pathogenic surfaces are identified, resulting in pro-inflammatory mediators (anaphylatoxins), opsonization, and targeted lysis secondary to the membrane attack complex (MAC).[19] Complement activation is seen immediately on initiation of ECMO.[20] There are three distinct pathways of complement activation: classical, lectin, and alternative. The classical pathway is principally mediated by the C1 complex binding to immunoglobulin patches on a pathogen; the lectin pathway is activated by microbial carbohydrates, and the alternate pathway is activated by the hydrolyzed form of C3.[21] All pathways converge, resulting in generation of C3 and C5 convertase and thus the major effectors of the complement system: anaphylatoxins, that is, the pro-inflammatory mediators (C4a, C3a, C5a), MAC, and opsonins (C3b).[19]

In adult patients on ECMO, there are rapid elevations of complement products C3b and sC5b-9 (fluid-phase MAC) on initiation of therapy, with a peak within 1 hour and normalization over several days.[22] This activation occurs via the alternative pathway. Similar data, describing elevations in C3a, are found in studies with neonates[20,23,24] and in experiments in vitro.[23,25] One neonatal study showed rises in C3a, C5a, and sC5b-9; however, in contrast to the limited adult data, here sC5b-9 levels remained elevated.[23,22] There is an additional in vitro association between complement activation and deterioration in blood rheology during ECMO.[26]

Over the past 20 years, circuit technology has improved with use of heparin-bonded circuits and centrifugal pumps. Centrifugal pumps are associated with less complement activation; therefore, in modern ECMO this is less likely to be problematic.[25]

Cytokines

Cytokines are a category of small proteins that are involved in cell signaling and the mediation of inflammation in innate immunity.[27] They include interleukins (ILs), chemokines, interferons, tumor necrosis factor (TNF), and growth factors. Cytokines are subject to close homeostatic control in health, with a balance of anti-inflammatory and pro-inflammatory activity; however, excess pro-inflammatory cytokines are seen during CPB.[28] Cytokine release stimulates further cytokine release, a process known as cytokine storm, resulting in the dysregulated production and aggravation of organ and tissue damage.[29]

The most studied cytokines in ECMO are IL-6, IL-8, and TNF-α. TNF-α is a protein that has a key role in a variety of inflammatory, malignant, and infectious conditions. The macrophage/monocyte lineage is the predominant source of TNF-α in inflammatory conditions.[30] TNF-α has several effects during inflammation. A program of membrane protein redistribution occurs, resulting in recruitment of adhesion molecules to endothelial cells, attracting leukocytes to sites of inflammation.[31] Vasodilatory effects result from stimulation of cyclooxygenase 2 and prostaglandins.[32] Additionally, a procoagulant effect occurs due to increased TF-like activity, which may lead to intravascular thrombosis.[33] In an animal study, levels of TNF-α rose rapidly after the initiation of ECMO.[34] This has also been seen in human data, where neonates who died on ECMO had higher levels of TNF-α than those who recovered.[35] It is hypothesized that the increase in level of TNF-α is the result of mobilization of preformed cytokines from tissue stores into plasma, resulting from mast cell degranulation, rather than an increase in tissue synthesis.[34]

Interleukin-6 is a multifunctional cytokine exhibiting functional pleiotropy that regulates the immune response, hematopoiesis, acute-phase response, and inflammation.[36] It is a potent inducer of C-reactive protein (CRP). Levels of IL-6 are consistently high in patients on ECMO.[34,37–39] In ECMO survivors, levels of IL-6 have been shown to undergo a rapid decline, while nonsurvivors have persistently raised plasma levels with similar patterns of CRP.[37] This coupling with CRP was not evident in a porcine ECMO study.[34]

Like IL-6, IL-8, a potent neutrophil activator, is found in higher levels during ECMO. This is consistent in experimental, animal, and human studies.[34,38–40] The development of extrapulmonary ARDS has been associated with higher levels of IL-6 and IL-8 than pulmonary ARDS in patients supported with ECMO. The presence of driving pressures of 19 cm H_2O or greater before the initiation of ECMO resulted in higher IL-8 levels in the same cohort.[38]

The Endothelium and Leukocyte Activation

The endothelium is the interface between blood and the underlying tissues, maintaining vascular tone, selective permeability, and thromboresistance.[41] On activation, it becomes involved in the inflammatory process with expression of leukocyte adhesion molecules, expression of prothrombotic mediators, cytokine production, and loss of vascular integrity.[41] Impaired endothelium-dependent vasodilation is a predictor of mortality in the critically ill.[42]

The use of ECMO is independently associated with endothelial activation,[34] which may lead to capillary leak syndrome with resultant systemic and pulmonary edema.[43] The oxygenator may play a significant role as the site of activation.[44] In neonatal studies, activated leukocytes adhere to the endothelium, contributing to edema formation.[45,46] The activation of leukocytes results in the release of inflammatory mediators, leading to an increased inflammatory burden in an already critically ill patient.[39] Complement plays a major role in neutrophil activation, in association with other pathways.[47] On activation, neutrophils release reactive oxygen species, chemokines, cytokines, and other primary and secondary granules.[48] In neonatal and laboratory studies, levels of neutrophil elastase increase quickly, returning to preextracorporeal support levels by 24 hours.[40,45] Neutrophil infiltration secondary to extracorporeal support is thought to result in end-organ dysfunction.[34] Neutrophils disappear from the systemic circulation, undergoing margination, and adhere to the pulmonary capillary endothelium, which may worsen pulmonary function.[20,40]

The neutrophil-to-lymphocyte ratio (NLR), a marker of inflammation and immunologic function, has been used as an indicator for postoperative outcomes in heart failure patients on ECMO.[49] A higher NLR is associated with poorer prognosis, although it is unclear whether this is an inflammatory response to the ECMO apparatus or more a reflection of more advanced cardiac deconditioning prior to ECMO. Higher levels of Ang-2, an endothelial biomarker, are associated with mortality in patients on V-A ECMO.[50]

Platelets and Von Willebrand Factor

Platelets have a major role in not only vascular integrity and hemostasis but also inflammation. Under normal conditions, platelet activation and aggregation are inhibited by prostacyclin and nitric oxide (NO); however in response to endothelial injury or exposure to a biomaterial, they adhere, forming a thrombus.[51] During shear stress, von Willebrand factor (vWF) forms a bridge between exposed collagen and platelet glycoprotein complexes.[52] Thrombocytopenia is a common problem in extracorporeal support, because of not only the circuit, but also the initial severity of critical illness.[53]

Exposure to a biosurface leads to fibrinogen adsorption within minutes, resulting in additional protein adherence (coagulation factors from the contact pathway, albumin, and immunoglobulins).[54,55] The development of a protein layer triggers the adherence of platelets.[56] Platelet activation is also mediated by complement.[57] Once activated, platelets change shape, releasing inflammatory mediators. These platelet granules contain chemokines, cytokines, adhesion factors, growth factors, and coagulation factors, which may act on other platelets, leukocytes, and endothelial cells.[58] Activated platelets bind with leukocytes, causing further release of inflammatory mediators.[59]

Large vWF multimers mediate platelet binding to the endothelium. The presence of an extracorporeal surface results in an acquired deficiency of these high-molecular-weight multimers due to shearing forces, which cause cleavage and the formation of much less effective small multimers.[60] Serologically, there is decrease of ristocetin cofactor activity and collagen-binding activity.[61] This effect occurs rapidly; however, on cessation of therapy levels return to normal within hours.[62] Deficiency is associated with mucosal, bronchial, or puncture site spontaneous hemorrhage.[63] The use of centrifugal compared to roller pumps has been shown to increase nonsurgical bleeding events, which, due to the shear forces, may be explained by acquired von Willebrand deficiency.[64] Acquired von Willebrand deficiency is common in ECMO, but only a small population of patients are tested. The extent to which it contributes to bleeding or how changes in ECMO management can influence high-molecular-weight vWF multimer levels is not clear.[65]

Fibrinolysis

Fibrinolysis ensures hemostatic regulation by converting plasminogen to plasmin using tissue plasminogen activator and urokinase.[66] Plasmin cleaves fibrin, generating soluble degradation products. Limited data are available, although the development of hyperfibrinolysis is associated with the use of extracorporeal support and may contribute to excess bleeding.[67,68]

Soluble fibrin is a useful marker to evaluate circuit clotting, helping to identify the appropriate timing of a circuit exchange,[69] where higher levels indicate a hypercoagulable state.[70] Soluble fibrin in plasma is an indicator of thrombin activation in the blood, with elevated levels serving as a marker of venous thrombosis.[71] D-Dimer, formed when cross-linked fibrin is proteolyzed by plasmin,[72] provides valuable diagnostic and prognostic information about the progression of clot formation within the oxygenator in the absence of other explaining pathology (e.g., DIC, sepsis, or trauma).[73]

Hemolysis

Hemolysis occurs when red cells rupture and release free hemoglobin into the plasma, resulting in tissue hypoxia and cell death.[74] Elevated levels of LDH are seen due to red cells

containing large amounts.[75] The etiology is multifactorial in extracorporeal support, with mechanical shear stress applied to the red cells from pressure gradients, high blood flow, exposure to the nonendothelialized circuit, and centrifugal pumps (compared to roller pumps) playing a role.[76–78] Hemolysis results in free hemoglobin binding with NO, leading to inappropriate vasoconstriction, endothelial dysfunction, and platelet aggregation.[75] It is further associated with renal failure and may induce multiorgan dysfunction.[79]

It is a common problem with up to 67% of patients displaying evidence of hemolysis during ECMO,[80,81] although more recent adult data have shown marked hemolysis occurring in only 3% of patients on extracorporeal support.[82] Hemolysis is associated with increased red cell transfusion, platelet transfusion, and higher mortality.[81,82] Levels of pfHb greater than 500 mg/L are an independent predictor of mortality.[83]

CLINICAL FEATURES AND DIAGNOSIS

The Inflammatory Response

Extracorporeal support is associated with a systemic inflammatory response. In preclinical ECMO, performed on healthy animals, the initiation of therapy is associated with the development of hypotension and tachycardia within 1–2 hours and capillary leak by 4 hours, with abdominal distention and ascites requiring greater volumes of fluid and blood products to support the circulation.[34] Similar effects have been described in humans, including multisystem organ dysfunction manifesting as reduced pulmonary compliance, decreased urine output, and hypotension due to capillary leak.[40,84,85] The effect is less pronounced with modern circuitry, however; in patients with advanced heart failure, those supported with ECMO preoperatively prior to left ventricular assist device implantation had higher vasopressor requirements to achieve normal mean arterial pressure targets. This may indicate that hypotension is enhanced by the synergistic effect of a cytokine storm caused by ECMO and CPB.[86]

There is wide variability in the management of infection in patients on ECMO. In a survey of ECMO centers across the world, white cell count (WCC) was the most commonly used laboratory test for surveillance of infection (80%), followed by CRP (75%), and procalcitonin (55%).[87] In addition to other clinical signs, changes in WCC, the presence of thrombocytopenia, and increasing levels of CRP (and/or procalcitonin [PCT]) were used as an indication for empiric antibiotic therapy. This is interesting given the reliability of PCT and CRP has not yet been established as a diagnostic test for infection in ECMO and can be raised due to SIRS from the underlying disease process or blood-biomaterial interaction.[88–90]

Thrombosis

The more common complications of ECMO relate to hemostasis, with hemorrhage and thrombosis often coexisting.[91] These can be difficult to balance, resulting in morbidity and mortality from not only the inflammatory response of the circuit, but also exacerbation of the underlying disease process.

Major thromboembolic events on V-A ECMO occur in 8% of patients and are most commonly related to circuit clotting.[92] Daily inspection of the circuit should occur to identify thrombi that may degrade gas exchange.[93] A rise in transmembrane pressure and a deterioration in postoxygenator gas exchange can predict the need for a circuit change. Intrinsic hematological problems (thrombocytopenia, hypofibrinogenemia, and elevated d-dimer) not dissimilar to DIC can also be precipitated. The d-dimer level, which can be elevated for several reasons, should be observed daily. An increase, in the absence of other explaining pathology, can be helpful in predicting the need for a circuit exchange.[94]

Pump thrombosis, associated with pump failure, results in a noisy pump head and often hemolysis. A sudden pronounced increase in pfHb (≥1000 mg/L) is associated with pump head thrombosis, necessitating a circuit change, thus normalizing the level.[82] Levels of pfHb should be routinely measured to detect early changes given that LDH may be an unreliable marker in the patient with sepsis.

Hemorrhage

Hemorrhage remains the most common complication of ECMO.[80,91] In one retrospective study, 60% of ECLS runs were complicated by hemorrhage.[95] The most likely areas for bleeding are the cannula site (37%); followed by hemothorax or tamponade (17%); then ear, nose, and throat (16%). Bleeding incidence is independently associated with severity of illness, higher activated partial thromboplastin time, and recent surgery—resulting in an increased risk of death.[95] An increase in blood product usage is independently associated with patient outcome.[96]

The pathological, pharmacological, and mechanical impact on clotting places the ECLS patient at risk of life-threatening hemorrhage, which may be precipitated by minor procedures or occur spontaneously. The underlying critical illness often leads to an imbalance between procoagulant and anticoagulant factors, further enhanced by the inflammatory effect of the circuit (resulting in thrombocytopenia, hyperfibrinolysis, DIC, and acquired von Willebrand syndrome). This, combined with large-bore arterial and venous access and systemic anticoagulation, puts patients at high risk from hemorrhage.

Bleeding can be catastrophic even with minor or no trauma and may be out of proportion to coagulation abnormalities.[97] Treatment involves preventive strategies with cessation of anticoagulation, transfusion of products, antifibrinolytics, or surgical control.

Hematological Monitoring

Transfusion of red blood cells is not without risk. A restrictive strategy of transfusion (>7 g/dL) is usually employed in critical care.[98] There is uncertainty regarding the optimal hemoglobin threshold for packed red cell transfusion in ECLS patients given the high incidence of hemorrhage and often critical oxygenation. Traditionally, a hematocrit of greater than 35%–40% has been targeted[99]; however, recently lower targets have been studied with a target Hb greater than 7 g/

dL[100–102] showing comparable results. There is some evidence to support higher mortality in patients with a greater number of blood transfusions[96,103]; however, these data are difficult to assess due to the large number of confounding factors, varying practices, and different modes of ECMO. The PROTECMO study aims to answer these questions.[104]

Thrombocytopenia is the most common hemostatic disorder in critical care and is associated with bleeding and increased mortality if moderate or severe.[105] Prophylactic transfusions in the nonbleeding patient are often given when the platelet level falls below 20×10^9/L, but much variation exits.[106] In ECMO the etiology of thrombocytopenia is multifactorial and related to underlying illness and the effects of the mechanical device. The duration of ECMO is not associated with the development of thrombocytopenia, but the severity of critical illness and platelet count at time of cannulation are.[53] Platelet counts of greater than 100×10^9/L are often targeted with supported guidance from the Extracorporeal Life Support Organization[107]; however, many centers will use a lower threshold in stable patients who are at low risk for intracranial haemorrhage.[99] In addition, there may be a role for assessing platelet function instead of counts per se.[108]

Fibrinolysis is common in extracorporeal support and can result in excessive bleeding.[109] Hyperfibrinolysis can be triggered by clot deposition within the circuit resulting in increased d-dimer levels and generalized coagulopathy-type bleeding (e.g., from mucous membranes).[97] A circuit change may be required to reverse this process. Cryoprecipitate is usually given when fibrinogen levels are less than 100–150 mg/dL.[99,107] Antifibrinolytics may also be required.[110]

MANAGEMENT

The identification of the inflammatory processes occurring in ECMO may allow us to develop targeted strategies and future developments for anti-inflammatory techniques aimed to reduce complications (Table 12.1).

Heparin-Bonded Circuits

The mainstay of management is systemic anticoagulation and the reduction of the circuit's propensity for hemostatic activation. There is extensive research into the use of heparin-bonded circuits in CPB, which is associated with shorter intensive care stay and duration of mechanical ventilation.[111,112] A heparin-coated surface results in less thrombogenicity, through reduced or selective adhesion of plasma proteins and contact activation, in addition to reduced activation of complement and other inflammatory mediators.[113] They reduce the risk of oxygenator failure[114] and may result in reduced systemic anticoagulation.[115–117]

Lower levels of systemic anticoagulation reduce side effects; however, with heparin the risk, although rare, remains of heparin-induced thrombocytopenia (HIT). The contribution of the circuit to the development of HIT remains unclear, with mixed results.[118–120]

Biopassive Surface Modifications

Other modifications to prevent cellular adhesion have been investigated, including phosphorylcholine (PPC) and poly-2-methoxyethylacrylate (PMEA). PPC mimics the main lipid group component of the cell membrane, which is nonthrombogenic in nature and associated with a favorable effect on platelets.[121] PMEA, an amphiphilic polymer, has been shown to reduce platelet activation and comparable in this ability to heparin-bonded circuits.[122] Future studies into omniphobic infused coatings is required as these appear to be associated with a significant reduction in thrombosis.[123] Despite ongoing research, circuit-related thrombosis remains a significant problem and still necessitates the use of systemic anticoagulation in most circumstances.

Nitric Oxide–Based Modifications

Nitric oxide can be used to minimize surface-induced thrombosis when incorporated into a circuit coating as a form of

Table 12.1 CURRENT AND FUTURE ECMO SURFACE MODIFICATIONS

SURFACE MODIFICATION	TECHNOLOGY	PROBLEMS
Heparin-bonded circuit	Reduces thrombogenicity	Systemic anticoagulation required
Biopassive surfaces: Phosphorylcholine (PPC), poly-2-methoxyethylacrylate (PMEA)	PPC: hydrophilic group of phospholipids in outer cell membrane PMEA: amphiphilic polymer Both show reduced platelet adhesion and aggregation	Systemic anticoagulation still required Further research required in ECMO
Nitric oxide (NO) releasing	1st generation: NO added to thin layer of plasticized PVC (polyvinyl chloride) 2nd generation: silica-based NO-releasing materials 3rd generation: embedded lipophilic donor complex Reduced platelet consumption and adhesion in all generations	1st generation: systemic release of nitrosamine 2nd generation: reservoir NO depletion and delay in release time 3rd generation: fibrinogen consumption Generally: finite reservoir (impractical for long ECMO run)
Endothelialization	In vitro: directly seeding autologous endothelial cells onto circuit; prevents thrombogenesis In vivo: induced self-endothelialization using endothelial progenitor cells	In vitro: cost-ineffective, months to years to complete In vivo: low endothelial cell proliferation activity

biomimetic surface. NO acts as a major regulatory factor in platelet inhibition by the endothelium. On binding with soluble guanylate cyclase, levels of cyclic guanosine monophosphate are increased, resulting in temporary direct platelet inhibition through reduced fibrinogen binding to IIb/IIIa receptors, inhibition of the phosphorylation of myosin light chains, inhibition of phosphorylation of protein kinase C, and modulation of phospholipase A_2- and C-mediated responses.[124] There is also a direct effect via calcium inhibition.

Nitric oxide has been studied extensively for incorporation with extracorporeal circulation. This can be achieved by two methods; the first involves infusing it into the sweep gas flow, and the second incorporates NO into the polymers of the circuit, from which it is locally released at the blood-biomaterial interface with no systemic effect.[125] There are broadly three generations of studies investigating the use of NO, the first involved NO added to a thin layer of plasticized polyvinyl chloride (PVC), showing reduced platelet consumption and adhesion in animal studies but with systemic release.[126,127] Second-generation studies included silica-based NO-releasing materials in rabbits without leaching of other compounds.[125] These coatings required thickening but were impractical for clinical use. Polymer matrices were designed and applied to the circuit[128] and subsequently tested in swine studies. This was associated with platelet activation, but the circuit was easily delaminated and the NO reservoir depleted.[125] Third-generation NO compounds have involved lipophilic NO donor complexes, eliminating issues with previous generations.[129]

Incorporating NO into the extracorporeal circuit has consistently been shown to reduce platelet activation and the requirement for systemic heparinization.[126] It may also prevent biofilm formation by the direct bactericidal effects of NO.[130]

A combined direct thrombin inhibitor (argatroban) and NO-releasing polymer has shown potential benefit as a nonthrombogenic surface coating. Its use resulted in increased platelet preservation in preclinical models.[131] Further data from a rabbit study have shown better efficacy and higher activity when argatroban is linked to a polyurethane silicone polymer. In this setting, there was less thrombus generation and a reduction in systemic heparinization compared to a control.[132]

Given the problems associated with a finite source of NO within the extracorporeal circuit, alternative structures have been investigated for local release. NO donor compounds S-nitrosothiols and N-diazeniumdiolates have been used as a source for NO in biomimetic surfaces.[133] Alternatives include metal organic frameworks for drug delivery[134,135] and nanotechnology.[136] Further research is required into the exact role of NO incorporated within extracorporeal circuitry.

Endothelialization

Endothelial cells maintain vascular integrity and the fluidity of blood through the secretion of pro- and anticoagulant factors.[137] Endothelialization of the biomaterial surfaces has been researched in order to reduce the adverse consequences of biomaterial interaction. This can be performed ex vivo by seeding autologous endothelial cells onto the blood-facing components of the extracorporeal circuit. This may be promoted by pretreating prosthetic material with fibrin, collagen, and/or matrix molecules, which encourage cell attachment and retention.[138] Fibronectin has also been used for surface endothelialization modifications.[139] Further research is required given the prolonged production times involved and the need to establish stability of the surface layer.[140] In vivo endothelialization describes an alternative approach using endothelial progenitor cells (EPCs) primarily derived from bone marrow and capable of differentiating into matured endothelial cells. These cells promote regeneration of a functional endothelium directly onto the blood-contacting surfaces of vascular devices after implantation.[141] Promising research has employed many techniques and homing factor mimetic molecules for biofunctionalization of synthetic graft materials. However, in order to be successful, further identification of highly specific EPC markers and their ligands for selectively attracting cells on artificial implants is needed.[142]

Factor XII Inhibition

Factor XII, an integral part of the contact system, is indispensable for thrombus stablization. It is an attractive target to interfere with thrombosis selectively given its pro-inflammatory and procoagulant effects with activation of the intrinsic coagulation system and kallikrein-kinin system,[143]; indeed, inherited deficiency results in protection against thromboembolism without affecting hemostasis.[144] Experimental evidence in animal models showed coating catheters inserted into the jugular vein with a factor XII inhibitor reduced thrombogenicity,[145] and the use of an antibody (3F7) provided thromboprotection equivalent to heparin without increasing bleeding in ECMO studies.[146,147] In addition to the effect on thrombosis, bradykinin production, known to increase microvascular permeability and inflammation, was abolished in a mouse model.[148] Strategies for inhibition are shown in Table 12.2.[143,149] The characteristics of each strategy vary, with antisense oligonucleotides (ASOs) having a long half-life and prolonged duration of treatment before therapeutic effect, which limit their clinical use.[150]

Future work should focus on larger animal studies with extracorporeal support before progression to human data. However, factor XII inhibitors are promising targets for new anticoagulants with an improved safety profile and clinical potential for reducing thromboinflammation.

Blood Purification Devices

The spectrum of blood purification consists of high-volume hemofiltration, hemoadsorption, plasma exchange, dialysis techniques, and hybrid systems.[151] Hemoadsorption devices, placed in series with the extracorporeal circuit, have been used to remove activated leukocytes and cytokines in an attempt to modulate the immune response.[152] The most data relating to this technique exist with its use in hemoperfusion during sepsis, which in meta-analysis, combined with other blood purification therapies, was associated with mortality reduction.[153] Blood purification devices have been compared: The

Table 12.2 STRATEGIES FOR FACTOR XII INHIBITION

STRATEGY	ACTION
Oligonucleotides (e.g., ASOs, RNA aptamers)	ASOs: bind to FXII mRNA and protein RNA aptamers: bind to FXII and FXIIa; do not interfere with active site
Monoclonal antibodies (e.g., 3F7)	Block activation or activity of factor XII
Biological inhibitors (e.g., corn trypsin inhibitor)	Bind to FXIIa or FXII
Nucleic acid–binding polymers	Inhibit polyphosphate-mediated coagulation
Low-molecular-weight molecules	Inhibit active site of factor XII

CytoSorb® (CytoSorbents Corporation, NJ, USA) device, which uses a hydrophobic resin made of polymer beads, can remove a wide range of inflammatory mediators at middle molecular weight, including cytokines. CytoSorb is inefficient for endotoxin removal, although the converse is true for Toraymyxin™ (Toray Industries, Tokyo, Japan), a device made of rolled woven polystyrene fibers with the antibiotic polymyxin B immobilized on the surface.[154] CytoSorb is licensed for use in Europe, although no recommendation is given within the surviving sepsis campaign guidelines regarding blood purification devices.[155] Small case control studies have shown benefit with CytoSorb in cardiac surgery through cytokine reduction in the perioperative period.[156–158] A randomized control trial has not shown any change in outcome in the perioperative course or reduction in the pro-inflammatory response acutely; however, there were higher IL-10 levels in those receiving the intervention, which may suggest a longer lasting anti-inflammatory effect.[159] Its use in ECMO has been studied only in case reports.[160,161] A multicenter randomized controlled trial is currently in progress to assess the reduction of pfHb and the incidence of acute kidney injury during cardiac surgery.[162] Mixed results on outcome have been shown with the use of polymyxin B in clinical trials to date.[163,164] The future should focus on whether these devices are able to address hemolysis, cytokine storm, and endotoxemia during ECMO.

Mesenchymal Stem Cells

There has been increasing interest in the use of mesenchymal stem cells (MSCs) in ARDS due to their immunomodulatory properties.[165] MSCs are isolated from tissue of mesenchymal origin, such as bone marrow, and retain the ability for multipotent differentiation.[166] They directly modulate the innate immune response during infection and inflammation in vivo, with the ability, depending on the environmental milieu, to produce pro- or anti-inflammatory effects.[167] A preclinical study in cardiac bypass demonstrated an amelioration of ischemia-reperfusion injury in those treated with MSCs[168]; however recent studies in ECMO have reported potential harms associated with intravascular MSCs mediated by a rapid decline in oxygenator function.[169,170] Further research is required to assess the role of cell therapy in this population.

CONCLUSION

- Extracorporeal membrane oxygenation is a life-saving technology in a wide range of situations.
- Circulation of blood in an extracorporeal state is an unnatural state and as such results in an inflammatory and coagulative response.
- Significant progress has been made in recent years in developing technological adaptations and clinical strategies to minimize and ameliorate the innate response to ECMO.
- Future research will bring improvements in these technologies as well as expanding our understanding of the complex effects of ECMO on the immune response during acute illness.

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REVIEW QUESTIONS

1. In response to the extracorporeal circuit, cytokines

   A. Cause vasoconstriction.
   B. IL-6 and IL-8 levels are reduced in ECMO patients.
   C. Result in anticoagulant effect.
   D. Can stimulate further cytokine release.

2. A 45-year-old has influenza-induced respiratory failure on V-V ECMO. You notice clot within the oxygenator. Which other sign may indicate thrombosis within the circuit?

   A. A fall in transmembrane pressure
   B. Improved postoxygenator pO_2
   C. Elevated d-dimer
   D. Hyperfibrinoginemia

3. Heparin-bonded circuits

   A. Eliminate the need for systemic anticoagulation
   B. Reduce complement activation
   C. Increase HIT
   D. Increase plasma protein and contact activation

4. A 34-year-old female is on V-V ECMO for *Strepococcus pneumoniae*. On day 5, the d-dimer is rising, LDH rises, and plasma fHb is greater than 1. The intervention likely to resolve this DIC picture is

A. CytoSorb
B. Heparin
C. Narrowing antibiotic cover
D. Circuit change

5. Based on the evidence, all of the following techniques have promising research into reducing the inflammatory response from the endothelial surface except

A. Mesenchymal stem cells
B. Endothelialization
C. Nitro oxide–releasing surface modifications
D. Argatroban

ANSWERS

1. D. Cytokines are a category of small proteins that are involved in cell signaling and the mediation of inflammation in innate immunity. Their release stimulates further cytokine release, a process known as cytokine storm, resulting in the dysregulated production and aggravation of organ and tissue damage.[29] Vasodilatory effects result from stimulation of cyclooxygenase 2 and prostaglandins and a procoagulant effect from increased TF-like activity.[32,33] IL-6 and IL-8 levels are increased on ECMO.[34,37–40]

2. C. A rise in transmembrane pressure and a deterioration in postoxygenator gas exchange can predict the need for a circuit change. [93] Intrinsic hematological problems (thrombocytopenia, hypofibrinogenemia, and elevated d-dimer) can occur due to thrombus in the circuit. An increase in the absence of other explaining pathology can be helpful in predicting the need for a circuit exchange.[94]

3. B. A heparin-coated surface results in less thrombogenicity through reduced or selective adhesion of plasma proteins and contact activation, in addition to reduced activation of complement and other inflammatory mediators.[113] They reduce the risk of oxygenator failure[114] and may result in reduced systemic anticoagulation.[115–117] Lower levels of systemic anticoagulation reduce side effects; however, with heparin the risk, although rare, remains of HIT. The contribution of the circuit to the development of HIT remains unclear with mixed results.[118–120]

4. D. This hematological picture is indicative of hemolysis occurring from red cell rupture and release of free hemoglobin into the plasma, resulting in tissue hypoxia and cell death.[74] Elevated levels of LDH are seen due to red cells containing large amounts.[75] The etiology is multifactorial in extracorporeal support, with mechanical shear stress applied to the red cells from pressure gradients, high blood flow, exposure to the nonendothelialized circuit, and centrifugal pumps (compared to roller pumps) playing a role.[76–78]

5. A. Mesenchymal stem cells directly modulate the innate immune response during infection and inflammation in vivo, with the ability, depending on the environmental milieu, to produce pro- or anti-inflammatory effects.[167] A preclinical study in cardiac bypass demonstrated an amelioration of ischemia-reperfusion injury in those treated with MSCs[168]; however, recent studies in ECMO have reported potential harms associated with intravascular MSCs mediated by a rapid decline in oxygenator function.

13.

HEPARIN ANTICOAGULATION FOR TRANSCATHETER AORTIC VALVE IMPLANTATION ON ECMO

Gianluca Paternoster, Marc O. Maybauer, and Filippo Sanfilippo

STEM CASE AND KEY QUESTIONS

A 34-year-old male patient was admitted to the Cardiovascular Surgery Department with acute on chronic systolic and diastolic heart failure due to biological aortic valve (AV) prosthesis degeneration and severe left ventricular (LV) dysfunction. The patient's medical history reported AV endocarditis followed by aortic valve replacement (AVR) in 2010 with all follow-ups performed at our center. Four years later, the patient developed *Enterococcus fecalis* infective endocarditis on the bioprosthetic AV; this was treated medically with a long course of antibiotics and healed without need for redo surgery.

During winter 2018, we admitted the patient through the Accident and Emergency (A&E) Department because of profound dyspnea and fever. At this time, the patient was tachycardic (115 beats/min) and tachypneic (30 breaths/min), systolic blood pressure was 85 mm Hg, oxygen saturation 85% on room air, and body temperature 37.8°C. He was initially treated with oxygen delivered via Venturi mask, one fluid challenge of 250 mL Ringer's solution, and antibiotics for possible pneumonia and sepsis; however, due to the known cardiac history, a transthoracic echocardiogram (TTE) was organized promptly and showed signs of severe LV failure, high LV filling pressure, and pulmonary edema. The prosthetic AV appeared thickened, and an advanced echocardiogram was requested. The troponin assay was negative, and there were no electrocardiographic changes suggestive for ischemia. Meanwhile, vasopressor support was started using norepinephrine up to 0.25 μg/kg/min to maintain a mean arterial pressure above 65 mm Hg; noninvasive ventilation was initiated in order to improve the cardiorespiratory function, but due to greatly increased work of breathing and progressive hypoxemia on arterial blood gas (ABG), the decision was made to intubate the patient with rapid sequence induction since the fasting time was unknown. Since the TTE was not fully satisfactory (poor acoustic windows), a transesophageal echocardiogram (TEE) was organized. The TEE showed moderate-to-severe LV chamber dilation with mildly increased wall thickness and severely reduced LV systolic function with an ejection fraction below 20%. The bioprosthetic AV appeared highly degenerated with heavy calcification, causing severe AV stenosis, with a mean pressure gradient of 55 mm Hg. The mitral valve was normal, and the right ventricular (RV) systolic function was within acceptable limits, with a tricuspid annular plane excursion (TAPSE) of 17 mm. The RV was mildly dilated with a tricuspid regurgitant jet velocity of 3 m/s. The pulmonary systolic pressure was estimated as 52 mm Hg due to a central venous pressure of 16 mm Hg.

In order to support the LV systolic function, epinephrine was initiated and increased up to 0.10 μg/kg/min. Blood cultures, procalcitonin, endotoxin, and interleukin (IL) 6 tests were performed; meanwhile, the body temperature slightly rose to 38.1°C. Despite maximal cardiovascular support and fluid resuscitation, the patient's condition further deteriorated in a short time frame of 12 hours, with hemodynamic instability persisting despite norepinephrine and epinephrine at rising dosages. The gas exchange worsened with a PaO_2-FiO_2 (fraction of inspired oxygen) ratio of 62 and positive end-expiratory pressure (PEEP) of 12 cm H_2O. Oligoanuria and metabolic and respiratory acidosis with increasing lactate of 12.2 mmol/L were observed.

A decision was made by the cardiac intensive care unit consultant, in agreement with the cardiac surgery and cardiology teams, to initiate veno-arterial (V-A) extracorporeal membrane resuscitation (ECMO) and stabilize the patient before any further treatments would be considered. V-A ECMO was implanted with right femoral vein and artery cannulation. Initial flow was 4.2 L/min with unfractionated heparin (UFH) infusion as first choice for anticoagulation. At the time of starting V-A ECMO, the patient had normal activated partial thromboplastin time (aPTT), slightly increased international normalized ratio (INR) (1.6), and normal platelets count (217.000/mm^3). There was just a mild increase in transaminases due to liver congestion.

The effect of UFH on coagulation in this patient was assessed by activated clotting time (ACT) in order to achieve a target range between 180 and 200 seconds. In the first 6 hours, we found lower ACT values than we expected and had to increase the heparin infusion repeatedly (ACT initially was 142 and gradually increased to 167 seconds); while we suspected low levels of antithrombin III (ATIII), this was not replaced until laboratory confirmation because the increased INR at baseline was believed to contribute to some degree of anticoagulation. Eventually, the laboratory confirmed ATIII activity of 47%, which fully explained the difficulty in achieving the ACT goal.

In this clinical case, we decided to keep ATIII levels above 80% in order to avoid the risk of fluctuations in anticoagulation and of using very high heparin doses. Once ATIII was replaced, the patient received an average infusion of 12–15 IU/kg/h of UFH during the whole ECMO run.

In the following 48 hours, the results of the blood cultures were negative, the patient's temperature dropped to 36.1°C without use of paracetamol, and the ABG results showed reduction of the metabolic acidosis with a normal $PaCO_2$. Urine output persisted low (around 0.3 mL/kg/h on high-dose furosemide infusion), and creatinine was slightly elevated (1.71 mg/dL) with normal potassium (4.4–4.9 mEq/L) levels. At that time, epinephrine could gradually be reduced and stopped, and the norepinephrine infusion could be reduced to 0.12 μg/kg/min. The decision was made to wait before institution of renal replacement therapy since the lactate was gradually normalizing. After normalization of ATIII levels, the heparin doses could gradually be reduced, and ACT was maintained stably in the target range.

On day 3 postadmission, the case was discussed in a multidisciplinary cardiac meeting in order to decide the best strategy of AV replacement for this gentleman, considering on one side the risks of redo surgery, in particular of bleeding while on V-A ECMO support and systemic anticoagulation, and on the other the negative results from a sepsis perspective (negative blood cultures, no appearance of endocarditis, and reducing levels of inflammatory markers). After the negative results of another set of cultures, the decision was made to attempt a high-risk transcatheter aortic valve implantation (TAVI) with a valve-in-valve procedure while on V-A ECMO with the surgical team in standby in case of complications. No changes in heparin doses were requested to perform the intervention. The procedure was uneventful, and soon after TAVI, the patient was weaned from norepinephrine.

A TEE performed 1 day post-TAVI (day 6 from admission) showed an already improved LV function with 35% ejection fraction while on V-A ECMO. On sedation hold, the patient was contactable and had a Glasgow Coma Scale score of 11 without neurological deficit. Gradual weaning from the ventilator allowed maintaining the patient on pressure support ventilation and reducing PEEP. Lactate levels were normalized, renal function gradually improved, and the patient became polyuric. About 4 days after TAVI implantation (day 10 from admission), the patient was successfully weaned from V-A ECMO with almost normalized LV ejection fraction (46%) and extubated 48 hours later. He was finally discharged home 17 days later with improved and acceptable LV function (ejection fraction 55%).

WHY WAS V-A ECMO USED IN THIS PATIENT?

Extracorporeal membrane oxygenation is a procedure providing circulatory and/or respiratory support. It can be used for veno-venous (V-V) circulation (V-V ECMO) to provide adequate oxygenation and carbon dioxide removal in isolated refractory respiratory failure of various etiologies or in a V-A ECMO configuration when support is required for cardiovascular function. In this case, V-A ECMO was used in order to manage cardiogenic shock in a young patient admitted with cardiac and respiratory failure. Cardiac failure was due to the degenerated AV bioprosthesis, with heavy calcifications determining a severe aortic stenosis; in turn, the patient developed respiratory failure due to high LV filling pressures and subsequent pulmonary edema, though it was not possible to exclude the concomitant presence of pneumonia due to fever during the winter period.

Both acute and end-stage cardiac failure are indications for V-A ECMO, which can be performed as a bridge to recovery, long-term assistance by other means of mechanical circulatory support such as left ventricular assist devices (LVADs), or transplantation. In this case, ECMO was implanted for cardiorespiratory support for acute cardiogenic shock due to severe increase in afterload resulting from severe AV stenosis determining LV decompensation and failure, with ejection fraction falling to extremely low values.

WHAT WAS THE RATIONALE FOR V-A ECMO IN THIS PATIENT?

Veno-arterial ECMO was instituted because the clinical condition deteriorated rapidly despite maximal cardiorespiratory support and signs of worsening systemic decompensation, with rising doses of vasoactive drugs, worsening renal function, mildly elevated transaminase and INR, severe respiratory failure, and a PaO_2/FiO_2 ratio of 62. Furthermore, considering the fixed increase in afterload due to the severe AV stenosis, LV conditions were not likely to improve by any pharmacological means but rather to deteriorate. V-A ECMO was useful to avoid further clinical deterioration and the detrimental effects of high-dose vasopressors on microcirculation and to buy time to discuss the best intervention for this patient. Indeed, without V-A ECMO institution, the most likely option would have been to bring the unstable patient to the operating room for an emergency redo AVR with a consequently high morbidity and mortality risk. After having bought time, ensured stability for the patient, and confirmation of no infective endocarditis, the multidisciplinary team meeting decided to perform a TAVI procedure in order to restore a "physiological" gradient through the AV and improve cardiac performance.[1]

WHY USE HEPARIN FOR V-A ECMO?

Several drugs are commercially available for anticoagulation and could theoretically be used during anticoagulation with ECMO (Table 13.1). Importantly, now there is availability of heparin-bonded ECMO circuits that require lower levels of anticoagulation than cardiopulmonary bypass (CPB). Such circuits are adopted by most centers.[2] Nonetheless, anticoagulation is still required for most ECMO cases, and heparin is the standard anticoagulation strategy for extracorporeal support, in particular for ECMO and CPB, while dialysis circuits are now also using alternative strategies of anticoagulation, such as the use of citrate calcium. In absence of contraindications, heparin is by far the most used strategy for anticoagulation for its easy titration and monitoring, low costs, overall familiarity

Table 13.1 DRUGS AVAILABLE FOR ANTICOAGULATION AND ADVANTAGES/DISADVANTAGES OF USE DURING EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO).

DRUG	ADVANTAGES	DISADVANTAGES
UFH	Familiarity with use Easy to antagonize (protamine)	Not linear anticoagulation effect Dependency from AT III levels Risk of HIT induction
LMWHs	Easy to administer Very Low risk of HIT	Accumulation during acute kidney injury Difficult to monitor No antagonist available Half-life too long for ECMO
DTIs	Independent from AT III levels Good dose response No HIT induction Mainly renal clearance (Bivalirudin) Mainly Hepatic Clearance (Argatroban)	Ceiling effect in aPTT (Bivalirudin) May interfere on INR (Argatroban) No antagonist available
Antiplatelet drug	Platelet consumption Inhibit coagulation at starting point	No antagonist available No anticoagulation provided Not enough scientific evidence Half-life too long for ECMO

ACT = Activated Clotting Time; aPTT = activated Partial Thromboplastin Time; AT III = Antithrombin III; DTIs = direct throbin inhibitors; HIT = heparing induced thrombocytopenia: LMWH = low molecular weigth heparins; INR = International Normalized Ratio; UHF = unfractionated heparin.

with its use, and the availability of an antidote (protamine, although it is very rarely used during ECMO runs). When starting ECMO, usually priming of the circuit with heparin is not necessary.

From a molecular perspective, heparin is a heterogeneous mixture of branched glycosaminoglycans in saccharide chains. UFH is a mixture of different molecular weight heparins (ranging from 3 to 30 kDa, although average molecular weight of most commercial preparations of UFH is between 12 and 15 kDa). Low-molecular-weight heparins and fondaparinux have been developed as alternative anticoagulants, but their use is not advantageous for ECMO and CPB, and therefore these are not discussed in this chapter.

Heparin is an indirect anticoagulant since it requires the presence of the enzyme inhibitor ATIII for its primary anticoagulant action. The binding of heparin with ATIII causes a conformational change in the latter, resulting in its activation through an increase in the flexibility of the reactive site loop. From a molecular perspective, UFH binds ATIII through a specific pentasaccharide sulfation sequence, and it is important to highlight that anticoagulation by UFH is influenced by the chain length of the heparin molecules. Once the UFH and ATIII have bound, such a molecular complex has a 1000 times higher inhibitory effect as compared with ATIII alone. Thus, in the presence of heparin the "activated" ATIII inhibits thrombin, factor Xa, and other proteases, such as factors IXa, XIa, and XIIa with higher activity.[3]

As previously reported, heparin molecules are made up of different lengths of saccharide chains, making it difficult to predict the degree of complex formation to ATIII and the inhibition level reached. Moreover, heparin's activity against proteases is variable. In particular, thrombin inhibition is size dependent and requires at least 18 saccharide units, while activity against factor Xa via ATIII requires only the pentasaccharide-binding site. This heterogeneity should be considered when discussing the choice of monitoring for anticoagulation.

HOW IS ANTICOAGULATION MONITORED?

Considering the variability in the effects of UFH, frequent adjustments of heparin doses are required throughout the treatment period, and regular monitoring of the anticoagulation effects is necessary. The two most commonly used methods of monitoring anticoagulation are aPTT and ACT, while others are less common (Table 13.2). Both aPTT and ACT are measured by the time between ex vivo contact activation of the coagulation cascade and the formation of fibrin/thrombin "gel" in the tube.

The monitoring of aPTT in order to check the effects of heparin is performed in the laboratory, which measures the time plasma takes to form a clot. The effect of UFH on coagulation assessed by aPTT reflects the classical interpretation of the "intrinsic" pathway starting with factor XII. For instance, a prolongation of aPTT could be due to an acquired

Table 13.2 COAGULATION TEST AVAILABLE FOR MONITORING ANTICOAGULATION DURING EXTRACORPOREAL MEMBRANE OXYGENATION.

COAGULATION TEST	ADVANTAGES	DISADVANTGES
ACT	Bedside Easy monitoring Point of care Whole blood test	Different devices and ranges Less accurate for ECMO (lower anticoagulation than during cardiac surgery)
aPTT	Consolidated use, accurate Easy interpretation	Time consuming Not available as point of care Inter-laboratory variance
Anti-Xa assay	Very sensitive to UFH effects	Time consuming Not available as point of care Bilirubin and free haemoglobin interference
ROTEM/TEG	Point of care	Time consuming Need for training

ACT = Clotting time; aPTT = activated partial thromboplastin time; ROTEM Rotational Thromboelastometry; UHF = unfractionated heparin;. TEG = Thromboelastography.

or inherited factor deficiency in this chain. But in some cases, it could also be due to other reasons, such as lupus anticoagulant or drug effects.

There are some disadvantages when using aPTT for monitoring anticoagulation on ECMO. The most important seems to be the variability between different laboratories, which is due to different commercially available reagents and the use of different devices across the institutions.[4] It is therefore difficult to identify a "normal range" for aPTT, but from a more practical perspective, one can assume that a value between 28 and 35 seconds is normal in most cases. A normalization of the value using a ratio has been proposed for the monitoring of aPTT in the attempt to reflect therapeutic anti–factor Xa heparin levels. Importantly, the aPTT should not be confused with prothrombin time (PT), which measures blood clotting time through a different pathway of the coagulation cascade, and it is not appropriate to monitor heparin activity. Nonetheless, in cases of liver failure or other reasons for systemic anticoagulation demonstrated by increased PT, clinicians should take this parameter into account when deciding the target level of anticoagulation with heparin during ECMO. In our case, we did not take INR into account, but on the other side, while we were not reaching ACT range, we were comforted by the presence of a slightly increased INR that may have counterbalanced the lower ACT values.

Alternatively, the ACT is a point-of-care coagulation test designed to monitor UFH therapy in clinical situations in which intensive anticoagulation is required. ACT has the advantage of being rapidly performed at bedside, although it has less precision than aPTT. The ACT was designed as a point-of-care test of high-dose anticoagulation during CBP, but later several modifications have been made to improve its accuracy also during monitoring of anticoagulation with lower UFH concentrations. The ACT is now a well-established "bedside" monitoring test for therapeutic anticoagulation. As compared with the aPTT, ACT relies on contact activation, and normal values are mostly reported in the range between 70 and 120 seconds, but sometimes it has also been reported as a ratio (measured value/reference value). Moreover, ACT results can be affected by several other factors, such as anemia, hypofibrinogenemia, thrombocytopenia, and other coagulation factor deficiencies, that contribute to the patient's overall anticoagulation state. Hypothermia and hemodilution can also affect an ACT for this reason, and our targets in this case were to maintain hemoglobin above 10 g/dL and core temperature not lower than 36°C, while avoiding hyperthermia. In contrast, aPTT is not influenced by platelet count and hematocrit. This condition might explain the fact that aPTT better correlates to heparin concentration during ECMO. As compared to aPTT, ACT remains less sensitive to low UFH dosages, which are more frequently used in ECMO settings because the lower levels of anticoagulation required as compared with CPB and because of the development of heparin-bonded circuits and cannulae. While aPTT can monitor UFH effects in both prophylactic and therapeutic ranges, ACT cannot be used to monitor prophylactic anticoagulation.[5]

It should be noted that anticoagulation level differs between V-V and V-A ECMO, the latter requiring a higher degree of clot inhibition. Indeed, it is usually accepted to run V-V ECMO with a target aPTT of 40–50 seconds, while a range of 50–60 seconds is used in most cases of V-A ECMO. Similarly, an ACT of 130–170 seconds and 160–200 seconds could be reasonable targets for V-V and V-A ECMO, respectively. However, these ranges are very flexible according to clinical conditions (i.e., evidence of bleeding or thrombosis); past medical history (i.e., history of thrombosis, presence of mechanical valves); and other coagulation derangements, such as increased INR and low platelets, to name a few. Therefore, there is no universally accepted range for anticoagulation on ECMO, and we would like to stress the importance of considering the underlying comorbidities, the degree of organ dysfunction, the presence of other coagulation abnormalities on laboratory tests, and of course the clinical conditions (evidence or suspicion of bleeding or clotting). Therefore, while the above numbers are a good "start with" strategy in most cases, variation of the target anticoagulation should be discussed case by case.

Less frequently adopted monitoring approaches for anticoagulation during ECMO are the anti-Xa assay test and viscoelastic tests. The first test aims to describe the end effects of UFH on factor Xa, and when performing the anti-Xa assay test, a known amount of factor Xa and ATIII are added to the sample. For such a simple reason, it is considered probably the best monitoring test to study the effects of UFH in patients undergoing ECMO support.[6] Compared with aPTT, the anti-Xa assay has a higher degree of correlation with heparin dose and variation of anticoagulation. Although not an extremely common clinical condition during ECMO, it should be noted that the anti-Xa assay test can be affected by hyperbilirubinemia, hemolysis, and high lipid levels. One of the main issues for this test is represented by the costs and the limited availability of anti-Xa assay tests in the laboratories.[7] Another option to monitor anticoagulation during ECMO is the use of viscoelastic tests.[8] Because of their ability to reflect all aspects of hemostasis, also taking into account clotting derangements due to ongoing critical illness (i.e., patients developing liver failure), viscoelastic tests such as thromboelastography (TEG) or tromboelastometry (ROTEM) have been used for patients on therapeutic anticoagulation on extracorporeal support. These tests are more informative than standard use of ACT or aPTT. While the use of TEG/ROTEM is recommended by the Extracorporeal Life Support Organization guidelines, these tests are more expensive, and they require training for the staff performing and interpreting results.

WHAT IS THE ROLE OF ANTITHROMBIN III?

An important as well as controversial point in the management of this patient was the finding of low ATIII levels. ATIII is a vitamin K–independent glycoprotein produced by the liver, and it is a natural inhibitor of all serine proteases; the majority of its anticoagulant effect results from inhibition of thrombin (factor IIa) and factor Xa. ATIII represents an important endogenous anticoagulant protein. and its action is potentiated by a factor of 1000 by the formation of complexes with heparin.[3]

In our case, we found low ACT values despite UFH anticoagulation at increasing dosages, and the gradual increase of ACT was lower than expected. We detected low ATIII activity levels and decided to replace ATIII in order to achieve stable ACT levels. On the other side, we did not increase UFH too rapidly since some degree of anticoagulation was present due to the mildly deranged INR. ATIII concentrates are commercially available, and several centers routinely administer ATIII when finding low ACT values despite relatively high heparin doses. One should bear in mind that ATIII costs are far higher than heparin vials, and for this reason not all centers practice routine ATIII replacement. The optimal strategy for ATIII replacement in patients receiving ECMO remains unknown.[9]

WHY PERFORM TRANSCATHETER AORTIC VALVE IMPLANTATION?

No medical therapy is available for treating AV stenosis. The primary treatment for severe AV stenosis is surgical AV replacement since conservative medical treatment has shown significantly worse outcomes than surgical replacement.[10] Indeed, survival rate at 3 years in patients with symptomatic AV stenosis undergoing surgery is 87%, while in those not treated surgically, it is 21%; the operative mortality rate in the surgical treatment of uncomplicated aortic stenosis is far less than 5%, but it is estimated that at least 30% to 40% of patients with severe aortic stenosis are not treated.[11,12] There are several reasons explaining the finding of underuse of surgical treatment of severe AV stenosis. Patients are often thought to be too old or frail, or they have severe LV dysfunction and/or comorbidities that affect the surgical expectations. Moreover, patients are not referred for surgery because they can be misdiagnosed (severity of the AV stenosis underestimated, especially in patients generating a relatively low gradient through the AV stenosis due to coexisting LV dysfunction) or are considered "symptomatic" for other reasons. In addition, patients can perceive temporary improvement in symptoms after medical therapy.[13] Nonetheless, the substitution of AV with a heart operation on CPB may not be tolerated by fragile patients, or anyway they may be exposed to high risk of short-term morbidity and mortality. Balloon AV valvuloplasty is not an effective alternative to surgical AV replacement because it provides symptomatic benefits only for a very limited time frame with minimal physiologic impact. In the 2017 European Society of Cardiology guidelines, balloon AV valvuloplasty has no true indication, but may be considered as a bridge to surgery or TAVI or diagnostically.[14] Similarly, the American Heart Association/American College of Cardiology guidance from 2017 suggested that percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or transcatheter AVR for symptomatic patients with severe aortic stenosis (class IIb; level of evidence: C).[15]

Patients deemed to have unacceptable surgical risks have the option of a valve substitution with the TAVI approach, which can be performed via transfemoral (most commonly); transapical (rare, used in patients with highly calcified aorta and femoral arteries); or transaortic (rare, small sternal incision and insertion via ascending aorta) routes. The results of TAVI in high-risk patients have been very promising,[16] and gradually patients with a lower baseline risk for surgery have been studied for TAVI. The overall results have been so promising that indications for TAVI have been gradually extended to intermediate and low-risk patients.[17–19]. The development of transcatheter devices has progressed rapidly during the last decade, and this approach continuously challenges surgical replacement as preferred (or only) option for treating severe symptomatic AV stenosis. The debate is still ongoing since also a correlation between outcome and procedural volume has been noted.[20] Recently, the Food and Drug Administration has expanded the indication for TAVI to patients at low risk for death or major complications associated with open-heart surgery.[21] Importantly, the presence of an already in situ bioprosthetic AV is not a contraindication for TAVI that can be performed with a "valve-in-valve" procedure as an alternative to reoperative surgery,[22] and it is currently approved for high-risk and inoperable patients, with favorable survival, sustained improved hemodynamic status, and excellent functional and quality-of-life outcomes. Challenges to the technique include higher rates of prosthesis-patient mismatch and coronary obstruction, compared to TAVI in native valves.

In the case described, the decision to perform a valve-in-valve TAVI was made on grounds of very sick patient conditions and extracorporeal support with expected high risk of perioperative complications, such as bleeding due to redo surgery on V-A ECMO and anticoagulation, low cardiac output syndrome, severe hypoxemia pre-ECMO institution, and worsening renal and hepatic function.

DISCUSSION

Despite recent significant advances in ECMO circuit technology, we are still far from having a satisfactory circuit design where no anticoagulation is needed, and it is likely that minor degrees of anticoagulation will still be administered for a while in patients receiving ECMO support. Blood proteins accumulate on the circuit membranes, leading to the activation of the coagulation cascade with platelet and leukocyte aggregation to the membrane surfaces. Once enzymes are activated, factor XIIa, complement components, kinin/kallikrein, and fibrinogen are cleaved, triggering the coagulation cascade and eventually leading to thrombus formation. Currently, heparin-coated membranes are utilized in many ECMO oxygenators, but this advance does not fully eliminate the risk of clot formation.

The aim of anticoagulation on ECMO is to prevent thrombosis while minimizing bleeding risks; thus, accurate anticoagulation management is indispensable. Various strategies of anticoagulation are available, but, as discussed previously, UFH administration remains the main anticoagulant used for ECMO (and CPB). A large survey confirmed that all responding centers used UFH as an anticoagulant, and that only 8% of respondents indicated use of alternative anticoagulation medications in the 6 months prior to the survey. Interestingly, the largely preferred method of anticoagulation

monitoring was the serial measurement of ACT, while ATIII levels were investigated by 82% of centers.[2]

During ECMO support, platelets are activated on contact with extracorporeal circuit surfaces and with high shear stress and turbulence within the circuit. Fibrinogen adsorption also contributes to platelet activation, and it is largely expected that the platelet count will drop within the first few hours and days of an ECMO run. Effects on the coagulation system include contact activation of the "intrinsic" pathway via exposure of circulating factor XII and prekallikrein to nonbiological surfaces, which triggers fibrinolysis and bradykinin release downstream. Exposure of negatively charged collagen in damaged endothelium also triggers activation of high-molecular-weight kininogen, prekallikrein, and factor XII. The so-called extrinsic coagulation pathway is activated via the exposure of subendothelia to circulating factor VIIa, which is the major pathway responsible for thrombosis and disseminated intravascular coagulation.

To prevent thrombosis, events at both corporeal (patient) and extracorporeal (ECMO circuit) levels and adequate anticoagulation strategies are indispensable. At present, UFH remains the main anticoagulant used for ECMO because it is inexpensive, it is dose dependent (although with some variability), has a rapid onset and short half-life, there is familiarity of use, and it is easily neutralized with protamine. However, monitoring of anticoagulation levels on heparin is not easy, mainly because UFH has unpredictable clinical effects. Always keep in mind that heparin-induced thrombocytopenia (HIT), a life-threating situation, may occur in up to 5% of patients.

The primary anticoagulant function of UFH is based on the ability of heparin to potentiate by a factor of 1000 of the effect of ATIII as a result of the formation of UFH/ATIII complex, resulting in the inhibition of free thrombin and factors XIa, Xa, IXa, and VIIa. UFH also has suboptimal pharmacokinetic properties in that it binds to plasma proteins, including acute-phase reactants, leading to heparin resistance, especially in acutely ill patients. The UFH/ATIII complex acts as a direct inhibitor of factor IIa (thrombin) and factor Xa, but the precise degree of inhibition of these factors and in particular of thrombin (its inhibition is size dependent) and thus anticoagulation depends on the heparin size molecules, which are present as a mixture in the vials. In brief, the larger the heparin molecule is, the stronger the interaction of the complex will be, in particular with thrombin. Hereditary, congenital, or acquired ATIII deficiency is associated with inadequate endogenous anticoagulation that predisposes patients to an increased risk of thrombosis in times of clinical physiological stress (e.g., surgery, trauma, or pregnancy).[23,24] It is also expected that ATIII levels drop in the first few days after ECMO initiation, and there is no univocal approach to replace ATIII to achieve normal levels. The main advantage of a strategy of replacing ATIII to normal values might be to achieve less heparin administration, but considering the costs of ATIII (much higher than heparin), such advantage may not be clinically meaningful. Moreover "heparin resistance," which might be corrected by ATIII therapy, is not entirely attributable to low ATIII levels, but may be conditioned by platelet counts (ineffective inhibition of platelet-bound thrombin), previous heparin use, age above 65, and low hemoglobin levels.[25]

The causes of bleeding are multifactorial in ECMO patients, as demonstrated in the various pathways that can be affected. Bleeding is a common and serious complication of ECMO and was described in up to 60%–70% of adults or children on ECMO. It includes surgical site bleeding, gastrointestinal bleeding, hemothorax, hemopericardium, and intracranial hemorrhage. The efficacy of an individual hemostatic agent may be difficult to evaluate in isolation in a research or clinical setting. We expect more developments of evidenced-based bleeding bundles/protocols tailored to the capabilities of each ECMO center.

Patients on ECMO represent a heterogeneous group from neonates with immature coagulation system compared to adults. Bleeding and thrombotic complications are the major contributors to morbidity and mortality during ECMO. However, all these conditions may impact the risk of bleeding and thrombosis. Although alternatives to UFH have been assessed, data are limited, and UFH remains the gold standard. Unfortunately, the optimal anticoagulation strategy with intravenous UFH during ECMO support remains a subject of intense debate. All methods for monitoring UFH anticoagulation (ACT, aPTT, antifactor X levels, viscoelastic tests) have their advantages and disadvantages. Although it has been done for decades, guiding UFH anticoagulation only on the basis of such tests, and in particular by ACT, has been declared an "unsafe practice" by some authors due to the poor correlation of ACT with UFH dosage.[26] The lack of evidence provided by some studies is the key limitation for defining the optimal anticoagulation strategy in ECMO patients. A meta-analysis of observational studies in V-A ECMO patients concluded that optimal targets and strategies for anticoagulation in V-A ECMO remain unclear, and the incidence of bleeding and thrombotic complications was comparable between different anticoagulation monitoring methods used, although UFH anticoagulation based on ACT seems to be associated with fewer major bleeding complications. On the other side, lower ACT targets increase the risk of thrombotic complications, while monitoring with aPTT is associated with more major bleeding complications but fewer thrombotic events.[27]

One of the most feared complications associated with UFH is the development of HIT, which consists of gradual development of thrombocytopenia and thrombosis due to abnormal formation of blood clots. HIT is a platelet-activating immune response triggered by the interaction of heparin with platelet protein (called platelet factor 4). Venous thrombotic complications and in the worst case the development of pulmonary embolism is more common than arterial thrombosis. When thrombosis is identified, the condition is called heparin-induced thrombocytopenia and thrombosis. Usually, HIT is associated with a rise in fibrinogen. The integration of the degree of thrombocytopenia, timing of platelet count fall, presence of thrombosis, and absence of other causes of thrombocytopenia is usually integrated in a scoring system (the 4 T's) for the evaluation of the risk of HIT. The

diagnosis is clinical and can be confirmed by functional assay (high specificity, low sensitivity) or immunoassay (low specificity, high sensitivity). The treatment of HIT requires stopping heparin treatment, protecting from thrombosis with the choice of an alternative agent that will not reduce the platelet count any further. Several alternatives are available for this purpose, such as bivalirudin,[28] which are discussed in detail in another chapter of this book.

CONCLUSION

- Extracorporeal membrane oxygenation is a highly invasive procedure that requires expertise with anticoagulation.
- The risk profile of ECMO anticoagulation management includes thrombosis and bleeding.
- Unfractionated heparin is the mainstay anticoagulant due to familiarity with its use, low cost, and availability of an antidote.
- Development of heparin-bonded circuits have decreased the level of anticoagulation required.
- Cases of prolonged ECMO runs without anticoagulation are described in the literature.
- Heparin carries the risk of drug-induced thrombocytopenia.
- In HIT, anticoagulation alternatives such as bivalirudin or argatroban should be instituted.

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REVIEW QUESTIONS

1. What are the correct characteristics of UFH when used in ECMO patients?

   A. Quick onset, fast offset, acceptable anticoagulation monitoring with point-of-care tests

B. Quick onset, slow offset, suboptimal anticoagulation monitoring with point-of-care tests
C. Quick onset, slow offset, acceptable anticoagulation monitoring with point-of-care tests
D. Quick onset, fast offset, suboptimal anticoagulation monitoring with point-of-care tests

2. Is INR monitoring relevant for anticoagulation during ECMO and heparin anticoagulation?

A. It is relevant because it describes the hepatic function that may worsen because of heparin.
B. It is relevant because it may contribute to anticoagulation derangement and risk of bleeding.
C. It is not relevant when heparin anticoagulation is monitored with aPTT.
D. It is partially relevant when heparin anticoagulation is monitored with ACT.

3. Regarding the anti-Xa level monitoring during ECMO support and anticoagulation with UFH:

A. It is a specific measure of the ability of UFH to inhibit factor Xa.
B. Elevated levels of plasma-free hemoglobin and bilirubin may interfere with its findings.
C. It is not more expensive than using aPTT, and it is available in most laboratories.
D. Although expensive, this point-of-care test makes easier and more accurate anticoagulation monitoring.

4. What are the characteristics of ACT point-of-care monitoring for anticoagulation in ECMO?

A. Cheap, whole-blood test
B. Slightly expensive, whole-blood test
C. Slightly expensive, serum blood test
D. Cheap, serum blood test

5. In patients with HIT:

A. Platelets are functionally inhibited and bleeding may occur.
B. It can occur in case of prolonged exposure to high doses of heparin.
C. Severe thrombocytopenia occurs around 1 week after exposure to heparin.
D. Moderate thrombocytopenia occurs soon after exposure to heparin.

6. Bleeding and severe complications of ECMO are described in

A. Usually less than 30% of cases
B. Up to 60%–70% of cases
C. Around 15% of cases when monitoring with aPTT
D. Around 20% of cases when monitoring with ACT

7. What is the main disadvantage of using UFH in ECMO patients?

A. Dependency from ATIII levels
B. Variability in the effects on factors III and XI
C. Need to monitor the levels of anticoagulation with viscoelastic tests
D. Poor information given by the aPTT

8. Heparin-induced thrombocytopenia

A. Is associated mainly with bleeding.
B. Is associated mainly with venous thromboembolism.
C. Is associated mainly with arterial thromboembolism.
D. Has similar incidence with bleeding and thrombotic complications.

ANSWERS

1—a
2—b
3—b
4—a
5—d
6—b
7—a
8—b

14.

BIVALIRUDIN FOR ALTERNATIVE ANTICOAGULATION IN HEPARIN-INDUCED THROMBOCYTOPENIA DURING ECMO

Cristina Santonocito, Filippo Sanfilippo, and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 40-year-old patient with known history of diabetes and hypertension but no other comorbidities was admitted to the Emergency Department with chest and back pain. The diagnosis of a type A aortic dissection with extension limited to the descending thoracic aorta was made, and the patient underwent surgery. He was admitted to the operating room in cardiogenic shock but neurologically intact. The dissection flap caused obstruction of the left coronary artery ostium, but only mild aortic valve (AV) regurgitation. An aortic graft with reimplantation of the coronary ostia was performed as an AV-sparring procedure, but the weaning from cardiopulmonary bypass (CPB) was difficult due to postcardiotomy biventricular failure, not responding to milrinone and norepinephrine infusion. Initially, an intra-aortic balloon pump (IABP) was positioned through the left femoral artery, but the situation rapidly deteriorated and required escalation to veno-arterial extracorporeal membrane oxygenation (V-A ECMO) using percutaneous peripheral cannulation through the right femoral artery and left femoral vein in order to close the patient's chest. The patient was brought to the intensive care unit (ICU) while on V-A ECMO, IABP, and a norepinephrine infusion at 0.22 μg/kg/min; at that time milrinone was already discontinued. Anticoagulation with unfractionated heparin (UFH) was initiated a few hours later since there were no clinical signs of bleeding, and the chest drains output was acceptable. Considering the postcardiotomy status, levels of activated partial thromboplastin time (aPTT) were initially aimed at 30–40 seconds and then escalated to 40–50 seconds to ensure no bleeding complications. Within hours, it could be escalated and kept between 50 and 60 seconds. The patient remained intubated and sedated. Renal, hepatic, and respiratory conditions improved over the following days, but the transesophageal echocardiogram showed persisting left ventricular (LV) failure, while the right ventricle (RV) fully recovered. No acute ischemic changes were seen on electrocardiogram, and the angiogram confirmed successful reimplantation of the coronary arteries into the graft.

Clinical conditions were stable throughout the V-A ECMO run with stable dosage of UFH around 13–16 IU/kg/h; only occasional transfusions of red blood cells were made (3 units in total), and no signs of bleeding or thrombosis were noted. However, after 1 week the patient gradually developed thrombocytopenia with a nadir of 38,000/mm^3 and a decrease of greater than 200% (platelets on admission 283,000/mm^3). Although V-A ECMO and to a minor extent the IABP could contribute to thrombocytopenia, the magnitude of platelet decrease and their nadir were greater than usually observed under these circumstances. There were only suspected but unproven signs of thrombosis at the skin level, but as no other causes were identified for the drop in platelet count, the suspicion of heparin-induced thrombocytopenia (HIT) was intermediate-high (6 to 7 points on the 4 T score (Thrombocytopenia degree, Timing of platelet count fall, Thrombosis or other sequelae, other causes of Thrombocytopenia; Table 14.1).

The immunoassay (high sensibility, though lower specificity) was not available at that time, and functional assay was sent to the laboratory with a negative. Nonetheless, the low sensibility of this test and the high clinical suspicion suggested HIT as the possible cause. A sample for immunoassay was collected and sent to the closest laboratory. Meanwhile, a collegial meeting between hematologist, ICU physicians, and cardiac surgeons resulted in the decision to immediately switch the anticoagulation strategy rather than waiting for the results of the immunoassay.

Ultrafractionated heparin was stopped and bivalirudin was introduced for anticoagulation on V-A ECMO. At that time, the aPTT was 58 seconds, and it was decided to start bivalirudin without a loading dose after stopping UFH. Bivalirudin continuous infusion was commenced at 0.5 mg/kg/h, maintaining the same aPTT target. A couple of days later, the results of the immunoassay returned positive for HIT, confirming the clinical suspicion supported by the results of the 4 T score.

On postoperative day (POD) 14, another meeting between ICU physicians, cardiologists, and cardiac surgeons took place. The LV systolic function was still very poor and showed no signs of recovery. When reducing V-A ECMO support, LV contractility remained poor both visually (eyeballing) and as estimated with conventional parameters and strain echocardiography; on the other hand, the RV function

Table 14.1 THE 4TS SCORING SYSTEM FOR HEPARIN-INDUCED THROMBOCYTOPENIA. THE 4TS SCORE IS THE SUM OF THE VALUES FOR EACH OF THE 4 CATEGORIES. SCORES OF 1–3, 4–5, AND 6–8 ARE CONSIDERED TO CORRESPOND TO A LOW, INTERMEDIATE, AND HIGH PROBABILITY OF HIT, RESPECTIVELY

4TS CATEGORY	2 POINTS	1 POINT	0 POINT
Thrombocytopenia	Platelet count drop over 50% and nadir ≥ 20.000/mm^3	Platelet count drop 30%–50% or nadir 10.000–19.000/mm^3	Platelet count drop <30% or nadir <10/mm^3
Timing of platelet count fall	Clear onset days 5–10 or platelet fall ≤1 day (prior heparin exposure within 30 days)	Consistent with days 5–10 fall, but not clear (i.e., missing platelet counts); onset after day 10; fall ≤1 day if prior heparin exposure 30–100 days ago)	Platelet count fall ≤4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction post-intravenous UFH bolus	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

UFH, unfractionated heparin.

was very good. Therefore, the decision was made to plan for a left ventricular assist device (LVAD) as bridge to transplantation. The patient underwent LVAD implantation 2 days later, and during the procedure, an additional bolus of 0.25 mg/kg bivalirudin was given. At that time, the platelet count rose to 67,000/mm^3 without transfusion. Although technically challenging considering the presence of the recently positioned aortic graft, the LVAD operation with V-A ECMO and IABP explantation proceeded without complications, and the patient returned to the ICU. He was extubated the day after and discharged to the cardiac surgery ward on POD 5 post-LVAD. The patient was instructed to avoid heparin for a long period and to seek medical advice if heparin was needed for any reason. The patient received a heart transplant 14 months later. During this operation, as a precaution, systemic anticoagulation for CPB was achieved with bivalirudin.

WHAT IS HIT?

Heparin-induced thrombocytopenia is a syndrome developing after exposure to heparin, and typically it is characterized by declining platelet counts about 5–10 days after heparin exposure in isolation (isolated HIT) or concurrently with thrombotic complications (heparin-induced thrombocytopenia and thrombosis, HITT).[1,2] An overall incidence of 2.6% of immune-mediated HIT in patients treated with UFH was found by a meta-analysis,[3] but its incidence in patients exposed to longer periods of anticoagulation (e.g., ECMO and ventricular assist devices) could be higher.[4,5] Moreover, thrombocytopenia is very common in ECMO patients, and differentiating between HIT and other causes such as platelet activation, hemodilution, and losses due to bleeding can be challenging, representing a clinical dilemma.

Thromboembolic complications of HIT can include pulmonary embolism, ischemic limb necrosis necessitating limb amputation, acute myocardial infarction, and stroke.[6] In general, arterial thromboembolism (ischemic cerebrovascular accident, digital ischemia, upper limb ischemia, axillary artery thrombosis, femoral artery thrombosis) is less common than venous thromboembolism (deep vein thrombosis, upper limb thrombosis, femoral vein thrombosis, inferior vena cava thrombosis, pulmonary embolism). Other sites of thrombosis may be the extracorporeal circuit and oxygenator and at the level of prosthetic valves in cardiac surgical patients.

As demonstrated by Choi et al. in their systematic review and meta-analysis of HIT in extracorporeal life support (ECLS) circuits, patients who develop HIT on V-A ECMO are more likely to experience more severe thrombocytopenia and arterial thromboembolism than those on veno-venous (V-V) ECMO who, at the opposite, experience mainly bleeding complications.[7] As most, if not all, patients on ECLS are exposed to UFH all over the world, it is imperative to know the pathophysiology and the clinical manifestations of HIT since its incidence is not negligible, and the HIT-related complications expose many patients to the risks of significant clinical complications.

Thrombocytopenia during ECLS is the major clinical sign triggering suspicion of HIT, though diagnosis of HIT in patients on ECLS is confounded by issues with the ECLS circuit itself and the variability in protocols for management of anticoagulation and transfusions.[8] Regarding thrombocytopenia and suspicion of HIT, the main factors that should be taken into account include the magnitude and the timing of platelet count drop,[9] all together with the presence of a thrombotic event[10] and the probability of other conditions that could be responsible for HIT. These factors are estimated by the 4 T score (Table 14.1). Importantly, in order to quantify the magnitude of decrease in platelets, the prenadir platelet count is defined as the highest measured platelet count at any time between initiation of ECLS and onset of suspected HIT.

WHAT ARE THE CRITERIA FOR A HIT DIAGNOSIS?

The diagnosis of HIT remains clinical, though it can be supported by confirmatory laboratory testing. The criteria for diagnosis of HIT include

- normal platelet count before starting heparin;

- thrombocytopenia, defined as a drop in platelet count by at least 30%, with a value less than 100×10^9/L or a drop of more than 50% from the patient's baseline platelet count;
- onset of thrombocytopenia typically 5–10 days after starting heparin, but it can occur earlier if recent heparin exposure occurred (within 100 days);
- acute thrombotic event (in this case, it will be named HITT);
- rule out other causes of thrombocytopenia;
- the resolution of thrombocytopenia after heparin stopped;
- HIT antibody serum conversion; and
- intermediate-to-high 4 T score (>3).[11]

WHAT OTHER SUPPORTING INFORMATION IS AVAILABLE FOR THE DIAGNOSIS OF HIT?

Apart from the use of the 4 T score, different tests are available in order to support the diagnosis of HIT. These tests could be grossly divided into immunoassays and functional assays. The choice of assay may be influenced by diagnostic accuracy, availability, cost, feasibility, and turnaround time.

In patients with suspected HIT, the American Society of Hematology (ASH) guideline panel recommended using the 4 T score to estimate the probability of HIT (Table 14.1). If there is an intermediate- or high-probability 4 T score, the ASH guideline panel recommended an immunoassay (strong recommendation). If the immunoassay is positive and a functional assay is available (either locally or as a send-out test to a reference laboratory), the ASH guideline panel suggests a functional assay.[12] As rule of thumb, it should be considered that immunoassay has high sensitivity but lower specificity; on the contrary, the functional assay has low sensibility and higher specificity.

If an enzyme-linked immunosorbent assay (ELISA) is used, a low threshold is preferred over a high threshold. In some settings, a functional assay may not be available, and decisions may need to be made on the basis of the results of the 4 T score and immunoassay. In general, the likelihood of HIT increases with a higher 4 T score and a higher ELISA optical density (OD). A functional assay may not be necessary for patients with a high-probability 4 T score and very strongly positive immunoassay (i.e., an ELISA value of 2.0 OD units). In some centers, a functional assay may be performed in tandem with an immunoassay for quality assurance or efficiency.[12]

Laboratory investigation involves first the immunological measurement of heparin dependent immunoglobulin (Ig) G antibodies (mainly targeted to heparin–platelet factor 4 [PF4] complexes). When positive, a functional assay for platelet activation, performed at a low- and high-heparin concentration, allows confirming this disease. In any case, if the immunoassay is negative, HIT can be excluded with a high probability, and heparin can be continued if the clinical examination favors this decision. Conversely, the higher the IgG antibody concentration (and affinity), the higher is the probability of developing HIT. The functional assay confirms platelet activation capacity of antibodies, therefore confirming the presence of HIT. The gold standard for testing antibody-dependent platelet activation is the C14-serotonin release assay, available only in very few laboratories working with radioisotopes. A simple, sensitive, and accurate flow cytometry assay now is available to all clinical sites, and it can be easily used for testing the capacity of heparin-dependent antibodies to activate platelets, at a low heparin concentration. This technique can be performed by any laboratory equipped with a flow cytometer and can make the HIT diagnosis rapidly available, which introduces a significant improvement for management of patients with HIT.[13]

WHICH CONDITIONS COULD LEAD TO THROMBOCYTOPENIA DURING ECMO?

Blood-device interaction leads to a widespread inflammatory and prothrombotic response. Consumption coagulopathy and dilution of coagulation factors occur during ECMO, mainly because of the priming at the initial stage and then due to progressive hemodilution and worsening clinical conditions. Platelet activation and aggregation persist, coagulation factor consumption continues, and fibrinolysis usually starts by day 5 of the ECMO run.[14] Moreover, when bleeding occurs, platelet consumption and loss can contribute to thrombocytopenia. Antithrombin III (ATIII) usually decreases with the institution of ECMO, contributing to a procoagulant state and decrease in heparin responsiveness.[14] In this regard, there is no agreement on the substitution of ATIII in case of decreased activity and on which is the best replacement strategy.

It should be noted that novel centrifugal pumps, polymethylpentene oxygenators, and heparin-coated circuits and cannulae have been developed with the aim of ensuring lower degrees of activation of the coagulation and inflammatory cascades, thus facilitating the management of patients under extracorporeal support. Indeed, numerous patients only require low doses of anticoagulants, and cases of prolonged ECMO support without anticoagulation, especially when V-V ECMO is concerned, have been encountered in our experience. Finally, from a technical perspective, it should be noted that use of larger cannulae could also decrease the risk of thrombosis.

WHICH ALTERNATIVES TO HEPARIN ARE AVAILABLE FOR ANTICOAGULATION DURING ECMO?

Unfractionated heparin remains the most common anticoagulant used for systemic anticoagulation of patients on ECMO (and CPB) for several reasons. Among them are the consolidated experience in its use, its low cost, and the availability of the reversal agent protamine, even though its use in rare in ECMO patients. However, when heparin is or becomes contraindicated, the direct thrombin inhibitor (DTI) bivalirudin represents a valid alternative. In the present stem case, bivalirudin was introduced as HIT was suspected, but a loading

dose was not administered since the patient was already anticoagulated and had recent major cardiac surgery. In a systematic review of the use of bivalirudin in patients supported by V-A or V-V ECMO, our group previously reported several case reports and series where loading doses of bivalirudin had been omitted[15]; whether or not the loading dose is given (usually 0.5 mg/kg seems reasonable, but it depends on the clinical conditions), the continuous infusion is usually reported between 0.3 and 0.5 mg/kg/h, although very high doses have been reported by Preston et al.[16] in a pediatric patient receiving plasma exchange (1.2–1.8 mg/kg/h). The short half-life of bivalirudin (25 minutes)[17] may be advantageous compared to other DTIs such as argatroban (39–51 minutes) and lepirudin (78 minutes) for titration of anticoagulation.[18,19] Moreover, argatroban and lepirudin may accumulate in hepatic and renal dysfunction, respectively, potentially leading to derangements of the anticoagulation target and thus a higher incidence of complications, while bivalirudin is cleared by a combination of renal (20% in patients with normal renal function) and proteolytic cleavage.[20] However, there are shortcomings with using bivalirudin for CPB. First, the tests to monitor the level of anticoagulation are aspecific. Second, there is no known reversal agent for bivalirudin, and data supporting the reversal of DTIs are limited, even if reversal of bivalirudin using recombinant factor VII has been described,[21] and its use in intractable hemorrhage in patients receiving ECMO seems promising. Third, bivalirudin loses efficacy in stagnant blood as it may happen during CPB due to the proteolytic cleavage of the drug.

Apart from the use of DTIs, the use of a glycoprotein (GP) IIb/IIIa inhibitor, such as tirofiban, followed by UFH was considered an alternative for anticoagulation during cardiac surgery in patients with HIT. More recently, due to the high postoperative bleeding incidence when using tirofiban and UFH, some authors described the use of cangrelor to block platelet aggregation as this is a significantly shorter acting agent. Cangrelor is a potent, rapid-acting, reversible antagonist of the P2Y12 receptor approved by the US Food and Drug Administration (FDA) in 2015 as an intravenous antiplatelet drug, and it could reduce the risk of significant bleeding compared with tirofiban. Therapeutic doses of cangrelor achieve platelet inhibition of up to 95% within 2 minutes. Complete recovery of platelet function is expected within 2 hours after the infusion is stopped. Sex, age, and renal or liver function do not affect its clearance, which makes this agent ideal for patients with multiple comorbidities. In addition to these favorable characteristics, the drug effect could be theoretically monitored with the VerifyNow Platelet Reactivity Unit Test, which measures the extent of platelet aggregation in the presence of P2Y12 inhibitors. The therapeutic effects of cangrelor can be maintained with continuous infusion, and its pharmacokinetic profile is characterized by rapidly achieved steady-state concentrations and a half-life around 3 minutes, so that cessation of its administration is associated with rapid removal, and normal platelet function is restored within 1 hour since its elimination is not deeply altered by renal and hepatic impairment.[22]

Some authors have already described the successful use of cangrelor with UFH for CPB in a patient with acute HIT[23–25] and in one case for a patient undergoing an urgent LVAD implantation.[26] Interestingly, in this case the patient was anticoagulated with bivalirudin, and when taken for urgent LVAD implantation, bivalirudin infusion was stopped and cangrelor with UFH was used for anticoagulation during CPB, with a loading dose of cangrelor (30 μg/kg) administered over a minute followed by continuous infusion at 4 μg/kg/min. Full-dose UFH for CPB (>300 U/kg) was given 10 minutes after cangrelor administration, and anticoagulation was monitored with activated clotting time (ACT).

Danaparoid is a valid alternative for anticoagulation of critically ill patients with HIT, but it does not seem to be ideal for extracorporeal circulation since it is a mixture of anticoagulant glycosaminoglycans (mostly heparan, dermatan, and chondroitin sulfate) with a long half-life.

WHAT MONITORING STRATEGY SHOULD BE USED?

A description of approaches to monitor anticoagulation with different assays and their advantages and disadvantages have been described in the chapter on traditional anticoagulation. In this chapter, we describe only particularities relative to alternative anticoagulation strategies.

Monitoring of anticoagulation with bivalirudin can be performed with the same methods used to measure anticoagulation levels on UFH. The two most common methods are ACT and aPTT, while the use of thromboelastography as described by Ranucci et al.[27] is less common.

Activated clotting time is an inexpensive bedside whole-blood assay that measures the degree of anticoagulation. In contrast to full anticoagulation with a target of 400–480 seconds for CPB, the target for ECMO is much lower. However, ACT monitoring alone may not provide an adequate representation of anticoagulation monitoring for patients requiring ECMO. Indeed, ACT values are also affected by several factors, and among them some are likely or certain in patients with HIT (thrombocytopenia, platelet dysfunction or inhibition, abnormal ATIII levels).[14]

The aPTT monitoring is a more precise approach for patients receiving anticoagulation with UFH or DTIs. It has been used with different target ranges, and these are not changed when switching from UFH to bivalirudin. Since bivalirudin directly inhibits thrombin (factor II), the monitoring of anti-Xa activity levels does not seem as reliable as during UFH anticoagulation. Some authors suggested combining anti–factor Xa with a whole-blood test capable of assessing the relative contribution of platelets and fibrinogen to clot formation. Viscoelastic tests (thromboelastography or rotational thromboelastometry) can be helpful in this context to diagnose an underlying hypo- or hypercoagulable state that may suggest a bleeding or thrombotic tendency, respectively. However, performing viscoelastic tests is a more challenging approach and also more expensive.[28].

ONCE HIT IS DIAGNOSED, WHAT SHOULD BE DONE?

From a clinical perspective, once the diagnosis of HIT has been established or it is suspected, heparin products must be avoided and alternative therapies for anticoagulation started.

Heparin-induced thrombocytopenia is a form of "acquired consumptive coagulopathy state" with a tendency toward thrombosis (and eventually bleeding for consumption of clotting factors and platelets); in the absence of risk factors for bleeding, alternative anticoagulation is usually started. In patients with stable clinical conditions, the therapeutic or prophylactic anticoagulation is started with danaparoid or DTIs, later switching to oral anticoagulants such as vitamin K antagonists (warfarin). It should be noted that once the HIT diagnosis is made, it is generally contraindicated to start warfarin as a choice for the switch due to its transient procoagulant effects in the first few days as result of the reduction of anticoagulant protein C levels.

The need for systemic anticoagulation, as in the case of patients undergoing ECMO, follows different rules than for other critically ill patients since the possibility of rapid modulation of the level of anticoagulation is of utmost importance. Therefore, bivalirudin seems at present the most reliable alternative and the one with the most experience available. Heparin should be immediately removed from "flush bags" connected to arterial or central venous catheters. It is advisable to reduce the possible factors that may contribute to development of thrombocytopenia, such as other drugs, if clinically possible. As an example, antibiotics like linezolid and vancomycin are among the most commonly reported drugs inducing thrombocytopenia.[29]

WHICH OTHER CONDITION MAY REQUIRE ALTERNATIVE ANTICOAGULATION FOR ECMO?

Another possible issue with anticoagulation for extracorporeal circuits is represented by the occurrence of heparin resistance (HR), commonly caused by low ATIII levels. This other challenge caused by the deficiency of ATIII can be managed with supplementary UFH to achieve the anticoagulation goal or with substitution of ATIII with administration of either fresh frozen plasma or ATIII concentrate. Although substitution therapy is the most physiological approach, the costs are higher than using a higher amount of UFH. On the other side, very high doses of UFH may increase the variability of its effect with fluctuating anticoagulation levels, thus exposing the patient to higher risks of bleeding or thrombosis.

IS HIT A PERMANENT CONDITION?

Heparin-induced thrombocytopenia is not a permanent condition, and after a period free from the trigger (heparin), the patient could be reexposed to heparin itself. HIT immune response is very transitory, with antibodies no longer detectable after a period of 40 to 100 days following the episode of HIT, depending on the laboratory test used. The risk of recurrent HIT has been estimated at around 2% to 5% if exposure happens 1 to 2 weeks after the first episode and is attributable to appearance of delayed-onset (or autoimmune-like) HIT antibodies, which activate platelets even in the absence of pharmacologic heparin.[30–32] The risk for inducing a second episode of HIT with reexposure to heparin seems relatively low, especially in nonsurgical patients, although higher than in the general population. Anyway, the daily monitoring of the platelet count after surgery is mandatory.

Even if a patient with previous HIT could still receive heparin after a while—though under strict clinical and laboratory control—in our case the patient was instructed to avoid heparin. Even if the heart transplant intervention happened well beyond the HIT event (14 months after), the team preferred to perform systemic anticoagulation for CPB with bivalirudin due to the highly challenging and risky operation. Indeed, the occurrence of HIT with potential bleeding and/or thrombosis after heart transplant could have tremendous complications. For instance, even a relatively small bleeding amount could increase the risk of septic complication with return to the operating theater, and a coronary thrombosis could increase the risk of graft failure.

DISCUSSION

Extracorporeal membrane oxygenation can provide cardiac and/or respiratory support, even for extended periods. V-V ECMO provides adequate oxygenation and carbon dioxide removal in isolated refractory respiratory failure, while V-A ECMO is used when support is required for cardiac function with or without respiratory failure.[33–35] The ECMO circuits are shorter than the traditional CPB circuit and are heparin bonded. Since also the ECMO cannulae are available as heparin bonded, lower levels of anticoagulation are now required for ECMO support[36] as compared to previous years.[6] As already described, UFH remains the anticoagulant of choice because of easy titration and monitoring, its low costs, the overall familiarity with its use, and the availability of an antidote (protamine). Nonetheless, the clinical use of UFH or, less commonly, of low-molecular-weight heparins[37] and fondaparinux,[38] may trigger HIT, which represents a potentially life-threatening immune disorder.[39,40] As described, HIT is an antibody-mediated reaction caused by circulating heparin–PF4 complexes leading to a transient prothrombotic condition.

Together with the clinical assessment using the 4 T score, laboratory testing represents an important component of an accurate HIT diagnosis. The assays available to assess HIT essentially fall into two categories: immunological assays and functional assays. As per recommendations of the ASH, we used the 4 T score to estimate the probability of HIT, and with an intermediate or high probability we should have performed an immunoassay. However, this was not immediately available for technical reasons, and we decided to perform

a functional assay, keeping in mind the limitations of this approach, in particular its low sensitivity. Indeed, the functional assay was negative for HIT. In this case, while sending out a sample for immunoassay to the closest available laboratory for confirmation, a multidisciplinary meeting decided that due to the critical conditions of LV failure and ECMO support in a patient with a type A aortic dissection and coronary graft, there was no time to send the sample for analysis in another center and wait for the results before switching anticoagulation strategy. Therefore, we proceeded immediately to switch from UFH to bivalirudin, ignoring the result of the functional assay because its low sensibility and the intermediate-high clinical suspicion suggested by the 4 T score. Diagnosis of HIT was confirmed after a couple of days by the sample sent out.

In the case of HIT/HITT during ECMO, very limited evidence is available for alternative strategies for anticoagulation. The medical treatment of HIT is mainly based on switching to DTIs with supportive therapy, such as platelet transfusion and/or plasmapheresis. Bivalirudin, a DTI, does not require ATIII and has additional activity against thrombin-mediated platelet activation; it is currently approved by the F DA for use during percutaneous coronary intervention/angioplasty. It has gradually become an accepted alternative in patients requiring anticoagulation in the setting of HIT/HITT. Bivalirudin is also recommended as a first-line strategy for intraoperative anticoagulation in patients with HIT/HITT requiring cardiac surgery,[41,42] and it is widely used during percutaneous coronary interventions.[43–45] Another possible issue with anticoagulation for extracorporeal circuits is represented by HR, commonly caused by low ATIII levels. This challenge is often managed with supplementary heparin and fresh frozen plasma or ATIII concentrate.[46] The first action in the presence of HIT suspicion is to withdraw heparin and to initiate an alternative anticoagulant. While vitamin K antagonists are not appropriate, anticoagulant options include fondaparinux; sodium danaparoid; direct oral anticoagulant, also known as novel oral anticoagulant (i.e., dabigatran, rivaroxaban, apixaban, and edoxaban); argatroban; and bivalirudin. However, if HIT is excluded, patients can benefit again from the high therapeutic and antithrombotic efficacy of this drug, which remains superior to all the substitutive anticoagulant treatments.

CONCLUSIONS

- During ECMO it is difficult to diagnose HIT.
- Thrombocytopenia is a very common finding for ECMO patients.
- It is mandatory to raise the suspicion of HIT/HITT and to investigate throughout the differential diagnosis.
- Bivalirudin is a valid option for systemic anticoagulation of patients with HIT.
- Bivalirudin has a short half-life, and it can be manageable in cases of renal and hepatic dysfunction.

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REVIEW QUESTIONS

1. Regarding anticoagulation, ECMO circuits, as compared with the traditional CPB circuits,

   A. Require lower levels of systemic anticoagulation as circuits are heparin bonded
   B. Require higher levels of systemic anticoagulation if circuits are not heparin bonded
   C. Require the same levels of systemic anticoagulation as circuits that are not heparin bonded
   D. Only rarely require systemic anticoagulation if the circuit is heparin bonded

2. Why is heparin commonly used as an anticoagulant for ECMO patients?

   A. Easy titration and monitoring
   B. Low costs and the overall familiarity
   C. Availability of an antidote
   D. A, B, and C

3. Which of the following anticoagulation treatments could potentially be used for ECMO patients?

   A. Unfractionated heparin
   B. Bivalirudin
   C. Fondaparinux
   D. A and B

4. Which of the following should not be used if HIT/HITT is suspected?

   A. Unfractionated heparin
   B. Lepirudin
   C. Fondaparinux
   D. A and C

5. Which of the following statements is correct?

   A. HIT is an immune disorder.
   B. HIT is a hereditary disorder.
   C. HIT is an organic disorder.
   D. HIT is a functional disorder.

6. Which of the following is among the factors to be considered in the score for the probability of HIT?

   A. The degree of thrombocytopenia is more important than the timing of platelet count decrease.
   B. A platelet count below 10,000/mm^3 would score 2 points.

C. Antibiotics should not be considered as other potential causes of thrombocytopenia since most patients are under antibiotics during ECMO.
D. The typical onset of HIT is between day 5 and 10 (unless there is previous heparin exposure within 30 days).

7. Which choice is among the factors to be considered in the score for the probability of HIT?

A. The presence of arterial thrombosis counts as 2 points, while venous thrombosis counts as 1 point.
B. The presence of suspected arterial thrombosis counts as 2 points.
C. A platelet decrease to 15,000/mm^3 would score 1 point.
D. The presence of possible other causes of thrombocytopenia scores 2 points.

8. Regarding the tests for HIT,

A. Heparin-PF4 antibody ELISA with optical density greater than 2.0 is strongly positive.
B. Heparin-PF4 antibody ELISA with optical density lower than 4.0 is considered negative.
C. Functional assays, such as the serotonin release assay, with optical density greater than 2.0 are barely positive.
D. Functional assays, such as the serotonin release assay, with optical density lower than 6.0 are considered negative

9. Which is true regarding the tests for HIT?

A. Both immunosorbent assays and functional assays have high sensitivity and specificity.
B. Both immunosorbent assays and functional assays have low sensibility and specificity.
C. Immunosorbent assays have high sensibility; functional assays have high specificity.
D. Immunosorbent assays have low specificity; functional assays have low sensibility.

10. When a patient on V-A ECMO is anticoagulated and subsequently develops HIT, which of the following is correct?

A. Direct thrombin inhibitors are one of the preferred alternatives.
B. Anticoagulation can be safely switched to warfarin.
C. Continue heparin associated with anti-platelets therapy with aspirin or clopidogrel
D. Combine bivalirudin with aspirin or clopidogrel

11. Which of the following treatments could be considered as alternative therapy to heparin in case of HIT?

A. Argatroban, Bivalirudin, Fondaparinux
B. Argatroban, Bivalirudin, Lepirudin
C. Argatroban, Lepirudin, Fondaparinux
D. Bivalirudin, Lepirudin, Fondaparinux

12. Which of the following statements is correct?

A. Bivalirudin, a direct thrombin inhibitor (DTI), does require antithrombin III and has not additional activity against thrombin-mediated platelet activation
B. Bivalirudin, a direct thrombin inhibitor (DTI), does not require antithrombin III and has additional activity against thrombin-mediated platelet activation
C. Bivalirudin, an antiplatelet drug, does not require antithrombin III and has additional activity against thrombin-mediated platelet activation
D. Bivalirudin, an anticoagulant drug, does require antithrombin III and has additional activity against thrombin-mediated platelet activation

13. Which of the following statements is correct?

A. Bivalirudin has similar half-life as lepirudin and argatroban
B. Bivalirudin is preferred over argatroban because it may accumulate in renal dysfunction
C. Bivalirudin is preferred over lepirudin because it may accumulate in hepatic dysfunction
D. Bivalirudin has a minor renal clearance and it is mostly eliminated via proteolytic cleavage

ANSWERS

1 A, 2 D, 3 D, 4 D, 5 A, 6 D, 7 C, 8 A, 9 C, 10 A, 11 B, 12 B, 13 D

15.

ARGATROBAN FOR ANTICOAGULATION IN PEDIATRIC AND ADULT ECMO

Massimo Capoccia, Janos Geli, and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 36-year-old man with known dilated cardiomyopathy was admitted to the Accident and Emergency Department of a university hospital with severe pulmonary edema. After initial antifailure treatment optimisation, further investigations showed severe biventricular systolic and diastolic dysfunction with a left ventricular ejection fraction of 15%, left ventricular diastolic diameter of 6.5 cm, moderate-to-severe mitral regurgitation and significantly reduced right ventricular longitudinal function (tricuspid annular plane systolic excursion, TAPSE, 0.9cm). Initial inotropic support only partially addressed the clinical picture. Therefore, veno-arterial (V-A) ECMO support was considered on symptomatic and prognostic grounds. Following percutaneous cannulation through the right femoral vein using a 23 French (23F) drainage cannula and left femoral artery using a 17F return cannula with a 5F left femoral distal perfusion cannula, full V-A ECMO support was initiated and pursued with a mean pressure of 80 mm Hg, a flow range of 4–4.5 L/min, and 4000–4500 RPM. Subsequently, partial support was considered to allow left ventricular ejection with a mean pressure of 70 mm Hg, a flow range of 3.0–3.5 L/min, and 3000–3500 RPM. Anticoagulation was maintained with heparin infusion and aPTT range of 50–60 seconds. On day 1 following ECMO insertion, a significant reduction in platelet count was observed, from 246 × 10^9/L (pre-ECMO) to 116 × 10^9/L with further reduction to 60 × 10^9/L by day 5. Although ECMO-related trauma was taken into account, heparin-induced thrombocytopenia (HIT) was considered as a potential cause. HIT testing was arranged, which came back positive with immunoglobulin (Ig) G at 1.2 U/mL but enzyme-linked immunosorbent assay () negative with IgG at 0.2 U/mL. Further reduction was observed on day 6, with a platelet count of 48 × 10^9/L. Despite significant progress, the patient was still in need of mechanical support; therefore, a decision was made to switch to argatroban infusion at 0.2 μg/kg/min adjusted to a partial thromboplastin time (PTT) range of 50–60 seconds. The decision-making approach proved successful, with a gradual increase in platelet count and successful weaning off ECMO support on day 12.

WHAT ARE THROMBIN AND ANTITHROMBIN?

Thrombin or coagulation factor II is a serine protease with a key role in hemostasis regulation and maintenance of blood coagulation. Thrombin converts fibrinogen to fibrin, leading to platelet aggregation and clot formation. Antithrombin (AT) is a $_2$-globulin synthesized in the liver with a major role as inhibitor of blood coagulation.[1]

WHAT IS HEPARIN, AND WHAT ARE ITS ADVANTAGES AND DISADVANTAGES?

Heparin is a glycosaminoglycan of varying molecular weight which, binds to antithrombin III (ATIII) to inactivate factors IIa and Xa.[2] Heparin is very well known and widely used. It is easy to monitor with activated partial thromboplastin time (aPTT) and activated clotting time (ACT). It can be reversed with protamine and is available at low cost. Heparin has a half-life of 60 minutes and is metabolized in the liver and the reticuloendothelial system. Nevertheless, pharmacokinetics can be unpredictable, with a nonlinear, variable effect. Besides, in view of a conformational change hiding the binding site, the complex heparin-AT will not inhibit thrombin already bound to fibrin, making it ineffective against preexisting clot.[3–5] aPTT monitoring is helpful for the evaluation of the intrinsic pathway starting with factor XII (FXII). A prolonged aPTT may be related to an acquired or inherited factor deficiency or to other reasons, such as lupus anticoagulant and drug effect. The aPTT assay is ideal for the monitoring of patients on heparin treatment, although it is time consuming and variability between laboratories is very well known. The ACT is the established bedside test and relies on contact activation, although it can be insensitive to low-dose heparin frequently used during ECMO support. The anti-Xa assay is probably the most reliable in relation to accuracy. This test measures the inhibition of activated FX (FXa) in relation to the common pathway. Nevertheless, it is time consuming and needs separate calibration for unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH). Finally, like the aPTT, the anti-Xa assay underestimates the presence of UFH in case of free hemoglobin or bilirubin in the plasma.[4]

WHAT IS HEPARIN-INDUCED THROMBOCYTOPENIA?

Heparin-induced thrombocytopenia (H)is secondary to either a nonimmune-mediated response (type 1) or an immune-mediated response (type 2) generating IgG antibodies against complexes between heparin and platelet factor 4 (PF4). The IgG-PF4 complex binds to platelets, causing their activation with thrombus formation in the circulation. The development of significant thrombocytopenia or a 30%–50% reduction from baseline after 5 days of heparin administration should raise suspicion, although the diagnosis is often challenged by other potential causes, such as sepsis.[6] A prompt diagnostic approach is required in patients with suspected HIT. The 4 Ts score is a clinical assessment tool with great potential but requires experience and is subject to relevant interobserver variability.[7,8] It is based on four typical clinical features of HIT: thrombocytopenia; timing of thrombocytopenia; presence of thrombosis or other clinical sequelae; and absence of other causes of thrombocytopenia.[8] The HEP (HIT expert probability) score is another clinical assessment approach based on more clinical features: magnitude of platelet count fall; timing of platelet count fall; nadir of platelet count; thrombosis; skin necrosis; acute systemic reaction; bleeding; and other causes of thrombocytopenia.[8] The clinical and immunologic response to heparin discontinuation in patients with HIT follows a predictable pattern consisting of five phases: suspected HIT (diagnosis made on clinical grounds while waiting for laboratory tests); acute HIT (diagnosis is confirmed by laboratory tests with significant increased thrombotic risk); subacute HIT A (platelet count has recovered); subacute HIT B (the washed platelet functional assay is negative); and remote HIT (anti-PF4/heparin antibodies are no longer detectable by immunoassay).[9]

WHAT ARE DIRECT THROMBIN INHIBITORS?

Direct thrombin inhibitors (DTIs) are anticoagulant agents which bind directly to thrombin without the need of a cofactor like AT to exert their effect. DTIs can inhibit both soluble thrombin and fibrin-bound thrombin.[10] Parenteral DTIs include argatroban, bivalirudin, and hirudin derivatives (lepirudin and desirudin). Dabigatran is the only oral agent. Lepirudin is no longer available due to discontinuation in 2012 by the manufacturer.[11,12]

WHAT ARE THE ADVANTAGES AND DISADVANTAGES OF DTIs?

Key advantages of DTIs include a more predictable anticoagulant effect compared with heparin because of the lack of binding to other plasma proteins; an antiplatelet effect; and the absence of immune-mediated thrombocytopenia.[10] Disadvantages include a higher cost than heparin; no specific antidote or reversal agent; potential destabilisation of existing clot. Nevertheless, their half-life is short, and the anticoagulant effect tapers off rapidly despite the presence of organ dysfunction in patients on ECMO support.[3,5,11]

WHY IS ARGATROBAN THE MOST SUITABLE DTI FOR V-A ECMO?

Argatroban is a small molecule that binds to the active thrombin site, reversibly preventing the activation of clotting factors (V, VII, XIII), fibrin formation, and platelet aggregation. It has a short half-life (45 minutes) and rapid onset of action and hepatic metabolism, which makes it safe in patients with renal impairment. It does not interact with heparin-induced antibodies.[6] Compared with veno-venous (V-V) ECMO, when the full ECMO flow is directed through the heart and the lungs, V-A ECMO bypasses these organs to the extent of the initiated flow. In the failing and not ejecting/contracting heart, the cardiac chambers potentially act as a natural reservoir that could lead to blood stagnation and risk for spontaneous intracardiac thrombosis. This must be avoided by maintaining partial V-A ECMO support and facilitating some degree of cardiac contraction, which subsequently may lead to aortic valve opening and blood flow through the heart and lungs. Intracardiac thrombus formation during V-A ECMO with heparin anticoagulation has been described but the pharmacokinetic properties of heparin (half-life 1–2 hours) may limit the risk of thrombus formation due to blood stagnation. Argatroban, which has a half-life of approximately 45 minutes, is still a suitable drug, while bivalirudin with its half-life of 25 minutes bears considerable risk for thrombus formation in patients on V-A ECMO during periods of poor contractility, when inotropes need to be started and time must be bought to place an intra-aortic balloon pump or Impella to help venting/unloading the left ventricle.[13]

HOW IS ARGATROBAN DOSED?

Argatroban does not require an initial bolus; the starting dose is 2 μg/kg/min for preserved organ function. In the presence of liver dysfunction or heart failure, dosage is reduced to 0.5–1.2 μg/kg/min.[9] Nevertheless, a 10-fold reduction in the dosage has been previously suggested due to significant bleeding.[11,14–17] Table 15.1 shows three examples of dosing regimen for argatroban in adult patients. However, the anticoagulation management of these patients is explained in more detail below. Table 15.1 can only be a suggestion; every center or user is responsible for their own dosing regimen and monitoring approach.

HOW IS ARGATROBAN MONITORED?

The target for dose adjustment of argatroban is aPTT monitoring with a range of 50–60 seconds. This is consistent with current guidelines recommending an aPTT target range of 1.5–2.5 times baseline. ACT monitoring, either alone or with aPTT, is less frequent, with a target range of 200–400 seconds.[11] However, in our experience, the three aPTT dose ranges are playing a significant role in anticoagulation management. The ultimate goal is to prevent clotting with a minimum risk of bleeding. Every individual patient and patient's condition need to be taken into account. For instance, in a postcardiotomy patient it may make sense initially not to give

Table 15.1 EXAMPLE FOR THREE APTT TARGETS AT 0.2 MCG/KG/MIN[a]

APTT RANGE	30-40	40-50	50-60
Infusion regime	aPTT < 25 increase by 0.2 μg/kg/min aPTT 26-29 increase by 0.1 μ/kg/min aPTT 30-40 no change aPTT 41-50 decrease by 0.1 μg/kg/min aPTT > 50 hold infusion for 1 hour and decrease by 0.2 μg/kg/min	aPTT < 21 increase by 0.2 μg/kg/min aPTT 21-29 increase by 0.15 μ/kg/min aPTT 30-39 increase by 0.1 μg/kg/min aPTT 40-50 no change aPTT 51-60 decrease by 0.1 μg/kg/min aPTT > 60 hold infusion for 1 hour and decrease by 0.15 μg/kg/min	aPTT < 31 increase by 0.2 μ/kg/min aPTT 3139 increase by 0.15 μg/kg/min aPTT 4049 increase by 0.1 μg/kg/min aPTT 5060 no change aPTT 6170 decrease by 0.1 μg/kg/min aPTT > 70 hold infusion for 1 hour and decrease by 0.15 μg/kg/min

[a]Infusion is started at 0.2 μg/kg/min; baseline aPTT before commencement of infusion, then 2 hours after, 2 hours after dose changes, then every 4 hours.

any anticoagulation at all because of the high bleeding risk and then on a daily basis increase the dose range step by step until anticoagulation matches the best possible clinical picture. If no clot formation in the circuit and oxygenator is observed without bleeding at the cannula sites or chest tubes, individually optimal anticoagulation has been achieved. Centers that prefer to measure ACT may see this effect already in a range between 160 and 220 seconds.

HOW DO WE MANAGE HIT IN THE PRESENCE OF HEPARIN-COATED CIRCUITS?

Managing HIT in the presence of heparin-coated circuits is an old issue where options have been previously explored,[18] although the best strategy for the management of HIT in ECMO patients with heparin-coated circuit remains not completely defined.[19] Temporary platelet inhibition with iloprost, a stable prostacycline analogue, has been used in patients with known HIT requiring reexposure to heparin for cardiac and vascular procedures.[20] Replacement of UFH with heparinoids (heparan sulfate and dermatan sulfate) and LMWHs such as dalteparin, tedelparin, and enoxaparin has been reported.[21,22] LMWHs act mainly against factor Xa, although cross-reaction with heparin is very well known, requiring platelet aggregation tests and frequent monitoring with factor Xa assay.[21,23] A combined use of LMWHs with heparin-bonded circuits has also been previously proposed.[23–25] Although the argument is based on the potential beneficial effect of decreased complement and granulocyte activation,[26–28] a major limitation of these circuits is the flow dependence of the anticoagulant effect and failure to reduce thrombin formation.[23,29] Heparin coating of the surface of ventricular assist devices (VADs) does not seem to enhance the formation of heparin/PF4 antibodies, although their presence is strongly related to an increased risk of thromboembolism in VAD patients.[30,31] Also heparin-bonded expanded polytetrafluoroethylene vascular grafts do not seem to generate heparin/PF4 antibodies.[32] The use of heparin-coated catheters in the presence of HIT can be addressed by their removal and commencement of alternative anticoagulant agents.[33]

Nevertheless, heparin-coated circuits during ECMO support remain a source of exposure for the patient to the drug, and the aim should be their replacement when possible.[19] The argument supporting the "endothelialisation" of heparin-coated circuits and therefore decreased exposure to the drug may not be that strong. The question is whether heparin-coated circuits are really needed.[36] Phosphorylcholine coating may be an alternative, with evidence to suggest that it may allow safe reduction of heparin administration with a decrease in blood loss and thromboembolic complications compared with uncoated circuits.[37–41] Despite this evidence, no randomized controlled trials have been designed to compare heparin coating with other biocompatible treatment.[36]

A recent review has addressed current and future developments in surface modifications to improve hemocompatibility and replication of the antithrombotic and anti-inflammatory properties of the endothelium with a view to reduce or even avoid systemic anticoagulation during ECMO.[42] Thought-provoking and controversial is the recent proposal for V-A ECMO support without routine anticoagulation.[43]

DISCUSSION

Bleeding and thromboembolic complications remain critical issues affecting the outcome of patients undergoing mechanical circulatory support. There is significant variability in the need for anticoagulation according to the device used. Consequently, a universal anticoagulation strategy cannot be recommended. The selection of drugs and their dosage is related to the type of device used, patient-specific factors, length of treatment, and the experience of the medical team.[44] Although heparin remains the most widely used anticoagulant for blood recirculating devices, its known side effects and consequences must be acknowledged. DTIs seem to have gained more popularity in recent years,[3,10,11] with argatroban as the likely most suitable alternative since initial reports.[45–49] It is argued that prevalence of HIT in ECMO patients is extremely low[50] making the need of alternative anticoagulation not completely justified. Nevertheless, argatroban may be a safe alternative even in the absence of HIT due to a potentially more significant platelet-preserving effect than heparin.[51] This aspect should be kept in mind considering that thrombocytopenia is more frequent in patients on mechanical circulatory support due to platelet activation, trapping, consumption, and trauma.[52]

Given the widespread use and experience with heparin as the anticoagulant, the proposal of an alternative on a more

routine basis may be difficult to accept. At the same time, there is a clear need of alternatives to counteract potential problems or an already compromised background, such as antithrombin deficiency.

Considerations about anticoagulation in the adult population may not necessarily apply to pediatric patients. The occurrence of HIT in children seems more limited compared to adult patients, although it may be underreported.[53] Traditional anticoagulant agents remain a contentious issue in children, and newer drugs may not necessarily be without significant risk. Besides, the available clinical experience with newer agents is not completely established.[54,55] Therefore, it is difficult to draw conclusions. Nevertheless, given the observed variability of AT concentration in children and the need for additional administration on ECMO,[56,57] argatroban may still be worth considering despite its increased risk of bleeding in the pediatric population.[55] The use of AT supplementation for heparin resistance remains controversial and affected by the potential inaccuracy of the diagnosis of heparin resistance based on current monitoring parameters and devices.[58] Therefore, the focus on alternative anticoagulant agents with particular reference to argatroban may well be justified.

CONCLUSION

- Heparin remains the most widely used anticoagulant drug.
- HIT is a known complication which can affect outcome.
- Alternatives are available.
- Argatroban may become the likely suitable candidate on a permanent basis.
- Argatroban does not require the presence of ATIII.

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REVIEW QUESTIONS

1. What is the half-life of (UFH)?

   A. 60 minutes
   B. 90 minutes
   C. 45 minutes
   D. 25 minutes

2. What is the half-life of argatroban?

   A. 60 minutes
   B. 90 minutes
   C. 45 minutes
   D. 25 minutes

3. What is the half-life of bivalirudin?

   A. 60 minutes
   B. 90 minutes
   C. 45 minutes
   D. 25 minutes

4. What is the suggested ACT range for argatroban during ECMO support?

   A. 400–800 seconds
   B. 200–400 seconds
   C. 400–600 seconds
   D. None of the above

5. What is the suggested aPTT range for argatroban during ECMO support?

   A. 50–60 seconds
   B. 30–40 seconds
   C. 60–70 seconds
   D. None of the above

6. When is HIT most likely to occur postoperatively?

   A. 2–3 days
   B. Between 5 and 10 days
   C. Almost immediately
   D. None of the above

7. Which patients with suspected HIT should receive empiric treatment while awaiting for laboratory confirmation?

A. Only those with high probability
B. Those with intermediate and high probability
C. All patients
D. None of the above

8. What is the anti-Xa range for heparin during ECMO support?

A. 0.2–0.39
B. 0.5–0.59
C. All of the above
D. None of the above

9. What is the impact of HIT in patients on V-A ECMO and V-V ECMO?

A. No real difference is observed.
B. Patients on V-A ECMO are more likely to experience more severe thrombocytopenia and arterial thromboembolism; those on V-V ECMO are more likely to require device or circuit exchange due to oxygenator thromboembolism.
C. Patients on V-V ECMO are more likely to experience more severe thrombocytopenia and arterial thromboembolism; those on V-A ECMO are more likely to require device or circuit exchange due to oxygenator thromboembolism.
D. None of the above.

10. Is it enough to stop heparin in patients who develop HIT?

A. Usually it is enough.
B. No, the prothrombotic state will require alternative anticoagulation with argatroban.
C. All of the above.
D. None of the above.

ANSWERS

1. A is the correct answer.
2. C is the correct answer.
3. D is the correct answer.
4. B is the correct answer.
5. A is the correct answer.
6. B is the correct answer.
7. B is the correct answer.
8. A is the correct answer.
9. B is the correct answer.
10. B is the correct answer.

16.

ECMO TRANSFUSION AND COAGULATION MANAGEMENT

Hergen Buscher and Shweta Priyadarshini

STEM CASE AND KEY QUESTIONS

A 45-year-old male was admitted to the intensive care unit following coronary artery bypass graft surgery for triple-vessel disease and bioprosthetic aortic valve replacement for severe aortic regurgitation. His left ventricle (LV) was moderately impaired before the surgery. He was unable to be weaned from cardiopulmonary bypass postoperatively and was placed on central veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO). Perioperative bleeding was significant and required the replacement of clotting factors and thrombocytes as per the institutional massive transfusion protocol. The postoperative transesophageal echocardiography (TEE) showed a severely impaired LV with a well-seated aortic valve prosthesis. His chest drain output remained at around 80–120 mL/h for the first 12–24 hours, and the ECMO circuit was run without any anticoagulation for the first 24 hours. He was anuric postoperatively and placed on continuous renal replacement therapy via the ECMO circuit.

The bleeding from the drains settled down, and he was started on heparin infusion on postoperative day 2 for anticoagulation of the ECMO circuit, aiming for low therapeutic range activated thromboplastin time (aPTT) of 40–60 seconds. He failed a weaning TEE study on day 3 and was taken to the operating theater, where the chest was closed, and the ECMO configuration changed to peripheral femoro-femoral V-A ECMO with a right femoral 25 French (25F) drainage cannula and left femoral 19F return cannula with a 7F distal perfusion cannula. The anticoagulation was paused perioperatively, and on his return from the operating theater, he was restarted on a heparin infusion, aiming for therapeutic range aPTT (50–70 seconds). An escalating dose of heparin was needed to achieve this target, and an antithrombin (AT) fraction of 35% was measured. With a spontaneous increase in AT over the following 2 days, the required heparin dose could be reduced.

He started becoming thrombocytopenic on day 5, reaching a nadir of 30 on day 5. No bleeding complications were noted. A rise in D-dimers and a fall in fibrinogen were also noted. The transmembrane pressures gradually increased, and numerous clots were seen on both the venous and arterial side of the oxygenator, which necessitated a semielective circuit change on day 6. TEE done on the same day showed a mild improvement in the LV function but inability to wean off V-A ECMO. There was a suspected clot at the apex of the LV. This raised the possibility of heparin-induced thrombotic thrombocytopenia syndrome (HITTS) and triggered a screening enzyme-linked immunosorbent (ELISA) test. Heparin was stopped, and argatroban infusion was started as an alternative to heparin for anticoagulation of the ECMO circuit and the suspected LV thrombus.

The HITTS screening test came back negative, and argatroban was replaced by heparin. On day 10, the patient was successfully decannulated from ECMO in the operating theater, and the intraoperative TEE showed no intracardiac clot. The patient required platelet transfusions on a few occasions to maintain his platelet count above 30,000/μL. The thrombocytopenia gradually resolved over a few days. The patient was weaned of all inotropes and vasopressors but required a tracheostomy on day 14 and remained dialysis dependent for another 4 weeks. Echocardiogram done at 8 weeks showed an improved LV ejection fraction of 45%, a normal right ventricle, and a well-seated prosthetic aortic valve. He was discharged to the rehabilitation ward on day 60 of his hospital admission.

WHAT ARE THE MAJOR HEMATOLOGICAL CHALLENGES FACED DURING ECMO AND WHY?

The major hematological challenges faced during ECMO are thrombosis, bleeding, hemolysis, and disseminated intravascular coagulation (DIC), some or all of which may occur concurrently. Besides the hematologic dysregulation seen in critical illness, there is activation of the inflammatory and coagulation cascade (both pro and anti) in ECMO patients due to continuous contact between the biomaterials of the ECMO circuit, including the cannulae, tubing, pump head, and oxygenator membrane, and the blood. This is further impacted by the anticoagulation required to maintain ECMO and the underlying conditions and organ failure.

The adverse effects of thrombosis can include oxygenator failure, pump malfunction, hemolysis, and thromboembolic events (including intracardiac clot, oxygenator failure, clots requiring circuit change, pump failure due to clot, stroke, limb ischemia from thrombotic event, pulmonary embolism,

or deep vein thrombosis).[1–3] The major bleeding events can include cannula site bleeding, surgical site bleeding, nasopharyngeal bleeding, pulmonary hemorrhage, gastrointestinal bleeding, and intracranial hemorrhage.[1,4–7]

HOW DO YOU APPROACH ANTICOAGULATION IN A PATIENT ON ECMO?

A bolus dose of 50–100 units/kg of unfractionated heparin (UFH) is administered at the time of cannulation and continued as a continuous infusion thereafter. The Extracorporeal Life Support Organization (ELSO) recommends using UFH targeting an activated clotting time (ACT) of 180–220 seconds, based on limited data and expert opinion. The ELSO guidelines also suggest that aPTT, anti–factor Xa (anti-Xa) activity levels, thromboelastography (TEG) or thromboelastometry (TEM) can be used to monitor anticoagulation in addition or as alternatives to the ACT.[8]

There are inadequate data to define the best monitoring tool for UFH in intensive care unit patients.

The ACT and aPTT are the most widely used assays either alone or in combination with the other assays. Both ACT and aPTT are heparin-monitoring assays and are based on activation of the intrinsic pathway of coagulation. Typical ACT targets in nonbleeding ECMO patients range from 160 to 220 seconds, depending on the analyzer, other hematologic parameters, and institutional practice.[9,10] Given the reduced thrombogenicity of modern ECMO circuits, in the absence of an indication for a therapeutic anticoagulation target, such as known hypercoagulable state or deep venous thrombosis, heparin is titrated to an aPTT typically less than the therapeutic range, ranging from 50 to 70 seconds or 1.5 to 2.0 times normal, with great variation in practice between centers.[11]

Anti-Xa may be a more accurate measurement of heparin effect and is used to guide heparin protocols in other prothrombotic states (e.g., lupus anticoagulant).[12]

There are no large randomized trials comparing these different monitoring strategies.

Whole-blood tests like TEG or TEM are offered as real-time bedside tests and give information on anticoagulation as well as a quantification of coagulopathies, including the impact of platelet count and function as well as hyperfibrinolysis. They have been shown to be beneficial in the management of bleeding, but no clear evidence exists in its use to guide anticoagulation.[13–15]

ARE OTHER ANTICOAGULANTS USED IN ECMO?

Low-molecular-weight heparin has widely replaced UFH in many areas. However, the lack of an antidote and a relatively long half-life have limited its use in ECMO, and studies are needed to assess its safety.

Anticoagulation can also be achieved using a direct thrombin inhibitor (DTI). Results from the ELSO survey indicated that the three most widely used DTIs are argatroban, bivalirudin, and lepirudin (Table 16.1). Unfortunately, the data for the use of DTIs in ECMO patients are limited. Areas of uncertainty are safe dosing regimens for these drugs, adequate monitoring, and whether they could ultimately replace UFH as the anticoagulants of choice in ECMO. A significant limitation of DTIs, compared to UFH, is the absence of antidotes.[16,17] Further and more detailed information on DTIs is provided in other chapters of this book.

WHAT ARE PRACTICE VARIATIONS IN ECMO PATIENTS WITH A HIGH BLEEDING RISK?

Anticoagulation in ECMO has been associated with severe bleeding, including cannulation site bleeding and surgical site bleeding requiring rethoracotomy.[1,4–6] There have been several advancements to mitigate the risk of thrombosis during ECMO, like polymethylpentene oxygenators, centrifugal pumps, and heparin coating of the ECMO circuit, which may allow a safe reduction of systemic heparinization. In postcardiotomy patients with significant bleeding risk after cardiopulmonary bypass, some centers have performed V-A ECMO without anticoagulation[18] or with lower anticoagulation targets. Thromboembolic events have been found to be similar between the lower ACT and higher ACT groups, while major bleeding has been found to be more common in higher ACT targets.[7]

It is considered to be safe to withhold anticoagulation during active bleeding and high bleeding risk. While this had been reported for days and even weeks in veno-venous (V-V) ECMO,[19] the risk of intracardiac thrombosis and embolization is higher in V-A ECMO.

WHAT IS HEPARIN RESISTANCE, AND HOW DO YOU MANAGE IT?

Heparin resistance can be defined as high doses of UFH, greater than 35,000 IU/d, required to raise the aPTT, ACT,

Table 16.1 **PHARMAKOLOGICAL DIFFERENCES BETWEEN UFH AND THE THREE MOST WIDELY USED DTIS**

	UFH	ARGATROBAN	BIVALIRUDIN	LEPIRUDIN
Half-life	1 to 2 hours	52 minutes	25 minutes	60 minutes
Elimination	Cellular uptake, renal	Hepatic	Enzymatic proteolysis	Renal
Ultrafiltration	Variable	Minimal	Yes	Yes
Antidote	Yes	No	No	No

or anti-Xa levels to within therapeutically desired ranges or the impossibility of doing so. The most common pathology responsible is the deficiency of AT.

Antithrombin can be replaced in the blood by administration of either AT concentrates or fresh frozen plasma, which contains a small amount of AT. The Rochester protocol[20] considered usage of AT concentrate in patients with levels less than 35% and evidence of heparin resistance. Literature, however, is limited, and the impact of AT administration on heparin requirements, bleeding, or thrombotic events is mixed.[21] Transition from heparin to DTIs such as bivalirudin has also been used in cases of heparin resistance.

WHAT IS THE THRESHOLD FOR RED CELL TRANSFUSION IN A PATIENT ON ECMO?

There are no standardized protocols regarding transfusion for patients requiring ECMO. Hemoglobin is essential to ensure oxygen delivery, which is particularly important in ECMO physiology, where oxygen saturation and/or circulating blood flow are low. However, a transfusion-limiting strategy may be beneficial to patients as frequent transfusion comes with its own risks. Multiple studies have shown that increased numbers of transfusions are an independent predictor of worse clinical outcomes among critically ill patients.[22]

Smith et al. showed that for patients being treated with ECMO for noncardiac indications, greater red cell transfusion requirement was independently associated with an increase in mortality.[23] Recent studies of ECMO in patients with acute respiratory distress syndrome have demonstrated that restrictive strategies targeting hemoglobin of 7.0 g/dL may perform just as well as a liberal target of 9.0 g/dL.[24] Cahill et al.[20] demonstrated that implementation of a standardized transfusion protocol (Rochester protocol), using more restrictive transfusion indications in cardiac ECMO patients, was associated with reduced blood product utilization, decreased complications, and improved survival.

It would hence be reasonable to state that a restrictive transfusion strategy be followed in ECMO patients aiming for hemoglobin greater than 7.0 g/dL. This target may be raised to more than 8.0 g/dL in bleeding patients and in nonbleeding patients with a clinical indication (i.e., untreated ischemic heart disease).

WHAT ARE THE CAUSES OF THROMBOCYTOPENIA IN A PATIENT ON ECMO?

The reasons for thrombocytopenia during ECMO are incompletely understood. Circulating platelets are consumed by binding of platelets, mediated by von Willebrand factor (vWF), to exposed collagen on the damaged vascular endothelium as well as platelet binding to the fibrinogen bound to the ECMO circuit. Platelets not only decrease in quantity, but also exhibit decreased binding affinity. Thrombocytopenia during ECMO may be explained by other reasons, such as severity of illness, use of platelet-lowering medications, numbers of organs with dysfunction, and precannulation platelet count. When adjusting for these factors, the link between thrombocytopenia and duration of ECMO has not been consistently reproducible.[25]

WHAT IS HITTS, AND HOW IS IT DIAGNOSED?

Heparin-induced thrombotic thrombocytopenia syndrome or heparin-induced thrombocytopenia (HIT) type II is an immune-mediated coagulation side effect of heparin therapy characterized by thrombocytopenia and a paradoxical prothrombotic state following heparin exposure. It is a challenging complication given the combination of thrombocytopenia, hypercoagulability, and need for continuous anticoagulation.

The concentration of circulating heparin–platelet factor 4 (PF4) complexes depends on both the propensity of heparin to bind to PF4 and the quantity of circulating PF4. During mechanical circulatory support, exposure of blood to the artificial circuit membrane increases platelet activation and may place patients at increased risk of heparin-PF4 antibodies as well as clinically significant HIT. This is well described in cardiopulmonary bypass, where greater than 50% of patients may have heparin-PF4 antibodies; however, only about 20% of patients have actual HIT type II, as demonstrated by confirmatory testing measuring in vitro platelet activation performed with a serotonin release assay.[26] An even smaller percentage of approximately 2%–3% develop clinical thrombosis.[27] The platelet activation that occurs with cardiopulmonary bypass also occurs with ECMO, though the frequency of HIT is unknown in this population. In relatively small, single-center case series, HIT was diagnosed in 0%–8% of patients supported with ECMO.[25,28]

HOW DO YOU MANAGE A PATIENT WITH HITTS?

Management of a patient with HITTS requires prompt diagnosis, immediate cessation of any heparin therapy, and administration of an alternative anticoagulant.

If suspicion of HITTS exists, the "4 T score" calculator can be used, taking into account: **t**hrombocytopenia (fall in platelets ≥ 50%, level usually < 60×10^9/L, but not below 20×10^9/L); **t**iming of thrombocytopenia (timing: days 5–10); **t**hrombosis; and absence of o**T**her potential causes of thrombocytopenia.[29] Unfortunately, all of these are typical features of ECMO itself, and the validity of the score has been questioned in ECMO.

If the clinical suspicion is intermediate to high, it is important to stop heparin, avoid platelet transfusion (as it may increase the generation of thrombi), and commence alternative anticoagulation while awaiting the result.

The ELISA measures levels of antibodies in the circulation against PF4 antigen. HITTS is excluded if there are fewer

than 0.4 optical density units or confirmed if there are more than 2.0 optical density units. Overall, the assay is rapid but unreliable due to a lack of specificity. It has been shown to be positive in 30%–39% of patients on ECMO despite HITTS having only a 1%–4% incidence in this population.[28]

A serotonin release assay can be performed, which helps to either confirm or exclude HITTS. This is a functional test of platelet factor 4 antibodies (it measures the ability of heparin antibodies from patient serum to activate test platelets). However, it usually takes much longer to get a result and rarely guides clinical management.

Following a diagnosis of HITTS, anticoagulation is typically achieved using a DTI. Results from the ELSO survey indicate that the three most widely used DTIs are argatroban, bivalirudin, and lepirudin. Unfortunately, the data for the use of DTIs for HITTS in ECMO patients are limited. Overall, areas of uncertainty are safe dosing regimens for these drugs in HITTS and whether they could ultimately replace UFH as the anticoagulants of choice in ECMO.

WHAT IS THE THRESHOLD FOR PLATELET TRANSFUSION IN A PATIENT ON ECMO?

Recommendations for management of thrombocytopenia vary widely by center and reflect institutional opinion since specific evidence-based recommendations do not exist. In a survey conducted by Bembea et al., platelet targets ranging from 20,000/μL to 100,000/μL were reported in different ELSO centers.[30] In addition, platelet dysfunction is common but not universally present in all patients.[31]

The targets used for transfusing platelets in the Rochester protocol[20] (bleeding patients with a count < 60,000/μL and < 30,000/μL in nonbleeding patients) potentially had significant clinical implications, such as decreased mortality and reduction of transfusion. It would be reasonable to transfuse platelets to at least 50,000/μL in patients with bleeding complications and prior to planned surgery.

WHAT IS THE APPROACH TO ANTICOAGULATION DURING THE ECMO WEANING PHASE?

Weaning of ECMO is the gradual reduction of ECMO support as organ function is recovering, and it is handled very differently in cardiac support when compared to respiratory support. The current ECMO systems have an optimal blood flow range within which clot formation in the device is relatively unlikely. The materials and components used as well as their size define this safe range.

During the initiation of ECMO, high blood flow and adequate size systems are chosen. A reduction of blood flow to minimal levels is specifically important during the process of weaning a patient off V-A ECMO, which may lead to blood flows below the optimal range. This should be counterbalanced by an increase in anticoagulation, more frequent screening for clot formation, and limiting low blood flow periods. It is important to know the safe blood flow ranges for each device used.

WHAT ARE THE IMPORTANT CONSIDERATIONS WHEN PERFORMING SURGICAL PROCEDURES IN A PATIENT ON ECMO? IS THERE OPTIMAL TIMING FOR TRACHEOSTOMY IN PATIENTS ON ECMO?

Surgical and interventional procedures are frequently needed to treat the underlying condition, facilitate treatment, or address complications during ECMO. Given the discussed ECMO-specific coagulopathies and bleeding risks, no procedure should be regarded as "routine" during ECMO. Even small interventions like the placement of a nasogastric tube can result in significant hemorrhage and should be undertaken with care. Akin to surgical procedures in non-ECMO patients, interruption of anticoagulation is possible and potentially safer if time allows. The ultimate decision should be made after discussion between the proceduralist and the ECMO specialist.

Optimal timing of tracheostomy in patients on ECMO is controversial at best, and the evidence is scarce. There are several potential benefits of an early tracheostomy, such as ability to wake more comfortably, effective mouth care, less incidence of ventilator-associated pneumonia, and possibility of oral intake and speaking. Safely waking up patients on V-V ECMO is controversial as the ability to breathe may be limited, with another major disadvantage of tracheostomy on ECMO being bleeding. A recent study by Kruit et al. reported a high incidence of bleeding (40%) associated with percutaneous tracheostomy insertion during V-V ECMO, albeit with a low incidence of significant bleeding (8%).

Given the risk of bleeding during ECMO is a potential deterrent in performing percutaneous tracheostomy at many centers, the safety of surgical tracheostomy in critically ill patients supported by ECMO has been explored, and when performed by an experienced operator, and with careful optimization of coagulation status, it may be a relatively safe procedure.[32]

DISCUSSION

Significant perturbations in hemostatic function are seen during extracorporeal therapies.[33] The mechanism is complex and relates to underlying pathology, blood-surface contact and pump mechanics (Figure 16.1).

The hemostatic perturbations are evidenced by platelet dysfunction and consumption, hyperfibrinolysis, or coagulopathy secondary to DIC. In fact, the hemostatic milieu during ECMO has been described as a mixture of the same processes that are observed during cardiopulmonary bypass and DIC (Table 16.2).[34]

Historically, bleeding had been reported in clinical trials where high anticoagulation targets were used, which contributed to excessive bleeding and mortality.[35]

The combination of endothelial damage, inflammation, organ failure, foreign surface contact, and anticoagulation may manifest as DIC and a resultant consumptive coagulopathy.[34]

This process can present in various stages during ECMO, and its phenotype may exhibit as a bleeding disorder and a

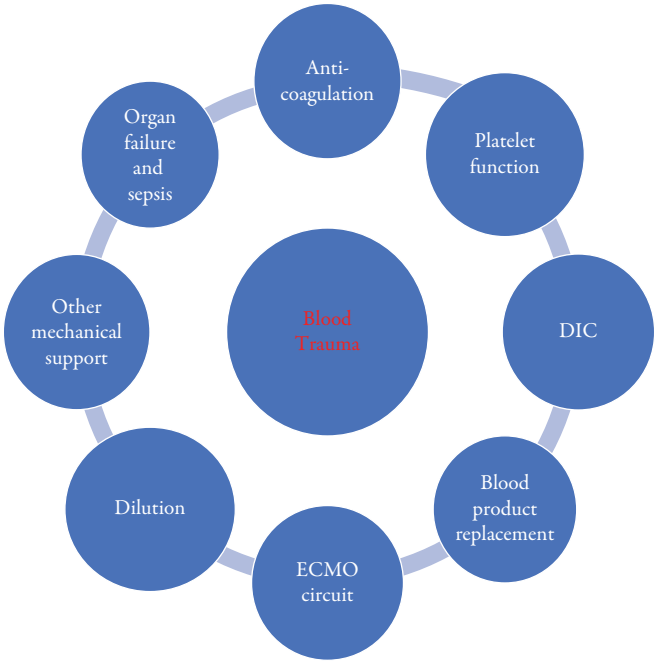


Figure 16.1 Perturbations in hemostatic function are seen during extracorporeal therapies. DIC, disseminated intravascular coagulation.

procoagulative state simultaneously. The genotype is, however, most often unknown and may involve platelet dysfunction,[31] up- or down-regulation of prothrombotic and fibrinolytic pathways and interaction with inflammatory responses.[36]

Current knowledge is insufficient to provide high-level, evidence-based recommendations on anticoagulation, management of bleeding, or transfusion triggers.[8] However, based on registry data, both bleeding and hemorrhagic complications are still the most commonly reported issues during ECMO and may have a large impact on morbidity and mortality.

Table 16.2 **THE HEMOSTATIC MILIEU DURING ECMO, CARDIO-PULMONARY BYPASS AND DIC**

	DIC	ECMO	CPB
Dilutional coagulopathy	-	+	++
Consumptive coagulopathy	++	++	-
Surface contact activation	-	++	+
Mechanical blood trauma	-	++	++
Thrombocytopenia	+	+	+
Platelet dysfunction	-	+	+
Anticoagulation	-	+	++
Fibrinolysis	+	(+)	++
Fibrinogen levels	-	+	-

CPB, cardiopulmonary bypass; DIC, disseminated intravascular coagulation.

DISEASE-INDUCED COAGULOPATHY

Inflammation, sepsis, trauma, major surgery, and massive transfusion are frequent traits of patients assessed for ECMO. All of these have significant impact on the coagulation system. Renal failure and liver failure are other complicating factors that will further induce coagulopathies. Endotoxins released during infections, tissue ischemia in shock, and exposure of endothelium after trauma or major surgery result in the clinical picture of systemic inflammatory response syndrome (SIRS), which has significant procoagulant effects through the expression of monocytes and tissue factor.[37] Excessive activation of protein C and fibrinolysis may further increase the consumption of clotting factors. This will eventually result in consumptive coagulopathy and an increase in hemorrhagic risk.

The coagulopathic effects of massive transfusion share many of the same processes as trauma, including hemodilution, hypothermia, and alterations in platelet function.[38]

ECMO-INDUCED COAGULOPATHY

There is a close relation between SIRS and triggering of the coagulation system. Contact between blood and the foreign surfaces triggers systemic inflammation, which stimulates the expression of tissue factor through monocyte and lymphocyte activation. This key molecule (tissue factor) initiates the activation of hemostasis, which can manifest as thrombosis leading to circuit dysfunction or thromboembolic events. The onset of clotting within the ECMO system results in damage to blood cells, which further exacerbates this process.[34,39]

The vWF acts as "glue" between the damaged vessels and platelets by binding to platelet receptor Glycoprotein Ib and exposed collagen. It also acts as a carrier for factor VIII, significantly increasing its half-life in the plasma. Because of its size of up to 20,000 kDa, high shear forces lead to sequestration and degradation of the vWF. The degradation of vWF hence impairs the activation and aggregation of platelets and may reduce the half-life of factor VII, thus reducing the activation of the extrinsic system.[40] This acquired vWF syndrome typically manifests with diffuse hemorrhage or unexpected bleeding after minor surgery.

ANTICOAGULATION

To counteract the prothrombotic effect of ECMO, UFH anticoagulation remains the gold standard during extracorporeal therapy. However, dosage and titration as well as stopping rules are not well defined and vary vastly in the literature.[7] Relative heparin resistance can frequently be observed, and this is often associated with AT deficiency. Some centers have integrated AT replacement in their anticoagulation guidelines, but no consensus exists in this regard.

During V-V ECMO, withholding anticoagulation or reducing it to a pure prophylactic dosing has been advocated,

but no high-level evidence comparing high- to low-dose therapy exists.[41] Alternative agents, including low-molecular-weight heparin as well as DTIs (argatroban and bivalirudin) have been suggested, but again, comparison data are lacking.[16,17]

Given the complex pro- and anticoagulant effects during ECMO, an individualized treatment aiming to suppress the excessive expression of tissue factor rather than chasing a specific coagulation test result would be most beneficial but has not been developed so far.

A conservative strategy for anticoagulation should be considered in situations where the bleeding risk is high, like during or after surgical procedures or interventions, or during thrombocytopenia or coagulopathy.

A liberal approach is useful when thromboembolic risk is high, like relatively low ECMO blood flow, poor LV ejection, or when clots have already been observed in the device or patient's vasculature.

CLINICAL COAGULATION MANAGEMENT DURING ECMO

The main goal during the management of the coagulation of patients on ECMO needs to be the continuous assessment of bleeding and thromboembolic risks.

This includes clinical examination and the recognition of potential or active complications and their early management. In addition, the ECMO circuit needs to be assessed for signs of clot formation (transmembranous pressure monitoring, visual inspection of all components, postoxygenator blood gases, among others).

Blood tests to assess the coagulation profile are frequently used, but no universal evidence exists on the value of each individual test and potential treatment algorithms. Tests can generally be used for the following purposes:

- Titration of anticoagulation
- Management of hemorrhagic complications
- Monitoring for ECMO circuit dysfunction
- Advanced testing for complex coagulation disturbances

TESTS TO TITRATE ANTICOAGULATION

The ACT, aPTT, and anti-Xa–based algorithms have been described to titrate UFH-based anticoagulation, and various target levels have been used to achieve this. AT levels have also been suggested to treat heparin resistance.[42]

However, since there is no head-to-head study comparing these approaches and due to the complex interaction with induced coagulopathies and various bleeding risks, it is unlikely that a universally agreed algorithm can be achieved.

Importantly, anticoagulation is an integral part of ECMO therapy and needs to be carefully controlled. This requires easily and swiftly available test results, local expertise, as well as clear algorithms to guide clinicians.[20]

TESTS TO MANAGE HEMORRHAGIC COMPLICATIONS

The most important management during major hemorrhage is to assess for surgical or interventional options, similar to patients not on ECMO.

Anticoagulation should be stopped if life-threatening bleeding occurs. Hemostatic resuscitation during major hemorrhage is paramount and requires point-of-care testing as well as clear algorithms to replace clotting factors and blood products. In addition to standard blood tests like platelet count or prothrombin time, viscoelastic testing (TEG or TEM) has been advocated and shown benefit in patients bleeding after cardiac surgery and trauma.[38] Since these pathologies share some common features with ECMO-induced coagulopathies and some initial studies have assessed their usage, it is reasonable to base clinical decisions on these tests.[15] Improved outcomes have most often been achieved when test results have been incorporated in treatment algorithms and massive transfusion protocols.

Any transfusion of clotting factors or blood products carries the risk of clot formation and ECMO circuit complications. Hence, overcoming these complications swiftly and decisively and staying vigilant during the treatment are important.

TESTS TO MANAGE CIRCUIT DYSFUNCTION

The ECMO circuit is best monitored using clinical assessment tools as described above. However, clot formation inside the oxygenator or other parts of the circuit can induce a consumptive coagulopathy that may display as a decline in fibrinogen and a rise of D-dimers.[43] Importantly, the trend rather than absolute number is important as is the exclusion of other processes explaining this.

Hemolysis can evolve secondary to an underlying medical problem or because of ongoing exposure of red cells to circuit surfaces.[44] This is often observed in the context of clot formation and circuit dysfunction. An acute rise in free hemoglobin, lactate dehydrogenase, or bilirubin may be an early marker of circuit failure even in the absence of other signs.

ADVANCED TESTING FOR COMPLEX COAGULATION DISTURBANCES

Many advanced hematological tests have been suggested in patients on ECMO. There is no evidence of additional benefit of most of these tests for the management of ECMO unless done for research purposes. Many ECMO patients present with complex and partially understood pathologies; hence, hematological consultation to rule out hematological conditions may be indicated.

Monitoring for HITTS remains challenging as the clinical screening test[28] is not very reliable in ECMO, and laboratory confirmation lacks specificity. It is concerning that HITTS incidence has a high variability and both over- and underdiagnoses may be associated with morbidity and mortality.[45]

MANAGEMENT OF THROMBOEMBOLIC COMPLICATIONS

Thromboembolic complications can originate from the arterial system, the venous system, or the ECMO circuit. Clot formation in the arterial system is particularly common in V-A ECMO in the context of low pulmonary blood flow and poor LV ejection. Minimal arterial pulse pressure (less than 15 mm Hg) is a sign of LV distention and intracardiac blood stasis. Ventricular and aortic valve thrombi can follow in hours and constitute an ECMO emergency because of the risk of embolic complications.

Deep venous thrombosis is often related to venous cannulation, and large thrombi have been identified in a quarter of all patients recovering from V-V ECMO.[46] Its frequency could be correlated to low anticoagulation targets during ECMO, and postdecannulation venous Doppler or computer tomographic assessments should be undertaken to identify patients in need for ongoing anticoagulation. Clot formation inside the extracorporeal circuit are important because of three reasons. First, obstruction of circuit components can cause sudden circuit failure. Second, clots may increase shear stress and initiate a consumptive coagulopathy followed by hemolysis and DIC. Last, embolic complications may have a direct impact on patient morbidity. Continuous monitoring and documentation of circuit function is essential for early identification of these complications.

MANAGEMENT OF HEMORRHAGIC COMPLICATIONS

Transfusion Trigger

The optimal transfusion trigger to treat anemia in critically ill patients has been investigated frequently over the past decade. In conclusion, liberal transfusion strategies aiming for hemoglobin levels above 9.0 g/dL have failed to show any benefit over more conservative approaches (7.0 g/dL).[22,47]

This is in contradiction to more classical guidance for ECMO where hemoglobin levels of well above 10 g/dL are targeted. Importantly, these recommendations are based on physiological considerations with the aim to increase oxygen delivery in situations where oxygen saturation and/or circulating blood flow is low. Clinical evidence extrapolated from the above trials suggests that transfusion-related complications may counterbalance this potential benefit, and conservative transfusion thresholds are safe.

Platelet transfusion is usually considered in the context of major hemorrhage, and the benefit is not clearly defined within the specific focus of ECMO treatment. Guidelines suggest their use during a massive transfusion protocol and when a specific nadir platelet count has been reached. During ongoing bleeding, this nadir is often quoted as a count of less than 60,000/μL and less than 30,000/μL in nonbleeding patients.[20] Coexisting coagulopathies should be taken into consideration. While platelet dysfunction has been documented frequently, it is rarely taken into consideration because of the lack of point-of-care testing.[33]

Desmopressin has been used to enhance platelet function, but no clear evidence exists on its benefit and safety.[48]

Clotting Factor Replacement

The replacement of clotting factors during major hemorrhage has been supported by guidelines and evidence outside of ECMO.[49] Since no specific ECMO-related studies exist, these principals should be applied to patients on ECMO. This includes massive transfusion protocols as well as the specific replacement of individual clotting factors. Factor replacement with fresh frozen plasma or cryoprecipitate or factor concentrates is used in different healthcare systems.

Tranexamic acid has recently become part of trauma protocols, but evidence of its use and safety in ECMO is mostly drawn from observational studies. Viscoelastic testing may help to identify patients at risk for fibrinolysis.[50]

It remains unclear if clotting factors should be replaced in the absence of major bleeding, and limiting such interventions to times where bleeding risk is high (e.g., during surgical interventions) is reasonable. The risk of clot formation is increased during transfusion and factor replacement as a result of which decline of the circuit function is possible, but catastrophic circuit failure is rare.[51] However, undertreatment of hemorrhagic complications can result in more severe coagulopathies and hence increase the need for blood products and clotting factors in the long run with more pronounced consequences for the patient and the ECMO circuit.

CONCLUSION

- Coagulation abnormalities during ECMO display features seen in cardiopulmonary bypass and disseminated intravascular coagulopathy.
- Hematological complications contribute to a large proportion of ECMO mortality and morbidity.
- Anticoagulation is an important treatment strategy during ECMO, but dosing recommendations and titration algorithms are largely based on expert opinion.
- Blood management strategies are most often extrapolated from other patient groups.
- ECMO centers should adopt policies for anticoagulation and blood management based on international guidelines and position statements, while more research is needed in both categories.

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REVIEW QUESTIONS

1. Which of the following is NOT a tool to assess the oxygenator function during ECMO?

   A. Visual inspection and documentation of clots
   B. Measurement of the pressure gradient across the oxygenator
   C. Doppler measurement of oxygenator flow
   D. Trend in fibrinogen and D-dimer over time

2. Which of the following is an advantage of DTIs when compared to UFH?

   A. Short half-life
   B. Easy to antagonize when overdosed
   C. Low risk of HITTS
   D. Clear monitoring and titration in patients with organ failure

3. Which statement is incorrect?

   A. Tissue factor plays a key role in the initiation of a procoagulative state during ECMO.
   B. High shear stress may reduce von Willebrand factor levels and in turn reduce platelet function.
   C. Activated clotting time and aPTT are common parameters to monitor anticoagulation in ECMO without clear evidence favoring one over the other.
   D. Thromboembolic complications are by far the most important complications during ECMO and require anticoagulation at all times.

4. Which statement is incorrect?

   A. Hemoglobin levels (together with circulating blood flow and oxygen saturation) determine the oxygen delivery to the tissues.
   B. A normal hemoglobin level should be maintained by adequate red cell transfusions.
   C. Early and aggressive treatment of bleeding complications is a good strategy to maintain appropriate hemoglobin levels.
   D. Blood transfusions have been shown to contribute to a pro-inflammatory state and may have unwanted side effects.

5. Which statement is correct in regard to HITTS?

   A. HITTS is a common condition during ECMO.
   B. HITTS can easily be diagnosed at the bedside.
   C. The best strategy to treat thrombocytopenia during HITTS is by platelet transfusion.
   D. Heparin should be stopped and replaced by a different agent as soon as suspected.

6. Which statement is incorrect?

   A. Viscoelastic testing has been proven to be equivalent to ACT when titrating anticoagulation.
   B. Viscoelastic testing can give specific information on the heparin effect on a blood sample.
   C. Viscoelastic testing assesses the whole ability of the blood to form a clot.
   D. Viscoelastic testing provides information on the presence of hyperfibrinolysis.

7. What statement is incorrect in regard to titration of anticoagulants?

   A. The risk for thromboembolic events is higher in V-A ECMO compared to V-V ECMO.
   B. A fixed target anticoagulation range should be maintained at all times during ECMO.
   C. If a poor LV ejection is observed during V-A ECMO, a liberal anticoagulation strategy may be indicated.
   D. Delaying the start of anticoagulation after major surgery may avoid hemorrhagic complications.

8. Which statement is correct?

   A. Hemolysis is always a sign of a failing ECMO circuit.
   B. Monitoring of serum bilirubin is an early indicator of hemolysis.
   C. Hemolysis can be a sign of exposure of red cells to the ECMO circuit.
   D. Ongoing red cell transfusion is a sufficient treatment for hemolysis during ECMO.

9. Which statement is correct in regard to the management of major bleeding during ECMO?

   A. Anticoagulation should never be stopped during ECMO.
   B. The replacement of clotting factors should be part of a protocol during massive transfusions.

C. Surgical intervention should be the last resource if no other treatment is successful.
D. Hemoglobin levels should always be maintained above 10.0 g/dL.

10. Which statement is incorrect?

A. Ultrasound evaluation of the venous system is useful during and after ECMO to demonstrate deep venous thrombosis.
B. Echocardiography may demonstrate LV clots during V-A ECMO.
C. Clotting of a distal perfusion cannula can critically reduce the perfusion of an upper limb.
D. Anticoagulation should be prolonged after the weaning of ECMO if thromboembolic disease had been identified.

11. Chose the correct statement:

A. Antithrombin should always be measured and replaced to normal levels during ECMO.
B. Antithrombin function is greatly augmented by heparin and leads to a dramatic increase in its effect on serine protease.
C. Heparin resistance is best treated by increasing the dose of heparin.
D. Antithrombin is a clotting factor that should be kept normal during major hemorrhage

12. Which statement is correct?

A. Major trauma is a contraindication to initiate ECMO.
B. Changing a central line during ECMO should always be done after anticoagulation was stopped for a minimum of 4 hours.
C. Placement of a chest drain during V-V ECMO is safer than without because oxygenation is maintained.
D. Surgical interventions and procedures during ECMO should be undertaken by experienced staff because of an increased bleeding rate even after cessation of anticoagulation.

ANSWERS

1.C, 2.C, 3.D, 4.B, 5.D, 6.A, 7.B, 8.C, 9.B, 10.C, 11.B, 12.D

PHARMACOLOGICAL CONSIDERATIONS FOR ECMO

17.

PHARMACOLOGICAL CONSIDERATIONS FOR ANALGESIA AND SEDATION OF ECMO PATIENTS

Joshua Chew, Vesa Cheng, and Kiran Shekar

STEM CASES AND KEY QUESTIONS

CASE 1

A 45-year-old man is admitted with severe community-acquired pneumonia and respiratory failure. He is intubated, mechanically ventilated, and is receiving low-dose vasopressor support. Over 24 hours, he develops severe acute respiratory distress syndrome (ARDS). As a management strategy, he has been deeply sedated, and a neuromuscular blocking agent (NMBA) infusion has been commenced. Over the following 2 days, he fails all conventional ARDS therapies, including protective lung ventilation, fluid restriction, and prone ventilation. He exhibits refractory hypoxemia with an arterial partial pressure of oxygen (PaO_2) of 40 mm Hg. The intensive care team initiates the patient on veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) through a femoro-femoral route as a bridge to recovery. The ECMO blood flow rate (EBFR) is set at 6 L/min, and the ventilator settings are set to achieve a driving pressure of less than 12 cm H_2O while maintaining a respiratory rate of 10 breaths/min and a positive end-expiratory pressure (PEEP) of 15 cm H_2O. Deep sedation and NMBA infusion are continued, but he is persistently hypoxemic despite the introduction of ECMO with a PaO_2 of 50 mm Hg.

CASE 2

A 20-year-old female with chronic lung disease in the context of cystic fibrosis (CF) is admitted with severe respiratory failure. She has been on the lung transplant waiting list. As there are no prospects of recovery from her current exacerbation, the decision is made to list her urgently for priority lung transplantation. She is intubated and mechanically ventilated. Over the next 12 hours, she develops severe hypercapnia and hypoxemia and is difficult to both ventilate and oxygenate despite the use of NMBA. She is then placed on V-V ECMO using a dual-lumen cannula inserted through the right internal jugular vein, and her physiology is optimized on EBFR of 3 L/min. She is subsequently extubated and undergoes rehabilitation with the efforts of her multidisciplinary team. Her respiratory drive is managed with CO_2 removal on ECMO as well as enteral benzodiazepines with the addition of low-dose dexmedetomidine for anxiolysis and analgesia. She undergoes lung transplantation on day 25 of her admission. With her preoperative optimization, she is finally able to be extubated on the day of transplant and is discharged to the ward 2 days after surgery.

CASE 3

A 50-year-old man is admitted with a week of increasing shortness of breath and syncopal episodes. Echocardiography reveals severe biventricular failure with no regional wall motional abnormalities. Over the next 24 hours, he displays increasing episodes of nonsustained, multifocal, ventricular tachycardia and progresses to severe cardiogenic shock with early end-organ dysfunction despite inotrope/inodilator therapy. Femoral arterial and venous sheaths are placed under local anesthesia to enable rapid ECMO initiation in the event of a cardiovascular collapse, and he was subsequently intubated. He is then placed on femoro-femoral veno-arterial (V-A) ECMO under transesophageal echocardiography guidance as a bridge to recovery/further decision-making. A myocardial biopsy and right heart catheterization were also performed once stabilized on ECMO. Lymphocitic myocarditis is noted on biopsy. Right heart catheter data is favorable for the insertion of a durable left ventricular assist device (LVAD) or urgent heart transplantation in the absence of cardiac recovery following a period of V-A ECMO support.

CASE 4

A 50-year-old man is admitted to the ICU following ECMO-assisted cardiopulmonary resuscitation (ECPR) and percutaneous coronary artery intervention. The patient suffered a witnessed out-of-hospital cardiac arrest and received immediate bystander cardiopulmonary resuscitation (CPR). The time to commencement of ECMO in the cardiac catheter laboratory from the time of cardiac arrest was 75 minutes. A computed tomographic (CT) scan of the head reveals no intracranial pathology. On day 1, he receives midazolam (10 mg/h) and fentanyl (200 μg/h) as well as cisatracurium (2 mg/h) to facilitate therapeutic hypothermia. Despite timely bystander

CPR and effective circulatory support with ECMO, he subsequently exhibits significant hepatic and renal dysfunction necessitating renal replacement therapy. Both sedatives and cisatracurium were ceased on day 2, but he remained unarousable on day 5. By this stage, there had been some improvement in both cardiac and hepatic function. Given the neurological status, he is scheduled to undergo a repeat CT of the head and an electroencephalographic (EEG) study.

WHAT CAN WE LEARN FROM THESE CASES?

These cases highlight the heterogeneity among patients supported with ECMO. These patients differ not only in terms of their underlying disease processes but also in their expected clinical trajectories and the likelihood of recovery or need for durable options. Thus, sedation management in these patients[1,2] goes beyond comfort and safety considerations.[3] These more case-specific considerations are the focus of discussion here.

WHAT ARE THE MAIN FEATURES OF CASE 1?

Case 1 highlights the issue of hypoxia with V-V ECMO, despite higher EBFR of 6 L/min.[4] Problems with the machine, access, or recirculation were appropriately excluded. This picture is not uncommon early in the course of V-V ECMO, where patients with little to no gas exchange occuring in native lungs become dependent on high ECMO blood flows (EBFs) to maintain oxygenation. This is often in the setting of a high cardiac output (CO) state, resulting in oxygenated ECMO blood admixing with deoxygenated native CO. This high CO state may be mediated through the hyperdynamic stage of sepsis. In considering oxygenation in terms of supply-demand balance, it would seem intuitive to further increase EBF in an attempt to improve oxygen supply but this would involve inserting another venous drainage cannula. Instead, an alternative approach would be reducing oxygen demand/consumption through physiological manipulation via sedative optimization.[5] Specifically, NMBA use can be important as well as the adjunctive use of agents such as dexmedetomidine with its negative chronotropic properties to further reduce CO and hence increase favorably the EBF/CO ratio.[4] This phase of minimal native oxygenation and low EBF/CO ratio typically resolves over a period of days. This allows for the cessation of NMBA and lightened sedation as those parameters improve.[6] Patients are increasingly kept awake or very lightly sedated as able, with the aim to facilitate spontaneous respiration, rehabilitation, and mobilization. This case highlights the dynamic nature of sedation during V-V ECMO through the patient's clinical course, as well as the role of sedation in management of refractory hypoxemia.

WHAT CAN WE LEARN FROM CASE 2?

Case 2 describes the use of ECMO as bridge to transplantation. In this context, the goals of care differ to case 1.[7,8] The availability of suitable donor lungs is an unpredictable endpoint. The maintenance of the patient's strength and conditioning, as well as motivation and positive psychology are important considerations. V-V ECMO can facilitate the ability for rehabilitation that would otherwise not be feasible with conventional therapies. In these patients, V-V ECMO at lower EBFR can normalize gas exchange to the point where extubation is possible and allow for greater engagement with rehabilitation and mobilization.

WHAT ARE THE SPECIFICS OF CASE 3?

The complexity of the third case lies in the ambiguity of the therapeutic endpoint. At a basic level, ECMO is organ support At a basic level, ECMO is organ support, and sedation and analgesia (S&A) facilitates this therapy. However, optimal S&A not only addresses this fundamental task but also accounts for the other context-specific goals of care. In case 1, resolution of the pathology was expected. In case 2, the chronic pathology would mean that it was unlikely to resolve to a level where the patient could be weaned from ECMO. Finally, in the third case, the prognosis of the pathology was yet to be determined. Thus, it could be termed that ECMO was a bridge to decision,[9,10] awaiting the declaration of the patient's clinical course. Aspects of case 2 where ECMO was used to facilitate rehabilitation would still be relevant and may even be important in influencing the patient's outcome.

WHAT IS THE PROGNOSIS FOR CASE 4?

The fourth case highlights the dilemma of neurological prognostication following ECPR.[11,12] There was a relatively prolonged "low-flow" time in this patient, with 75 minutes elapsing until the commencement of ECMO and a "high-flow" state.[13] This is likely to contribute to the failure to wake despite a 4-day sedation-free window and normalization of hepatic function. In this circumstance, clinicians have to exclude the influence of any residual sedative drugs or their metabolites prior to neurological assessment and prognostication. Clinicians are often concerned that the ECMO circuit may act as a reservoir for sequestered drugs, and that this may potentially prolong their effects after the cessation of infusions via redistribution.

HOW DO WE SET THE GOALS FOR S&A IN ECMO

Sedation and analgesia in ECMO at an elemental level involve drug choice, dose, and the management of safety and comfort. Beyond this, the optimal strategy would be determined by clinical context and the above vignettes demonstrate a range of goals where ECMO and the level of sedation are manipulated to advantage the patient. The following sections address these concepts in further detail.

WHAT ARE THE ROLES OF SEDATION AND ANALGESIA ON ECMO?

Implementation of ECMO is a last line treatment option for patients with cardiorespiratory failure unresponsive to maximal

conventional therapies.[10,14] In this, it is important to consider the nature of the therapy and the underlying pathology, which is inherently severe in nature. Furthermore, S&A will need to adapt to the clinical course of the patient, and therefore remain fluid. To outline the roles of S&A, they can be broadly classified as

1. Patient comfort
2. Physiological control
3. Patient safety

Patient Comfort

Extracorporeal membrane oxygenation is invasive in nature and for this reason necessitates analgesia and sedation. The concept of S&A for invasive life support therapies is not foreign to intensive care, and principles from S&A in other intensive care or critically ill patients can be extrapolated. The underpinning precept of this role is to maintain comfort, and this patient-centered goal is balanced against either inadequate or excessive sedation—both of which are accompanied with deleterious effects. The details of this risk-benefit equation is further elaborated in the section on risks and benefits in this chapter.

Physiological Control

Moreover, S&A has a role in physiological control: facilitating the management of ventilation strategies, optimizing oxygen consumption and circuit flows. This may mean avoiding spontaneous ventilation on initial venous cannula insertion, or employing a "lung rest" strategy in an ARDS patient, or maintaining tube tolerance and the prevention of ventilatory dyssynchrony. Given that this is a patient population that has failed maximal attempts at other conventional therapies, it would be safe to assume that the patient would exhibit extremes of cardiorespiratory physiology. Thus, in order to facilitate a "salvage" therapy, especially in the respiratory failure patient, the manipulation of the balance between oxygen consumption and delivery will be essential. That is, the optimization of circuit flows or oxygen delivery and a reduction in oxygen consumption are not peripheral considerations but central. This is pertinent particularly at the commencement and stabilization phases of therapy. Indirectly, there may also be advantageous byproducts of sedative agents on CO influencing shunt through native lung units not participating in gas exchange for certain patients.[15] Generally speaking, achieving physiologial control favors deeper sedation.

Patient Safety

Last, patient safety is paramount. This is applicable in aiding cannulation, avoiding air emboli during venous cannulation, and the avoidance of cannula kinks, "suck-down" phenomena, dislodgement, or decannulation. Accidental decannulation can frequently be fatal.[16] Coughing can induce suck down or chatter and result in hemolysis in the circuit. In general, to prioritize safety would mean increased sedation potentially with the addition of neuromuscular paralysis; although as seen in the cases presented at the start of this chapter, this may undermine other therapeutic goals. There exists a conceptual balance in optimal S&A depth, and this must factor in not only the individual patient, but also the center's experience, culture, resources, and staffing.[16]

WHAT ARE THE GUIDING PRINCIPLES OF SEDATION AND ANALGESIA ON ECMO?

Sedation and analgesia on ECMO are conceptually guided by the roles defined in the previous chapter, but in a more apparent sense by clinical endpoints and pharmodynamic interplay. Fundamentally, there is a targeted sedation level that is generally achieved with a "balanced" combination of opioid and hypnotic. This targeted level of sedation to akin to the tale of Goldilocks, in that too little or too much would be undesirable. Moreover, the goals should change during different phases of ECMO therapy, and will be different based on modality—be that V-V ECMO, V-A ECMO, or ECPR. In general, increased sedative drugs are required during the cannulation and establishment of ECMO, and also with the use of V-V ECMO when compared to other modalities.[17]

The Extracorporeal Life Support Organization (ELSO) recommends sedating a patient to the point of light anesthesia during cannulation and for the first 12 to 24 hours. After the patient is stable on ECMO, all sedation and narcotics should be stopped long enough to allow for a thorough neurologic examination. Then S&A may be resumed depending on the patient's level of anxiety and discomfort. Sedation should be minimal, but it is important to ensure the patient does not pull on cannulae and tubes, and risk decannulation or occluding access or return lines. Common reasons for impediment to venous blood drainage is patient anxiety, movement, or coughing. Choice and dosing of S&A should suitably address these.[18]

Sedation should be sufficient to avoid increases in the native metabolic rate. Beyond this, metabolic rate may be therapeutically lowered by means of systemic paralysis and cooling. S&A issues regarding these interventions are applicable as they are for other mechanically ventilated patients. That is, S&A is required in the paralyzed patient, and the management of shivering may necessitate pharmacological interventions. ELSO further recommends holding S&A long enough to do a neurologic examination daily (a daily drug holiday), and this should also give clinicians information as to how their patient will cope with lighter sedation.[18]

Despite the above recommendations from ELSO, specific practice varies greatly among institutions, as seen in large international surveys.[2] This highlights that there are probably many ways to achieve similar goals and that local context will influence the details of institutional practice.

HOW ARE SEDATION AND ANALGESIA MONITORED ON ECMO?

Previous sections have highlighted the importance of achieving specific sedation depths. Therefore, monitoring, recording, and tracking sedation, as for any other key physiological variable, is necessary. This can be done according to local practices—be that an objective scoring system or other means. Although some guiding principles of S&A can be ECMO specific, the monitoring tools for sedation or pain are generally not.

Much of the rationale and evidence surrounding monitoring and the use of objective scoring systems is extrapolated from other intensive care data. There is a general trend toward standardization of care; as such, objective scoring systems combined with sedation protocols have been successfully implemented in many intensive care units (ICUs). Moreover, the use of objective scoring systems and sedation protocols that allow lighter sedation with daily interruptions have been shown to reduce morbidity in the ICU.[19] This has become extrapolated to those on extracorporeal life support (ECLS) and integrated into ELSO guidelines.[18] Various objective scoring systems exist for sedation and pain, but covering these in detail would be outside the scope of this chapter. Multiple large surveys have shown that the vast majority of centers use a validated sedation scoring tool and pain assessment tool. The most common of these were the *Richmond Agitation Sedation Scale* and the *Critical Care Pain Observation Tool*. This was similar in both high- and low-volume centers. Less common was ECMO-specific sedation protocols, although, as one might expect, these were marginally more common in high-volume centers.[2,20]

Moreover, other tools have been used and implemented in this population to guide S&A. Bispectral (BIS) monitoring, a proprietary depth of anesthesia monitor based on a processed EEG signal has been implemented, although not formally evaluated in this patient population.[19] BIS is predominantly used in anesthetic practice and there may be a role to extend its use to this setting, but further studies demonstrating its validity are required.

WHAT ARE THE PHARMACOKINETIC/PHARMACODYNAMIC CONSIDERATIONS FOR SEDATION AND ANALGESIA ON ECMO?

There is a multitude of sedative or analgesic agents that can be used solely, or in combination to achieve desired clinical endpoints. The choice of agent should also consider the interplay of pharmacokinetics/pharmacodynamics (PK/PD) in a critically-ill[21] host and the extracorporeal circuit. Most commonly, an opioid will be used to address analgesia in combination with a sedative agent to achieve a sedation level ranging from anxiolysis to deep sedation or even anesthesia. There can be synergism from the combination of these agents; thus, dose-dependent side effects of any one agent can be minimized while achieving a similar endpoint. In addition to core S&A agents, the use of potential adjuncts is discussed.

A fundamental concept in drug selection will be pharmacokinetics. The critically ill population demonstrates pronounced alterations in pharmacokinetics, and this is further compounded by the use of ECMO.[22] As a consequence, resulting pharmacokinetics are a result of the reciprocity between patient, drug, and circuit factors, including alterations in CO, organ perfusion or drug clearance, volumes of distribution, and circuit sequestration.[23] The ability to predict and manage these perturbations is essential for providing directed pharmacotherapy. This results in a triad of interactions: patient-drug (which are not necessarily ECMO specific), patient-circuit, and drug-circuit interactions.

Patient-circuit interactions would include changes to CO, organ perfusion, or drug clearance and volumes of distribution. The circuit and its priming fluid may be conceptually akin to adding another drug compartment or altering the volumes of existing comparments in a multi-compartmental pharmacokinetic model. Moreover, this patient-circuit interaction will be influenced by the specific circuit, its volume, the effects of non-pulsatile flow on organ perfusion, and the interplay between an extracorporeal circuit and host - with potential systemic inflammatory response syndrome (SIRS) phenomena.

Drug-circuit interactions have been the subject of much pharmacokinetic study in the literature. Most agents commonly used for the purpose of sedation/analgesia have been discussed in the literature but evaluated only to varying degrees. It is important to note the study design utilized in the literature; which ranges from ex vivo studies (where a drug is circulated through an ECMO circuit and drug loss evaluated), to retrospective data collection of doses in clinical patients, to prospective dosing and plasma level studies. Further prospective pharmacokinetic studies in larger populations are needed, and we are waiting the results of the ASAP ECMO (Antibiotic, Sedative and Analgesic Pharmacokinetics during Extracorporeal Membrane Oxygenation) study[24] to narrow this knowledge gap.

Drug adsorption and sequestration are influenced by the physicochemical properties of the administered agent—including molecular size, degree of ionization, lipophilicity, and protein binding. The degree of lipophilicity, indicated by the octanol/water partition coefficient (log *P*) and the percentage of plasma protein binding, has a significant impact on drug sequestration in the ECMO circuit.[25–27] To generalize, a rapidly acting drug that acts on the central nervous system would likely have a high degree of lipophilicity in order to act on its target receptor. Hence, S&A acting on the central nervous system would generally fall in this category and be subject to drug-circuit interactions based on this physicochemical property. Drugs with high log *P* values (around 2.0) will have a propensity to be very soluble in organic materials such as the polyvinyl chloride tubing used in the ECMO circuit. However, one must note that there is little known about the adsorptive capacity of the circuit over long periods of time as most studies have only looked at the 24-hour period. ECLS, however, can often extend beyond this time frame, and thus the age of the circuit then becomes another pharmacokinetic variable.[28]

WHAT ARE THE AGENT-SPECIFIC FACTORS THAT INFORM THE CHOICE OF SEDATIVE AND ANALGESIC DRUGS ON ECMO?

Analgesics

Opioids are indispensable analgesics used in intensive care. There is a familiarity and proven track record with this class of drug in the critically ill population. Their class effects of respiratory depression and sedation are typically thought of as adverse effects, but in the ECMO patient may be used to manage 'air hunger' and tube tolerance. Moreover, there can be synergism seen with many commonly used sedatives when they are used in conjunction. This drug class is relatively hemodynamically stable compared with other S&A drugs and the inclusion of opioids can reduce the dose requirements and dose-dependant hemodynamic effects of other agents. By definition, drugs of this class will mediate their effect through the opioid receptor, and this gives similar pharmacodynamic profile amongst individual agents within this class. With the exception of methadone, the other opioids discussed can be thought of as pharmacodynamically uniform. Thus, their selection would then be based on pharmacokinetic differences. Most commonly used opioids in intensive care have been addressed in the ECMO literature. These include fentanyl, morphine, hydromorphone, sufentanil, alfentanil, and remifentanil.

The most commonly used opioid in international surveys remains fentanyl.[2,20] Fentanyl is highly lipophilic and has been shown to have a mean drug loss of 97% into an ex vivo ECMO circuit at 24 hours.[29] It has also been shown in some, but not all, studies to require dose escalation over time.[19,30] The demonstration of ex vivo circuit drug loss and potential clinical dose escalation has not seemed to have curbed the usage of this opioid despite the suggestion that ECMO introduces significant pharmacokinetic variability. Proponents have described the advantage of inactive metabolites as a reason its use, particularly in patients with renal dysfunction. Familiarity and its common use in the ICU for non-ECMO patients likely also influence its popularity.

Morphine is another commonly used opioid that, unlike fentanyl, appears to be minimally sequestrated in ex vivo models, with less than 1% drug loss at 24 hours.[29] However, despite the ex vivo models, morphine was similarly shown to require dose escalation over time, and this correlated with decreasing plasma concentrations.[19] Interestingly, its active metabolites were also shown to decrease in plasma concentration: morphine-3-glucuronide by 36% and morphine-6-glucuronide by 35%.[31] Acknowledging the phenomenon of dose escalation, based on the limited clinical data, it has been suggested as a superior alternative to fentanyl.[32]

Alfentanil, a highly ionized, rapidly acting, synthetic opioid has been used and described in ECMO patients. It has been shown to have no difference in patient outcomes when compared with fentanyl.[33] Other clinical data is limited.

Sufentanil is an exceptionally lipophilic and highly protein-bound drug. Sufentanil exhibited an increased volume of distribution for ECMO patients when compared to the non-ECMO population. Pharmacokinetic data would suggest that a higher rate of infusion is required in the ECMO population, with the exception of the hypothermic patient whose clearance is markedly reduced.

Enteral methadone has been used as an adjunctive opioid. It has been described that its long duration of action can be advantageous in this setting. With its use as an adjunct, it has been shown to temper escalation of other sedatives/analgesics,[35] and may have a role in reducing withdrawal symptoms when ceasing other opioids.

Sedatives

Midazolam, a commonly infused short-acting benzodiazepine, in ex vivo models has been shown to be significantly sequestrated with only 13% drug recovery at 24 hours.[29] In vivo studies have been conflicting however. They have ranged from dose requirements being twice as high as non-ECMO comparators, to having decreased daily dose requirements in another group.[30, 19, 36] On further appraisal of this discrepancy, the group who showed decreased dose requirements used what previous papers would term "high-dose" fentanyl and targeted much lighter sedation scores. Overall, it can be anticipated from expected pharmacokinetic changes on ECMO that higher loading and maintenance doses should be considered.[32] Despite this need, midazolam use remains popular, and this may be due to the more hemodynamically stable profile when compared to propofol.

Propofol, a phenol intravenous sedative, is a highly lipophilic and highly protein-bound drug. It had particularly advantageous infusion kinetics, with a short context-sensitive half-time even with prolonged infusion. It has been demonstrated to be significantly sequestered within the ECMO circuit and even theorized to undergo oxidative breakdown. In an ex vivo model of a whole-blood primed ECMO circuit, 70% of propofol drug concentration diminished within the first 30 minutes of the experiment, and after 5 hours only 11% of the initial propofol concentration remained.[37] Based on this limited data, it appears that higher doses of propofol may be required over time for equivalent sedation, but this is yet to be correlated with in vivo data incorporating plasma level analysis. Moreover, maximal doses need to be further defined in this population in the context of the risk of propofol-related infusion syndrome if higher dosing regimens are suggested for these patients. Initially, concerns were expressed regarding premature oxygenator failure with propofol secondary to adsorption to the membrane oxygenator. However, this has not translated to any decrease in oxygenator life span in a clinical study comparing to ECMO patients who did not receive lipid via propofol or total parenteral nutrition.[38] Propofol remains popular in both high- and low-volume centers internationally.[20]

Thiopentone, a barbiturate agent, is not a routinely used sedative in the ICU. It is limited by its sustained infusion kinetics and prolonged effect after continuous infusion. In an ex vivo study, highly protein-bound thiopentone had only 12% drug recovery at 24 hours, that is to say that most of the drug was lost to the circuit.[39] Further clinical study for this agent is warranted, although similar to most agents, the expectation is that increased doses would be required to achieve the same plasma concentrations.

Dexmedetomidine, a highly selective, centrally acting, alpha-2 agonist has gained popularity in the ICU for its

Table 17.1 SUMMARY OF CONSIDERATIONS OF SPECIFIC SEDATIVES/ANALGESICS DURING ECMO

SEDATIVE/ ANALGESIC	PHYSICOCHEMICAL PROPERTIES	PHARMACOKINETIC IMPLICATIONS[a]	DOSING	OTHER CONSIDERATIONS
Fentanyl	High lipophilicity Relatively high protein binding	High sequestration	Higher initial loading dose and higher daily doses	No active metabolites in patients with renal impairment
Morphine	Relatively lipophilic Moderate protein binding	Minimal-to-moderate sequestration	Modest increases in initial loading dose and daily doses	May have fewer drug-circuit interactions (cf. fentanyl)
Midazolam	Highly lipophilic Highly protein bound	High sequestration	Higher initial loading dose and higher daily doses	May have more hemodynamically stable profile cf. propofol
Propofol	Highly lipophilic Highly protein bound	High sequestration	Insufficient data	Not associated with reduced membrane oxygenator lifespan
Dexmedetomidine	Moderate lipophilicity Highly protein bound	Moderate-to-high sequestration	Higher initial loading dose and higher daily doses	Negative chronotropic effect. May be useful to achieve lighter sedation

[a]Minimal sequestration is determined by log *P* less than 2 and protein binding less than 60%. Moderate sequestration is determined by log P between 2 and 3 and protein binding greater than 60%. High sequestration is determined by log P greater than 3 and protein binding greater than 60.

absence of respiratory depression, promotion of a more physiological sleep-wake cycle, potential reduction of delirium,[17] and unique sedation profile characterized by being relatively rousable yet able to tolerate invasive therapies. Similarly, as for other sedatives, it appears to be significantly lost through circuit adsorption. 50% of dexmedetomidine was sequestered to an infant circuit after 48 hours; this was comparatively more when compared with midazolam in the same study.[40] However, as referenced in the case studies, it is also important to note that the agent also has a negative chronotropic effect. This may be desirable in select patients 1. Internationally, it remains popular, particularly for targeting lighter sedation after the establishment phase of ECMO has been completed.[20] It can be used both as a sole agent or in addition to other sedatives.

Ketamine, a phencyclidine derivative, has many pharmacodynamic properties that are distinct from traditional γ-aminobutyric acid (GABA)–receptor mediated, or opioid receptor–mediated agents. It is not commonly used as a sole sedative agent, but rather, as an adjunct. It has characteristic dissociative effects at higher doses and nonopioid-mediated analgesia seen even at low doses. Its adverse psychomimetic phenomena may be reduced through lower doses and the avoidance of boluses. Hence, it is typically used an a adjunct via low-dose infusion.[32] An initial retrospective study showed a sedative-sparing effect with concurrent decrease in vasopressor requirements,[41] but this was not seen in a subsequent randomized controlled trial (RCT) in V-V ECMO.[42] A potential limitation of this RCT may have been the use of sedation protocols not designed to suit ketamine's pharmacodynamics. It titrated agents to respiratory rate, which is generally preserved with ketamine.

Lastly, oral benzodiazepines and antipsychotics have been used in similar doses across both ECMO and non-ECMO populations and provided comparable, predictable and familiar results. Anecdotally, they have been shown to be useful adjuncts in reducing dose escalation of other sedatives and prevent withdrawal after the cessation of prolonged benzodiazepine infusions.

In summary, firm guidelines on agent choice do not exist. Common practice would suggest an initial combination of propofol or midazolam with a rational opioid choice. There could be consideration for use of dexmedetomidine either in combination or as a sole agent, and it may have a particular role in targeting lighter sedation when this is appropriate for the patient. Consideration should also be given to adjuncts, either routinely or in difficult patients. These choices should be further shaped by local practices and potentially standardized at institutions. It has become apparent that international S&A practices varies, and this has made it difficult to compare reporting of dosages between clinical studies. Certainly, vigilance regarding common pharmacokinetic alterations while on ECMO is advisable. A synopsis of key pharmacokinetic considerations for use of commonly used sedatives and analgesics during ECMO is provided in Table 17.1.

WHAT ARE THE RISKS AND BENEFITS OF SEDATION AND ANALGESIA ON ECMO?

The risk-benefit profile of S&A in ECMO has patient comfort, safety, and physiological control balanced against the risks that accompany excessive sedation. Safety issues have been elicited previously and include the risk of air emboli, cannula kinks, suck-down phenomena, dislodgement, or decannulation. Physiological parameters of relevance include metabolic demand, ventilation management, CO, and sequelae of cooling (i.e., shivering) if applicable. These were outlined in the section of this chapter discussing the roles of S&A.

The risks of oversedation are mostly extrapolated from the non-ECMO population, where less sedation confers advantages such as patient interactiveness, early assessment of neurology, early weaning from mechanical ventilation, oral

feeding, and active mobilization. The avoidance of excessive sedation has been shown to improve outcomes in critically ill patients.[43,44] Moreover, there may also be the minimization of ICU morbidity related to the risk of infections, duration of mechanical ventilation, inotrope and vasopressor requirements, drug withdrawal, posttraumatic stress, and length of hospital stay.[17] More specifically, the use of continuous sedative infusions, as opposed to intermittent sedation or no sedation, is an independent predictor of longer duration of mechanical ventilation and longer ICU and hospital stay. Prolonged high cumulative doses of opioids and benzodiazepines have been associated with tolerance, physical dependency, and subsequent withdrawal. Deeply sedated patients are also at risk of having more traumatic recollections of their ICU experience than lightly sedated patients.[2] It would stand to be biolgically plausible that all these benefits are equally applicable to the ECMO patient. Notably, this is reflected in ELSO guidelines suggesting daily sedation holds with the consideration of reinstating sedation only if beneficial. Thus, the concept of "awake" ECMO and lighter sedation is attractive for the appropriately selected patient. As discussed in cases 2 and 3, it could be seen that a lighter sedation protocol would enhance active mobilization and facilitate rehabilitation in order to optimize successive treatments. Addressing these broader goals while promoting oral feeding and minimizing posttraumatic stress disorder may provide holistic care to the appropriate patient.

Conversely, one must acknowledge issues pertinent to the ECMO patient and weigh the above benefits against potential pitfalls. Deeper sedation may be required to successfully employ a "lung rest" strategy or reduce the distress of a hypercarbic-driven respiratory drive with an intolerance of mechanical ventilation. Spontaneous ventilation in the context of their underlying lung disease may not prove to be a viable option for all patients. Attempts to reduce sedation and wake patients who have been made volume deplete in an attempt to optimize native lung function may induce a precipitous drop in blood flow, and this could lead to a hypoxic crisis if oxygenation is reliant on ECMO. Greater intravascular volume is anecdotally associated with fewer cardiovascular perturbations on reducing sedation, but this may not be appropriate for all patients.[16] Moreover, in a review of 110 patients, there was no short-term survival benefit, and there is an increased incidence of cannulation site bleeding with lighter sedation.[45] It is also important to consider the phase of ECMO therapy, with ELSO guidelines suggesting light anesthesia during the first 12–24 hours of therapy.[18]

In summary, robust, ECMO specific data is limited but the above highlights the issues as pertinent to S&A in ECMO. S&A needs to be individualized to patient, pathology, modality, prognosis and phase of ECMO therapy.

WHAT ARE THE CONSIDERATIONS FOR SEDATION AND ANALGESIA IN V-V ECMO AND EXTRACORPOREAL CARBON DIOXIDE REMOVAL?

When differentiating the S&A considerations between ECMO modalities, patient factors and indication for therapy are most relevant. V-V ECMO is now an established therapy for patients with ARDS and refractory hypoxia failing conventional therapies.[46,47] This scenario, as seen in case 1, generally means high-acuity pathology, little physiological reserve, and usually, the reliance on extracorporeal oxygenation. Thus, the considerations of ECMO in such a situation would give priority to safety, the facilitation of circuit flows, and facilitating lung protective ventilation. All of which culminate in favoring deeper sedation at least until some resolution or stabilization of the underlying physiology.

In a prospective study, patients who received V-V ECMO had significantly higher opioid requirements when compared to their V-A ECMO counterparts. Approximately half of these patients had ARDS and required increased doses to facilitate optimal ventilation parameters.[19,36]

Contrast this with case 2. Again, this case describes ECMO use as a rescue therapy for hypoxia failing conventional therapies, but instead of a bridge to recovery, ECMO is used as a bridge to transplant. It is likely the above considerations would remain relevant in the initial phase, but negotiating other treatment goals of active mobilization and rehabilitation shifts the risk-benefit relationship to attempting a lighter sedation protocol as soon as feasible.

A primary reason for sedation during V-V ECMO is to tolerate endotracheal intubation. Conversion to tracheostomy[48,49] may be considered early in patients expected to require longer term mechanical ventilation, as this is associated with reduced sedation requirements. In select patients, ECMO or $ECCO_2R$ may provide sufficient gas exchange to facilitate extubation. Early extubation has advantages in avoiding ventilator-associated complications as well as sedation-related complications. This may be especially relevant to immunosuppressed patients[50–52] and is a subject for future research.

Hypercapnia and respiratory acidosis, although usually well tolerated, are a barrier to implementing ultraprotective lung ventilation in patients who do not develop refractory hypoxemia. This has renewed interest in extracorporeal CO_2 removal ($ECCO_2R$).[14] Flow rates are significantly reduced in $ECCO_2R$ and reliance of sedation to facilitate optimal flows is less of an issue. Moreover, the control of CO_2 may reduce respiratory distress and reduce sedation requirements in and of itself.

WHAT ARE THE CONSIDERATIONS FOR SEDATION AND ANALGESIA IN V-A ECMO?

Using ECLS to provide temporary mechanical circulatory support (MCS) to patients with acute, refractory cardiac failure is a rapidly evolving area. Intervention is often time critical; and mortality is higher than ECLS for isolated respiratory failure. Central V-A ECMO has been traditionally applied as a bridge to recovery in patients who fail to wean from cardiopulmonary bypass after cardiac surgery. Central V-A ECMO outside of this setting is uncommon in adults. Femoral V-A ECMO avoids sternotomy, and can be more rapidly achieved. Hence, it is more commonly used in adults requiring urgent cardiac support. Peripheral V-A ECMO is a treatment option

for patients with acute cardiac failure refractory to conventional management. As seen in case 3, ECMO was used as a bridge to decision. Further evolution and clinical assessment will then guide whether the subsequent trajectory is as a bridge to recovery or a bridge to treatment—in the form of a durable LVAD or transplant. Alternative scenarios may be more clear in their clinical course and therefore in the goal of ECMO. The utility of peripheral V-A ECMO lies in the ability for rapid initiation; this is most apparent in ECPR.

Awake V-A ECMO is increasingly common, and patients can be safely cannulated under local anesthesia and minimal sedation. This may be preferable in some patients as there is a significant risk of deterioration during the process of endotracheal intubation, which can be performed after successful commencement of V-A ECMO. In extremely anxious patients, intubation may be performed after placing venous and arterial sheaths in the femoral vein and artery. As stated previously, when compared to V-V ECMO, V-A ECMO patients had lower opioid requirements. However, despite this, they generally had deeper sedation scores. This has been hypothesized to be related to the the underlying circulatory derangement and higher critical illness severity scoring of these patients. This deeper level of sedation may actually reflect cerebral dysfunction rather than pharmacological effect.[17]

WHAT ARE THE CONSIDERATIONS FOR SEDATION AND ANALGESIA IN ECPR?

Peripheral V-A ECMO is used to provide cardiopulmonary support during cardiac arrest when conventional CPR and life support have failed to establish adequate circulation. It has been shown to promote survival in select children and adults. Outcomes are still reliant on effective CPR with minimal delay, and this is a key consideration in the selection of ECPR candidates. The ability to rapidly restore circulation and achieve organ perfusion with ECMO is a paradigm shift from the traditional adult life support algorithm. The interventions of conventional adult life support intend to provide some flow, as opposed to no flow, to achieve some organ perfusion whilst either defibrillation restores native rhythm or other underlying causes are reversed. The circulatory restoration achieved with ECLS far exceeds that which can be achieved with high quality conventional CPR, and this means that the time taken to complete other definitive treatments is much extended. For example, a cardiac arrest that had timely ECLS could have percutaneous coronary intervention at a much later time than would be thought reasonable with just external chest compressions. In this regard, ECPR is usually used as a bridge to treatment.

As discussed with V-A ECMO considerations, these patients are likely to have deep "sedation scores", possibly exclusive of pharmacotherapy effect. A low Glasgow Coma Scale score would accompany an arrest almost by definition. As with the other scenarios, the goals of treatment inform the considerations for S&A. Once stabilized on MCS, targeted temperature management may be instigated as per local practices, and sedation tailored to facilitate this. Moreover, as seen in case 4, neuroprognostication will become essential to guide management, and sedation will often need to be weaned for further assessment.[11,12] A significant number of patients will be diagnosed as brain dead, and may enter an organ donation pathway. When performing sedation holds for neurological assessment and the diagnosis of brain death, it is important for clinicians to consider ECMO related pharmacokinetic derangements. Namely, the redistribution of sequestrated drug. It is also important to consider patient pathology affecting drug metabolism. For example, the patient may have hepatic dysfunction secondary to an ischemic hepatopathy, altered liver blood flow affecting metabolism of high extraction ratio drugs, or hypothermia lowering metabolic activity.[53] Generally speaking, ECPR is associated with reduced S&A dose requirements.

WHAT NOVEL SEDATION AND ANALGESIA OPTIONS EXIST FOR ECMO?

The facets of S&A comprise of depth, monitoring, and agent choice. Therefore, novel options or alternate practices can address depth, monitoring, or agent choice. Firstly, the concept of awake ECMO[54] is relatively new but is becoming more established. The label of awake ECMO is somewhat reductive, and could mean different things across institutions. Patient selection, timing, and targeted sedation scores may vary; but generally, sedation is minimized to the level where patients are able to interact.

Furthermore, the use of additional monitoring tools may further refine sedation practices. EEG-based monitors such as BIS may offer objective and titratable endpoints for sedation. This may particularly useful in ECMO, as compared with other ICU patients, for a number of reasons. Neuromuscular blockade is frequently employed (removing interaction and movement from assessment), pharmacokinetics in ECMO are variable, and the underlying pathology may make typical dosing ranges unsuitable. Experienced bedside staff and accurate sedation scoring would still remain a cornerstone, but the addition of processed EEG monitors may aid assessment. For example, the presence of burst suppression and low BIS would indicate oversedation and this may correlate with poorer outcomes. However, the use of these tools in this setting requires further evaluation.

Finally, drug choices or routes that are less commonly used have been published in ECMO literature. Of particular mention, oral adjuncts, have been used with positive results. These include antipsychotics, enteral methadone, and enteral lorazepam.[55] Moreover, inhalational agents have been used in ECMO, including those with severely compromised lung function on V-V ECMO. Despite tidal volumes less than 350 mL, targeted sedation with volatile anesthetics has been shown to be feasible, and a dose-response relationship appears to exist.[56] This may bypass traditional challenges of intravenous agents and may represent a reliable, titratable sedative agent with minimal metabolism. These agents may also have the benefit of bronchodilation and improved ventilation-perfusion matching in certain patients.

HOW IS SEDATION AND ANALGESIA INDIVIDUALIZED WITH A HOLLISTIC APPROACH?

Patient-centered, individualized, holistic care is a goal of modern medicine. This must also operate within a framework of standardized, large-scale, evidence-based care; and these seemingly opposing constructs need be reconciled. The Society of Critical Care Medicine's clinical practice guidelines for the management of S&A, as well as clinical trials, reported improved outcomes with algorithm-based approaches to sedation management. They reinforce structured management that can be patient-tailored, and include the use of sedation protocols.[57] Algorithms should be consistent with 'best practice', comprehensive, and fluid enough to meet the nuanced needs of each individual.

Using a previous case as an example, a holistic approach for case 2 should incorporate multiple considerations. Prior to her acute illness, there should have been appropriate patient and family discussions regarding priorities of her care. Acknowledging that there may be the possibility of longer-term ECMO as a bridge to transplant, clincians should consider the use of internal jugular, dual-lumen access for reduced infection rates and ease of care. Given the increased risk of a distal intestinal obstruction syndrome in the context of her CF, a reduced opioid infusion regimen should be trialled.[58] Hollistic care would also consider sedation weaning and extubation for all the reasons discussed in previous sections, but also for the ability to eat, drink, and vocalize. Some aims of holistic care are more difficult to quantify, but emphasize the whole patient, the promotion of their agency, well-being, psychology and motivation in conjunction with traditional goals of organ support and symptom control.

DISCUSSION

As emphasized in the case scenarios and through the above sections—context defines the goals of treatment. We have discussed cases that used ECLS as "bridges" to either decision, recovery or treatment, be that transplant or durable LVAD. This and the expected clinical course of the pathology inform S&A. Generally, heavy sedation or light general anesthesia is advocated with commencement of ECLS. Following this, sedation should be regularly reviewed, and in general, the patient progressed towards less sedation. Other treatments, like extubation or tracheostomy, may need to be instigated to allow for this reduction of S&A.

The prediction of PK/PD derangements are crucial to the use of drugs in ECMO.[23,25–27] The introduction of ECLS is generally associated with increased dose requirements, and this is more pronounced in highly lipophilic and protein-bound drugs.

The body of literature regarding S&A in ECMO has been growing steadily and should inform practice. It is important to note what has been demonstrated in ex vivo studies as well as dose-plasma concentration clinical studies. Additionally, retrospective dose-reporting ex vivo studies, as well as retrospective and prospective clinical studies that may or may not include plasma concentration analysis. Currently, a prospective, pharmacokinetic, observational study, ASAP ECMO,[24] is waiting analysis, and this may provide robust PK data that may further inform practice.

CONCLUSION

- Sedation and analgesia is central to the management of patients on ECMO. It is important for patient comfort, safety, and physiological control.
- Sedation and analgesia is typically achieved with a combination of commonly used ICU drugs, namely opioids, midazolam, propofol and dexmedetomidine. It can also incorporate other adjunctive agents.
- Sedation and analgesia management on ECMO is context-specific and the goals of therapy need to be defined as early as possible.
- To guide S&A management, institutions need to decide on appropriate monitoring of sedation, and this includes the use of objective tools.
- Agent choice can be rationalized based on PK/PD considerations, organ impairment, physiological goals, as well as clinician/institution preference.
- Pharmacokinetic/pharmacodynamic alterations can be considered in the framework of patient-drug, patient-circuit, or drug-circuit interactions.
- Finally, clinical care should be holistic and consistently consider individualization within a best practice framework.

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REVIEW QUESTIONS

Several answers may be correct.

1. Which of the following are considerations for S&A in ECMO?

A. Allowing for early mobilization
B. Decreasing patient oxygen consumption
C. Reducing suck-down phenomena
D. All of the above

2. Which of the following are ELSO recommendations?

A. Sedating the patient to the level of light anesthesia for the first 48 hours.
B. After neurological examination, resume S&A depending on patient's level of anxiety and discomfort.
C. Common reasons for impediment to venous blood drainage are patient anxiety, movements, or coughing.
D. The use of dexmedetomidine is encouraged as a delirium-prevention agent.

3. Which of the following statements regarding monitoring of sedation is true?

A. Only the Richmond Agitation Sedation Scale is validated for monitoring in ECMO patients.
B. Low-volume centers do have ECMO-specific sedation protocols.
C. BIS monitoring would be particularly helpful in the unparalyzed patient.
D. High-volume centers did not rely on objective sedating scoring tools.

4. Which of the following pharmacokinetic factors would result in increased dosage requirements?

A. Nonbiological circuit inciting a host SIRS
B. Reduced liver blood flow for a high extraction ratio drug
C. Hypothermia
D. Highly lipophilic opioid

5. Which drug factors would favor drug adsorption to the circuit?

A. A log *P* less than 2.0
B. High plasma protein binding
C. High degree of ionization at physiological pH
D. A weak acid drug with a pKa of 11

6. Which of the following statements regarding opioids in ECMO is true?

A. In ex vivo studies, the mean loss of fentanyl (as a percentage) was greater than that for morphine.
B. In a study looking at plasma concentration of a patient on morphine and ECMO, only morphine plasma concentrations decreased, and morphine-6-glucuronide concentrations were unaffected.
C. Alfentanil has been shown to reduce time to decannulation when compared with fentanyl.
D. Core body temperature and body weight are significant variables for sufentanil pharmacokinetic modeling.

7. Which of the following statements regarding sedatives in ECMO is true?

A. Midazolam loading doses are higher, but maintenance dosing appears to remain similar.
B. Propofol adsorbs to the membrane oxygenator, and this will need to be changed more frequently.
C. Dexmedetomidine is an ineffective respiratory depressant and does not control the "air hunger" seen in hypercarbic patients.
D. Inhalational agents can only be used when tidal volumes are greater than 350 mL. Otherwise, they will not work reliably.

8. Which of the following statements regarding adjunctive agents is true?

A. Oral benzodiazepines can reduce withdrawal after the cessation of a prolonged midazolam infusion.
B. In sedation protocols that use respiratory rate, adjunct ketamine infusion can reduce this and allow the down-titration of opioids.
C. Oral antipsychotics need to be used in supramaximal doses due to the pharmacokinetic considerations of ECMO.
D. Oral methadone reduces dose escalation of other sedatives/analgesics.

9. Which of the following are potential advantages of an awake ECMO technique?

A. Reduced catheter site bleeding
B. Reduced rates of posttraumatic stress disorder
C. Reduced tolerance of opioids and benzodiazepines
D. Short-term survival benefit

10. Which of the following regarding V-V ECMO is true?

A. There are reduced opioid requirements when compared with V-A ECMO.
B. $ECCO_2R$ can facilitate extubation.
C. The sedation for V-V ECMO patients should only be lightened once they are decannulated.
D. Inadvertent decannulation is usually well tolerated.

ANSWERS

1D, 2B,C, 3B, 4A,D, 5B,D, 6A, 7C, 8A,D, 9B,C, 10A,B

18.

CHALLENGES OF ANTIMICROBIAL THERAPY IN ECMO PATIENTS

Vesa Cheng, Mohd H. Abdul-Aziz, and Kiran Shekar

STEM CASE AND KEY QUESTIONS

A 50-year-old man was admitted with severe respiratory failure following a week of flu-like illness. Influenza A was isolated from his nasopharyngeal aspirates on admission. He was mechanically ventilated for worsening respiratory failure and fatigue. Oseltamivir (75 mg orally twice daily) was commenced on admission to the intensive care unit (ICU). After initial improvement, he had worsening acute respiratory distress syndrome (ARDS) on day 4, necessitating veno-venous (V-V) extracorporeal membrane oxygenation (ECMO). His condition was further complicated by septic shock and acute kidney injury, for which he received renal replacement therapy (RRT). Multiple cavitating lesions were noted on a computed tomographic scan of the chest, and methicillin-sensitive *Staphylococcus aureus* was isolated from the bronchial aspirates. A percutaneous tracheostomy was performed on day 12 to facilitate awakening, rehabilitation, and bronchial toilet as needed. Significant agitation and encephalopathy were noted, which improved with discontinuation of oseltamivir.

There was little improvement in his pulmonary status over the next 65 days, and he remained fully ECMO dependent. There were multiple subsequent intercurrent infections and episodes of sepsis during the ECMO run, which were treated with pipercillin-tazobactam, vancomycin, meropenem, and caspofungin. *Candida albicans* was isolated from blood cultures on day 30, and *Aspergillus fumigatus* was isolated from his bronchial washings on day 50. Serum galactomannan antibodies were found to be significantly high, suggestive of invasive aspergillosis. Significant hemoptysis arose, which was managed conservatively. He was commenced on intravenous voriconazole. Finally, gradual improvement in pulmonary gas exchange and compliance occurred from day 90, and he was finally liberated from ECMO on day 112. He was liberated from mechanical ventilation 4 days later and was discharged to the ward with ongoing RRT and remained on enteral voriconazole.

This case highlights the complexities involved in antimicrobial therapy in ECMO patients. The patient initially presented with a community-acquired flu pneumonitis complicated by a secondary staphylococcal pulmonary infection requiring ECMO support. He then developed multiple infections on ECMO requiring antimicrobial therapy. The patient was critically unwell, which predisposed him to ICU-acquired infections and critical illness-related alterations in pharmacokinetics/pharmacodynamics (PK/PD). These PK/PD alterations can be further exacerbated in the presence of ECMO and may result in antimicrobial drug failure or toxicity. The solution is not a "one-size-fits-all" approach each individual antimicrobial used in this patient. A thorough understanding of each drug's physicochemical structure, PK/PD profile, and the common types of infections in ECMO patients is essential in working toward the resolution of infections in this group of critically ill patients.

WHAT IS THE EPIDEMIOLOGY OF INFECTIONS DURING ECMO?

Patients can present with infections and related cardiorespiratory failure that may necessitate ECMO support or more commonly may develop infections on ECMO. Given the challenges of diagnosing infection on ECMO, the true burden of infection on ECMO may be underestimated.

Infections Acquired Prior to ECMO Initiation

Both bacterial and viral pneumonia are common indications for V-V ECMO.[1–3] One of the most widely reported indications for V-V ECMO in ARDS is influenza A (H1N1); a significant increase in the use of ECMO for this indication was seen during the 2009 H1N1 pandemic.[3] These patients often develop coinfections with *S. aureus*, multidrug-resistant Gram-negative bacteria, candida, and aspergillus species, which may risk lower survival compared with influenza alone.[3,4] Likewise, concomitant nonpulmonary infection acquired at the time of initiation of ECMO for ARDS may predict worse outcomes.[5] It is important to note that culture positivity may not represent true infection, and detection of these organisms prior to the initiation of ECMO may or may not have contributed to the cardiopulmonary failure that necessitated ECMO. While infectious etiologies may account for a relatively small proportion of the indications for nonarterial (veno-arterial [V-A]) ECMO in cardiac failure, certain subpopulations warrant consideration. Both acute myocarditis, which is often attributable to infection, and sepsis-associated cardiomyopathy are typical indications for V-A ECMO.[3,6,7]

The Extracorporeal Life Support Organization (ELSO) Registry data[3] identified 5492 positive cultures prior to the initiation of 17,374 distinct ECMO runs for respiratory failure (32%). Positive cultures prior to ECMO appeared to be much more common in cases of ECMO initiated for respiratory failure. Preexisting culture positivity was much lower for cardiac indications (8.8% of cardiac failure runs; 7% of runs for extracorporeal cardiopulmonary resuscitation [ECPR]), with the respiratory tract microbiological samples yielding most of the positive cultures. Regardless of ECMO indication, *S. aureus* and yeast were the most common respiratory tract pathogens reported. Notably, influenza A was the most commonly identified organism in the respiratory tract in patients receiving ECMO for respiratory failure, accounting for 13% of all organisms identified. *Staphylococcus* and *Streptococcus* species were the most common isolates from the bloodstream across all ECMO indications. Yeast, *Escherichia coli*, and *Enterococcus* species were common pathogens isolated in the urine.

Infections Acquired During ECLS

Variable rates of infections acquired during ECMO have been reported in the literature. Patients receiving ECMO may develop typical ICU-acquired infections, such as ventilator-associated pneumonia (VAP) and bloodstream or urinary tract infection. ECMO-related infections may arise from cannulation site infections or mediastinitis in the setting of central cannulation.[3,8,9] Based on ELSO Registry data, Bizzarro et al.[10] reported a 21% prevalence rate of infections on ECMO. However, infection rates of between 9% and 65% have been reported during ECMO.[3,8,11] Based on published literature, incidence of infection on ECMO ranges from 10.1 to 116.2 per 1000 ECMO days.[12] Patients receiving ECMO for respiratory failure appear to develop the highest rate of culture positivity (65%), whereas ECPR is associated with the lowest rate (22%). The distribution of pathogens during ECMO appears to be similar to the pre-ECMO distribution pattern. Yeast and *S. aureus* were the most common organisms isolated in the respiratory tract during ECMO across all indications. *Staphylococcus* species, yeast, and *Enterococcus* species were among the organisms isolated most frequently from blood cultures. Although the quality of data is not robust, infections acquired during ECMO may affect patient survival. The survival rates for patients developing infection on ECMO were 54% versus 61% for respiratory failure and 38% versus 44% for cardiac failure.[10] It is important to note that these data refer only to organisms identified on culture, and it is not possible to discriminate between colonization and true infection.

WHAT ARE THE RISK FACTORS FOR INFECTION ON ECMO?

The risk factors for infections on ECMO are not fully elucidated. Based on observational data, several potential risk factors have been identified. Apart from critical illness itself, immune dysregulation may play a significant role. Although ECMO duration has frequently been associated with the development of nosocomial infections,[3,8,11,13] it is not clear whether these infections result from longer ECMO runs or in fact are a contributing indication to longer runs. Equally, patients may die from an overwhelming infection early despite ECMO support; therefore, the causation-versus-association debate is yet to be settled. The extracorporeal circuit may affect the immune system through contact activation, endothelial dysfunction, coagulation activation, or neutrophil and platelet activation with consequent release of pro-inflammatory mediators,[14] resulting in a hyperinflammatory state. Equally, ECMO may exert anti-inflammatory effects through improvements in organ function and the minimization of secondary injuries, such as ventilator-induced lung injury resulting from damaging conventional mechanical ventilation techniques.[3,15] Immunocompromised patients appear to have worse outcomes when compared to immunocompetent patients. A multicenter observational study of 203 immunocompromised patients receiving ECMO for severe ARDS reported a 50% incidence of VAP. Cannula-associated infections were identified in 10% of patients.[2,16,17] The 6-month survival in this cohort was only 30%. However, infections acquired during ECMO did not independently predict mortality, and the poor outcome may likely have resulted from nonresolution of an underlying disease process or other complications that may arise during ECMO.

In addition, older age, greater pre-ECMO severity of illness, underlying autoimmune disorders, circuit configuration, and performance of procedures during ECMO have all been implicated as risk factors for infections during ECMO.[3,9,13,18] It is unclear whether the site and number of ECMO cannulae are associated with an increased risk of infection. Cannula site infections were more common with a surgical approach than a percutaneous approach (28% vs. 17%) in a recent propensity-matched analysis from 814 patients.[19] Central ECMO has been associated with greater risk of infection in pediatric studies.[12,20] Studies prior to the introduction of modern ECMO circuitry indicated an increased incidence of bloodstream infections in ECMO patients compared with non-ECMO critically ill patients.[21] ICU practices and technology both have evolved since, and more data are needed to substantiate these findings.

WHY IS IT IMPORTANT TO ACHIEVE OPTIMAL ANTIMICROBIAL THERAPY IN PATIENTS ON ECMO?

Optimal antibiotic therapy has been shown to have the greatest impact on infected patients' survival when compared with other treatment strategies, such as the use of antithrombin III,[22] activated protein C,[23] and intensive insulin therapy.[24] Severe infections leading to sepsis and septic shock are prominent contributors to morbidity and mortality in critically ill patients. Data from a large study suggested that 26.7% of patients who are admitted to the ICU were diagnosed with sepsis, with corresponding mortality rates of 32.2% and 54.1% in patients with sepsis and septic shock, respectively.[25] A point-prevalence study reported that 51% of ICU patients were classified as infected on the day of study with a corresponding

mortality rate of 25.3%.[26] Prompt initiation of antimicrobial therapy that is active against the causative pathogen also plays a crucial role in the treatment of patients with sepsis and septic shock.[27]

The provision of artificial cardiopulmonary support, such as ECMO, has been a significant advancement in the area of intensive care medicine. However, the introduction of multiple indwelling devices is associated with increased risk of developing infections when compared to ICU patients not on ECMO.[11,13,28] The ELSO reported an adult nosocomial infection rate of 20.5% in patients receiving ECMO.[10] Among ECMO patients, nosocomial infections can increase the risk of mortality by 38%–61%.[10,18] A study suggested that bloodstream infection is the most common type of infection during ECMO use.[29] Understanding the loci of infection and the type of pathogen to guide the selection of antimicrobial therapy therefore becomes a significant determinant of survival for infected critically ill patients on ECMO.[30,31] The challenges associated with optimizing antimicrobial dosing is due not only to ECMO-related physiological changes but also to the lack of robust bedside endpoints that could guide the dosing of antimicrobials in ECMO. The risk of suboptimal antimicrobial exposure that ECMO could cause may contribute to treatment failure and/or development of antimicrobial resistance.[32]

WHAT ARE THE KEY DIAGNOSTIC CHALLENGES TO ANTIMICROBIAL THERAPY ON ECMO?

The challenges of detecting infections during ECMO can potentially delay their prompt recognition and treatment. Equally, response to antimicrobial therapy may also be difficult to ascertain. Temperature management on ECMO can mask fever or hypothermia.[3,12,33] The presence of infiltrates on chest radiographs used to help identify VAP[34] may be difficult to interpret when extreme lung-protective ventilatory strategies, which may result in significant atelectasis and volume loss, are employed. Equally, the routine inflammatory markers such as C-reactive protein or proposed markers for infection such as procalcitonin have not been validated for ECMO patients. In a small case-control study,[35] these markers showed good sensitivity (87%) but poor specificity (26%). Another small study did not demonstrate any association between procalcitonin and infection on ECMO.[36] To overcome this uncertainty, many centers perform daily blood cultures for infection surveillance,[37] which may result in greater culture positivity rates with limited ability to clinically correlate to confirm an active infection. In addition, diagnosis of infection in a patient on ECMO can be confounded by bacterial colonization in the ECMO circuitry.[11] Kim et al. investigated 13 patients on ECMO who developed bloodstream infections, of which only six cases had recorded cannula colonization.[38] On the contrary, 34 patients did not develop a bloodstream infection, of which three patients had recorded cannula colonization. It is therefore important to supplement microbiological findings with the clinical picture of infection and also treat an infective presentation empirically without microbiological guidance. Techniques such as rapid genome sequencing may allow better identification of pathogens and remains an area of further research.

Furthermore, colonization can also occur within the oxygenator. The artificial surfaces within the oxygenator are commonly covered with debris made up of fibrinogen that is in constant contact with the patient's blood. Raad et al. demonstrated the affinity of coagulase-negative staphylococci and *Candida* species binding to fibronectin and thus the possibility of colonization of the membrane lung surfaces and production of biofilms.[39] This supports the ELSO Registry noting the two pathogens along with *Pseudomonas aeruginosa*, Enterobacteriaceae, *S. aureus* and *Enterococcus* species to be the most frequent causative pathogens in ECMO patients.[10] Although invasive lines can be removed or changed, it is often not feasible to do this for patients dependent on ECMO for survival. It is therefore imperative for sterile practices and optimal antimicrobial dosing in a patient on ECMO to prevent selection pressure to more resistant organisms.

WHAT ARE THE KEY THERAPEUTIC CHALLENGES TO ANTIMICROBIAL THERAPY ON ECMO?

The most prevalent types of infections in ECMO patients are bloodstream infections, lower respiratory tract infections, and urinary tract infections.[11] Empirical antimicrobial therapy is often used when clinical signs of infections such as biomarkers and microbiological cultures return supportive of the presence of infection. The Surviving Sepsis Campaign[40] recommends the use of broad-spectrum antibiotics in the initial management of patients with sepsis and septic shock. However, once the pathogen(s) are identified and their susceptibilities become available, empiric antimicrobials should be deescalated to more narrow spectrum agents to promote therapeutic appropriateness and reduce costs.[41] In order to accurately dose and choose the most appropriate antimicrobials, it is imperative for quick microbiological and susceptibility testing. This will guide not only our choice of antimicrobials but also the dosing to ensure sufficient concentrations of the agent are available at the site of infection.

Altered PK/PD on ECMO: The Known Knowns

The process of optimizing antimicrobial therapy has been a key area of research in recent years. The extreme physiological derangements in our ICU patients has been a well-established phenomenon, and the dosing of antibiotics in these patients has been a daunting challenge for many clinicians.[32] Antimicrobial effects have been highly associated with the pharmacological property of the drug. Two principle areas of pharmacology are PK and PD. Antimicrobial killing efficacy has been highly associated with the attainment of a PK/PD target. Dosing antimicrobials based on PK/PD principles has been shown in preclinical studies to minimize the risk of emergence of resistance by avoiding ineffective antibiotic exposure, which consequently exerts a selective pressure to more resistant pathogens, rather than eradicating them.[42]

The introduction of ECMO further deranges physiological changes found in the critically ill patient, effectively moving our PK/PD target by increasing the volume of distribution (V_d) and changing the clearance (Cl) of the drugs.[43] The enlargement of V_d is thought to be due to the ECMO-related change in apparent V_d of the drug by either drug sequestration into the circuit or hemodilution. The key predictor of whether the drug will be sequestered into the circuit has been associated with the physicochemical properties of the drug and its potential interaction with the ECMO circuit. Two key physicochemical properties that are associated with drug loss to the circuit are lipophilicity and high protein binding.[44]

Altered PK/PD on ECMO: The Known Unknowns

Although the final effects on PK has been well established, the exact mechanisms of these phenomena are still unknown. It is unclear how ECMO can increase and decrease Cl of different drugs. It is proposed that degree of perfusion to vital organs such as the liver and kidneys may play a role,[43] balanced with the potential enhanced Cl resulting from increased cardiac output secondary to systemic inflammatory response syndrome as well as aggressive fluid therapy and inotropic support.[45,46] Furthermore, ECMO is rarely used in silo within the ICU. Dosing of drugs during the concomitant use of other extracorporeal devices such as RRT needs to be established. The combined effects of drug sequestration and dialytic clearance need to be quantified to optimize dosing strategies of this very common group of patients. Another area of the unknown is the relationship between ECMO blood flow rates and the degree of drug sequestration into the circuit. These known unknowns require robust clinical studies to provide guidance in optimal antimicrobial dosing in ECMO management.

Altered PK/PD on ECMO: The Unknown Unknowns

In addition to the above, there are emerging data that ECMO may further exacerbate PK derangements through the hepatic cytochrome pathways, ultimately affecting drug metabolism. It is unclear how this occurs, but it may be due to altered hepatic perfusion leading to changes in hepatic efficiency.[44] The same theoretical phenomenon is applicable to the kidneys and will need to be further investigated to better define this unknown area.

Finally, the individual components of ECMO can be made with a variety of different materials. The continual drive to create better and more efficient circuits will be very present with the advancements in science and technology. The endless pursuit of quality and practice improvement may improve clinical practice but may continue to challenge our current understanding of optimizing PK/PD of antimicrobials in this patient population.

Emergence of Antimicrobial Resistance on ECMO

The recent surge of multidrug-resistant organisms combined with the diminishing antibiotic pipeline has highlighted the need to optimize the use of existing antimicrobials, particularly in the ICU.[32] Pathogens isolated in the ICU differ from the general wards as they are commonly less susceptible to common antimicrobials.[47,48] As discussed previously, the introduction of ECMO exposes a patient to significantly more invasive devices. A study conducted by Yeo et al. evaluated the impact of infection on biofilm formation on the surfaces of ECMO catheters. Bacteria can adhere to ECMO catheters, proliferate, and form biofilm, which subsequently releases bacteria into circulation and causes rapid septic deterioration, which is a critical clinical problem.[49] When microorganisms form mature biofilms on catheters in patients, the infections become resistant to antibiotics and can advance into systemic conditions because biofilms act as pathogen reservoirs.[50,51] Yeo et al. found 28 of 81 patients on ECMO had biofilms on the ECMO catheters, of which 16 returned with culture-positive results.[49] Microbiological results were found to be predominantly carbapenem-resistant *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus epidermidis*, methicillin-resistant *S. aureus*, and *Candida* spp.,[49] all of which are considered multidrug-resistant organisms.

HOW CAN CLINICIANS OVERCOME THE CHALLENGES OF ANTIMICROBIAL DRUG DOSING ON ECMO?

A comprehensive approach that incorporates knowledge of drug physicochemistry, altered PK/PD during ECMO, available population PK data, and therapeutic drug monitoring (TDM) is recommended in order to optimize antimicrobial drug therapy during ECMO.

Physicochemical-Based Approaches for Choosing Drugs

Understanding drug physicochemistry is key to predicting the degree of drug loss to the ECMO circuit. Drugs that exhibit high lipophilicity (log *P*) and high levels of protein binding have been associated with greater levels of sequestration into the ECMO circuit.[52] Although more robust studies are needed to guide the optimal dosing strategy in these patients, the physicochemical-based approach provides concrete advice in choosing the correct drug. For example, drugs such as ceftriaxone are 85% or greater protein bound and highly likely to be adsorbed into the ECMO circuit, ultimately reducing the concentration of drugs available at the infective site.[43] The physicochemical-based approach will suggest that ceftriaxone will not be the best choice of drug in a patient on ECMO as it will require a higher dose to attain the PK/PD target necessary for optimal bacterial kill and increase the risk of adverse events. An alternative could be the piperacillin/tazobactam combination, which is relatively hydrophilic and has lower protein binding and thus does not necessarily require dose adjustments in the setting of ECMO.

Population PK Modeling-Based Approaches for Choosing Dose

There are currently studies that are investigating the drug concentrations of patients on ECMO (PHARMECMO study,[53] the ASAP ECMO [Antibiotic, Sedative and Analgesic

Table 18.1 SUMMARY OF DOSING RECOMMENDATIONS FOR RELEVANT ANTIMICROBIALS

ANTIMICROBIAL	PHYSICOCHEMICAL PROPERTIES[52,55,56]	PHARMACOKINETIC IMPLICATIONS[A,B]	DOSING AND MANAGEMENT RECOMMENDATION
β-Lactams[57–59]	• Relatively hydrophilic • Variable protein binding	• Minimal-to-moderate sequestration • Enlarged V_d	• As per critically ill dosing strategy • Utilize TDM if available
Aminoglycosides[60,61]	• Hydrophilic • Relatively low protein binding	• Minimal sequestration • Higher V_d • Decreased CL	• Insufficient data • Utilize TDM-guided dosing
Vancomycin[62,63]	• Hydrophilic • Moderate protein binding	• Minimal sequestration • Higher V_d	• As per critically ill dosing strategy • Utilize TDM if available
Fluoroquinolones[64]	• Relatively hydrophilic • Low-to-moderate protein binding	• Minimal sequestration	• As per critically ill dosing strategy
Caspofungin[65,66]	• Low lipophilicity • Highly protein bound	• Minimal-to-moderate sequestration	• Insufficient data
Voriconazole[65,66]	• Low lipophilicity • Moderate protein binding	• Moderate sequestration	• Higher initial loading and daily doses • Utilize TDM if available

CL, clearance; TDM, therapeutic drug monitoring; V_d, volume of distribution.

[a]Minimal sequestration characterized by log *P* <2 and protein binding less than 60%; moderate sequestration determined by log *P* between 2 and 3 and protein binding greater than 60%; high sequestration determined by log *P* > 3 and protein binding greater than 60%.

[b]Arbitrary cutoff points for degree of sequestration and protein binding.

Pharmacokinetics during Extracorporeal Membrane Oxygenation] study.[54] The ASAP ECMO study aims to utilize a PK modeling-based approach to identify the dosing strategies that are most likely to achieve the PK/PD targets. Building on fundamental PK/PD principles, the study aims to utilize mathematical models to predict the likelihood of target attainment for patients on ECMO. Once these studies become available, ECMO dosing guidelines can be formulated to assist clinicians choose the correct dose for this patient population. A summary of recommendations based on physicochemistry and available PK data can be found in Table 18.1.

Therapeutic Drug Monitoring–Based Approaches to Confirm Adequacy of Dosing

Until the population PK data become available, it would be prudent to use a physicochemistry-based choice of drug or, if it is not possible, regular dosing review with TDM. TDM is highly warranted in critically ill patients due to the various and at times confounding factors that could interfere with achieving sufficient yet safe concentrations of antimicrobials for our patients. TDM is strongly recommended to guide effective antimicrobial treatment to confirm the adequacy of dosing in treating the infection and preventing the emergence of multidrug resistance.[53]

WHAT IS THE ROLE OF PROPHYLACTIC ANTIMICROBIALS AND OTHER STRATEGIES IN PREVENTING INFECTION ON ECMO?

Despite a lack of supporting data and the ELSO Infectious Disease Task Force recommending against this practice, antibiotic prophylaxis during ECMO is still common.[3,37,55,56] Such indiscriminate use of antimicrobials not only makes detection and interpretation of microbiological results difficult, but also induces selection pressures for the emergence of antimicrobial resistance. Many other infection prevention practices, including cannula maintenance strategies, vary significantly across centers.[3,37] ELSO recommends use of sterile techniques, the adherence to VAP prevention guidelines, the avoidance or removal of unnecessary invasive devices or interventions, and the adherence to general ICU infection control practices.[3,11,56] ECMO may allow endotracheal extubation in selected patients and may provide lower risk of VAP. Furthermore, prevention of infection can be aided by the identification of patients who may benefit from early extubation, such as patients with primarily cardiac failure, who have relatively preserved gas exchange, and patients with respiratory failure supported with ECMO as a bridge to lung transplantation; these are the typical candidates for extubation.[57] Immunosuppressed patients with respiratory failure on ECMO may potentially benefit from early extubation if feasible.[17] Other infection prevention strategies such as selective digestive tract decontamination,[58] use of antibiotic-impregnated cannulae and dressings, tissue adhesives to secure cannulae,[59] and daily chlorhexidine bathing,[60] merit further investigation prior to global adoption into clinical practice.

WHAT ARE THE POTENTIAL NOVEL APPROACHES/ADJUVANTS TO ANTIMICROBIAL THERAPY ON ECMO?

The advancements in antimicrobial therapy on ECMO are in tandem with improvements in the literature on antimicrobial

therapy in the critically ill population. Real-time TDM, even if available as a qualitative test, may be an important step forward in achieving therapeutic concentrations and avoiding drug toxicities. Use of extended infusions for drugs such as for β-lactams and vancomycin merits further consideration. Development of novel biomarkers for both detection of infection and assessing response to antimicrobial treatment may serve as a useful guide. A better understanding of immune dysregulation on ECMO may enable development of immunomodulatory therapies in the future. Extracorporeal blood purification techniques,[61] such as high-volume filtration or hemoadsorption, may warrant further research. Antimicrobial stewardship is critical, and daily ward rounds with an infectious disease specialist may help overcome some of the challenges of antimicrobial therapy during ECMO.

DISCUSSION

Patients may present with infections that prompt ECMO initiation or may develop nosocomial infections while on ECMO. These infections during ECMO add to both patient mortality and morbidity and are therefore of crucial importance for clinicians to understand the complexities associated with treating infections while patients are on ECMO. First, one of the biggest challenges in this area of medicine is that there is still a void in standardizing the definition of infections in patients on ECMO; this is therefore the first step toward developing best practice guidelines for antimicrobial use during ECMO. To differentiate between colonization and false positives from true infections, one must first have a good understanding of the infective picture and also the resultant changes from the initiation of ECMO (e.g., temperature regulation and augmentation to biomarkers). This foundational step is often facilitated by efficient microbiological and susceptibility testing. Second, and often the most critical to therapeutic success, is the selection of optimal drug therapy in this group of patients with extreme physiological derangements with subsequent altered PK and drug exposure. As the extent of these derangements remains poorly elucidated in adult ECMO patients, these decisions should be formed on the sound ground of the antimicrobial stewardship. That is, the initial selection of a broad-spectrum antimicrobial for empiric therapy and regular review for deescalation to more narrow-spectrum antimicrobials when further microbiological and susceptibility data become available. However, further understanding of drug physicochemical properties is required to optimize the choice of antimicrobials in the context of ECMO. Utilizing a physicochemical-based approach to counterbalance the V_d and Cl changes associated with ECMO-induced PK changes will assist in the attainment of PK/PD targets. Finally, the dose of the antimicrobial agent may be empiric at first but should be subsequently guided by TDM, where available, to ensure that PK/PD targets are attained.

Novel approaches to this problem are being explored, and clinicians have been eager for the results to assist in the navigation of this area of many "known unknowns" and "unknown unknowns." International collaborative research projects are the key to conduct adequately powered high-quality clinical trials in this fast-evolving area of critical care medicine. Until more robust dosing data become available, it is important that clinicians appreciate the challenges of optimal antimicrobial therapy during ECMO to choose the right antimicrobial agent, at the right time, and at the right dose. Understanding the challenges of diagnosing infection in patients on ECMO and the risks of indiscriminate antimicrobial use is critical to delaying the emergence of multidrug-resistant organisms and subsequent difficult-to-treat infections.

CONCLUSIONS

- Both detection of an active infection and optimal antimicrobial management during ECMO are challenges.
- Traditional biomarkers such as C-reactive protein and procalcitonin are of little value.
- A knowledge of physicochemistry of antimicrobials, critical illness, and ECMO-related alterations in PK/PD can assist in optimizing antimicrobial therapy.
- There is no role for prophylactic antimicrobials on ECMO.
- Therapeutic drug monitoring, where available, should be utilized.
- Adherence to general infection prevention polices in the ICU and timely deescalation or cessation of antimicrobials are important.

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REVIEW QUESTIONS

1. The most common type of infection during ECMO use is

   A. Soft tissue infection
   B. Lower respiratory tract infection
   C. Bloodstream infection
   D. Urinary tract infection

2. Which of the following is an independent risk factor for the development of nosocomial infections in patients on ECMO?

   A. Cannula site
   B. Older age
   C. Veno-arterial mode
   D. Flow rate

3. Which two of the following pathogens are reported to be the most frequent causative pathogens on the ELSO Registry?

   A. *Acinetobacter baumannii*
   B. *Candida albicans*
   C. *Staphylococcus aureus*
   D. *Escherichia coli*

4. In order to accurately dose and choose the most appropriate antimicrobial, it is important to have

   A. Local antibiograms
   B. Access to broad-spectrum antimicrobials
   C. Good hand hygiene
   D. Microbiological and susceptibility testing

5. Which of the following is a key physicochemical property associated with drug loss to circuit?

   A. Lipophilicity
   B. Hydrophilicity
   C. Molecular weight greater than 500
   D. Number of hydrogen donor groups greater than 5

6. What might you expect to observe with a hydrophilic drug like vancomycin in a neonate on ECMO?

   A. A relatively large increase in the V_d requiring a loading dose escalation
   B. A relatively large decrease in the Cl requiring a loading dose decrease
   C. No change in V_d with hydrophilic drugs
   D. A relatively large increase in the Cl requiring a dose escalation

7. What might you expect to observe with a hydrophilic drug like vancomycin in a large 100-kg adult on ECMO?

   A. A relatively large increase in the V_d requiring a dose escalation
   B. A relatively small increase in the V_d requiring a larger loading dose only
   C. A large increase in the Cl requiring a dose escalation
   D. A relatively small increase in the Cl requiring a dose escalation

8. The apparent ECMO-induced changes in V_d is thought to be due to

   A. Third spacing
   B. Interactions with the ECMO circuit
   C. Changes to drug physicochemical properties
   D. Clearance by the ECMO circuit

9. The potential increase in drug Cl observed in patients on ECMO is likely due to

   A. Degradation of drug in the oxygenator
   B. Perfusion into polyvinyl chloride cannula
   C. Interactions with the ECMO circuit
   D. Increased cardiac output

10. Antimicrobial dosing in ECMO should be

    A. Facilitated with efficient microbiological and susceptibility testing
    B. Managed carefully with structured TDM systems
    C. Guided by antimicrobial stewardship principles
    D. All of the above

11. The ELSO Infectious Diseases Task Force recommends

A. Against the use of antimicrobial prophylaxis
B. Changing colonized ECMO circuitry
C. Routine use of antimicrobial prophylaxis
D. Routine use of antifungal prophylaxis

12. Which of the following is the best indicator to diagnose infection in an ECMO patient?

A. Raised C-reactive protein
B. Two independent sets of positive blood cultures
C. Elevated procalcitonin levels
D. Infiltrates on chest x-ray

13. Which of the following drugs requires a dosing schedule higher than that recommended for the critically ill population?

A. Piperacillin/tazobactam
B. Vancomycin
C. Voriconazole
D. Cefepime

14. The key PK alterations observed during ECMO are

A. Drug sequestration/degradation in the circuit
B. Increased V_d
C. Increased or decreased Cl
D. All of the above

15. Pharmacokinetics includes measurements of the rate of all these parameters except

A. Absorption
B. Distribution
C. Metabolism
D. Excretion
E. None of the above

ANSWERS

1C, 2B, 3BC, 4D, 5A, 6A, 7B, 8B, 9D, 10D, 11A, 12B, 13C, 14D, 15E

19.

VASOPRESSOR AND INOTROPIC SUPPORT IN ECMO PATIENTS WITH REFRACTORY SHOCK

Michael D. Harper and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 42-year-old female patient presents to an outlying hospital brought in by emergency medical services from her home. The patient was severely hypotensive and hypoxic, refractory to appropriate intravenous fluid resuscitation (30 mL/kg of crystalloid) and oxygen supplementation by nonrebreather face mask, respectively. She rapidly progressed to requiring orotracheal intubation and mechanical ventilation and had escalating vasopressor requirements in order to maintain mean arterial pressure (MAP) greater than 65 mm Hg. Consultation was placed to an extracorporeal membrane oxygenation (ECMO) center due to refractory hypoxic and hypercapnic respiratory failure despite appropriate ventilation strategies according to ARDSnet guidelines; she developed progressive multisystem organ failure as well. At this point, a rapid screen for influenza had returned positive for influenza A, and a sputum culture had a Gram stain notable for gram-positive cocci in clusters. The mobile ECMO team arrived to assess the patient for candidacy for ECMO support, and a bedside echocardiogram was performed by the ECMO attending physician. In the parasternal long axis and subcostal four-chamber views, there was severe biventricular failure noted with left ventricular ejection fraction (LVEF) of less than 5%. The patient was on 3 μcg/kg/min of norepinephrine, 180 μg/min of phenylephrine, 0.04 unit/min vasopressin, and 1 μg/kg/min of epinephrine. Based on the echocardiographic findings and the vasopressor and inotropic requirements, the decision was made to cannulate the patient for veno-arterial (V-A) ECMO at the bedside due to the associated vasoplegia and likely septic cardiomyopathy. Cannulation strategy was for a 23French (23F), single-lumen multistage venous drainage cannula via the right common femoral vein, a 17F, single-lumen arterial cannula via the left common femoral artery, and a 7F, single-lumen, wire-reinforced sheath in antegrade fashion into the superficial femoral artery, all placed under ultrasound-guidance in percutaneous fashion via a modified Seldinger technique. She was then transported to the regional ECMO center for further care.

With the application of V-A ECMO, vasopressor support was initially weaning; however, her vasoactive infusions never weaned below 0.2 μg/kg/min of norepinephrine, 0.1 μg/kg/min of epinephrine, and 0.04 unit/min of vasopressin. The use of methylene blue (MB) at a dose of 2 mg/kg did not improve the MAP or allow any weaning of vasoactive infusions. At this time, angiotensin-2 infusion was initiated at 20 ng/kg/min, and after titration to 40 ng/kg/min the norepinephrine and vasopressin were able to be weaned completely. The epinephrine infusion was decreased to 0.02 μg/kg/min for inotropic support and to aid with left ventricular (LV) unloading given her persistent low ejection fraction and narrow pulse pressure, which was concerning for LV distension. Pulmonary capillary wedge pressure (PCWP) was measured to be less than 15 mm Hg and pulse pressure maintained above 20 mm Hg with application of low-dose epinephrine, so there was no need for mechanical LV unloading. Initial attempts to transition from epinephrine to dobutamine or milrinone were unsuccessful due to blood pressure intolerance to the vasodilation. By hospital day 7, all vasopressor support had been weaned with exception of the low-dose epinephrine (0.02 μg/kg/min) for continued LV unloading. By day 7, the LVEF had improved to 15%–20%, and epinephrine had been discontinued and she was transitioned to milrinone at 0.25 μg/kg/min, but as cardiac function began to improve and the acute respiratory distress syndrome (ARDS) (related to her H1N1 influenza and methicillin-resistant *Staphylococcus aureus* pneumonias) persisted, she began to eject a larger volume of hypoxic blood from her LV. This could not be mitigated with ventilatory support, and she began to develop Harlequin syndrome, necessitating conversion of her ECMO support from V-A to veno-arterio-venous (V-AV) to allow the LV to eject oxygenated blood. This was achieved by placing a 20-cm, 15F, single-lumen cannula into the right internal jugular vein with its tip terminating at the superior cavoatrial junction. In the following 7 days, her septic cardiomyopathy resolved with no further inotropic support required, and she successfully passed a weaning trial from arterial support. She was then taken to the hybrid operating room and surgically decannulated with simultaneous conversion to single-site veno-venous (V-V) ECMO utilizing a dual-lumen, bicaval cannula via the left subclavian approach. She was successfully weaned from ECMO after a total of 112 days of support. Her hospitalization was complicated by an acute kidney injury requiring continuous renal replacement therapy (CRRT), prolonged mechanical ventilation requiring tracheostomy, and disseminated intravascular coagulation. All these issues

ultimately resolved completely with return to near-normal baseline.

WHAT IS APPROPRIATE VASOPRESSOR UTILIZATION AND MANAGEMENT IN SEPTIC SHOCK?

After initial fluid resuscitation has been administered (30 mL/kg as per the 2016 Surviving Sepsis Campaign Guidelines), if hypotension persists the first-line vasopressor is norepinephrine.[1] This has been demonstrated in multiple trials and verified in subsequent meta-analyses with head-to-head comparison with dopamine and epinephrine. In studies comparing norepinephrine to other agents, there is a clear mortality benefit with its use over other vasopressors, also with decreased incidence of arrhythmias.[2–5]

Norepinephrine is a catecholamine vasopressor agent that stimulates α_1- and α_2-adrenergic receptors, causing vasoconstriction with an increase in systemic vascular resistance (SVR) and inhibiting endogenous norepinephrine release, respectively. Additionally, norepinephrine has activity at β_1-adrenergic receptors leading to an increase in both heart rate and cardiac output.[2] Pharmacologic activity of norepinephrine results in a predominantly α-adrenergic profile. Utilization of norepinephrine should be towards achievement of a goal MAP. The 2016 Surviving Sepsis Campaign Guidelines recommend a MAP target of 65 mm Hg, and all patients should be resuscitated to this target at the time of initial treatment.[1]

Several studies have examined MAP targets between the ranges of 65 and 85 mm Hg, and they have found no difference in mortality despite clear physiologic responses to increased perfusion pressure.[6–9] There is evidence of a subset of patients who may benefit from higher MAP targets; patients with preexisting hypertension prior to onset of their shock state have been shown to have a decreased incidence of renal replacement therapy (RRT) with MAP targeted to 85 mm Hg.[9] This was not a primary endpoint in the study, and further study is warranted in order to make a definitive statement about this treatment effect. In a pilot study by Lamontagne et al., 118 patients were randomized to either a MAP target of 60–65 or 75–80 mm Hg in the setting of vasodilatory shock irrespective of admitting diagnosis. There was no difference in mortality and an apparent trend toward increased cardiac arrhythmias in the higher MAP group. It was noted that with age greater than 75 years, there was a mortality benefit with a MAP target of 60–65 mm Hg.[10] It is important to understand that this study was not powered to make any conclusive statements in this regard, and that further trials are needed to better define MAP targets in vasodilatory shock.

To better answer the question of whether patients with chronic hypertension benefit from higher MAP targets, a meta-analysis was performed, and 894 patients were enrolled and analyzed. Patients who had been on vasopressors for greater than 6 hours prior to randomization to a higher MAP target had an increased risk of death. Lower blood pressure targets were not associated with adverse events in any subgroup, even the chronically hypertensive.[10] The takeaway message from this review is that there is not a one-size-fits-all approach to the application of vasoactive drugs in patients with vasodilatory shock. The authors can state that targeting a MAP of 65 mm Hg as an initial point of resuscitation is appropriate and supported by the literature.

We cannot recommend for, or against, the targeting of higher or lower MAP in these patients based on the currently published literature but would recommend that individual clinicians assess their patients and consider the physiologic implications of their respective treatment regimens given their past medical history. Adjustment of resuscitation targets should occur as historical and demographic information from the patient becomes available.

WHAT WERE THE BENEFITS OF ANGIOTENSIN II INFUSION IN THIS PATIENT?

Angiotensin II (AngII) is a hormone that is part of the renin-angiotensin-aldosterone system. Renin is produced in response to hypotension, renal sympathetic activity, or decreased delivery of Na^+ and Cl^- to the macula densa. Renin will cleave angiotensinogen to angiotensin I (AngI), which is then converted to AngII by angiotensin-converting enzyme (ACE), which is primarily located within the lung. In recent years, it has been studied in the setting of hypotension refractory to catecholamines and vasopressin infusions. The ATHOS-3 trial was a randomized, double-blind, placebo-controlled study examining the effect of AngII in patients with circulatory shock that was refractory to the equivalent of 0.2 μg/kg/min of norepinephrine. The primary endpoint of the study was achieved in 69.9% of patients receiving the study drug versus 23.4% in the placebo arm.[11] In the setting of refractory hypotension, it is clearly an efficacious drug to use. The trial was not powered for mortality, and though there was not a statistical difference in mortality between groups, there was a clear trend toward improved mortality in the treatment arm. Subsequent analysis of blood sampled from enrolled patients examined the ratio of AngI to AngII at the time of enrollment. The findings were consistent with a pathologic decrease in conversion of AngI to AngII in patients experiencing catecholamine-refractory hypotension.

Recent use of ACE inhibitors (ACEi's) was noted to contribute to marked elevation of this ratio, as well.[12] This elevated ratio of AngI to AngII has been previously described as conferring increased risk of mortality in patients with sepsis.[13] Acute renal failure is a common sequelae of critical illness, especially with persistent hypotension. Subgroup analysis of patients receiving RRT at the time of enrollment in ATHOS-3 who received AngII were shown to have lower 28-day mortality (30% vs. 53%) and increased rates of liberation from RRT (38% vs. 22%).[14] There is concern about the use of AngII in ECMO patients related to its possible prothrombotic activity,[15] but in a series of ECMO patients who received AngII, there were no reported thrombotic complications.[16] It has also been reported for successful use in vasoplegic shock after cardiopulmonary bypass (CPB) without thrombotic complications.[17] The patient described in the stem was on toxic doses of catecholamines and maintained dependence on vasopressin despite institution of V-A ECMO. With the addition of

AngII, we were able to wean these drugs and eventually wean RRT. More studies remain to be performed in order to determine the most appropriate role for this agent; we can safely recommend it as a second- or third-line agent in patients with hypotension refractory to standard vasopressor therapy.

WHAT IS APPROPRIATE INOTROPE UTILIZATION AND MANAGEMENT IN CARDIOGENIC SHOCK?

The question of what intrope utilization and management in cardiogenic shock (CS) is less readily answered in the current published literature. CS or low cardiac output state (LCOS) does not have a consensus definition; criteria that are sometimes utilized to define LCOS or CS are cardiac index less than 2.2 L/min/m^2 with the assistance of inotropes or less than 1.8 L/min/m^2 on no inotropic support. The most consistent portion of existing definitions is end-organ dysfunction due to hypoperfusion secondary to reduced cardiac output.[18] A Cochrane Database review published in 2018 compared the use of multiple inotropic agents, and of the included 13 trials, there was no evidence to support one agent over another.[19] Twelve of the 13 included studies were underpowered or had design flaws leading to potential bias. Levy et al. published their trial comparing epinephrine to norepinephrine plus dobutamine in CS patients due to acute myocardial infarction and found equivalent ability of each agent to increase arterial pressure and cardiac index; however, epinephrine use was associated with a higher rate of refractory shock.[20]

Dobutamine

Dobutamine is an inotropic agent with primarily β_2-receptor activity. It increases cardiac output both inotropically and chronotropically. The benefits to its use are decreased end-diastolic right ventricular and LV pressures in addition to the increased cardiac output. Negative associated effects center on an increase in myocardial oxygen consumption and a decrease in SVR.[21] The ADHERE trial demonstrated a concerning association between increased mortality in patients with acute heart failure with decompensation who were treated with dobutamine. This is not from a prospective, controlled, population of patients, but should certainly be taken into consideration when considering inotropic agents for use in CS.[22]

Milrinone

Milrinone is a phosphodiesterase-3 inhibitor that increases cytosolic cyclic adenosine monophosphate (cAMP) concentrations through impaired degradation. The downstream effect of milrinone administration is an influx of calcium within the cardiac myocytes, thus increasing contractility. Smooth muscle is relaxed via myosin light chain kinase inhibition, causing venous and arterial vasodilation, decreasing SVR. When administered, the heart rate, stroke volume, and cardiac output will all be increased. Myocardial oxygen consumption is unchanged, differing from the pharmacologic profile of dobutamine.[23] The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study evaluated patients admitted with acute decompensated heart failure (without associated shock) and randomized them to receive either placebo or milrinone for 48 hours. There was no difference in duration of hospitalization, but a nonsignificant increase in mortality in the milrinone group was observed. Adverse events of new-onset atrial dysrhythmias and hypotension were noted in the treatment arm as well.[24] Based on these concerning data for decompensated heart failure, milrinone is only recommended with the presence of shock state.

Levosimendan

Levosimendan is a calcium-sensitizing inotropic agent that exerts its effect by binding to cardiac troponin C within the cardiac myocytes, sensitizing the myofilaments to calcium. It also has a vasodilatory effect through the opening of potassium channels sensitive to adenosine triphosphate in the vascular smooth muscle, causing relaxation.[21] Both in the SURVIVE trial and in previous studies, levosimendan was demonstrated to decrease B-type natriuretic peptide (BNP) more so than dobutamine.[25] In the SURVIVE trial, there was no difference in all-cause mortality at 180 days after admission for acutely decompensated heart failure, but this is a difficult patient population to study, and mortality does not tell the entire story. Patients receiving levosimendan with a prior history of heart failure had a trend toward lower risk of death as compared to those receiving dobutamine. Patients receiving levosimendan also had more of a decline in systolic and diastolic blood pressure as compared to dobutamine. There was no other significant difference between the two groups. As in other trials examining the role of inotropes in patients with a heart failure diagnosis, the treatment of acutely decompensated heart failure without evidence of CS with levosimendan has also been shown to increase 90-day mortality.[26] As we are focusing purely on patients in CS, we can recommend the use of levosimendan as it has been demonstrated to be, at minimum, noninferior to dobutamine. It is clearly efficacious at decreasing PCWP and unloading the LV through increased inotropy given the decreased BNP production with its administration demonstrated in SURVIVE.

Epinephrine

Epinephrine has traditionally been one of the mainstays of treating shock of all causes. It is a catecholamine vasopressor/inotrope with both β- and α-adrenergic activity, functioning to increase SVR, heart rate, and cardiac output. Appropriate pharmacologic management in the setting of CS had not been well studied in randomized controlled trials (RCTs), and in 2017 the American Heart Association made the recommendation that RCTs in this area be performed to determine the optimum regimen.[27] In a trial comparing the use of epinephrine versus norepinephrine in CS patients after acute myocardial infarction, Levy et al. found a significant trend to incidence of refractory CS in patients receiving epinephrine as compared to norepinephrine (37% vs. 7%).[20] For this reason,

the trial was halted early. Of note, there was no difference in cardiac index evolution over the study period (from 0 to 72 hours). This study, and others, raised significant concern about the use of epinephrine in CS.

A subsequent meta-analysis was performed and examined outcomes in a total of 2538 patients with nonsurgical CS treated with inotropes and/or vasopressors. The use of epinephrine was associated with a threefold increased risk of death in CS patients as compared to other vasopressor/inotropic agents, except for those receiving V-A ECMO support.[28] This exclusion of patients receiving ECMO for increased risk of death cannot be definitively explained from the study, but the supposition is that the combination of unloading and circulatory support decreases myocardial wall stress, allowing increased coronary perfusion, and lower overall dosing (presume earlier withdrawal vs. non-ECMO) as compared to those not receiving ECMO support. Epinephrine increases myocardial oxygen consumption and interferes with calcium homeostasis more than other catecholamines.[29] We know from the CardShock trial that cardiac and renal biomarkers are significantly elevated in the first 96 hours of CS in patients receiving epinephrine as compared to other vasopressor/inotrope combinations. This difference remains after adjustment for pre-enrollment cardiac arrest and in the subgroup of patients without cardiac arrest in their course. Patients receiving epinephrine in this study had an increased incidence of encephalopathy and had higher concomitant requirements for norepinephrine or dobutamine.[30] Serum lactic acid levels were significantly elevated as compared to patients receiving other vasopressors, a finding well documented with its use. Outside of its use in patients on V-A ECMO or other high-volume acute extracorporeal life support/mechanical circulatory support therapies, we cannot recommend the use of epinephrine in patients in CS.

Dopamine

Dopamine is a catecholamine hormone and neurotransmitter with activity in the central nervous system and in peripheral tissues. Peripherally circulating dopamine does not cross the blood-brain barrier, so these two systems do not directly interact. At low doses, dopamine binds dopamine receptors in the renal artery, inducing vasodilation, at doses 5–15 μg/kg/min both α- and β-receptors are activated with resultant increases in heart rate, cardiac contractility, and cardiac output; above 15 μg/kg/min, the primary effects are α-mediated with increasing blood pressure.[31] The activity of dopamine as both a chronotrope and inotrope has potential benefit in the setting of bradycardia and CS, respectively, and at higher doses the vasopressor activity with greater α-stimulation has been utilized in shock of all etiologies. The increased risk of morbidity and mortality noted with its use in sepsis has been outlined in this chapter.

In the treatment of CS, dopamine has been compared with norepinephrine by Rui et al. in a meta-analysis of nine studies including 510 patients. This revealed that the use of dopamine increased 28-day mortality, arrhythmic events, and gastrointestinal reaction in patients with CS regardless of etiology of shock state.[32] In examining the meta-analysis performed by Fawzy and colleagues, the presence of cardiac risk factors along with the use of dopamine in the setting of septic shock conferred a significant increase in risk of death associated with its use.[5] The SOAP II trial evaluated first-line vasopressor utilization in patients with generalized shock with a CS subgroup identified. Dopamine use was associated with a higher rate of arrhythmias in the general study population and the CS subgroup and was associated with an increased risk of mortality in the CS subgroup alone.[33] While there were certainly design flaws in this study (CS patients were defined as a group by etiology, and acute myocardial infarction or heart failure variables were not reported), the results are consistent with those reported in other trials. For these reasons, we cannot endorse the use of dopamine in patients with CS, regardless of presence or absence of ECMO support.

WHAT IS THE ROLE OF METHYLENE BLUE IN SEPTIC SHOCK AND VASOPLEGIA SYNDROME?

Methylene blue is a thiazine dye that has been primarily used for the treatment of methemoglobinemia; of pharmacologic interest is the ability of MB to inhibit both constitutive and inducible nitric oxide synthase (NOS) and guanylate cyclase. Guanylate cyclase catalyzes the conversion of guanosine triphosphate to cyclic guanosine 3′,5′-phosphate (cGMP). Production of cGMP, upregulated in the setting of nitric oxide (NO) abundance, is well implicated in the pathophysiology of septic shock and vasoplegia syndrome (VS).[34] cGMP has a dual effect on vascular tone by decreasing the sensitivity of myosin contractions due to calcium exposure, decreasing intracellular [Ca^{2+}] through the activation of calcium-sensitive potassium channels (decreases intracellular calcium concentrations) and by inhibiting calcium release from the sarcoplasmic reticulum.[35] Attempts to intervene in this pathway pharmacologically have been made in multiple studies. In 2004 Watson and colleagues published their experience with NG-methyl-L-arginine hydrochloride, a nonspecific competitive NOS inhibitor, showing increased mortality with broad NOS inhibition.[36] Attention was then turned to cGMP as a more appropriate physiologic target.

Vasoplegia syndrome remains a vital condition in need of research and novel therapeutic interventions. The onset of VS in cardiothoracic surgery patients is well known to confer an increase in morbidity and mortality.[37,38] With a known profile of preoperative risk factors for VS in the cardiac surgical population (i.e., preoperative use of ACEi's, calcium channel blockers, and heparin), it has been evaluated to prophylactically administer MB during cardiac surgery. Özal et al. randomized 100 patients undergoing coronary artery bypass grafting (CABG) to receive either MB at a dose of 2 mg/kg 1 hour before surgery or nothing. None of the patients receiving MB went on to develop VS compared to 26% of the control arm. Patients receiving MB also had a shorter average intensive care unit (ICU) length of stay and shorter duration of hospitalization.[39] Cho and colleagues performed a similarly structured trial with 42 adult patients who were to undergo valve

replacement surgery due to infective endocarditis. Patients were randomized to receive either MB 2 mg/kg or saline 20 minutes prior to initiation of CPB. There was no difference in vasopressor requirements between treatment arms, but there was a significant decrease in required blood products transfused (packed red blood cells and fresh frozen plasma).[40]

Methylene blue use in the setting of ARDS, pulmonary hypertension, and lung transplantation remains rife with potential for concern. NO inhibition or blockade can increase the pulmonary vascular resistance (PVR) through the same pathways as the SVR, and in the ARDS patient (especially while on V-V ECMO) the risk of right ventricular dysfunction is compounded with an already increased PVR related to the underlying disease process.[41] Worthy of separate discussion is the administration of MB in patients receiving lung transplantation with VS as decreases in endogenous NO and cGMP levels are associated with primary graft failure.[42] For this reason, there is limited reported use in this population, despite preoperative ECMO utilization correlating with an increased risk of developing VS in thoracic organ transplantation.[43] Concomitant utilization of inhaled NO might be sufficient to mitigate the theoretical risk of increased PVR with systemic administration of MB and to minimize the risk of MB-induced graft dysfunction/failure after lung transplant, but this has not been studied to date. Avoidance of bolus dosing of MB and the utilization of a continuous infusion has been suggested as well. It should be noted, however, that while increases in right ventricular end-diastolic pressure (RVEDP) and PVR are documented with the utilization of MB in these scenarios, clinically significant changes in pulmonary arterial and right ventricular hemodynamics are not reported within the literature as evidenced by PubMed and OVID searches at the time of this writing.

Methylene blue administration is not without risk. Serotonin syndrome is a definite concern as MB has a monoamine oxidase inhibitor effect. Infusion of MB in a patient with recent utilization (within at least 2 weeks) of any serotonergic antidepressant should be done with caution due to the risk of developing serotonin syndrome.[44] Extreme caution should also be utilized in the use of MB in ECMO circuits utilizing a thermoplastic polyurethane heat exchanger membrane oxygenator. MB has been shown to cross into the water bath of heater-cooler units in this type of oxygenator, and at least in one study has been demonstrated to cross back into the circuit after a wet prime was stored for 30 days.[45,46]

Overall, MB is a safe medication to use, not only in the setting of VS but also as a preventive measure when VS is a concern. Its use in ECMO is safe and has reasonable literature to support it; however, understanding of the ECMO circuit and equipment composition is essential when employing new medications, therapies, and techniques.

WHAT IS THE ROLE OF HYDROXOCOBALAMIN IN A PATIENT SUCH AS THE ONE PRESENTED?

The micronutrient vitamin B_{12} (hydroxocobalamin) is a US Food and Drug Administration–approved agent utilized for the treatment of cyanide intoxication. Cyanide is inactivated through binding with the cobalamin molecule and is then renally excreted.[47] Currently, hydroxocobalamin is of pharmacologic interest in patients with VS (in both cardiac and noncardiac cases) because of its ability to both scavenge gasotransmitters (NO, H_2S, CO) and inhibit NOS.[48] As of the writing of this chapter one of the most comprehensive publications to date on the use of hydroxocobalamin in VS patients is a review article summarizing seven case series published on the use of hydroxocobalamin in VS.[49] There are no published RCTs on the use hydroxocobalamin in VS to date; there are several publications of larger, single-center case series.

Cios et al. published their experience with hydroxocobalamin in after left ventricular assist device (LVAD) implantation VS with a series of 10 patients receiving 5 g of hydroxocobalamin intravenously over 15 minutes for refractory VS (this is the most consistently referenced/utilized dosing schema). Six out of 10 patients had an increase in MAP greater than 15% from the premedication baseline; the other four patients had either an increase in MAP with associated increased vasopressor dosing or no response at all.[50] This is an interesting study but does not readily generalize to ECMO patients due to the complex physiology related to LVAD patients, especially at the time of implantation.

A subsequent case series by Shah and colleagues retrospectively reviewed 33 patients who had post-CPB VS, 24 of which had a greater than 33% reduction in vasopressor dosing at 30 minutes after administration of hydroxocobalamin.[51] Armour et al. noted a mean increase in systolic blood pressure of 14 mm Hg from the 30 minutes preceding hydroxocobalamin administration and the subsequent 30 minutes in 24 cardiac surgery patients.[52] Both studies are very promising but are unfortunately confounded by roughly 50% of patients in each series having also received MB. Also, without supporting experience reported in the literature, we cannot recommend for the routine use of hydroxocobalamin in VS outside of the setting of CPB-related VS. The effect of this drug has yet to be formally studied in ECMO patients; indeed, only a handful of case reports of its use in ECMO are published in the literature. In one such report, the case of a 10-year old patient who had concomitant cyanide and carbon monoxide intoxication requiring V-V ECMO is described. ECMO support was only present for 24 hours and was then weaned.[53] The patient did not have VS, and there were not any ECMO-related complications reported.

There is potential for toxicity with hydroxocobalamin administration. Common side effects are chromaturia and erythema. Oxalate crystal production in the urine was noted in more than 50% of healthy recipients.[54] Because of the red color of the medication, its administration is known to cause abnormalities in laboratory studies, specifically causing false elevation in hemoglobin, serum glucose, and coagulation studies.[55] Finally, Seelhammer and colleagues reported a case of cobalt toxicity in a patient who developed VS while receiving a simultaneous heart and kidney transplantation. V-A ECMO was required in order to successfully separate from CPB. Over the first month of care in the ICU after transplant, the patient received a total of 15 g hydroxocobalamin.

Subsequent nutritional assays were performed, and a serum cobalt level was measured at 307 ng/mL (>5 ng/mL is considered toxic). Analysis of transplanted renal biopsy was notable for an oxalate crystal nephropathy. Cobalt and hydroxocobalamin assays were performed on the effluent fluid from CRRT, and neither was noted to be cleared by this modality. Intermittent hemodialysis was not possible due to the presence of hydroxocobalamin in the effluent falsely triggering a blood leak alarm.[56] This patient had multisystem organ dysfunction and ultimately transitioned to comfort care, but this cannot be directly attributed to cobalt toxicity related to hydroxocobalamin administration.

The takeaway message is that more studies are needed to determine the efficacy of hydroxocobalamin in VS and whether it is safe to use in ECMO patients. We can only recommend its use in VS if MB is not an option due to presence of glucose-6-phosphate dehydrogenase deficiency or recent use of antidepressants, placing the patient at risk of serotonin syndrome with MB administration.

WHAT IS THE RATIONALE FOR USING VASOPRESSIN IN CIRCULATORY SHOCK?

Vasopressin (arginine-vasopressin, AVP) is a nonspecific agonist on V1a, V1b (V3), and V2 receptors (R). It is produced in the hypothalamus and stored in the posterior pituitary. Its release is triggered by hyperosmolar plasma and urine and by hypotension and hypovolemia. V1aR agonism leads to systemic vasoconstriction and has been described as having a potential for pulmonary and coronary vasodilation. The V1b (formerly known as V3) receptor releases corticotropin as a stress response to shock states, and the V2R induces water reabsorption in the renal collecting ducts and releases coagulation factors in the liver, such as von Willebrand factor.[57] AVP has been shown to reduce nitrosative stress and to improve cardiopulmonary functions in animal models.[58]

Since Landry and colleagues observed depletion of vasopressin plasma concentrations in patients with septic shock, AVP has been commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock.[59] AVP became the focus of numerous research projects, finally resulting in the Vasopressin and Septic Shock Trial (VASST).[60] In this multicenter, randomized, double-blind trial, the investigators compared low-dose AVP (0.01–0.03 U/min) added to open-label norepinephrine versus norepinephrine alone in 778 patients with septic shock. Even though the authors showed no significant difference between the AVP and norepinephrine groups in 28- or 90-day mortality rates and no difference in the overall rates of serious adverse events, they could show that effectiveness of the dose of AVP differed depending on the severity of shock. In the two prespecified strata of low severity of shock (baseline norepinephrine 5–15 μg/min) and high severity of shock (baseline norepinephrine 15 μg/min), very different results were observed. Low-dose AVP (0.03 IU/min) reduced mortality in the low severity of shock group by almost 10% ($P < .05$), and this result persisted over 90 days, suggesting that the earlier AVP is used the better the outcome may be.[61]

The VANISH trial examined the effect of early vasopressin versus norepinephrine on kidney failure in patients with septic shock. The findings suggested less need for RRT in the AVP group (25.4% vs. 35.3%), which trended to have lower creatinine levels and higher total urine output. However, there was no difference in outcome or mortality due to the limited number of patients involved in the trial.[62]

This trend, however, has been confirmed by the VANCS trial, which compared vasopressin versus norepinephrine in patients with vasoplegic shock after cardiac surgery. This study revealed significantly fewer complications such as renal failure as well as less mortality in the vasopressin group.[63]

Recent consensus guidelines suggest that low-dose (0.03 units/min) AVP may be added as a second-line agent after norepinephrine.[1]

WHAT IS THE VALUE OF VASOPRESSIN ANALOGUES IN CIRCULATORY SHOCK?

While V1aR-mediated vasoconstriction is a wanted effect in septic shock, some of the V2R-mediated effects such as hypercoagulation, antidiuresis, selective vasodilation, and central nervous system changes are adverse. This led to the hypothesis that a selective V1aR agonism would be superior to AVP in the treatment of septic shock. Terlipressin used to be the most selective, clinically available V1R agonist that has a higher selectivity for the V1R than AVP (V1/V2 ratio 2.2 vs. 1) and may be more potent in restoring catecholamine-refractory septic shock. Unfortunately, terlipressin has a prolonged effective half-life as compared to AVP (50 vs. 6 minutes) and was traditionally used as a splanchnic vasoconstrictor in hepatorenal syndrome and gastrointestinal bleeding in liver cirrhosis. The TERLIVAP study suggested that continuous low-dose infusion of terlipressin (1.3 μg/kg/h) reduced catecholamine requirements more effectively and with less rebound hypotension than AVP (0.03 U/min), which was attributed to better V1R agonism.[64]

This naturally led to investigations into pure V1aR agonists such as selepressin, which has been shown in animal studies to block vascular leaking more effectively than AVP because of its lack of agonist activity at the vasopressin V2R.[65] In clinical trials of septic shock patients, selepressin in a dose of 2.5 ng/kg/min rapidly replaced norepinephrine while maintaining adequate MAP.[66] The evidence behind current guidelines remains scarce and controversial. Emerging new evidence points to novel alternative agents such as the V1aR agonist selepressin. However, further research is needed to elucidate its full potential.[67]

HOW CAN LEFT VENTRICULAR UNLOADING BE ACCOMPLISHED PHARMACOLOGICALLY, AND WHY IS THIS IMPORTANT?

While restoring systemic circulation, V-A ECMO can lead to LV distension due to the increase in afterload related to retrograde blood flow. Complications of LV distension can include pulmonary edema and increasing left ventricular end-diastolic pressure (decreasing the coronary perfusion pressure and

increasing myocardial oxygen consumption). There are clear indications to proceed to mechanical LV unloading either by decreasing afterload (intra-aortic balloon pump) or decreasing preload (Impella or surgical LV vent), and that has been PCWP greater than 20 mm Hg, pulse pressure less than 20 mm Hg, or echocardiographic evidence of LV blood stagnation. In the setting of these findings, there is a mortality benefit associated with achieving LV unloading (regardless of strategy). A recent meta-analysis performed by Baldetti et al. demonstrated this but showed a benefit in preload reduction over afterload reduction in their analysis of 3930 patients.[68]

These devices should be employed where there is clear need, but we would recommend against their use unless there is evidence of pharmacological failure of inotropes or a contraindication to their use. Instances where the use of pharmacologic LV unloading on V-A ECMO should not be employed would be in the setting of untreated ischemic coronary disease and refractory ventricular arrhythmias. We would recommend the use of epinephrine at low dose (0.01–0.04 μg/kg/min) in patients with low SVR and milrinone at 0.25 μg/kg/min or dobutamine at 3–5 μg/kg/min in patients maintaining MAP greater than 65 mm Hg. Milrinone has the benefit of not increasing myocardial oxygen consumption as compared to dobutamine, as well as favorably improving right heart function through reduction of PVR.[23]

DISCUSSION

The answer to how to manage vasopressors and inotropes is not an easy one when trying to apply the current literature, which almost exclusively describes non-ECMO patients. Let us first examine patients on V-V ECMO support, who are primarily patients with infectious pneumonia progressing to ARDS.[69] In the setting of hypotension requiring vasopressor support with infectious pneumonia, the Surviving Sepsis Guidelines would still be applicable; thus, norepinephrine should be our first-line vasopressor in this setting. Our current clinical practice would indicate addition of a second agent, vasopressin being the agent of choice per the Surviving Sepsis Guidelines, with norepinephrine dosing reaching 0.1 μg/kg/min with MAP less than 65 mm Hg. Based on the results of the ATHOS-3 trial, it would be reasonable to consider AngII as a second- or third-line agent in this patient population; however, we recommend caution with the use of this agent in ECMO patients due to only limited anecdotal experience reported to date. Additionally, there is some concern with its use in patients with ARDS as there is potential for AngII to induce a fibroproliferative inflammatory state in hypoxic lungs.[70] That being said, the interventional arm of ATHOS-3 was composed of 24.7% ARDS patients and had a lower incidence of respiratory complications in the interventional arm as compared to the control arm,[16] so this risk has not yet borne out in the clinical data. Furthermore, the concern to induce an inflammatory response with fibroproliferation mediated by AngII at AT1 and AT2 receptors has been shown to be mitigated by ACE2 expression (ACE2 gene knockout mice demonstrated its protective role in a mouse model of ARDS).[70] However, with ACE2 activity cleaving AngII to angiotensin (1–7), there appears to be conflict in the data that are present. AngII utilization clearly has a mortality benefit in patients with an elevated Ang1:2 ratio,[13] signaling that the vasodilatory effects of angiotensin (1–7) are nonbeneficial in patients with hemodynamic collapse in the setting of ARDS. Clearly, further study is needed to unravel this complex physiology and the interplay between potential therapeutics and the underlying disease state.

Patients with severe respiratory failure requiring V-V ECMO support and a hyperdynamic state (i.e., elevated cardiac output and tachycardia) can be difficult to manage. Decreasing adrenergic activity can be necessary in order to achieve an adequate balance between oxygen consumption and oxygen delivery. One method by which this may be achieved is with the use of β-blockers; with negative effects on inotropy and chronotropy, the native cardiac output can be more closely matched to ECMO flows and oxygen saturation increased and oxygen delivery (DO_2) potentially increased.[71] With this strategy, hypotension can occur, and vasopressors to increase SVR may need to be given if a balance between oxygen saturations and hypotension may not be achieved with β-blocker dose adjustment alone. In this setting, our recommendation would be to utilize phenylephrine, a pure α-agonist, to achieve the target MAP without any increase in heart rate or cardiac output. Phenylephrine has been widely used in the setting of obstetric anesthesia to counteract the inherent vasodilatory effect.[72] Recent publications in the anesthesia literature point toward the likely benefit of norepinephrine versus phenylephrine due to the increase in cardiac output as well as blood pressure and the decreased incidence of bradycardia.[73] These effects (increased cardiac output and no decrease in heart rate) are the opposite of what is trying to be achieved in this described setting. By giving an agent to maintain MAP with the application of β-blockade and phenylephrine (if needed), cardiac output can be much more readily matched to ECMO flow. Similar effects can also be achieved using vasopressin.

Vasopressor and inotropic management in V-A ECMO patients is a more complicated endeavor. Peripheral V-A ECMO increases LV afterload via retrograde blood flow in the aorta.[74] To the failing heart, this has the potential to increase LVEDP and LV stress (both of which exacerbate myocardial ischemia), which is known to delay recovery from CS.[75] The practice we utilized in the care of the patient in this case was to employ inotropes (initially epinephrine at low dose: 0.01–0.04 μg/kg/min; and then transitioned to milrinone at 0.25–0.5 μg/kg/min) to achieve a pulse pressure greater than 20 mm Hg and a PCWP less than 18 mm Hg. In our experience, if this can be achieved, mechanical unloading is not necessary. What is not known is if the effect of LV pressures on the ailing myocardium are binary (above *X* mm Hg = bad, below *X* mm Hg = good) or exist on a continuum (above *X* mm Hg = bad, the further below *X* mm Hg you can get = best). Many RCTs and meta-analyses have been performed looking at the benefits of LV unloading on V-A ECMO for acute myocardial infarction, postcardiotomy CS, and myocarditis, with mortality benefit noted in those patients that received it compared to those who did not.

But, it is not clear if patients with low left-sided pressures on V-A ECMO plus inotropes will also benefit from further unloading. Placement of additional support devices confers increased risk of complications, and a clear inflection point of where to escalate to a multidevice strategy versus pharmacological management alone has not yet been identified.

Careful selection and implementation of inotropes must be made, as well. These patients can be sensitive to vasodilatory stimuli and vasodilating inotropes can cause significant decrease in SVR, leading to hypotension. Additionally, these agents are arrhythmogenic, so a careful balance must be struck: pharmacologic LV unloading to decrease left-sided filling pressures, thereby decreasing risk of arrhythmias, but avoidance of higher doses to avoid precipitating arrhythmic events. In CS patients on V-A ECMO with preserved SVR, our practice is to initiate inotropic support with milrinone in order to achieve the previously mentioned hemodynamic targets. If the patient also has vasodilation necessitating vasopressor support, we recommend low-dose epinephrine (0.01–0.04 μg/kg/min) for inotropic support and the addition of norepinephrine to achieve MAP greater than 65 mm Hg. Vasopressin had been our preferred second-line agent, but with increasing experience of AngII in vasoplegic patients on V-A ECMO or during/after cardiac surgery, it has been a useful tool to rapidly deescalate the total catecholamine dose. Finally, the role for continuous and serial examination cannot be understated. The effect on patient hemodynamics of vasopressor and inotropic agents that then directly affect ECMO flows is significant. As SVR and MAP increase, resistance on the centrifugal pump increases and flow decreases. This can lead to a low-flow state and result in organ hypoperfusion.

CONCLUSION

- Norepinephrine is the first-line vasopressor supported by guidelines.
- Vasopressin presently is the second-line vasopressor supported by guidelines.
- Stress dose steroids should be started with introduction of a second vasopressor.
- Angiotensin II is a very promising new drug that our group presently uses as a third-line vasopressor in refractory shock.
- More research on AngII is needed for consideration into guidelines.
- Methylene blue may temporarily improve hemodynamics.
- Epinephrine is a useful inotrope in the hypotensive V-A ECMO patient requiring LV unloading.
- Milrinone is a useful inotrope in the hypertensive V-A ECMO patient requiring LV unloading.
- If milrinone and/or epinephrine administration is not sufficient to achieve LV unloading in V-A ECMO patients, mechanical means of LV venting should be pursued.
- Presently, there is no evidence for the use of dopamine in the adult ECMO patient.

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REVIEW QUESTIONS

1. Which drug stimulates the V1a receptor only?

   A. Terlipressin
   B. Vasopressin
   C. Selepressin
   D. Desmopressin

2. Water reabsorption in the renal collecting duct is promoted by which vasopressin receptor?

   A. V1a receptor
   B. V2 receptor
   C. V1b/V3 receptor
   D. Oxytocin receptor

3. Which drug requires the least RRT in cardiac surgical patients?

   A. Epinephrine
   B. Norepinephrine
   C. Desmopressin
   D. Vasopressin

4. First-line vasopressor therapy in ECMO patients with septic shock should be with which vasopressor agent, regardless of ECMO modality?

   A. Norepinephrine
   B. Vasopressin
   C. Angiotensin II
   D. Epinephrine

5. For the patient described in this case, what would be an appropriate MAP to target with vasopressor therapy?

   A. 85 mm Hg
   B. 75 mm Hg
   C. 65 mm Hg
   D. 55 mm Hg

6. In patients with hypotension refractory to standard vasopressor therapy, AngII has been effective in achieving appropriate MAP. What other improvement was demonstrated in patients receiving AngII in the ATHOS-3 trial?

   A. Lower mortality
   B. Increased liberation from RRT
   C. Increased cardiac output
   D. Decreased lactic acid

7. What laboratory abnormality was noted in patients in whom catecholamine-refractory hypotension occurred in the ATHOS-3 trial?

   A. Low ionized calcium
   B. Elevated serum lactic acid
   C. Increased serum AngI:AngII
   D. Low serum cortisol

8. In the Levy trial comparing norepinephrine plus dobutamine versus epinephrine in CS, what difference was noted in patients receiving epinephrine?

   A. Increased myocardial oxygen consumption
   B. Increased requirement for RRT
   C. Decreased incidence of delirium
   D. Increased incidence of refractory shock

9. Hemodynamic effects of dobutamine include all of the following EXCEPT

   A. Increased LV end-diastolic pressure
   B. Decreased right ventricular end-diastolic pressure
   C. Increased cardiac output
   D. Increased heart rate

10. Which of the following statements regarding the use of milrinone is TRUE?

   A. In patients with acutely decompensated heart failure without CS, milrinone infusion showed a tendency toward decreased mortality.
   B. Myocardial oxygen consumption is increased with its administration.
   C. The inotropic effect of milrinone is mediated by increased calcium influx due to increased cytosolic concentrations of cAMP.

D. Inhibition of phosphodiesterase-3 leads to increased PVR.

11. The SURVIVE trial showed which of the following differences between levosimendan and dobutamine?

A. Increased mortality in patients receiving dobutamine
B. Decreased serum BNP in patients receiving levosimendan
C. Increased systolic and diastolic pressures in patients receiving levosimendan
D. Lower risk of death in chronic heart failure patients receiving dobutamine

12. Which of the following statements regarding the use of epinephrine in CS is FALSE?

A. In patients with CS not receiving V-A ECMO, the use of epinephrine confers a threefold increased risk of death.
B. Epinephrine use is associated with decreased serum lactic acid as compared to other catecholamines.
C. The CardShock trial demonstrated increased serum cardiac and renal biomarkers as compared to other vasopressor/inotrope therapies.
D. The use of epinephrine is associated with increased myocardial oxygen consumption and disrupted calcium homeostasis more so than other catecholamines.

13. The SOAP II trial had which of the following findings?

A. Increased survival in patients with septic shock receiving dopamine infusion
B. Decreased incidence of arrhythmias in patients receiving dopamine infusion
C. No difference in mortality between dopamine as compared to norepinephrine
D. Increased mortality in patients with CS receiving dopamine infusion

14. Which of the following is NOT an action (either direct or indirect) of MB?

A. Inhibition of induced and constitutive NOS
B. Inhibition of guanylate cyclase
C. Decreased cytosolic calcium concentrations
D. Increased calcium release from sarcoplasmic reticulum

15. The use of MB should be considered in all the following patients except

A. 34-year-old female with CS on 0.15 μg/kg/min of norepinephrine with low SVR, MAP 58 mm Hg, and long-standing use of a selective serotonin reuptake inhibitor for major depressive disorder
B. 58-year-old male undergoing elective cardiac surgery with preoperative medications including ACEi
C. 46-year-old female with CS due to acute myocardial infarction and CS refractory to vasopressors and inotropes requiring V-A ECMO with persistently low SVR
D. 67-year-old male undergoing emergent CABG with severe VS on onset of CPB

16. Which of the following statements about the use of hydroxocobalamin in patients with shock is correct?

A. There is potential for cobalt toxicity with high-dose therapy in patients with renal dysfunction.
B. Hydroxocobalamin has been well studied in VS and is superior to MB.
C. Hydroxocobalamin is an inhibitor of inducible NOS but is unable to scavenge circulating gasotransmitters.
D. Only in rare cases does oxalate crystal formation occur in the urinary tract.

17. Failing to adequately unload the LV after initiation of V-A ECMO support can lead to which of the following hemodynamic changes?

A. Decreased LV end-diastolic pressure
B. Increased coronary perfusion pressure
C. Increased LV end-diastolic pressure
D. Decreased PCWP

ANSWERS

1C, 2B, 3D, 4A, 5C, 6B, 7C, 8D, 9A, 10C, 11B, 12B, 13D, 14C, 15A, 16A, 17C

ECMO IN NEONATAL AND PEDIATRIC RESPIRATORY DISEASE

20.

ECMO FOR MECONIUM ASPIRATION SYNDROME

Avideh Rashed and Rachel L. Chapman

STEM CASE AND KEY QUESTIONS

A 42 weeks' gestational age, 3800-g female was delivered via emergent cesarean (C-) section secondary to failed induction of labor and fetal distress after an uneventful pregnancy. Thick meconium was noted prior to delivery. On delivery the infant was hypotonic and cyanotic with poor respiratory effort. The patient was dried, stimulated, suctioned, and provided positive pressure ventilation with 100% FiO_2 (fraction of inspired oxygen) at 30 seconds of life with improvement in tone and respiratory effort; however, the patient continued to require oxygen via face mask and had significant respiratory distress and was transported to the neonatal intensive care unit (NICU).

An initial chest x-ray (CXR) revealed hyperinflated lung fields with bilateral patchy infiltrates throughout (Figure 20.1). She was intubated and subsequently placed on a high-frequency oscillatory ventilator for severe hypoxemia and hypercarbia. Oxygen saturation monitoring revealed up to a 20% discrepancy between upper lower extremity saturations, which worsened with agitation. Blood gases showed persistent hypoxemia and respiratory acidosis. Clinical assessment was most consistent with meconium aspiration syndrome (MAS) complicated by persistent pulmonary hypertension of the newborn (PPHN). She was started on broad-spectrum antibiotics and intravenous fluids. She was given exogenous surfactant with transient improvement, but despite maximum respiratory support on high-frequency ventilation (HFV) and 100% oxygen, she remained hypoxemic, with a pre-post ductal saturation gradient. Capillary refill was delayed with tachycardia and decreased mean arterial blood pressures, which improved with two normal saline boluses and initiation and titration of dopamine, with maintenance of mean arterial blood pressures between 45 and 55 mm Hg while receiving 10 μg/kg/min of dopamine. An echocardiogram (echo) confirmed the presence of pulmonary hypertension, with suprasystemic pulmonary pressures, right-to-left shunting across the patent ductus arteriosus, and an otherwise structurally normal heart. Right-sided function was mildly depressed, but left-sided function was within normal limits with moderately decreased filling of the left ventricle. Inhaled nitric oxide (iNO) was initiated at 20 ppm with only modest improvement in oxygenation.

A cranial ultrasound was structurally normal without evidence of hemorrhage. A surgical consultation was obtained. Her oxygenation index (OI) ranged from 30 to 50 with preductal saturations remaining persistently less than 90% and postductal arterial blood gases with partial pressure of oxygen (PaO_2) less than 40 on a mean airway pressure of 16. Given that the patient met physiological criteria for extracorporeal membrane oxygenation (ECMO) and had no clear contraindications, a decision was made to proceed with veno-venous (V-V) ECMO, and consent was obtained from the family.

The circuit was blood primed, and the multidisciplinary team reviewed roles, precannulation checklist, prepared blood products, heparin bolus and drip, and emergency medications. During the cannulation, the patient developed worsening hypoxemia and was hand-ventilated throughout the procedure. She was successfully cannulated with a 13 French (13F), double-lumen cannula, and ECMO flow (utilizing a centrifugal pump) was titrated up to 100 mL/kg/min with improvement in saturations to the low 90s. While awaiting CXR to confirm appropriate placement of the V-V catheter, the ECMO specialist noted significantly negative venous pressures, leading to decreased ECMO flow and patient desaturation. While troubleshooting the etiology of decreased venous return, a saline bolus was administered with transient improvement. The CXR revealed the cannula tip was in the superior vena cava. The cannula was advanced into the right atrium, with improvement in venous return and oxygen saturations, and flow was titrated up to 120 mL/kg/min with saturations maintained in the low 90s. The FiO_2 was slowly decreased to 0.4, and HFOV settings were reduced to minimize barotrauma. The sweep flow was titrated to normalize carbon dioxide levels while weaning ventilator support. Dopamine was weaned off within the first few hours after cannulation.

Flow requirements remained stable over the next 36 hours. The patient was transitioned to conventional ventilator rest settings, utilizing a high positive end-expiratory pressure (PEEP) lung-protective strategy (PEEP of 10). Nitric oxide was discontinued. Worsening opacification was noted in bilateral lung fields over the first 24 hours, but compliance and CXR improved over the next few days, and both flow and sweep were able to be weaned.

She was anticoagulated with unfractionated heparin, with goal anti–factor Xa (anti-Xa) levels of 0.5–0.7, which were maintained throughout the run. Plasma free hemoglobin levels were monitored and remained between 30 and 50 until

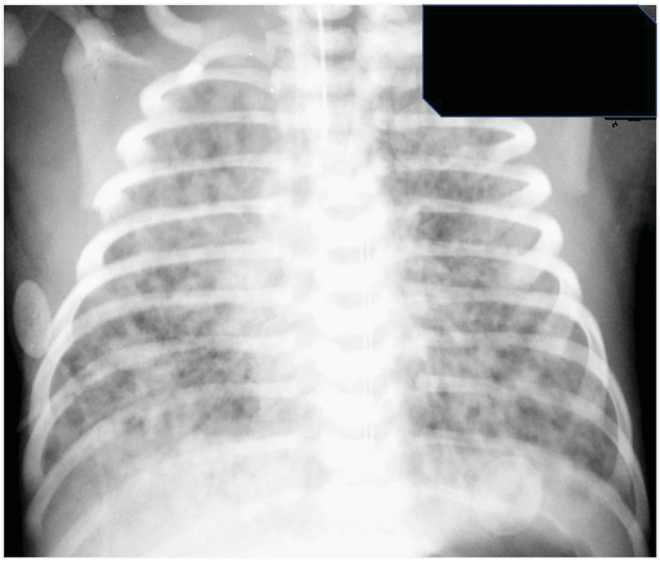


Figure 20.1 Anterior-posterior chest x-ray demonstrating coarse patchy opacities throughout both lung fields with hyperinflation down to the 10th thoracic rib, consistent with MAS.

ECMO day 6, when the level rose to 65, at which time an increased thrombus was noted in the venous limb of the circuit and in the oxygenator, with mildly increased transmembrane gradient. At this time, the patient had been weaned to 70 mL/kg/min of flow, was euvolemic, and with improved lung compliance and clearing CXR. A decision was made to trial off ECMO with a plan to change the circuit if the patient was not ready to come off. She tolerated the trial well and was decannulated on ECMO day 6 and successfully extubated to nasal cannula on hospital day 10.

The patient was monitored closely for neurologic complications with daily cranial ultrasounds, which remained normal, and with 24-hour video electroencephalogram (EEG) followed by continuous cerebral function monitoring, which remained reassuring. The remainder of her hospital course was notable only for dysphagia, which improved with feeding therapy, and she was discharged home on hospital day 20 with planned follow-up in the neonatal follow-up clinic.

WHAT IS THE PATHOPHYSIOLOGY OF MAS?

Meconium consists of amniotic fluid, epithelial cells, lanugo, mucus, bile, and pancreatic enzymes and first appears in the fetal intestines in the third month of gestation. Meconium is normally not passed until after delivery, typically in the first 24 hours in term and near-term neonates, but fetal passage complicates approximately 10%–25% of deliveries, with MAS occurring in approximately 5%.[1,2] The major risk factors for intrapartum passage of meconium and for MAS include late-term or postterm pregnancy and evidence of chronic or acute placental insufficiency and fetal distress.[2–4]

Meconium aspiration syndrome is defined as the presence of respiratory distress in the setting of meconium-stained amniotic fluid, without an alternative explanation. Severe MAS is defined as disease requiring more than 48 hours of assisted ventilation, typically with associated pulmonary hypertension.[1] Severe MAS typically involves multiple physiologic processes, outlined in Figure 20.2, all leading to hypoxemia and acidosis, complicated by persistent pulmonary hypertension, with associated shunting of oxygenated blood right to left across the patent ductus arteriosus, further contributing to cyanosis. In a subset of patients with MAS who suffered from chronic intrauterine hypoxia, there may also be an element of muscularization of the pulmonary capillary bed, further contributing to the pulmonary hypertension.[4] Severe MAS may also be complicated by comorbidities, including hypoxic-ischemic encephalopathy (HIE), sepsis, and bacterial pneumonia, all of which can further exacerbate the complex physiology.

HOW HAVE CHANGES IN PERINATAL MANAGEMENT ALTERED THE INCIDENCE OF MAS?

Changes in perinatal management over the recent decade have included guidelines around the management of late-term and postterm pregnancies to minimize the risk of both stillbirth and MAS, as well as changes in management of meconium-stained infants on delivery.

The American College of Obstetrics and Gynecology has provided consensus recommendations regarding the management of late-term and postterm pregnancies, including the role of fetal monitoring as well as induction of labor to minimize the perinatal risks to the mother and fetus.[5] A recent systematic review including 7781 infants in 11 trials demonstrated a 23% reduction in the relative risk of MAS with induction versus expectant management.[6]

Historically, the management of neonates with meconium-stained fluid included deep suctioning of the oropharynx on delivery, as well as intubation and suctioning of the neonate, in an attempt to decrease the incidence of MAS.[7–9] In 2005, the Neonatal Resuscitation Program, American Heart Association, and American Academy of Pediatrics no longer recommended suctioning of the oropharynx by the obstetric provider at the time of delivery and recommended intubation of only nonvigorous meconium-stained infants.[10] As of 2015, recommendations were revised such that routine endotracheal suctioning of nonvigorous infants born through meconium-stained amniotic fluid was also no longer recommended.[11–13] This change was prompted by the lack of evidence to support immediate endotracheal suctioning in these infants and concern that the risk of intubation and increased time to positive pressure ventilation would potentially be more harmful for the infant. Two studies subsequently analyzed the effect of this practice change, utilizing the Vermont Oxford Network Database and the California Perinatal Quality Care Collaborative Database, and both found a decrease in NICU admissions secondary to MAS with no change in the number of infants with severe respiratory distress and similar incidence of infants requiring invasive respiratory support, iNO, or ECMO.[14,15]

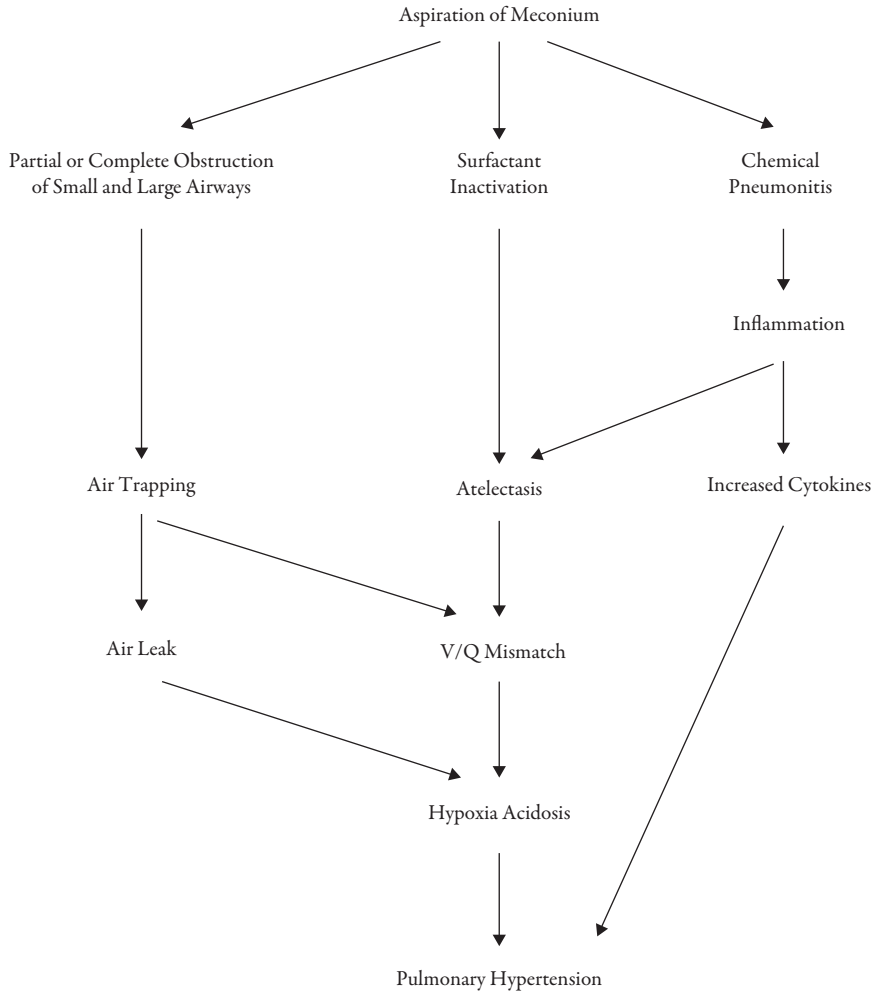


Figure 20.2 Pathogenesis of meconium aspiration syndrome.

HOW ARE NEONATES WITH MAS CURRENTLY MANAGED PRIOR TO CONSIDERATION OF ECMO?

Treatment of MAS is guided by the pathophysiology of the disease, the severity of symptoms and response to therapy, and the presence of comorbid conditions, such as sepsis or HIE. Infants born in the presence of meconium-stained fluid with evidence of cyanosis and/or respiratory distress at delivery should be transferred to a NICU for close monitoring and potential need for escalation of care. While patients with mild disease may only require supplemental oxygen, those with moderate-to-severe disease will require additional support.

Supplemental oxygen should be provided to achieve normal oxygen saturations, typically via nasal cannula or oxygen hood in patients with mild disease. The presence of moderate-to-severe respiratory distress and/or significant respiratory acidosis and hypoxemia should prompt early consideration of intubation and mechanical ventilation. While noninvasive support may be considered, these modalities should be used with caution given the risk of air trapping and air leak. The ventilation strategy utilized should take into account the risk of air trapping, uneven ventilation, and ventilation-perfusion mismatch, with consideration of the use of HFV in the setting of air leak.[16,17] Serial CXRs can be helpful to monitor degree of inflation and to assess for evidence of air leak. Staff should be made aware of the risk for air leaks and be prepared for emergency thoracentesis in the setting of acute pneumothorax.

When intubation and ventilation are required, exogenous surfactant administration should be provided to address surfactant inactivation and improve compliance. The use of surfactant to treat MAS was initially described in a retrospective case series in 1996 with demonstration of improvement in oxygenation.[18] Subsequent randomized controlled trials as well as a systematic review of the evidence have demonstrated a reduction in the need for ECMO in neonates with MAS, with a pooled number needed to treat (NNT) to prevent one additional need for ECMO of 6 (95% confidence interval 3–25) in the 2014 Cochrane review.[19–21] Surfactant provided as lung lavage either instead of or in addition to bolus surfactant dosing has also been studied, with demonstrated reduction in duration of mechanical ventilation and hospitalization.[22–23] While the optimal number of doses of surfactant and optimal method of delivery (intermittent dosing vs. surfactant lavage) may not be clear, multiple studies have demonstrated significant benefit in reducing the need for ECMO in patients with MAS.

Patients with MAS requiring mechanical ventilation should have an umbilical arterial line placed to allow for close monitoring of arterial blood gases and invasive blood pressure monitoring, as well as an umbilical venous catheter to provide central access for fluid and medication administration. The OI is a useful tool for following patients at risk for ECMO and takes into consideration both the amount of mean airway pressure used and the FiO_2 utilized to achieve the PaO_2: OI = ((Mean Airway Pressure × FiO_2) × 100)/PaO_2. The OI is a useful metric to help guide decision-making regarding potential need for transfer to an ECMO center. If a patient is not in an ECMO center, consideration should be made for transfer early in the course of the disease, depending on the capabilities of the NICU, as well as of the transport team, including the capability to provide iNO and/or HFV on transport.

The patient with MAS must be monitored closely for evidence of PPHN, which should include continuous monitoring of pre- and postductal arterial saturation. The preductal saturation should be monitored via the right hand, while either lower extremity can be utilized to measure a postductal saturation. A lower postductal saturation may be seen with PPHN (>5%–10%) and can be more pronounced with agitation. In the setting of suspected pulmonary hypertension, an echo should be obtained to rule out cyanotic cardiac disease, assess degree of pulmonary hypertension, and assess cardiac function.

Initial management of associated PPHN includes optimization of oxygenation, avoidance of acidosis, maintenance of a low-stimulation environment, and use of sedation to minimize agitation. Perfusion and blood pressure should be monitored closely with a goal of maintaining adequate perfusion and blood pressure within the normal range, typically targeting a mean arterial blood pressure between 40 and 55 mm Hg in a full-term neonate. Fluid boluses may be administered with normal saline if concerned for poor perfusion, followed by consideration of vasopressors for persistent hypotension, with dopamine typically utilized as a first-line agent. The presence of PPHN requiring more than 70% oxygen or with an OI greater than 15 should prompt consideration of initiation of iNO, a selective pulmonary vasodilator that has been approved by the Food and Drug Administration (FDA) for use in term and near-term neonates with hypoxemic respiratory failure since 1999. iNO stimulates soluble guanylate cyclase within the smooth muscle cells of the pulmonary arterioles to produce cyclic guanosine monophosphate (cGMP). cGMP decreases the calcium concentration within the cell and induces smooth muscle relaxation and pulmonary vasodilation. iNO acts only on ventilated alveoli, inducing vasodilation of the pulmonary vascular bed to the ventilated alveolus, thus minimizing ventilation to perfusion mismatch (V:Q mismatch). Because iNO combines with hemoglobin to form methemoglobin, it does not cause systemic vasodilation, making it an ideal agent for treating PPHN.[24,25]

Multiple randomized clinical trials have demonstrated efficacy of iNO for treatment of neonatal hypoxemic respiratory failure, with the majority including substantial numbers of patients with MAS as the underlying disease process.[26–31] A recent systematic review of 17 clinical trials of iNO in term and late-preterm neonates with hypoxemic respiratory failure demonstrated a pooled NNT to prevent one infant from requiring ECMO of 5 (95% confidence interval 4–8), supporting the use of iNO at an initial concentration of 20 ppm, excluding infants with diaphragmatic hernia.[32] Additional medications have been utilized for pulmonary hypertension management, including prostacyclin analogues and phosphodiesterase inhibitors, some of which are playing an increasing role in the management of neonatal pulmonary hypertension, but in the absence of large clinical trials, these have not yet become routinely utilized in the management of acute PPHN.[25]

Fluid and electrolyte management should include careful attention to maintaining serum calcium and glucose within normal range. Supportive care for neonates with MAS also includes management of comorbidities, with the most common being pneumonia and/or sepsis, as well as HIE. Broad-spectrum empiric antibiotics are typically administered, with duration of treatment guided by culture results and patient condition. Of note, the literature is very limited regarding the benefit of antibiotics in MAS in the absence of proven sepsis or pneumonia, as demonstrated in a recent systematic review.[33] Therapeutic hypothermia is recommended as an effective therapy to reduce the incidence of death or major neurologic disability in term and late preterm neonates with moderate-to-severe HIE.[34] The hemodynamic and acid-base consequences of sepsis and/or HIE as well as with therapeutic hypothermia can be particularly difficult to manage and may increase the potential need for ECMO in these patients.

WHAT IS THE EVIDENCE FOR USE OF ECMO IN MAS?

The first case report of the successful use of neonatal ECMO described by Dr. Robert Bartlett in 1976 was in a postdates neonate with MAS complicated by PPHN who survived after treatment with veno-arterial (V-A) ECMO.[35] Three subsequent randomized trials have demonstrated the efficacy of ECMO for neonatal hypoxemic respiratory failure, with approximately more than one-third of patients in the three trials having a primary diagnosis of MAS.[36–38] The Extracorporeal Life Support Organization (ELSO) Registry has been collecting data from all ELSO centers since mid-1987 and has demonstrated consistently excellent survival in patients with MAS, remaining greater than 90% since 1987 and in the most recent 5 years (Figure 20.3).[39]

HOW HAS THE USE OF ECMO FOR MAS CHANGED OVER TIME?

As demonstrated in Figure 20.4, from the January 2020 ELSO Registry international summary, the use of ECMO for MAS was the most common indication for ECMO up through the mid-1990s and now accounts for approximately 10% of neonatal respiratory ECMO (see discussion for further detail).[39]

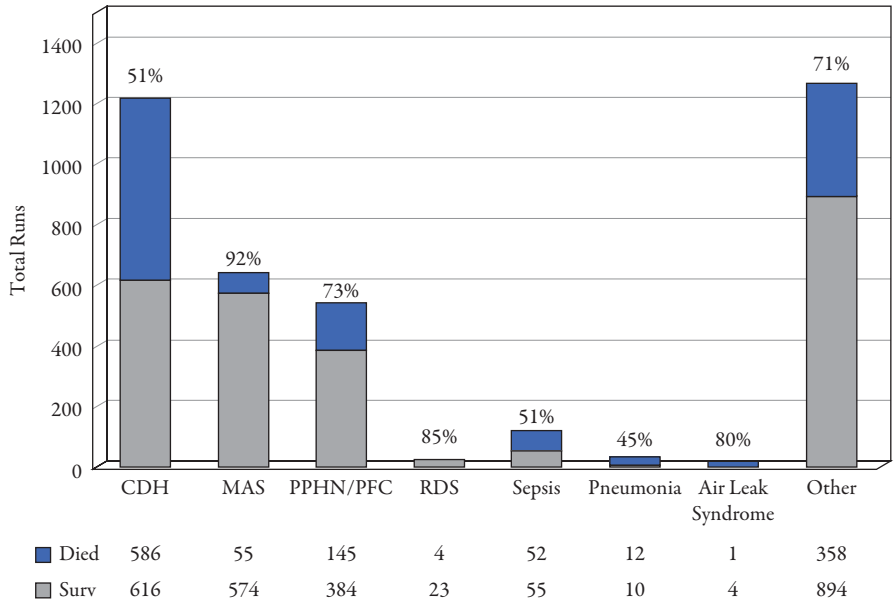


Figure 20.3 *Neonatal ECMO survival by year and diagnosis: January 2015–January 2020. ECLS Registry Report. International Summary Trend Report, January 2020:1–47.* ELSO, Ann Arbor, MI, USA. Reprinted with permission.

WHAT ARE THE INDICATIONS AND CONTRAINDICATIONS FOR NEONATAL RESPIRATORY ECMO?

The most common indications and contraindications for ECMO are summarized in Box 20.1 and Table 20.1 from the ELSO neonatal ECMO patient care guidelines.[40] Infants with severe MAS with persistently high ventilator and oxygen requirements despite optimal medical management, and without clear contraindications, should be evaluated for possible ECMO, which includes screening for contraindications (cranial ultrasound to rule out hemorrhage, echo to rule out structural heart disease) and surgical consultation.

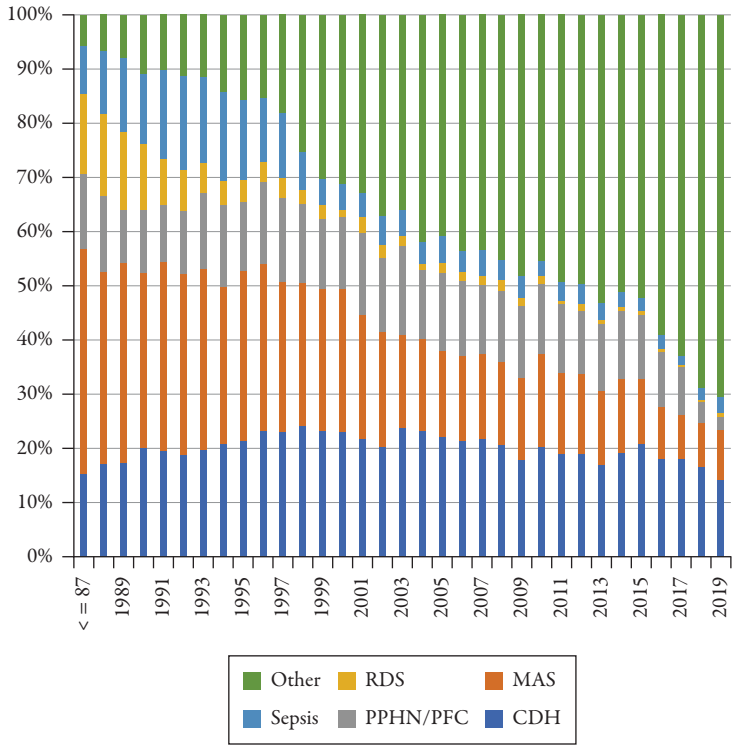


Figure 20.4 Neonatal ECMO cases by year and diagnosis. Primary diagnosis of MAS is in orange and has continued to decrease over time, currently accounting for approximately 10% of neonatal respiratory ECMO cases.
ECLS Registry Report. International Summary Trend Report, January 2020:1–47. ELSO, Ann Arbor, MI, USA. Reprinted with permission.

Box 20.1 **POTENTIAL INDICATIONS FOR NEONATAL ECMO**

Oxygenation index > 40 for > 4 hours

Failure to wean from 100% oxygen despite prolonged (>48 hours) maximal medical therapy or persistent episodes of decompensation

Severe hypoxemic respiratory failure with acute decompensation (PaO_2 < 40) unresponsive to intervention

Severe pulmonary hypertension with evidence of right ventricular dysfunction and/or left ventricular dysfunction

Pressor resistant hypotension

Box adapted with permission from Rintoul N and Gray B, *ELSO Neonatal Respiratory Failure Supplement to the ELSO General Guidelines*, December 2017:1–34.

WHAT RISKS SHOULD BE DISCUSSED WITH THE FAMILY DURING THE CONSENT PROCESS FOR ECMO IN THIS CASE?

Consent for ECMO should include a discussion of the surgical risks, as well as the risks specifically related to ECMO, including patient and circuit complications, need for systemic anticoagulation and blood products, and risk of death and long-term neurodevelopmental disabilities. Specific discussion regarding typical duration of ECMO support is critical, including discussing that ECMO support will be discontinued if it becomes clear that the baby's condition is not reversible or there have been severe complications, including bleeding and/or neurologic complications.

WHAT FACTORS INFLUENCE THE DECISION REGARDING MODE OF ECMO IN A NEONATAL RESPIRATORY PATIENT SUCH AS THIS ONE?

The choice of V-V versus V-A ECMO depends on several factors. The first consideration is whether there is a need for hemodynamic support in addition to pulmonary support. An assessment of cardiac function by echocardiography and of the need for significant pressor support can aid in this decision.

Table 20.1 **CONTRAINDICATIONS TO NEONATAL ECMO**

CONTRAINDICATIONS	RELATIVE CONTRAINDICATIONS
Lethal chromosomal disorder or other lethal anomaly	**Irreversible organ damage (unless considered for organ transplant**
Irreversible brain injury	**<2 kg**
Uncontrolled bleeding	**<34 weeks' postmenstrual age**
Grade III or greater intraventricular hemorrhage	**Mechanical ventilation greater than 10–14 days**

Table adapted with permission from Rintoul N and Gray B, *ELSO Neonatal Respiratory Failure Supplement to the ELSO General Guidelines*, December 2017:1–34.

When the cardiac function is preserved and the need for vasopressor support is thought to be primarily related to pulmonary hypertension, V-V ECMO should be strongly considered if otherwise feasible and given the delivery of highly oxygenated blood directly into the right side of the heart with potential to decrease the pulmonary vascular resistance, improve right-sided function, and subsequently improve return to the left side of the heart. Patient size is also an important consideration given that the smallest V-V cannula currently available is a 13F cannula. V-A ECMO should be considered if there is evidence of concurrent septic shock, severe right heart failure, myocardial dysfunction in the setting of asphyxia/prolonged hypoxemia/acidosis, or if the size of the patient eliminates the option of V-V cannulation.

WHAT IS THE DIFFERENTIAL FOR THE ETIOLOGY OF DECREASED VENOUS RETURN IN THIS CASE?

The etiology of decreased venous return could include hypovolemia, cannula malposition, tamponade physiology, or obstruction within the ECMO circuit. Venous return can also be limited by the size of the cannula (resistance to flow is inversely related to the radius of the cannula to the fourth power). Addressing this situation requires teamwork between the ECMO specialist, bedside nurse, and physician to quickly troubleshoot and identify the most likely etiology. It is often reasonable to administer a fluid bolus to attempt to restore venous return while examining the patient and circuit. A stat CXR and echo may help to identify possible cannula malposition as well as evidence of air or fluid in the pleural or pericardial space. The specialist will inspect the circuit to ensure no kinks or clots are causing obstruction.

In this case, cannula malposition was high on the differential given that the difficulty occurred shortly after cannulation and prior to verifying cannula placement by CXR or echo. Venous return and oxygenation improved after advancing the cannula into the correct position. During cervical V-V cannulation, a double-lumen cannula is placed into the right internal jugular vein with the tip located at the junction between the inferior vena cava and the right atrium with the infusion limb directed toward the tricuspid valve to optimize venous return and minimize recirculation.

WHAT FACTORS CONTRIBUTED TO DECIDING ON ANTICOAGULATION GOALS FOR THIS PATIENT?

Anticoagulation is required in order to minimize thrombosis in the circuit and is typically achieved with the use of unfractionated heparin. The goal of anticoagulation is to strike a balance between minimizing bleeding in the patient and minimizing thrombosis in the circuit. It is important to assess risk factors for intracranial hemorrhage in each patient, including prematurity, pre-ECMO severe acidosis, pre-ECMO cardiopulmonary resuscitation (CPR), HIE/therapeutic hypothermia, and sepsis.[40–44] In our institution, anti-Xa levels are utilized to monitor adequacy of anticoagulation, with a goal

anti-Xa level of 0.5–0.7 IU/ mL for standard-risk patients and 0.3–0.7 IU/mL for high-risk patients (<37 weeks, history of HIE, severe acidosis or CPR prior to cannulation, preexisting low-grade hemorrhage, or concern for ischemia). This patient had a normal screening head ultrasound and no risk factors for hemorrhage, so the patient was managed using our standard risk strategy.

WHAT STRATEGIES CAN BE UTILIZED TO MINIMIZE THE INCREASED RISK OF HEMOLYSIS WITH A CENTRIFUGAL PUMP IN NEONATES?

Centrifugal pumps are the primary pumps utilized in pediatrics and adults, with many advantages, including a smaller system and increased safety. Multiple studies have raised concern regarding increased rates of hemolysis in neonates and small infants supported with a centrifugal pump.[45–51] Potential risk factors for increased hemolysis in smaller patients include cannula size potentially causing increased shear stress, increased fragility of neonatal red cells, and increased transfusion need in smaller patients. A recent large propensity-matched retrospective cohort study of 8366 infants less than 10 kg in the ELSO Registry supported with ECMO between 2011 and 2016 with either a roller or centrifugal system demonstrated increased mortality and ECMO complications among those supported with centrifugal pumps, with hemolysis meeting criteria as a full mediator for the difference in mortality.[51]

While it is likely that the recent studies will influence the pump type for neonates moving forward, many neonatal programs utilize centrifugal pumps at this time. Potential strategies to minimize the risk of hemolysis include carefully managing preload and afterload to minimize the revolutions per minute required to maintain desired flow, optimizing anticoagulation to minimize circuit thrombosis, and minimizing transfusions by lowering the hematocrit threshold.

WHAT IS THE ROLE OF NEUROMONITORING FOR THE NEONATAL ECMO PATIENT?

Neonates treated with ECMO are at significant risk for neurologic complications, including intracranial hemorrhage, cerebral ischemia/infarction, and seizures. Between 2013 and 2017, central nervous system (CNS) hemorrhage (intraventricular and/or intracerebral) occurred in 12% of neonates undergoing respiratory ECMO, of whom 39% survived; CNS infarction occurred in 4%, of whom 33% survived; and electrographic seizures occurred in 4%, of whom 46% survived according to the ELSO Registy.[39] Neuromonitoring while on ECMO may include head ultrasounds, cerebral tomography (CT), continuous EEG, as well as cerebral near-infrared spectroscopy (NIRS) monitoring.

The role for serial cranial ultrasounds to assess for intracranial hemorrhage is well established. Previous studies have shown that the majority of hemorrhages occur within the first 5 days, although late hemorrhages can occur.[51,52] Including a mastoid view may better identify posterior fossa hemorrhage.[53] A surveillance strategy that includes daily head ultrasounds for at least the first 5 days, with the frequency thereafter based on risk factors and presence of any abnormalities, is a reasonable approach. In the setting of abnormalities on cranial ultrasound or neurologic findings with a normal ultrasound, head CT should be considered to help identify ischemia, infarction, or hemorrhage not well visualized by ultrasound.

The incidence of seizures on ECMO may be as high as 20% with continuous monitoring, with a high frequency of subclinical seizures demonstrated by Lin and colleagues and an association with higher incidence of death or neurologic impairment.[54] The American Clinical Neurophysiology Society currently recommends the use of continuous EEG monitoring in all critically ill neonates, including those on ECMO, given the potential for benefit in neurodevelopmental outcome with reduction of seizure burden.[55]

The use of cerebral NIRS to trend cerebral saturations is emerging in the NICU, including ECMO patients, but the utility and potential for early identification and of risk for neurologic injury have not yet been clarified.[56,57]

Magnetic resonance imaging (NRI) has been shown to be superior for identifying brain injury in patients who have been treated with ECMO, with a recent retrospective study of patients treated with ECMO between 2005 and 2015 demonstrating evidence of intracranial injury on MRI in 46% of 81 neonates studied.[58]

WHAT FOLLOW-UP WOULD BE RECOMMENDED FOR THIS BABY?

Prior to discharge, the patient should undergo MRI to identify specific risks for neurologic impairment, complete a hearing screen, and be evaluated by physical and occupational therapy. She requires follow-up to assess for short- and long-term complications, which should include assessments of growth and lung function as well as neurodevelopmental follow-up to screen for developmental delays, including hearing, speech, cognitive, and motor outcomes; and an assessment for learning disabilities and attention deficit disorder as she enters the school years.[59] Follow-up is typically coordinated through a neonatal follow-up program. Patients should also be referred for early intervention assessment and services.

DISCUSSION

Since the first neonatal patient was cannulated for respiratory failure secondary to meconium aspiration in 1975, ECMO has played an important role in the management of MAS.[35] In 1985, the first prospective trial was published by Bartlett and colleagues.[36] This trial utilized a randomized play-the-winner study design and included a total of 12 patients, 1 randomized to conventional therapy and 11 randomized to ECMO, with 100% survival in those treated with V-A ECMO. A subsequent prospective adaptive randomization trial enrolled 39 patients with predicted mortality of more than 85% and demonstrated 95% survival in the 28 patients receiving ECMO versus 60% survival in the 10 patients allocated to conventional therapy.[37] Based on these trials, ECMO was introduced

as a rescue therapy for neonates with hypoxemic respiratory failure. ELSO was established in 1989 to support the ECMO community and to maintain a registry with a goal of capturing data on all patients receiving ECMO; ELSO has been maintained since that time.

A multicenter, randomized, controlled trial with longitudinal follow-up was subsequently completed in the United Kingdom, including patients without contraindications with an OI greater than 40 for at least 3 hours, utilizing both V-A and V-V ECMO, and demonstrated efficacy with survival of 59% of those allocated to ECMO versus 32% of those allocated to conventional treatment, with an NNT to prevent one death at discharge of 4 (95% confidence interval 3–7).[38]

Approximately one-third of the infants randomized to each group had a primary diagnosis of MAS. Of note, the study design allocated patients to transfer to an ECMO center, and not all patients allocated to ECMO received ECMO (78 of 93 subjects received ECMO), but the analysis was completed as intention to treat. At 1 year of age, 60% of survivors in the ECMO group were alive without severe disability, compared to 40% in the conventional treatment group.[60] Follow-up at 4 years was notable for 50% of the ECMO-allocated children with no disability, compared to 37% of those allocated to conventional therapy.[61] Follow-up of 90 children available for assessment at 7 years was notable for an increased incidence of behavioral difficulties in the conventional group, with similar rates of learning problems in both groups.[62]

As was demonstrated in Figures 20.3 and 20.4, MAS was the most common indication for ECMO until 1998 and now accounts for approximately 10% of neonatal respiratory ECMO cases, with 92% survival over the past 5 years.[39] This change came about during the same time period that surfactant and iNO for patients with MAS were increasingly utilized, which likely influenced the need for ECMO.[63] Several retrospective studies have examined the changing population of neonatal ECMO patients in the era of multiple pre-ECMO therapies.

A single-center retrospective review of neonatal patients with hypoxemic respiratory failure during two different epochs demonstrated decreased use of ECMO with increased use of HFV, surfactant, and MAS in the second epoch, with 21 of the 49 patients (43%) in the early epoch (1993–1994) and 13 of 49 patients (28%) in the second epoch requiring ECMO. Of particular interest is the change in primary diagnosis of those requiring ECMO; 63% of the neonates in the early cohort but only 39% of those in the later cohort had a diagnosis of MAS or PPHN, with sepsis/pneumonia the most common indication in the second cohort.[64]

Gill and colleagues specifically examined outcomes of neonates with MAS in the ELSO Registry, with a hypothesis that the use of newer therapies may delay the initiation of ECMO and lead to worse outcomes.[65] Among 3235 patients with complete data treated with ECMO for MAS between 1989 and 1998, mortality was significantly higher in those patients in whom ECMO was initiated later, with 4.8% in those cannulated within the first 24 hours, 7.7% cannulated between 24 and 48 hours, and 6% cannulated between 48 and 71 hours. There were also significant differences in time to decannulation and duration of ventilation with later cannulation. The authors concluded that delays in utilizing ECMO related to trying other therapies may lead to worse outcomes.

The most recent retrospective review of the ELSO Registry between 1996 and 2003 assessed the impact of pre-ECMO management with newer therapies, including iNO, surfactant, and HFV.[66] The use of ECMO declined by just over 25% between the two time periods, with no significant change in mortality, with a 45% decrease in the number of neonates cannulated for MAS. In this study, there was no significant difference in the duration of ECMO support or in duration of mechanical ventilation between the groups, but the age at cannulation was slightly older in those on ECMO between 2000–2003 and 1996–1999, with an increase in mortality with increased age at cannulation. On multivariate analysis controlling for potential confounders, surfactant administration was associated with decreased mortality and iNO administration with decreased need for CPR prior to cannulation.

Since the first patient was placed on ECMO for MAS, ECMO has remained a beneficial therapy for patients with severe MAS. While the need for ECMO has decreased with the advent of additional beneficial therapies, there remains a need for ECMO support in patients with refractory hypoxemic respiratory failure. The available data are unclear whether for some patients early ECMO may lead to better outcomes, and these are questions that should continue to be addressed, particularly if further advances in ECMO technology may allow for minimizing anticoagulation and options for additional strategies for neuroprotection. The outcome for patients with comorbid sepsis and/or HIE with MAS deserves additional investigation, as the outcomes for these patients are likely significantly less favorable than those for patients with MAS alone.

CONCLUSIONS

- Meconium aspiration syndrome was the predominant primary diagnosis treated with ECMO in the 1980s and early 1990s, with survival rates of more than 90%, short runs, and favorable long-term outcomes.
- The use of surfactant and iNO to address surfactant inactivation and PPHN has been associated with a decreased need for ECMO for neonates with MAS in randomized controlled trials.
- Patients with MAS without significant comorbidities remain excellent candidates for V-V ECMO.
- There is a growing concern regarding the increased risk of hemolysis with centrifugal ECMO in neonates and whether roller pumps should be the preferred support mode for neonates to optimize outcomes and minimize complications.
- There is need for further short- and long-term outcome data for the current population of patients requiring ECMO for MAS, particularly with associated HIE, to understand the additional risks for these patients.

- Additional strategies for optimizing neuromonitoring and neuroprotective strategies for neonates requiring ECMO should remain a research priority.

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REVIEW QUESTIONS

1. Which of the following statements is NOT true?

   A. The first neonatal patient placed on ECMO was for MAS in 1976.
   B. Surfactant administration decreases the need for ECMO in MAS.
   C. Inhaled NO is FDA approved for neonates older than 34 weeks' gestational age with hypoxemic respiratory failure.
   D. Meconium aspiration syndrome remains the commonest indication for neonatal ECMO.
   E. The first prospective trial of ECMO for neonatal hypoxemic respiratory failure utilized a play-the-winner randomization design.

2. Which of the following statements is incorrect?

   A. Intubation of all neonates born through meconium-stained fluid is beneficial in preventing MAS.
   B. Standardized guidelines for monitoring and induction of labor in late-term pregnancies have been associated with a decrease in the incidence of MAS.
   C. Minimal stimulation and sedation are recommended for patients with PPHN.
   D. Patients with MAS are at risk for pneumothorax.
   E. Pre- and postductal saturations should be monitored in patients with MAS.

3. Which of the following is NOT a contraindication to ECMO?

   A. Lethal chromosomal anomaly or congenital malformation
   B. Grade III intraventricular hemorrhage
   C. Birthweight of 1.5 kg
   D. Late premature infant at 36 weeks' gestational age
   E. Massive subgaleal hemorrhage

4. Which of the following likely contribute to the increased risk of hemolysis in neonates on centrifugal ECMO?

A. Cannula size
B. Gestational age
C. Increased transfusion need
D. Increased fragility of red blood cells
E. A, C, and D

5. Which of the following may be used in addition to a detailed clinical examination to assess for patients at risk for neurological complications and neurodevelopmental disability?

A. Cranial ultrasound scans (CUS)
B. Electroencephalography
C. Near-infrared spectroscopy
D. Magnetic resonance imaging
E. All of the above

ANSWERS

1. D
2. A
3. D
4. E
5. E

21.

ECMO FOR NEONATAL PULMONARY HYPERTENSION AND ASSOCIATED DISORDERS

Billie Lou Short

STEM CASE AND KEY QUESTIONS

A 32-year-old primiparous woman presents in labor at 41 weeks' gestation. Her pregnancy has been complicated by maternal tobacco use. During the second stage of labor, she has a fetal heart tracing showing late decelerations and thick meconium (MEC)–stained amniotic fluid is noted. She progresses in labor, and a vaginal birth is anticipated. The pediatric team is called to attend the birth.

WHAT CAUSES PULMONARY HYPERTENSION IN THE NEWBORN?

Persistent pulmonary hypertension of the newborn (PPHN) has been a common finding in diseases that require extracorporeal membrane oxygenation (ECMO) treatment in the newborn population.[1,2]

This postfetal pathophysiologic condition can be either the primary cause for respiratory failure (i.e., idiopathic PPHN) or a secondary cause in such diseases as meconium aspiration syndrome (MAS), sepsis/pneumonia, and congenital diaphragmatic hernia (CDH) patients. In the last 3 years, data from the ELSO Registry (January 2020) showed that 32% of the neonatal respiratory ECMO cases are CDH patients, with 17% MAS and 14% idiopathic PPHN. When the ECMO course for these patients does not follow the routine course, a differential for other disease states needs to be considered, including surfactant protein deficiency, alveolar capillary dysplasia, or congenital heart disease.

WHAT IS THE INCIDENCE OF MECONIUM ASPIRATION?

Meconium is a sterile substance composed of debris from desquamated cells, amniotic fluid, and bile. It is found in the fetal intestinal tract as early as 12 weeks' gestation, but meconium passage into amniotic fluid is uncommon before 34 weeks' gestation. In contemporary studies, meconium is seen in 8% to 10% of term deliveries. The prevalence of MEC is strongly correlated with gestational age and increases almost linearly from 37 weeks' to 42 weeks' gestation.[2–5]

Although MEC-stained amniotic fluid is frequent, MAS occurs infrequently, and the incidence has been progressively decreasing during the last four decades. MAS occurs in approximately 2% to 3% of infants born through MEC-stained fluid, yielding an incidence of 1 to 2 per 1000 live term births per year. Severe MAS, requiring either mechanical ventilation or continuous positive airway pressure, occurs in less than 1% of infants born through MEC-stained fluid and represents only one-third of newborns diagnosed with MAS. The risk of MAS markedly increases with advancing gestational age beyond 39 weeks' gestation. Additional risk factors associated with MAS include abnormal fetal heart rate tracings, abnormal fetal growth, maternal tobacco use, and increasing consistency of the MEC in the amniotic fluid. Of infants with MAS significant enough to require mechanical ventilation, only a small percentage will worsen and require ECMO. These infants have a degree of PPHN associated with their MAS.[1–7]

SHOULD THE PEDIATRIC TEAM INTUBATE AND SUCTION THE INFANT IF THICK MEC IS NOTED IN THE INFANT?

Multiple interventions to prevent MAS and its complications were recommended in the 1970s and 1980s based on biologic plausibility and nonrandomized studies, including tracheal intubation and suctioning. Later studies showed no difference in the incidence of MAS and/or respiratory support required between those intubated and those not, and many tracheal complications were noted in the intubated population.[2–7] Therefore, this procedure is no longer recommended. The incidence of MAS and mortality related to MAS has progressively declined since the 1970s, most likely because of obstetric practices that have decreased the incidence of birth beyond 41 weeks' gestation. Currently, there is insufficient evidence to recommend amnio infusion, intrapartum suctioning by the obstetrician, or routine tracheal suctioning in either vigorous or nonvigorous infants with MEC noted at birth.

WHEN SHOULD THE INFANT BE CONSIDERED FOR ECMO THERAPY?

Most infants with MAS can be managed on conventional ventilation, but a small percentage will go on to require high-frequency ventilation (HFV) techniques and/or inhaled nitric oxide (iNO; Figure 21.1).[1–3] After they have failed these

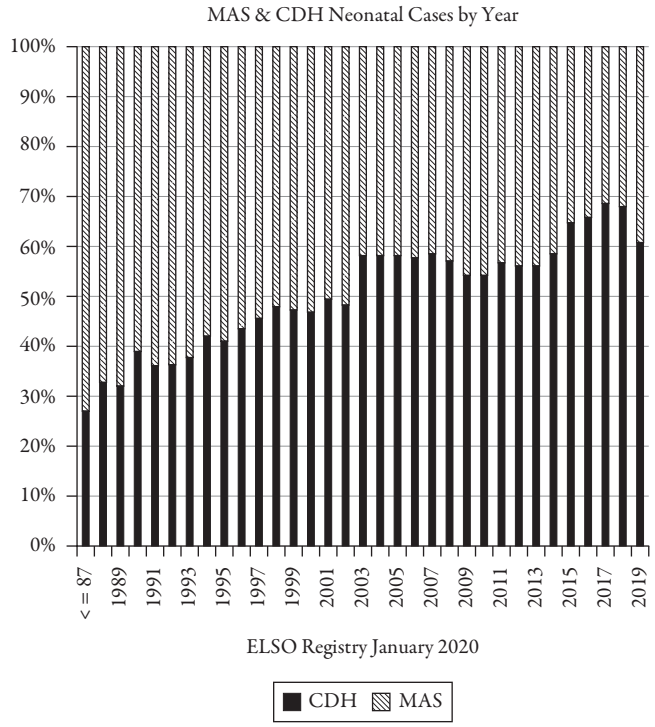


Figure 21.1 Data from the ELSO Registry outlining the incident of the MAS population and CDH population.
ECMO from 2015 to present. Data from the January 2020 report with permission from ELSO.

treatments, they should be considered for ECMO therapy, but more importantly they should be referred and transported to an ECMO center prior to meeting ECMO criteria. It is exceedingly difficult to transport when the infant has failed HFV/iNO.

The most common parameter indicating the need for ECMO is the oxygen index (OI).[8] The OI is calculated by dividing the product of the fraction of inspired oxygen (FiO_2) (times 100) and the mean arterial pressure (MAP) by the post-ductal partial pressure of oxygen (PaO_2):

$$OI = FiO_2 \times MAP \times 100/PaO_2$$

An OI of 40 for at least 2 hours has been used to indicate a mortality rate of 80% in the neonatal population; so, OI of 40 or greater is used to indicate that ECMO is required. It is important that infants should be transferred to an ECMO center prior to an OI of 40. Depending on circumstances, an OI of 30 should indicate that the infant may continue to deteriorate, and consultation with an ECMO center is recommended.

WHAT STUDIES ARE NEEDED PRIOR TO ACCEPTING THE PATIENT FOR ECMO?

Pre-ECMO studies that should be undertaken are related to the potential risk associated with the ECMO procedure (i.e., hemorrhage secondary to the heparinization required). Therefore, a head ultrasound (HUS) should be obtained to rule out an intracranial hemorrhage; coagulation studies should be done to determine baseline anticoagulation requirements of the infant. Infants in septic shock can already have prolonged bleeding times and require less anticoagulation initially. Congenital heart disease can mimic neonatal respiratory failure, so a cardiac echocardiogram (ECHO) should be done to rule this out.

A GRADE I INTRAVENTRICULAR HEMORRHAGE IS NOTED ON THE HEAD ULTRASOUND. SHOULD THIS BABY GO ON ECMO?

Infants with grade I intraventricular hemorrhage (IVH) can be placed on ECMO with appropriate monitoring of coagulation requirements, keeping the heparin dose as low as possible and following daily HUS studies. If the IVH extends to a grade II or III, you may need to take the patient off ECMO.

The infant is now on high-frequency oscillatory ventilation (HFOV) and iNO with an OI consistently greater than 30. The infant was transferred to an ECMO center and stabilized on the HFOV. Two hours later, the OI increased to 50 despite increasing ventilator settings, and the decision was made to place the infant on ECMO.

WHAT SHOULD YOU DISCUSS WITH THE PARENTS IN GETTING ECMO CONSENT?

The survival for a MAS infant is around 92% (Figure 21.2), so you can be optimistic that the infant will make it off ECMO, but you should discuss the limitations of ECMO (i.e., treatment does not improve with ECMO runs greater than 21 days, with the average run 6–8 days; intracranial hemorrhage risk is low, around 4%, but if an intracranial hemorrhage is noted, ECMO will need to be discontinued; other bleeding can occur, and if noted will require special treatment, and the baby may need to come off ECMO if the bleeding cannot be controlled. It is important to also discuss equipment failures, which are rare but can happen. The ECMO team is trained to change equipment if needed. After ECMO, the infant will need to be followed in a neurodevelopmental clinic. Although the majority do well, there is a small percentage that may develop developmental issues.

THE INFANT IS NOW 14 DAYS ON ECMO WITH NO IMPROVEMENT. WHAT SHOULD BE CONSIDERED?

Most MAS/PPHN infants are off ECMO by 8 days, so courses beyond that time are concerning for an underlying disorder. If you are out to 21 days, one should consider congenital surfactant deficiencies, alveolar capillary dysplasia, or CHD; the commonest cardiac lesion that mimics lung disease is total anomalous pulmonary venous return (TAPVR).[9–11] If the baby was unstable when the ECHO was done and a full ECHO study could not be done, the first item would be to repeat the ECHO, but studies on ECMO can be difficult, so a cardiac catheterization may be required. TAPVR draining below the diaphragm can be difficult to diagnose if

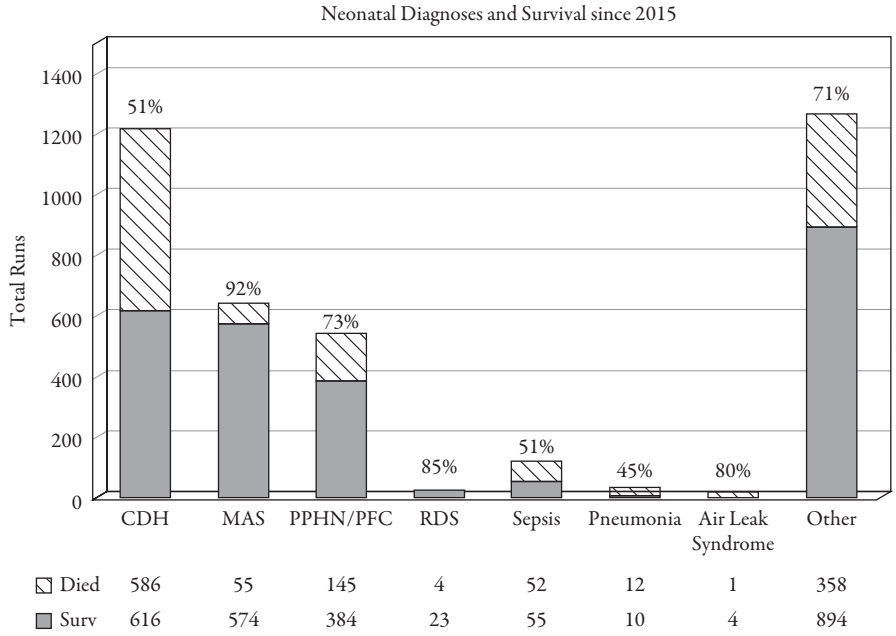


Figure 21.2 Data from the ELSO Registry on survival of neonatal respiratory failure cases. Data are from the January 2020 report with permission from ELSO.

a full ECHO study could not be completed. Genetic studies for surfactant protein deficiencies should be sent and consideration for a lung biopsy to diagnose alveolar capillary dysplasia. Of note, cases of alveolar capillary dysplasia have been diagnosed on cardiac catheterization, where an abnormal blush transition into the lungs was noted. The unusual case can be due to significant lung injury pre-ECMO causing a chronic lung disease situation. In these cases, steroids may help, but if there is no major improvement, the above measure need to be undertaken.

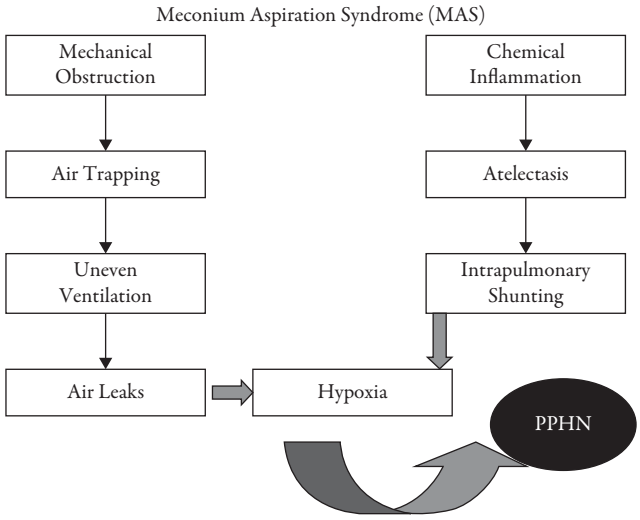


Figure 21.3 Schematic of the pathophysiology of MAS from mechanical obstruction to chemical inflammation, resulting in potential air leaks and development of PPHN.

DISCUSSION

The typical MAS/PPHN patient who requires ECMO therapy has been on maximal conventional ventilation, HFV, and iNO.[1,2] The infant with MAS not only has MAS with the known areas of lung collapse and combined with areas of overdistention of the lungs (Figures 21.3 and 21.4), but also has a component of PPHN, making their pre-ECMO management very difficult.[1–3] A small percentage of MAS infants have sustained severe hypoxic-ischemic encephalopathy and may be on a cooling protocol to minimize brain injury. These infants can be managed on ECMO with continued cooling,[12,13] and of interest there have been no reported coagulation issues while cooling.

PRE-ECMO MANAGEMENT

The goal for management of the MAS/PPHN infant is to maintain oxygenation and ventilation in a normal state until the body can absorb the meconium, and the pulmonary hypertension will resolve, usually taking 5–7 days for improvement.[1,2] In severe cases with persistent hypoxia and/or hypercarbia despite maximal ventilation, ECMO is the next treatment modality. Pre-ECMO studies should include a HUS to rule out intracranial hemorrhages, coagulation studies to have a baseline on coagulation status, and a cardiac ECHO to rule out cardiac disease. Days on the ventilator indicate the disease severity, and around 7–10 days the infant will move into chronic lung injury from ventilation. Many will not consider ECMO for these patients if over 10 days of ventilation, but experience in our chronic lung disease patients indicates that ECMO may be an appropriate therapy for these

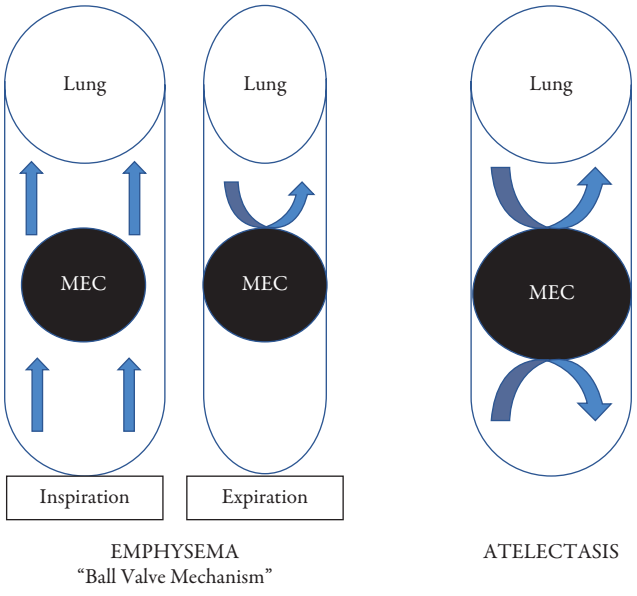


Figure 21.4 Schematic of the air-trapping phenomenon noted in MAS leading to areas of collapse and areas of overdistention.

patients. OI levels consistently over 40 indicate high mortality, and most will use this as an indication for the need for ECMO therapy.

Pneumothorax is a risk in the MAS population related to the unequal ventilation in these infants. A chest tube placed less than 8 hours prior to being placed on ECMO with heparinization can be a risk for chest tube bleeding and must be monitored closely for this risk.

ECMO MANAGEMENT

Most MAS infants can be managed with veno-venous ECMO if there is not a significant cardiac component to their disease state.[14] Patients who have required high pressor support and have OIs greater than 50 can require veno-arterial ECMO. Most of these infants are on maximal pressor support, requiring volume resuscitation.

CANNULATION

The team required for cannulation includes the neonatal medical team who will manage ventilation and sedation, the surgical team, and the ECMO specialist team. Communication between all team members is essential for successful cannulation. Heparinization is usually achieved with a heparin bolus of 100 units/kg to achieve the activated clotting time (ACT) over 250 seconds to prevent catheter clotting. This bolus should be given when the surgeons have isolated the vessels and are ready to place the catheters. Sedation and paralysis for the patient is provided by the medical team. The most common medications include a paralytic, such as vecuronium, and morphine or fentanyl for pain management. Surgeons will isolate the vessels. At this point, the heparin bolus should be given; after waiting 5 minutes, then they will place the catheter(s). Placement will be confirmed by x-ray. At this point the surgeon will work with the ECMO specialists to connect the catheters to the circuit. ECMO blood flow should be increased slowly until a flow rate, estimated to be 60% of the cardiac output, 120 mL/kg/min, is achieved. This level of support is usually sufficient in the MAS/PPHN patient. Infants with sepsis may require higher flow, up to 80% bypass. Ventilator settings should be reduced during this time to "rest settings." These settings may vary per institution, but in general, rest settings are peak inspiratory pressure (PIP) 15–18 cm H_2O, positive end-expiratory pressure (PEEP) 5–6 cm H_2O, and FIO_2 0.21.

DAILY MANAGEMENT

The initial days on ECMO usually require ECMO blood flows of 120 mL/kg/min to maintain rest settings with normal blood gases. The x-ray may worsen over the first few days, and then a gradual improvement in aeration will occur over the next several days. If the x-ray does not improve by 5–6 days, consider if ventilator settings need to be increased. It is important with low ventilator settings to keep sedation low and have the infant breathing on their own. The infant can open their own lungs better than trying to open with higher ventilator settings. As the lungs improve on x-ray, the ECMO blood flow can be weaned; most measure blood gases every 2–4 hours and wean by 10–20 mL if the patient's PaO_2 is greater than 60–80 torr. A gradual reduction in ECMO flow until 60–80 mL/kg/min is considered *idling*; if this level is maintained for 4–6 hours with good blood gases, the patient is ready to decannulate. A trial off ECMO, as some do, is not required in the MAS/PPHN population; if they idle successfully, decannulation can be achieved. If patients are still on high ECMO flow at 10–12 days, an underlying process should be considered.[9–11] Review of the initial ECHO should be undertaken, and if the study is not conclusive for all four pulmonary veins returning to the left atrium, a repeat ECHO should be done; consideration for a cardiac catheterization should be undertaken. Genetic testing for genetic causes of surfactant deficiency should be sent. If there is no improvement by 21 days, then there should be strong consideration for other disorders, including alveolar capillary dysplasia. A lung biopsy may be required. Steroid therapy may also be attempted to support any case with chronic lung injury. We usually limit our ECMO runs for MAS/PPHN infants to 21 days.

Routine care includes nutrition through total parenteral nutrition, as with term infants (e.g., starting at 80 mL/kg/day, increasing to 100 to 120 mL/kg/day by the end of the ECMO run). Some centers start enteral feeds. Attention to gastroenteric status is required, in this instance, because one case of necrotizing enterocolitis has been noted in our center in this population.

Sedation should be minimized so the infant will breathe effectively. This will help to open the collapsed lungs in a gentle fashion. Morphine either as needed or as a drip is effective to keep the patient calm. Nursing techniques are key, with swaddling and other measures. Parents should be encouraged to interact with the infant.

Coagulation is maintained through a heparin drip titrated using various coagulation methods.[15,16] It is beyond the scope

Table 21.1 REPRESENTATIVE OUTLINE OF TYPICAL COAGULATION MANAGEMENT ALGORITHM FOR NEONATAL RESPIRATORY FAILURE PATIENTS ON ECMO

UNFRACTIONATED HEPARIN (UFH) LEVEL (UNITS/ML)	ACTIONS
<0.2 Or ACT < 160 second	**IMMEDIATELY INCREASE HEPARIN INFUSION BY 20% AND NOTIFY PROVIDER.** Repeat UFH in 4 hours after heparin infusion change. The intensive care unit (ICU) provider may determine a larger change is warranted.
<0.4	Increase heparin infusion by 10% and notify provider. Repeat UFH in 4 hours after heparin infusion change.
Goal (0.4–0.6)	No change. Is ACT out of range high? Platelet count > 100 K/μL? Fibrinogen < 150 mg/dL? Consider cryo to achieve desired fibrinogen level to reduce volume administration.
>0.6	Decrease heparin infusion by 10% and notify provider. Repeat UFH in 4 hours after heparin infusion change.
>0.8	**IMMEDIATELY DECREASE HEPARIN INFUSION BY 20% AND NOTIFY PROVIDER.** Repeat UFH in 4 hours after heparin infusion change. The ICU provider may determine a larger change is warranted.
Heparin management notes	1. Initial heparin bolus of 100 units/kg when instructed to do so by cannulating or ICU physician. 2. Start heparin infusion at 50 units/kg/h when ACT drops below 250 seconds. 3. Check UFH every 4 hours until two consecutive checks are therapeutic, then check every 8 hours. 4. Maintain ACT range of 200–220 seconds or as indicated by provider's order. 5. Obtain ACTs every 1 hour until two consecutive UFHs are within range, then every 2 hours. 6. If any two consecutive UFH results are out of range (high or low), obtain ACTs every 1 hour until the UFH values are therapeutic. 7. If ACT is out of range, recheck immediately. If repeat ACT is still out of range, send UFH stat. 8. Managing heparin drip with ACT value may be warranted until UFH results are available. If ACT < 180 with no UFH results, increase heparin by 10%.

of this chapter to cover all the coagulation methods used, but know that this management in this population is less complex than in cases where there is bleeding postsurgery, as with the CDH or postoperative cardiac patients, which makes coagulation management complex. Routine coagulation measurements are listed in Table 21.1. It is common to require platelet transfusions daily due to the circuit and membrane trapping platelets.

DECANNULATION

When the patient has successfully idled for 4–6 hours with stable blood gases, you can consider decannulation. Taking the patient off ECMO requires the same team; again, communication is especially important across team members in this process. The ventilator should be increased to ensure proper ventilation (i.e., PIP 25–28 cm H_2O, PEEP 5–6 cm H_2O, respiration rate 30–40 breaths/min, FiO_2 0.3). The patient will need to be paralyzed and sedated (vecuronium/fentanyl); ensure there is no respiratory effort, for the venous catheter on occasion can be difficult to remove, and side holes can be out before the catheter is completely out of the patient. If the patient inhales during this process, an air embolus can occur. Use a ventilator inspiratory hold during removal to the venous catheter will help prevent this.

After the catheters are out, the patient will metabolize the heparin very quickly, so heparin reversal is usually not required.

POST-ECMO CARE

Adjust the ventilator settings as needed. Many will extubate within 24–48 hours to nasal cannula or high-flow nasal support. Enteral feeds can be started in 24 hours, advancing over the next 72 hours. Many infants will take oral feeding very slowly. This will improve over the next week. Brain magnetic resonance imaging should be done for many findings are not found on the HUS done while on ECMO.[17–19] Most infants are followed up in a neurodevelopmental clinic, because although neuroimaging may be good, there are about 30% who require special needs care when they go to school.[20,21]

In general, the long-term outcome of the MAS/PPHN infant is good, with those with severe development delays having abnormal neuroimaging indicating brain injury prior to ECMO. If there is a family history of asthma, these infants are at risk for developing asthma later in life. To date, there is no evidence that these infants will develop adult-onset pulmonary hypertension.[22]

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REVIEW QUESTIONS

1. Name the major risk associated with placing a MAS infant on ECMO that you would discuss with the family during your consent process?

A. A 15% risk of intracranial hemorrhage, resulting in the need to come off ECMO
B. Bleeding risk for the chest tube placed 6 hours before going on ECMO
C. Neurologic injury, primarily from the pre-ECMO period when the infant was hypoxic
D. B and C
E. None of the above

2. Veno-venous ECMO is the typical form of extracorporeal life support for the MAS/PPHN patient. List the limitations of this type of ECMO therapy.

A. Blood pressure maintenance when cardiac function impaired
B. Increased risk for intracerebral hemorrhage
C. Oxygenation limitations due to recirculation at higher veno-venous ECMO flows
D. A and C
E. A, B, and C

3. If the patient is now 21 days on ECMO with no improvement in pulmonary function, what would be your next consideration?

A. Cardiac disease; repeat ECHO
B. Genetic disorders, such as alveolar capillary dysplasia
C. Acute respiratory distress syndrome with significant lung damage; may require more time
D. Genetic disorders such as surfactant B disorder
E. All the above

4. For the patient in question 3, what maneuvers would you try to improve lung function?

A. Give surfactant
B. Increase the ventilator PIP and PEEP
C. Change to HFV
D. Consider steroid treatment
E. All the above

5. Which of the following is true for the idiopathic PPHN patient requiring ECMO?

A. Survival in about 92%.
B. Their typical ECMO run is 6–8 days.
C. They risk development of adult pulmonary hypertension later in life.
D. Treatment before ECMO can include iNO, which is a platelet inhibitor that should not be a risk on ECMO.
E. None of the above.

ANSWERS

1. D
2. D
3. E
4. E
5. B

22.

ECMO FOR CONGENITAL DIAPHRAGMATIC HERNIA

Carl Davis

STEM CASE AND KEY QUESTIONS

A 3.1-kg baby girl was born at 39 weeks' gestation with an antenatal diagnosis of right congenital diaphragmatic hernia (CDH) made at a detailed fetal anomaly scan at 20 weeks. Her care was transferred to the regional fetal medicine unit with access to co-located neonatal, neonatal surgery, and extracorporeal membrane oxygenation (ECMO) services. Antenatal investigations included regular fetal ultrasound examinations and second and third trimester fetal magnetic resonance imaging (MRI). She was seen by fetal medicine, pediatric surgery, and neonatology. Her calculated observed-to-expected total fetal lung volume (O:E TFLV) was 18%.

Following induction of labor, her mother gave birth to her by spontaneous vaginal delivery at 10:00. She was immediately intubated and ventilated and transferred to the neonatal intensive care unit (NICU) once stable. Continuous mandatory ventilation (CMV) was commenced (28/5 with inspiratory time [Ti] 0.5 seconds at a fraction of inspiratory oxygen [FiO_2] of 0.95). Arterial blood gas on CMV showed poor carbon dioxide (CO_2) clearance with partial pressure of carbon dioxide ($PaCO_2$) of 16.9 kPa (127 mm Hg). An early echocardiogram (at 3.5 hours) showed right-to-left shunting at atrial and ductal levels, and very poor cardiac contractility was identified so she was commenced on inhaled nitric oxide (iNO) at 20 ppm. As CMV parameters (above) were maximal accepted, she was converted to high-frequency oscillatory. ventilation (HFOV) to aid CO_2 clearance. Arterial PCO_2 was reduced to 9 kPa (68 mm Hg) on HFOV settings of mean arterial pressure (MAP) 16 cm H_2O, delta P 36, at 8 Hz, but oxygen saturation (SaO_2) remained at 70% despite FiO_2 of 0.9–1.0. As ECMO criteria were met and following discussion with her parents, veno-arterial (V-A) ECMO was commenced at 11 PM.

She was supported with flows of 350 mL/min, and the ventilator was on CMV settings of 20/4, FiO_2 0.4. A decision was made to repair the defect early, and this was undertaken after 36 hours on ECMO. The defect was graded as a C defect, and repair was undertaken with a GoreTex™ 1-mm graft. Heparin was discontinued as surgery commenced (and was discontinued for 6 hours total). Tranexamic acid was also commenced at the time of surgery and continued postoperatively. Floseal® and Surgicel® Fibrillar™ were applied above and below the patch. The abdomen required a further GoreTex graft as a primary closure was not possible. The procedure was well tolerated.

Perfluorocarbon was instilled during the postoperative period to clear debris and recruit the lungs with the ventilator on continuous positive airway pressure settings (lung distension protocol). This was used for 5 days. Progress was slow, with very little improvement during the first 6 days. Ductal flow was now bidirectional; the right ventricle (RV) appeared hypertrophied, but the left ventricular (LV) function showed improvement when ECMO flows were weaned.

At 6 days on ECMO, the abdominal patch was removed, and a 50-mL collection of blood was removed. No apparent source was identified. A small clot was identified at the end of the endotracheal tube at bronchoscopy and removed. Over the next few days, ECMO flow was slowly weaned, and the patient was decannulated to HFOV on day 10 of ECMO.

The patient slowly improved on HFOV with maximum treatment for pulmonary hypertension (PH), including milrinone, iNO, sildenafil, and Prostin. The abdominal patch was downsized and later removed. The post-ECMO course was complicated by an episode of sepsis, and she developed a chylothorax that required drainage. Both resolved. She remained intubated for a total of 39 days and was discharged (corrected age 49 weeks) on 0.1 L/min O_2. An echocardiogram prior to discharge showed no evidence of PH, although she was discharged on oral sildenafil.

A cranial ultrasound on day 27 suggested a right middle cerebral infarction, and this was confirmed on MRI. She has been followed up in a multidisciplinary clinic for 18 months and is making very good progress. Her left arm is less dexterous than the right, and she cruises around the furniture. She will have a formal neurodevelopmental assessment at 2 years. She remains on 0.1 L/min O_2 at night and during naps.

WHY DO I USE ECMO IN PATIENTS WITH CONGENITAL DIAPHRAGMATIC HERNIA?

Congenital diaphragmatic hernia is the reason I became interested in ECMO. The frustration of seeing babies with CDH not survive to the point of surgical repair due to inability to achieve physiological stability encouraged me to see ECMO as the solution. Over 30 years later, I realize how naïve I was, but I still believe ECMO has an important role in optimizing outcome in CDH. This chapter gives the reader an objective

outline of its role in the management of CDH when conventional treatments are failing.

WHAT IS THE PROBLEM WITH CONGENITAL DIAPHRAGMATIC HERNIA?

Abdominal viscera, including liver, spleen, stomach, and intestine, can herniate into the chest from around the 10th week of gestation (when the physiological exomphalos reduces). Lung growth and development are impaired through limitation of space, reduced fetal breathing movements, and loss of fetal lung liquid. This leads to variable degrees of pulmonary hypoplasia. The combination of pulmonary hypoplasia, PH, and cardiac dysfunction are the main determinants of postnatal survival (Figure 22.1). Though CDH has high mortality compared to other pediatric surgical congenital anomalies, improvement in survival has occurred through antenatal diagnosis and advances in neonatal care that includes ventilation strategies to avoid lung injury and targeted therapy for PH.[1] Antenatal diagnosis facilitates identification of associated anomalies (especially cardiac) and chromosomal defects and informs prenatal counseling and delivery in a specialist unit that has all treatment modalities available, thus avoiding the need for postnatal transport with potential separation of mother and baby.

CAN WE IDENTIFY HIGH-RISK CDH, AND HOW DO WE PREDICT SURVIVAL?

To date, we have no clinically useful definitive prenatal or postnatal accurate predictors of survival, either with or without ECMO support.

WHAT ARE THE PRENATAL PREDICTORS OF OUTCOME?

Currently, we can expect upward of 75% of CDHs to be antenatally diagnosed at a fetal anomaly scan, usually performed between 18 and 20 weeks' gestation. Some services report detection at booking scans, but this is unusual. The most widely used prenatal predictors of outcome is the lung-to-head ratio (LHR) assessed by ultrasound, best reported as the O:E LHR. The second predictor is TFLV measured on maternal MRI, also best expressed as O:E TFLV, and is usually measured during the late second or early third trimester. The presence of liver in the chest has a negative impact on survival. Based on the above data, in 2009 a European group of clinicians[2] recommended stratification of risk based on O:E LHR (or O:E TFLV) and liver position:

1. Fetuses with an O:E LHR less than 15% have virtually no chance to survive, such that the hypoplasia is "extreme." The liver is typically up in these cases. Morbidity rates in these patients are unknown, given the few reported cases.
2. Fetuses with an O:E LHR from 15% to 25% have "severe" pulmonary hypoplasia. Their predicted survival rate is less than 20%, less if the liver is up. The rate of bronchopulmonary dysplasia (BPD) in the (rare) survivors is greater than 75%.
3. Fetuses with an O:E LHR between 26% and 35% (irrespective of the liver position) and those with an O:E LHR between 36% and 45% and liver up have "moderate" hypoplasia. They have a predicted survival rate around 50% (range 30%–60%). The rate of BPD is around 30%.
4. Fetuses with an O:E LHR between 36% and 45% with liver down and those with an O:E LHR greater than 45% have "mild" hypoplasia and are likely (>75%) to survive. In the latter group, the rate of BPD is around 10%.

Outcomes given for the groups above have been contested, particularly groups 2 and 3, where many clinicians feel the quoted survival rates are overly pessimistic.

The above risk stratification has been used as entry criteria for two fetal tracheal plugging (FETO) trials: The TOTAL trial for assessed moderate lung hypoplasia (25%–34.9% O:E LHR and 35%–44.9% O:E LHR with liver in chest) and the TOTAL trial for measured severe (<25% O:E LHR) lung hypoplasia. The moderate lung hypoplasia trial has closed to recruitment, and published results are expected soon. The randomized trial for treatment of severe left CDH has just been published and confirmed benefit of FETO with 40% survival

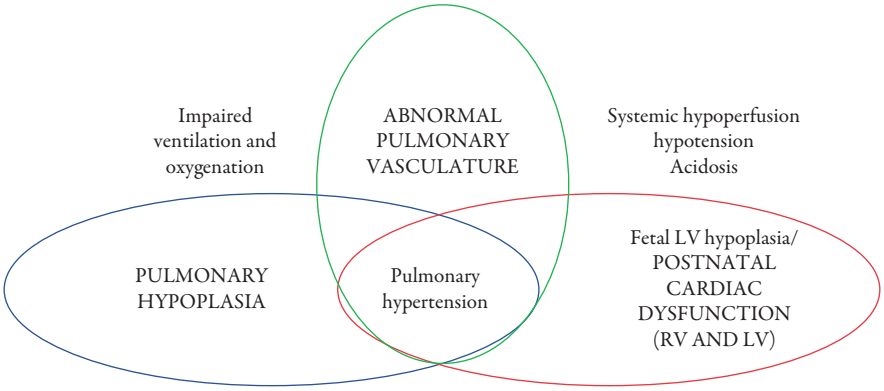


Figure 22.1 Pathophysiological model of CDH.
Modified from Kinsella et al, J Peds 2018

in the treated group (16/40) *vs* 15% (6/40) in the conventional group.[3]

The risk of this antenatal intervention is a higher likelihood of preterm delivery, reducing the potential role for ECMO.

It is important that prenatal outcome assessment data and prenatal counseling details are available to clinicians to aid parent counseling and clinical decision-making postnatally. Other measurements, particularly around cardiac and pulmonary artery structure and function, are still not sufficiently reliable to be useful when counseling prospective parents (Figure 22.3).

WHAT ARE POSTNATAL PREDICTORS OF OUTCOME?

Postnatal predictors of outcome have been studied extensively, but none has proven popular in the clinical setting. Rather, they are useful when performing retrospective reviews. Some of these include the following:

- Best PaO_2 in first 24 hours[4]
- Best or worst $PaCO_2$ in first 24 hours 9[5]
- PF-PCO_2 score in first 24 hours (where PF is PaO_2/FiO_2)[6]
- CDH Study Group Predictive Score[7]
- Biventricular dysfunction in the first 48 hours[8]

Defect size is probably the most significant determinant of outcome (mortality and morbidity).[9] However, the grade of defect only becomes available at the time of surgical repair, so it is not available when making clinical decisions early in the postnatal period.

WHAT ARE THE CRITERIA FOR CONSIDERING ECMO SUPPORT IN CDH?

Guidelines on management of CDH have been outlined in a CDH EURO Consortium Consensus paper (updated in 2015).[10] From this consensus came the following recommendations for ECMO use (grade of recommendation = D):

- Inability to maintain preductal saturations greater than 85% or postductal saturations greater than 70%.
- Increased $PaCO_2$ and respiratory acidosis with pH less than 7.15 despite optimization of ventilator management.
- Peak inspiratory pressure greater than 28 cm H_2O or mean airway pressure greater than 17 cm H_2O is required to achieve saturation greater than 85%.
- Inadequate oxygen delivery with metabolic acidosis as measured by elevated lactate of 5 mmol/L or greater and pH less than 7.15.
- Systemic hypotension, resistant to fluid and inotropic therapy, resulting in urine output less than 0.5 mL/kg/h for at least 12–24 hours.
- Oxygenation index of 40 or greater present for at least 3 hours.

I support these guidelines but would typically limit the maximum peak inspiratory pressure to 25 cm H_2O.

WHAT ARE CONTRAINDICATIONS FOR ECMO IN CDH?

The usual absolute and relative contraindications to providing ECMO support apply, such as severe cardiac anomalies, severe chromosomal anomalies, grade 2 or greater intracranial hemorrhage, severe coagulopathy, gestation less that 34 weeks, and birth weight less than 2000 g.

ARE THERE GUIDELINES FOR THE USE OF ECMO IN CDH?

The Canadian Congenital Diaphragmatic Hernia Collaborative has published a comprehensive clinical practice guideline for managing CDH; the guideline extends from prenatal care to long-term follow-up.[11] The guideline stresses the need for multidisciplinary care throughout. The guideline for use of ECMO in CDH is as follows: "Extracorporeal life support should be discussed during pre-natal counselling and may be considered as a therapeutic rescue option in those centres that offer it." The collaborative stressed that ECMO rates for CDH are low in Canada, and that "available evidence does not suggest a survival benefit to its use."

WHAT IS THE BEST TYPE OF ECMO SUPPORT FOR CDH?

Options include

- Veno-arterial ECMO
- Veno-venous (V-V) ECMO
- Veno-arterio-venous (V-AV) ECMO

There are proponents of V-A and V-V support, and many will employ the mode most appropriate for an individual patient.[12] The different physiological effects of each mode mostly revolve around reduced pulmonary flow and efficient cardiac offloading in V-A and normal pulmonary flow with well-oxygenated blood in V-V ECMO, with the potential benefit of right common carotid artery preservation in V-V ECMO. Some infants are undoubtedly too unstable to manage with V-V ECMO support because of cardiac instability, and a number will be unsuitable because of relatively low birth weight, further complicated by a smaller caliber internal jugular vein in CDH compared to controls.[13] The Mannheim group always offers V-A ECMO and at lower flows than traditionally used (50–100 mL/kg/min), aiming to offload about one-third cardiac output from the RV via the ECMO circuit. A systematic review has failed to show benefit of one over the other with

the above caveats.[14] Personal and institutional preferences are likely to be the main determinants of ECMO mode.

Though somewhat cumbersome, V-AV ECMO allows support to be titrated from predominantly V-A to predominantly V-V as the patient tolerates. This facilitates weaning. Figure 22.7 shows examples of chest radiographs taken for cannula position for each modality.

HOW TO CANNULATE FOR ECMO INITIATION?

Support for V-A ECMO is typically achieved through open right neck cannulation of the internal jugular vein and common carotid artery. V-V double-lumen cannulation can be performed percutaneously under ultrasound guidance. In both techniques, echocardiography is essential to ensure appropriate venous cannula placement. Mediastinal shift makes chest radiographs more difficult to interpret, and inadvertent azygos vein cannulation is a possibility. Cannulation technique is comprehensively covered elsewhere in this book or the *ELSO Red Book*.[15]

WHAT ECMO CIRCUIT COMPONENTS MAY BE USED?

Considerations for ECMO involve the choice of roller or centrifugal pumps. There have been a number of reviews of the high instance of hemolysis when using some centrifugal pumps in neonatal ECMO.[16] This can be more pertinent in CDH as the ECMO runs tend to be longer. It is essential to ensure that if a centrifugal pump is chosen, it is not a type associated with a significant risk of hemolysis. Centrifugal pumps are available with pediatric heads that are less prone to hemolysis in neonates.

HOW LONG CAN ECMO RUN FOR CDH PATIENTS?

The longer ECMO runs for CDH require fastidious patient management throughout. Avoiding complications is essential, and careful fluid management is essential to prevent the patient becoming overloaded. Judicious use of diuretics is often appropriate, and, where necessary, renal support should be commenced early to prevent this complication. ECMO runs for CDH beyond 4 weeks are associated with very poor outcomes.

WHY MIGHT ECMO WORK IN CDH?

In CDH, the three main causes of physiological instability are pulmonary hypoplasia, PH, and intrinsic cardiac dysfunction. In severe pulmonary hypoplasia, severe PH is inevitable. However, the PH can be disproportionately severe in apparently less significant pulmonary hypoplasia (based on prenatal indices of severity and visual inspection of the lung at surgical repair). Unrelieved PH will result in RV failure as a secondary consequence but does not readily explain the left and biventricular dysfunction seen in the early postnatal period. An approach to medical management before and during ECMO, based on these underlying pathophysiologies, is discussed below and summarized in Figure 22.8.

WHAT MEDICAL MANAGEMENT SHOULD WE USE DURING ECMO?

Medical management during ECMO should identify, as far as possible, and address the underlying pathophysiological reasons for ECMO support, specifically cardiac dysfunction, pulmonary hypoplasia, and LV dysfunction (Figure 22.8).

Left Ventricular Dysfunction

Early postnatal LV dysfunction is increasingly recognized as a contributor to disease severity, mortality, and indication for ECMO in CDH.[17,18] LV dysfunction, resistant to medical therapy, can be identified on echocardiogram. It can lead to severe hypotension, hypoperfusion, and metabolic acidosis and is an indication for early ECMO support. LV dysfunction may additionally contribute to increased pulmonary vascular resistance (PVR) in CDH by increasing pulmonary venous pressure. V-A ECMO provides LV support.

Left ventricular dysfunction typically improves in the first days of life.[19] In the absence of associated severe PH or ventilation failure, our experience is that CDH patients with severe LV dysfunction will demonstrate rapid echocardiographic and clinical improvement, usually allowing them to be weaned from ECMO support, with the ongoing support of inotropes if needed, prior to surgical repair.

Severe Pulmonary Hypertension

Increased PVR in CDH is considered to be due to structural and functional abnormalities in the pulmonary vasculature, though LV dysfunction may also contribute to "postcapillary" PH. Severe PH, characterized by oxygenation failure, RV dilation and dysfunction, is an important potential indication for ECMO support. Frequent echocardiography is important to help assess pulmonary artery pressure (PAP), before and during ECMO, accepting that all infants will have elevated PAP and PVR immediately after birth. Some echocardiographic measures, notably tricuspid regurgitation velocity, have inherent limitations.

Pulmonary vascular resistance should be minimized during ECMO by optimizing ventilation, sedation, fluid balance, and judicious use of neuromuscular blockade. We recommend a systematic approach to use of pulmonary vasodilator therapy, targeting the endogenous nitric oxide pathway (using iNO and intravenous sildenafil) and prostacyclin pathway (using milrinone, a phosphodiesterase 3 inhibitor, and prostacyclin analogues). Clinical and echocardiographic measures of PAP and PVR are used to assess response, which may be variable between individual cases.[20,21] We maintain ductal patency, using prostaglandin E_1 (PGE1) infusion if needed (closing ductus in the presence of systemic or suprasystemic PAP and

RV dilation/dysfunction), to reduce RV afterload and support the systemic circulation. Direction of ductal shunt should be monitored regularly. If the shunt reverses to become predominantly left to right, then PGE1 should be discontinued, allowing ductal constriction, to reduce the risk of pulmonary hemorrhage.

Early CDH repair, on ECMO, may be indicated in cases with severe PH to optimize lung inflation and optimize PVR.

Ventilation Failure

Severe hypercarbia and respiratory acidosis, as a consequence of severe pulmonary hypoplasia, are also potential indications for ECMO, particularly if the patient has demonstrated potential reversibility of lung dysfunction. The aim of respiratory management on ECMO is optimal lung recruitment, not for gas exchange per se, to prevent decruitment or overdistention, both of which may exacerbate PH/PVR and lung injury. Our practice is to maintain a low rate of conventional ventilated breaths (typically at PIPs of 15–20 cm H_2O and rates of 10–20 breaths/min), guided by blood gas and chest x-ray.

If ventilation failure is the primary indication for ECMO, early repair on ECMO may be appropriate to optimize lung recruitment and function and facilitate weaning.

HOW IS WEANING FROM ECMO SUPPORT BEGUN?

Weaning should be commenced when there is objective evidence of improvement in underlying pathophysiology. Our practice is to optimize inotropic and pulmonary vasodilator support to facilitate weaning and maintain stability after ECMO support is withdrawn. Ventilation should be gently increased to recruit endogenous lung function, with consideration of HFOV to provide continuous distending pressure if required. Selective use of bronchoscopy may help to remove trachea-bronchial secretions and assess airway patency, but with care to avoid pulmonary hemorrhage.

WHAT ARE SURGICAL OPTIONS FOR CDH IN THE CONTEXT OF ECMO SUPPORT?

There are a number of scenarios that determine the timing of diaphragmatic hernia repair in relation to the potential need for ECMO support:

1. CDH repair before ECMO
   A. ECMO not envisaged
   B. ECMO planned as "rescue"
2. CDH repair on ECMO
   A. Repair early on ECMO
   B. Repair late on ECMO (rescue)
3. CDH repair after ECMO

Repair Before ECMO

a. *ECMO not envisaged*

Usually, the need for ECMO support after repair occurs if the patient decompensates when ECMO was not considered necessary or likely preoperatively.

b. *ECMO planned for rescue*

The alternative scenario, as suggested by David Kays,[22] is to repair very high-risk diaphragms very early after birth and use ECMO as a rescue therapy.

Repair on ECMO

Repair of CDH on ECMO confers a three-fold higher odds of mortality than repair after ECMO.[23]

There are two schools of thought regarding timing of repair on ECMO support:

a. *Repair early on ECMO*

What is early? Certainly, it is within the first 72 hours, and many would advocate repair on the morning following commencing ECMO support. Repairing the defect early on ECMO allows the team to focus further management on optimizing the infant to a position fit for decannulation. Early repair may pre-date any complications that can arise during a longer ECMO run. Some surgeons believe that coagulation is less impaired in the early stages of ECMO support as there are more "native" products in the circulation. Reduction of the herniated contents gives optimal space for both lungs to expand and achieve their maximal function, corrects mediastinal shift, and may assist cardiac function. Repair on ECMO in the critical care setting, without the need to move to the operating room, can be achieved with minimal physiological impact in the vast majority of cases. Defect size, lung size, and any other surgical issues will be identified, and enteral nutrition can be introduced. The main downside to early repair is the risk of postoperative hemorrhage and the lack of time for spontaneous reversal of the process that led to ECMO support. Those repaired early on ECMO (<72 hours) have a small but significantly better outcome than those not repaired during the ECMO run (87.1% vs. 78.4%, $P = .002$), at the cost of a longer ECMO run (median 240.6 vs. 196.8 hours, $P = .001$). This latter group includes patients repaired after the ECMO run and those never repaired.[24]

b. *Repair late on ECMO*

Late repair on ECMO is not ideal but may be necessary in those that fail to decannulate without repair. In this setting, ECMO support is typically weaned fairly rapidly following repair to facilitate early decannulation and minimize bleeding complications. The

downside is that the patient may have developed complications related to the relatively long ECMO run, and the lungs will still be negatively impacted by the herniated viscera.

Repair After ECMO

Repair after an ECMO run has been shown to give the best results where ECMO is needed. The challenge is early, accurate identification of patients that are capable of weaning from ECMO without the requirement to repair the defect before decannulation. My view is that these patients typically have either suboptimal pre-ECMO management, have a sudden decompensation requiring ECMO, or the main cause of pre-ECMO instability is cardiac dysfunction that often improves with time. Infants with very small lungs and ventilatory failure are less likely to wean off ECMO support pre-repair.

HOW IS RIGHT VERSUS LEFT CDH APPROACHED?

Right- and left-sided CDH should be approached similarly in most respects. A recent study has shown no difference in outcome or ECMO use between right and left CDH.[25] The Congenital Diaphragmatic Hernia Study Group (CDHSG) registry data (2007–2016) confirmed that a greater proportion of larger defects are right sided; 9.7% grade A defects are right sided versus 21.1% grade D defects.

When considering the need for surgery on ECMO for right CDH, I am of the opinion that early surgery (certainly within 72 hours of ECMO support) is better. Especially in large right-sided defects, the liver is a major obstruction to lung expansion, and there are clear merits to reducing the herniated liver early in the ECMO run to facilitate decannulation.

WHAT ARE THE TECHNICAL ISSUES IN CDH REPAIR ON ECMO?

Bleeding is the main risk for repairing CDH on ECMO. This risk can be reduced by optimizing coagulation factors preoperatively, meticulous use of diathermy during surgery, and certain procoagulant measures postoperatively. Aminocaproic acid (Amicar™) or tranexamic acid should be used perioperatively. They should be given as a bolus immediately preoperatively and run as an infusion peri- and postoperatively.[26] It is my practice to discontinue heparin for 4–6 hours peri- and postoperatively while maintaining high ECMO flow, followed by 10 units/kg/h for the following 24 hours. It is prudent to have a preprimed circuit available in the event of circuit clots developing. The Rotterdam group has previously published their protocol for repair on ECMO and reported low rates of postoperative bleeding.[27]

The diaphragmatic defects that require repair on ECMO tend to be large, and the surgeon will, almost certainly, need a prosthetic patch to achieve the repair. My personal preference is 1-mm GoreTex™. Care must be taken to ensure sutures do not injure intercostal vessels when fixing the patch to the ribs posteriorly. Polytetrafluoroethylene pledgeted sutures can help reduce bleeding risk, and tissue glue also helps. Minimal mobilization of the posteromedial rim of diaphragmatic muscle is appropriate, just enough to take a suture. I dome the patch in large defects as the lung is usually relatively small, and there is less chance that a further abdominal patch will be required to accommodate the reduced herniated viscera without causing a rise in intra-abdominal pressure. A drain may be inserted through the repair to give an indication of blood loss postoperatively. This is useful in the short term but is unreliable later as the drain tends to occlude with clot. I do not advocate routine use of suction on the drain. Nonessential extra surgical interventions that would risk bleeding should be avoided. In very challenging cases (often right sided), the main aim of surgical repair is to separate the abdominal and thoracic viscera. Tacking a patch in place while avoiding high-risk sutures should be the aim. A more robust repair can be delayed until after successful weaning from ECMO when bleeding risk is lower.

DISCUSSION

Congenital diaphragmatic hernia has an incidence of 1 in 2000–5000 live births. The diaphragmatic defect (80%–85% left sided) is of varying size.

Single-institution reports on outcomes for CDH have been unreliable as they are dependent on referral patterns (including termination rates), availability of advanced therapies (including ECMO), associated anomalies, and variability in the severity of the defect. The first attempt to address this was the publication of two articles in the *Journal of Pediatric Surgery* in 1997, comparing similar survival rates between Boston Children's Hospital and Toronto Sick Children's Hospital, despite each center having different management strategies.[28,29] This generated much discussion at the time.

Today, there are two very important resources on outcomes in CDH:

1. The Extracorporeal Life Support Organization (ELSO) Registry has been collecting data since the mid-1980s. CDH is an important subset of the neonatal respiratory ECMO cohort. In the 1990s, CDH comprised 19% of all neonatal respiratory ECMO cases reported to ELSO. In the period 2015–2019, CDH accounted for 32% of neonatal respiratory ECMO cases. Reported survival in the registry has stubbornly hovered around 50% throughout the last three decades. There is evidence, however, that ECMO is currently being used in a higher risk CDH cohort based on defect size compared to past decades.[30]
2. The second source is the CDHSG, which first met in 1991.[31] The associated registry has been collecting CDH data since 1995. In 2007, CDHSG introduced a grading system to assess defect size at surgery. Defects were graded A, B, C, or D, and a diagrammatic representation was published to assist the surgeon (Figure 22.2). As defect size has since been shown to be the major determinant of outcome in CDH, the CDHSG introduced a staging

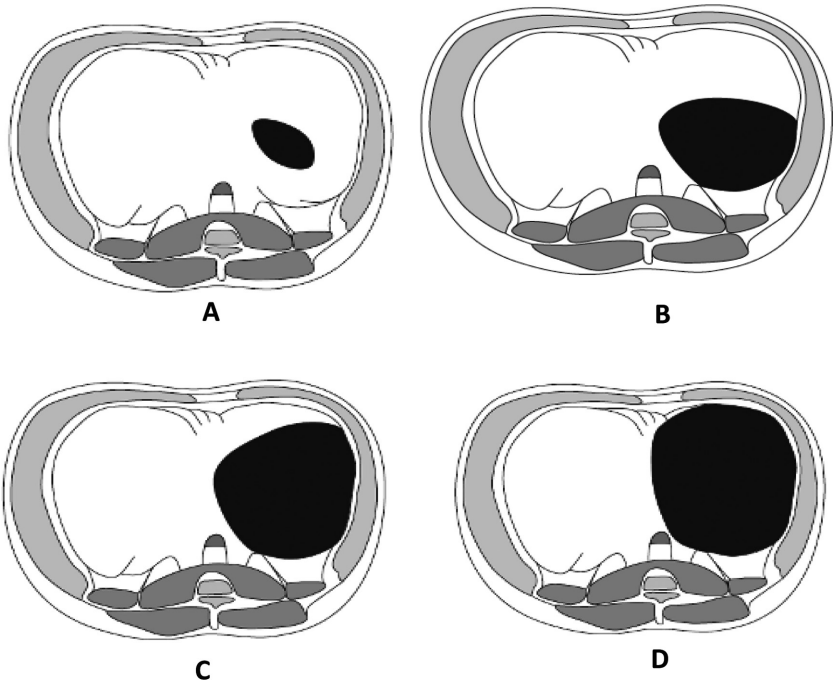


Figure 22.2 International CDH Study Group grades of left sided CDH defect size at open surgery as seen from the abdomen

system (stages 1 to 5), based on defect size and the presence or absence of major associated cardiac or chromosomal abnormalities, to allow more structured reporting of outcomes for individual institutions.[32] CDHSG reports for individual institutions submitting data now allow the institutions to benchmark against the registry results.

There have only been three randomized controlled trials (RCTs) of ECMO versus conventional treatment that included CDH patients. Morini et al. conducted a systematic review of these RCTs and of nonrandomized studies comparing mortality when ECMO was not available with a period when ECMO was available. Mortality was classified as "early" (before hospital discharge) and "late" (after discharge). In the non-RCTs, patients were classified as "ECMO" and "non-ECMO" candidates. Both early and late mortality were significantly lower when ECMO was available than when ECMO was unavailable. This difference in mortality was observed in "ECMO candidates" but not in "non-ECMO candidates." The RCTs comparing ECMO and conventional ventilation included 39 infants with CDH. The early mortality was significantly lower with ECMO compared to conventional ventilation. Late mortality was similar in the two groups. They concluded that non-RCT studies suggested a reduction in mortality with ECMO but that differences in the indications for ECMO and improvements in other treatment modalities may have contributed to this reduction. The meta-analysis of RCTs indicated a reduction in early mortality with ECMO but no long-term benefit.[33]

In the United Kingdom and Ireland, BAPS-CASS undertook a prospective study[34] of 219 babies with CDH admitted to all 28 neonatal surgical units over an 18-month period in 2009–2010.Median number of cases per unit was 5 and varied from 1 to 18. For those who were stabilized and repaired, there was a 98% 30-day survival rate. Five of the 28 centers offered ECMO, but only 4% of the entire cohort received ECMO support. The diagnosis was made postnatally in 39%, and 25% of these did not require preoperative ventilation. All prenatally diagnosed babies were ventilated from delivery. The non-repair rate was 16% (24% prenatal, 4% postnatal diagnosis). The methodology of this national study only identified babies admitted to neonatal surgical units. The calculated prevalence of 1.7 per 10,000 live births (1:5880 live births, compared to the predicted 2.66 per 10,000 live births) suggest a number of babies did not reach neonatal surgical units. The primary repair rate of 65% is also much higher than the equivalent CDHSG rate of 47%.

The ELSO Registry consistently reports a 50% survival to discharge for babies with CDH who receive ECMO, and CDH now accounts for over 32% of all neonatal ECMO support (19% in the mid-1990s). The International CDH Database presently reports an overall 70% survival in reported cases, up from 63% in the mid-1990s.[35,36] This improvement has been associated with an increased rate of repair on ECMO from 23% to more than 50% over the same period. CDHSG Registry data on use of ECMO and outcomes for those requiring ECMO are shown in Figures 22.4 and 22.5.

A recent CDHSG study of centers that have continuously entered data in the registry from 1995 were analyzed in 5-year eras (5015 patients). Birth weight, 5-minute Apgar, incidence of agenesis, ECMO use, and rate of repair did not vary over time. Overall, mortality decreased over time: Era 1 (30.7%), Era 2 (30.4%), Era 3 (28.7%), Era 4 (26.0%), and Era 5 (26.0%) ($P = .04$). Risk-adjusted mortality showed a trend favoring significant improvement in Era 5 compared to Era 1 (odds ratio [OR] 0.79, 95% CI 0.63–1.01; $P = .06$)

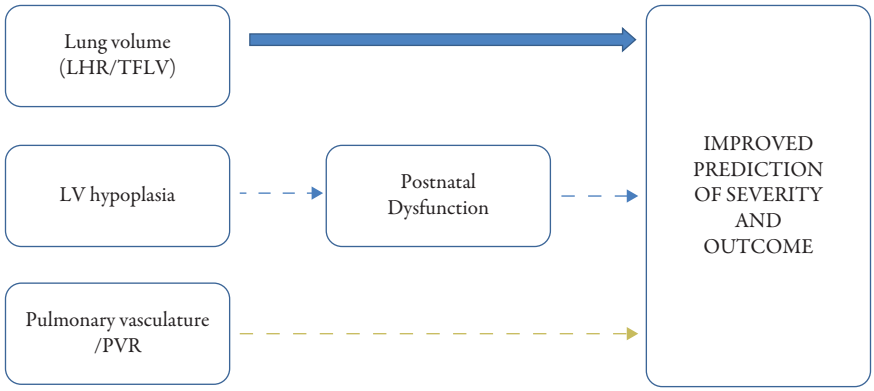


Figure 22.3 Measurements that will aid counselling of parents and likely need for ECMO in CDH
Courtesy of Dr Neil Patel

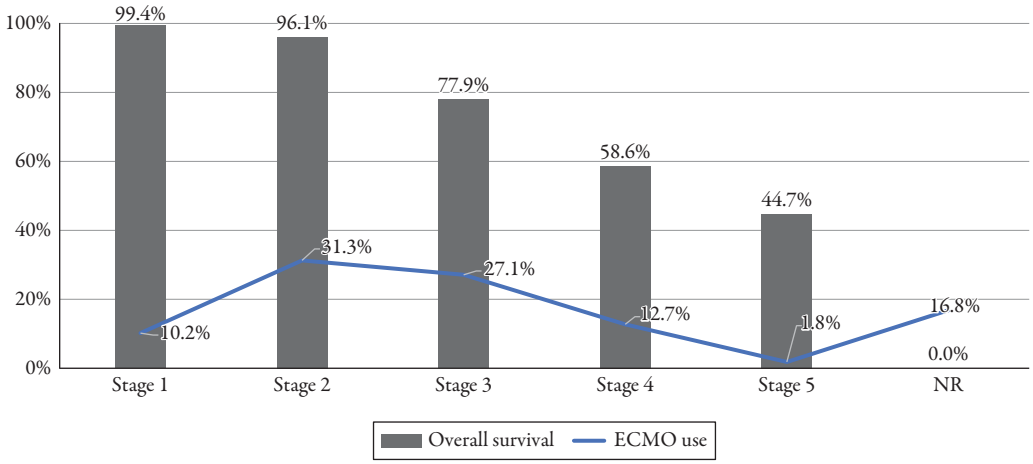


Figure 22.4 Overall survival and ECMO use according to stage. Data from the first 10 years collecting defect size by grade at surgery in the CDHSG Registry (2007–2016). NB Defect size is not available for the "no repair" (NR) group so they could not be staged.

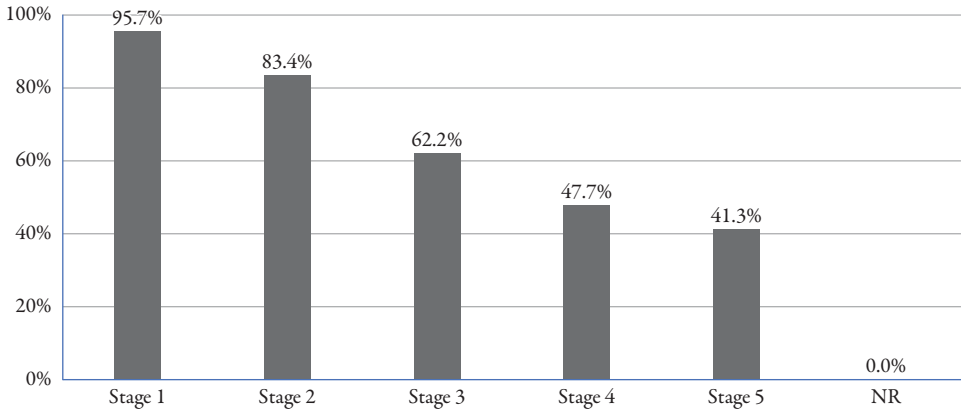


Figure 22.5 ECMO survival by stage. Data from the first 10 years collecting defect size by grade at surgery in the CDHSG Registry (2007–2016). NB Defect size is not available for the "no repair" (NR) group so they could not be staged.

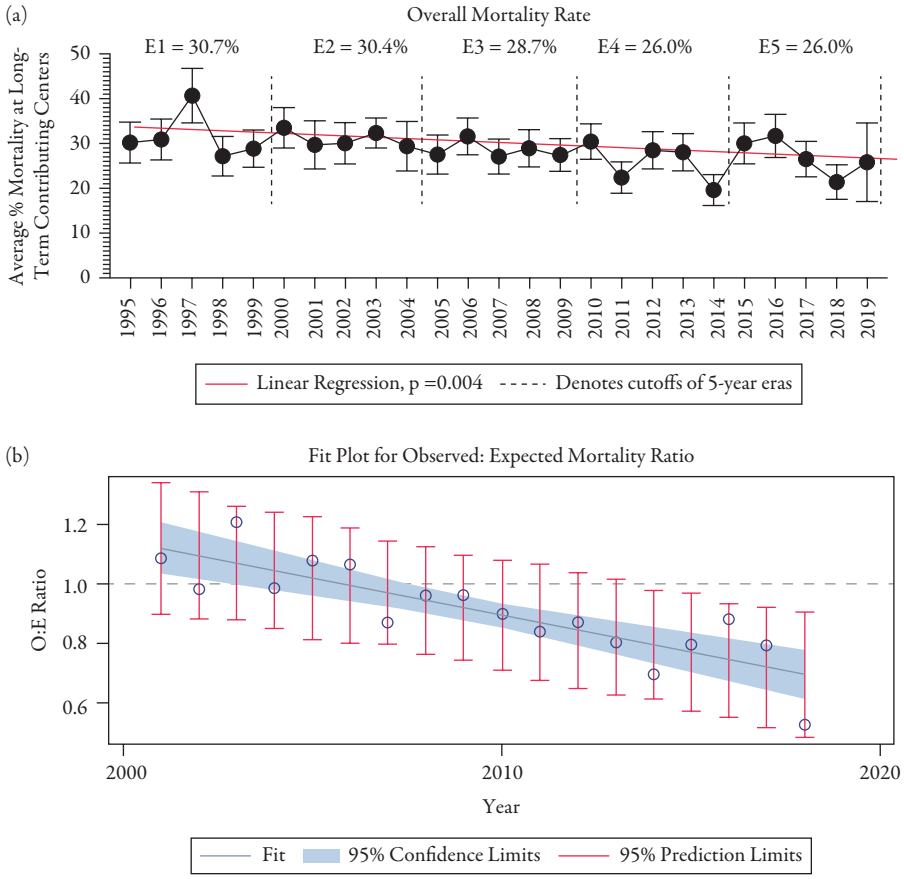


Figure 22.6 a) Average mortality of centers by year. Data points represent mean + standard error of the mean. Overall mortality by era (E1-E5) is listed and separated by grey hash lines. b) Fit plot of O:E mortality ratio using 1995-2000 as a reference and adjusted for birth weight, Apgar at 5 minutes, presence of a major cardiac anomaly, prenatal diagnosis, and center volume. O:E ratio of 1 is denoted by the grey hash line.

(Figure 22.6a). O:E mortality improved over time (slope: -0.02, $P < .01$), with the most significant improvement occurring in the last 5 years (Figure 22.6b).[37]

In an attempt to determine the impact of ECMO in a clinical setting, International CDH Registry data (2007–2019) have been further analyzed by Jancelewicz et al. Applying propensity scoring, they analyzed three groups of patients: (a) the total cohort, (b) a high-risk cohort (lowest $PaCO_2$ 60 mm Hg or greater or 8 kPa during the first 24 hours), and (c) a medium-risk cohort with documented PH and ventricular dysfunction. As expected, overall survival was lower for ECMO versus no ECMO in the overall cohort (54% vs. 77%). However, there was an almost three-fold advantage to ECMO in the high-risk cohort (41% vs. 14%) and a 2.3-fold improved survival for the ECMO patients in the medium-risk cohort (47% vs. 20%). The ECMO survival advantage was primarily in high-volume centers in high-risk patients.[38]

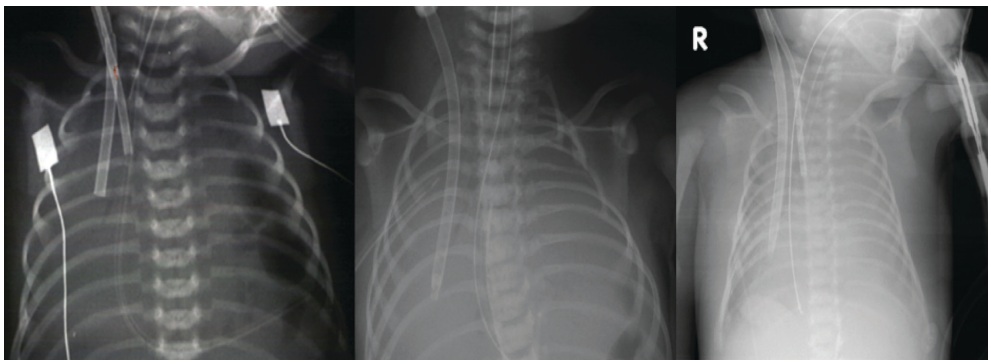


Figure 22.7 Chest radiographs of V-A ECMO, V-V double lumen ECMO and V-AV ECMO in patients with left CDH (from left to right).

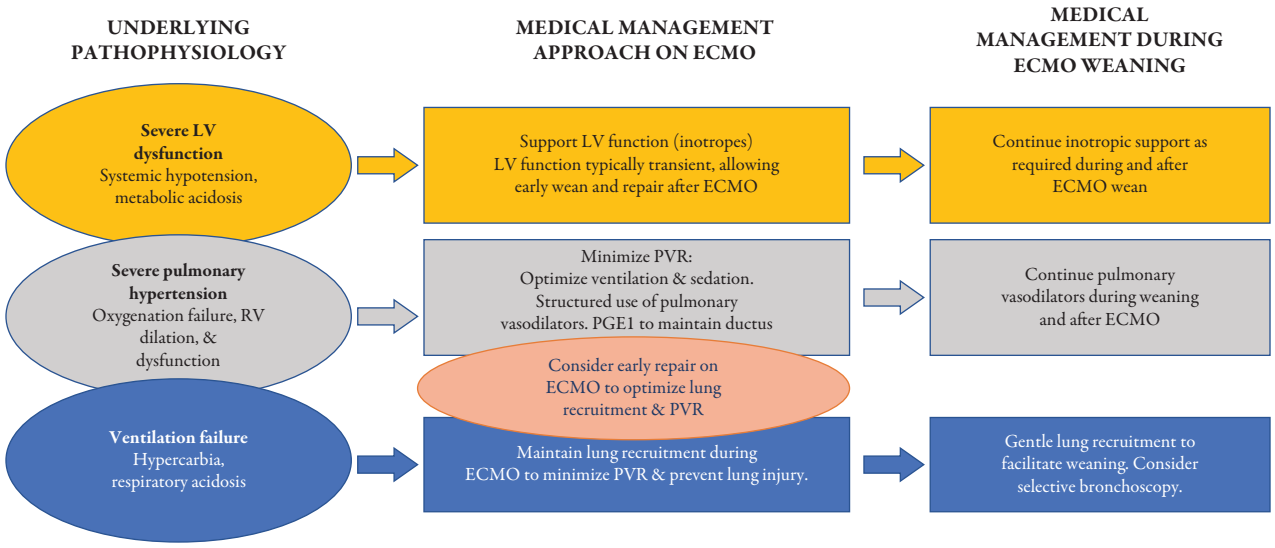


Figure 22.8 Possible Management strategies in CDH requiring ECMO, based on likely underlying main pathophysiology. *Courtesy of Dr Neil Patel*

Overall, a combination of prenatal predictors of outcome, followed by postnatal risk stratification based on known measurable risks and response to treatment, while taking into account parental preference, will determine whether offering ECMO is potentially valuable or likely futile. EXIT to ECMO has been offered in CDH but is no longer recommended (Jay Wilson, personal communication).

A study of CDH patients treated with ECMO in the United Kingdom in the 1990s demonstrated a significant mortality over the first year of life, with 63% being weaned from ECMO, 58% surviving to hospital discharge, and just 37% surviving to 1 year of age. Comorbidities were common in the survivors.[39] Local data now show 82% weaning from ECMO and 48% surviving to 1 year.

The American Academy of Pediatrics has published guidelines on long-term follow-up for CDH.[40] It stressed the need for a multidisciplinary approach and a schedule of monitoring based on severity. As CDH survivors who have received ECMO support are likely to be at the more severe end of the spectrum, this carefully orchestrated follow-up is essential to identify problems early and help these patients achieve their maximum potential. This is also a group where transition to adult services will be essential and can be challenging.

CONCLUSION

- CDH repair without the need for ECMO is best.
- There is huge variation in approach to the provision of ECMO in CDH.
- If ECMO is needed, repair after ECMO has the best outcome, but accurate identification of suitable candidates is challenging.
- Repair on ECMO is associated with bleeding complications.
- The early versus late debate has yet to be resolved, but early repair is probably best in high-risk cases.
- A pathophysiological approach, assessing and understanding the relative contributions of pulmonary hypoplasia/ventilation failure, PH, and LV dysfunction, can inform ECMO decision-making.
- ECMO improves outcomes in high-risk CDH.
- Care on ECMO must be meticulous as runs are usually long, and complications must be avoided to achieve a successful outcome.
- Morbidity is high in patients who receive ECMO for CDH, so multidisciplinary follow-up is essential.

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REVIEW QUESTIONS

1. Which of the following is correct regarding antenatal diagnosis of CDH?

   A. Is unusual
   B. Can be expected in 75% of cases
   C. Is made on computed tomography
   D. Is normally detected at a booking scan

2. Which of the following is the best indicator of outcome in CDH?

   A. Lung-to-head size ratio on fetal ultrasound
   B. Weight at birth
   C. Apgar score at 2 minutes
   D. Defect size at surgery

3. Which of the following is true regarding fetal circulation?

   A. It requires low PAP.
   B. Most RV blood flow goes to the lungs.
   C. Blood flows from the placenta to the baby via the umbilical arteries.
   D. None of the above.

4. Which of the following is (approximately) correct regarding reporting of ECMO results in CDH?

   A. ELSO reports 75% survival.
   B. ELSO reports 25% survival.
   C. ELSO reports 50% survival.
   D. None of the above.

5. Which of the following is correct regarding surgery for CDH?

   A. Best result is surgery on ECMO
   B. Best result is surgery before ECMO
   C. Best result is surgery after ECMO
   D. None of the above

6. Which of the following is a marker for PH?

   A. Right-to-left ductal flow
   B. Bidirectional ductal flow
   C. Significant tricuspid regurgitation
   D. All of the above

7. Which of the following statements is false?

   A. Inhaled nitric oxide has proven benefit in CDH.
   B. ECMO is contraindicated in the presence of grade 1 intraventricular hemorrhage.
   C. Liver up on fetal MRI or ultrasound predicts a poorer prognosis.
   D. Prostaglandin E_1 infusion is used to maintain ductal patency.

8. Which of the following is false regarding right-sided CDH?

   A. Right-sided defects tend to be larger.
   B. Defect is right sided in 15%–20% of CDHs.
   C. Right-sided defects are unsuitable for thoracoscopic repair.
   D. Overall outcome is worse in right-sided defects.

9. Which of the following is true regarding repair of CDH?

   A. Surgical repair is contraindicated if still on iNO.
   B. Surgical repair is contraindicated if on HFOV.
   C. A Ladd's operation should be performed at the same time as repair of CDH.
   D. Type C and D defects require patch repair.

10. Optimal repair of CDH on ECMO includes which of the following?

   A. Use of electrocautery exclusively
   B. Use of aminocaproic acid (Amicar) or tranexamic acid
   C. Discontinuing heparin around surgery
   D. All of the above

11. A 2-day-old, 3.5-kg neonate with a left-sided CDH is being ventilated on HFOV (MAP 24 mm Hg, delta P 40, frequency 10 Hz, FiO_2 95%). PCO_2 has increased to 13 kPa (97 mm Hg) on arterial blood gas. Which of the following statements is true?

   A. Surgical repair should be arranged urgently.
   B. Increasing frequency to 12 Hz may improve CO_2 clearance.
   C. ECMO support should be considered.
   D No changes are required as permissive hypercapnia is the gold standard treatment.

ANSWERS

1B. Currently, one can expect antenatal diagnosis in 75% of cases, usually at the detailed scan undertaken at 18–20 weeks. Improvements in fetal ultrasound mean some cases can be detected at a booking scan. A computed tomographic scan is normally contraindicated in pregnancy.

2D. All answers are markers of severity, but defect size at surgery is the best indicator of outcome.

3D. In fetal circulation, RV output mostly bypasses the lungs because of high PVR and enters the systemic circulation via the ductus arteriosus. Maternal blood flows to the fetus via the umbilical vein.

4C. Typically, overall survival for ECMO in CDH as reported by ELSO is 51%. This has changed very little over the last number of decades.

5D. None of the above—Miserable question I know. Best results are repair without ever needing to use ECMO. Second best is repair after ECMO.

6D. All the above are markers of PH. Signs of reducing PAP include a shift from right-to-left flow to left-to-right flow (via bidirectional flow) and reduction in the degree of tricuspid valve regurgitation.

7A. Inhaled nitric oxide has not been shown to be beneficial in CDH.

8C. Overall outcome in right-sided defect has been much debated, but as right-sided defects have been shown to be larger and thus associated with a higher incidence of associated anomalies (CDH International Study Group

database), the mortality is higher. Suitable cases may be repaired thoracoscopically.

9C. Larger defects (C and D) require patch repair. A Ladd's operation is not necessary as there is not true malrotation, just relative nonrotation. Judgment should be exercised regarding widening the mesenteric base if noticeably narrow. By definition, this is not identified at thoracoscopic repair. Inhaled no and HFOV (if used) are not contraindications to surgical repair of CDH, especially if undertaken at the bedside with minimal disturbance to the stable baby.

10D. Bleeding is the single biggest issue with repair of CDH on ECMO. Optimizing coagulation, use of procoagulants, and stopping heparin for a number of hours during and after surgery all contribute to lowering the likelihood of postoperative bleeding.

11C. ECMO support should be seriously considered as HFOV is failing. MAP is higher than ideal for HFOV, so present settings are not acceptable. The aim is low pressure (midteens at most) to protect the lungs. Increasing frequency will likely result in a higher PCO_2.

23.

EVIDENCE AND MANAGEMENT OF A RARE PRESENTATION IN NEONATAL ECMO

Zeenia C. Billimoria and Thomas V. Brogan

STEM CASE AND KEY QUESTIONS

A term female infant was delivered to a 33-year-old gravida 4, para 3, mother with good prenatal care and uncomplicated pregnancy via spontaneous vaginal delivery assisted by vacuum extraction. Maternal prenatal laboratory studies were normal except for positive group B *Streptococcus* screening. Fetal distress occurred during labor, and the infant was delivered through meconium-stained fluid. She was flaccid and had no spontaneous respiratory effort. She required positive pressure ventilation with face mask followed by intubation in the delivery room. Thick meconium was suctioned from her mouth, esophagus, and trachea. Apgar scores were 0, 4, 6, and 7 at 1, 5, 10, and 15 minutes of life, respectively. Her venous blood gas showed a pH of 6.55, PCO_2 of 76, PO_2 of 27, and base excess of -30. The infant was started on a therapeutic hypothermia protocol and ampicillin and gentamicin. A blood culture grew group B *Streptococcus* at 13 hours of life.

In the first 36 hours of life, she developed multiorgan failure. Echocardiography showed a structurally normal heart with evidence of persistent pulmonary hypertension of the newborn (PPHN). She was treated with stress dose hydrocortisone and high doses of dopamine and epinephrine drips. Still, she had persistent lactic acidosis (11–16 mmol/L). She required 100% inspired oxygen via mechanical ventilator with inhaled nitric oxide at 20 ppm to maintain arterial oxygen saturation greater than 90%. Her transaminases and renal indices were elevated. She demonstrated anemia, thrombocytopenia, and coagulopathy as well, requiring multiple blood products.

Due to worsening distributive and cardiogenic shock, she was placed on veno-arterial extracorporeal membrane oxygenation (V-A ECMO) at 45 hours of life. She was cannulated with an 8 French (8F) arterial cannula in the internal carotid artery and 10F venous cannula in the internal jugular vein. Despite ECMO flows of 140 mL/kg/min, lactic acidosis persisted (15–20 mmol/L). She also experienced capillary leak, and her urine output dropped. She was started on continuous renal replacement therapy (CRRT) to assist with electrolyte homeostasis and excessive volume removal. Despite excellent oxygen delivery with ECMO and inotropic support, as well as fluid management with CRRT, she had worsening organ failure and evidence of severe inflammation. She was started on therapeutic plasma exchange (TPE) to provide improved clearance of inflammatory mediators. She tolerated the first treatment with TPE but required calcium chloride boluses and a calcium chloride infusion to maintain ionized calcium greater than 1.0 mmol/L. She also remained on inotropic support with dopamine and epinephrine drips during TPE to maintain adequate blood pressure. Three courses of TPE were performed.

By day 4 of ECMO, she weaned off her epinephrine infusion, and dopamine was lowered to 10 μg/kg/min. The lactic acidosis improved to 7 mmol/L. Metabolic workup, including acylcarnitine profile, urine organic acids, plasma amino acids, and pyruvate level, were suggestive of lactic acidosis likely as a result of sepsis. By day 5 of ECMO, all vasopressor support was discontinued. She tolerated fluid removal of approximately 100 mL/kg/d. Throughout her ECMO run, she had oozing from all her access points, and hence anticoagulation with heparin was managed conservatively to maintain an activated partial thromboplastin time (aPTT) of 80–120 seconds and anti–factor Xa 0.1–0.3 IU/mL. Her conjugated bilirubin was elevated at 8.8 mg/dL, making interpretation of anti–factor Xa challenging. By day 6 of ECMO, she had achieved significant diuresis with improvement in edema. She was successfully decannulated after 6 days on ECMO.

The infant was weaned off the ventilator and transitioned to nasogastric feeds. Magnetic resonance imaging of her showed no evidence of ischemia or infarction, and hippocampal volumes appeared normal. She was discharged home 6 weeks after cannulation without need for respiratory support. She was feeding 50% of her goal nutrition volume by mouth and the remainder by gavage.

WHAT ARE THE BIOCHEMICAL AND CLINICAL SEQUELAE OF NEONATAL SEPSIS?

Activation of toll-like receptors (TLRs) results in the initiation of the innate immune system and the release of pro-inflammatory cytokines and chemokines.[1] TLRs are activated by intracellular and extracellular pathogens and mediators released by dying or damaged cells. Production of pro-inflammatory cytokines leads to activation of endothelial cells, resulting in leukocyte recruitment. Neonates have poor cellular chemotaxis, which can result in rapid spread of infection.[2]

A fine balance between pro- and anti-inflammatory mediators helps contain pathogens locally and prevent systemic activation of inflammatory cascades, resulting in systemic inflammatory response syndrome (SIRS).[3] Complement components play an important role in innate immunity. They are responsible for coagulation, pro-inflammatory cytokine production, and leukocyte activation. Dysregulation in the complement system results in the untoward effects of SIRS and septic shock, such as disseminated intravascular coagulation (DIC) and adrenal insufficiency.[1,4] DIC is associated with the formation of microthrombi in the peripheral vasculature, resulting in platelet consumption and thrombocytopenia.[5] Mechanical shearing of red blood cells by intravascular fibrin strands results in anemia.

Endothelial activation secondary to expression of TLRs results in local microvascular occlusion and can progress to DIC. Pulmonary endothelial activation can result in respiratory failure and PPHN.[1]

The inflammatory cascade results in abnormal peripheral vasoregulation and may be accompanied by myocardial dysfunction, resulting in hypotension.[6] Circulatory failure due to inadequate cardiac output in conjunction with poor peripheral vasoregulation can result in multiorgan dysfunction syndrome (MODS) due to compromised perfusion to kidneys, liver, intestines, and brain.

HOW ARE NEONATES WITH SEPSIS MANAGED?

Early treatment with broad-spectrum antibiotics based on an infant's age and likely pathogens is the mainstay of therapy.

The initial resuscitation in neonates with sepsis includes management of airway, breathing, and circulation. Neonates with sepsis may present with respiratory failure requiring noninvasive respiratory support or escalation to intubation with mechanical ventilation.[7] Circulatory failure should be assessed by monitoring clinical, hemodynamic, and oxygen utilization variables.[8] Clinical signs include hypothermia or hyperthermia, peripheral vasoconstriction with capillary refill time greater than 2 seconds (cold shock) or peripheral vasodilation (warm shock) and tachycardia followed by hypotension. Hemodynamic monitoring with invasive arterial blood pressure is necessary to determine vasomotor state. Maintaining adequate blood pressure enables adequate perfusion to vital organs such as the brain, adrenals, and kidneys. Tissue oxygen delivery and utilization and organ perfusion are measured by surrogate markers such as serum lactate and urine output.

The American Heart Association and the American Academy of Pediatrics developed the neonatal resuscitation program[9] and pediatric advanced life support[10] guidelines for establishing emergent vascular access in critically ill neonates. In newborns, umbilical venous and arterial catheters are placed, while an intraosseous needle may be used in older infants. Early rapid fluid resuscitation with crystalloid solutions (20 mL/kg normal saline boluses) is recommended to prevent circulatory compromise.[11,12] Clinical and hemodynamic variables such as heart rate, blood pressure, and capillary refill time should be assessed with each fluid bolus.

Dopamine (5–20 μg/kg/min) and epinephrine (0.01–0.3 μg/kg/min) are typical first-line inotropes and vasopressors used to maintain adequate cardiac output. At lower doses, epinephrine has greater β- and less α-adrenergic effect, resulting in dilation of the peripheral vasculature. Epinephrine also increases delivery of lactate to the liver as a substrate for gluconeogenesis, which can increase plasma lactate levels, rendering the interpretation of this parameter difficult. Critically ill infants are likely to have relative adrenal insufficiency[13] and may benefit from stress dose hydrocortisone during septic shock.

Neonates with PPHN secondary to septic shock benefit from correction of metabolic acidosis and addition of inhaled nitric oxide,[14] which unload the right heart and improve oxygenation. Milrinone may be added to improve cardiac contractility and pulmonary vasodilation.[15]

HOW DOES THERAPEUTIC HYPOTHERMIA AFFECT MANAGEMENT OF NEONATES WITH SEPSIS?

Neonates 36 weeks or older with biochemical and clinical evidence of moderate-to-severe hypoxic ischemic encephalopathy are treated with therapeutic hypothermia for 72 hours to decrease risk of death or disability.[16] Neonates with sepsis can present with birth asphyxia and encephalopathy.[17] Hypothermia can decrease the body's immune response by affecting neutrophil release and function, decreasing leukocyte chemotaxis, suppressing phagocytosis and killing of pathogens, and delaying pro-inflammatory cytokine release.[18] Hypothermia can also decrease efficiency of blood clotting by causing changes in platelet number and function, fibrinolysis, and clotting enzyme function.[19]

WHAT IS THE UTILITY OF EXTRACORPOREAL THERAPIES IN NEONATES WITH SEPSIS?

Extracorporeal therapies include ECMO, CRRT, and blood purification processes such as TPE.

In neonates with refractory septic shock and respiratory failure secondary to PPHN unresponsive to pulmonary vasodilators, ECMO is a viable therapy.[20,21] Approximately 10% of all neonatal respiratory ECMO runs in the Extracorporeal Life Support Organization (ELSO) Registry were due to sepsis and had a survival rate of 72%.[20]

The proposed benefits of CRRT include management of fluid overload, clearance of lactate, normalization of electrolyte and metabolic parameters, removal of inflammatory mediators, and reversal of coagulopathy.[22]

The 2010 American Society of Apheresis gave TPE a category III recommendation (i.e., data are unclear on the use of apheresis), stating that the optimum role of apheresis therapy is not established, and decision-making should be individualized.[23] Single-center case series have shown that TPE can be performed safely and may be beneficial in neonatal septic shock patients on ECMO.[24]

DISCUSSION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[25] Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.[25] Sepsis remains a leading cause of neonatal morbidity and mortality. The epidemiology of neonatal sepsis has evolved with time.[26] The incidence of early-onset sepsis (infection in the first 72 hours of age) has decreased due to universal screening and intrapartum antibiotic prophylaxis for group B *Streptococcus.*[27] It occurs in 0.77 to 1 per 1000 live births based on positive blood cultures within the first 72 hours of life.[28] The incidence of late-onset sepsis (infection > 72 hours of age) has remained unchanged.[28]

Sepsis can result in a systemic inflammatory response due to an imbalance between pro- and anti-inflammatory mediators with pathological crosstalk between inflammatory and coagulation cascades, complement activation, and neuroendocrine signals.[29] Pro-inflammatory cytokines or mediators of sepsis include tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin (IL) 1β, IL-6, IL-8, IL-12, and IL-18.[1] There is a simultaneous increase in anti-inflammatory cytokine production with TGF-β, IL-4, IL-10, IL-11, and IL-13, countering the actions of pro-inflammatory cytokines. A hyperinflammatory response has untoward effects on the cardiopulmonary system, vascular endothelium, and gut, precipitating progressive organ dysfunction.[29] Endothelial disruption in patients with sepsis results in rapid and multifaceted interactions between circulating platelets, endothelial cells, and subendothelial structures. Platelet aggregation to the endothelium is facilitated by cellular receptors such as integrins and selectins and by adhesive proteins, such as von Willebrand factor (vWF) and fibrinogen.[30] Larger vWF multimers have much stronger hemostatic competency than smaller molecules. The size of vWF multimers is regulated by ADAMTS-13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13), also known as vWF-cleaving protease. Decreased levels of ADAMTS-13 result in increase in platelet-vessel wall interactions, leading to thrombotic microangiopathy. Clinically, this presents as MODS and thrombocytopenia-associated multiorgan failure (TAMOF).[31,32]

Supportive therapy with fluid resuscitation, blood pressure management, and respiratory support and treatment with broad-spectrum antibiotics remain the cornerstone of therapy for neonatal sepsis. Extracorporeal therapies with varying success such as ECMO, CRRT, and blood purification with TPE have been reported in the literature.

The first study utilizing ECMO in neonates with respiratory failure was published in 1985 by Bartlett et al.; it showed survival in all 11 patients treated with ECMO and death of 1 patient treated with conventional medical therapies.[33] In 1989, O'Rourke et al. demonstrated a 97% survival rate in 39 neonates with severe PPHN.[34] The UK Collaborative ECMO Trial Group in 1996 showed a relative risk of death of 0.55 when comparing the ECMO group to the conventional medical therapy group.[35] ECMO has been proven to be an effective therapy, and its utilization in neonates has increased over time.[36] A large retrospective review of prospectively collected data from the Pediatric Health Information System database collected by the Children's Hospital Association from 2004 to 2012 showed 49% of infants less than 1 year of age admitted to a pediatric intensive care unit with severe sepsis needed ECMO support. Thirty-four percent required both ECMO and CRRT. Mortality was higher when more than one extracorporeal therapy was utilized.[37] In the ELSO 2017 international summary report, 10% of neonates with respiratory failure receiving ECMO had sepsis. The survival rate for this population was 72%. A nationwide review of neonates and children with pulmonary hypertension receiving ECMO support from 2009 to 2012 had a higher incidence of sepsis and mortality as compared to those not receiving ECMO support.[38] Neonates with viral sepsis who receive ECMO are at increased risk of mortality.[39] Survival in neonates receiving ECMO for sepsis depends on severity of illness, type of pathogen, and early recognition and treatment. An important complication of ECMO, hemolysis, can lead to worsening of microvascular thrombosis, potentiate sepsis-induced organ failure, and worsen mortality.[22,40] The risk of hemolysis can be mitigated by using appropriate size cannulas, avoiding excessive pump speeds, and maintaining the negative inlet pressure close to the specified pressure drop given by the manufacturer for the flow rate.[22]

The use of CRRT in smaller, younger patients has increased with time. A large single-institutional review of pediatric patients utilizing CRRT over a 10-year period showed 23% of infants less than 1 year old utilizing both ECMO and CRRT concomitantly for diverse etiologies.[41] Benefits of CRRT include decreased fluid overload, management of acute kidney injury, clearance of lactate, binding of inflammatory markers, and reversal of coagulopathy. Mortality is higher in neonates requiring ECMO and CRRT, likely reflecting severity of illness for selection to receive CRRT.[37] In general, early use of CRRT in septic patients with MODS has been associated with decreased mortality in children, even when adjusted for severity of illness.[42] Data on CRRT use in neonates with sepsis are lacking.

Therapeutic plasma exchange is the process of selectively removing the patient's plasma and replacing it with fresh frozen plasma, colloids such as albumin, or crystalloids. Apheresis is the removal of a targeted cell or substance from blood. Apheresis includes plasmapheresis (the removal of plasma) and cytapheresis (the removal of blood cells). Plasmapheresis, the process of separating the patient's plasma from whole blood, can be performed by two different techniques: centrifugation or filtration.[43] Centrifugation plasmapheresis allows for whole blood to be spun so that the four major blood components (red blood cells, white blood cells, platelets, and plasma) are separated out into layers by their different densities. This is typically performed by blood bank teams, and there is no limit on the size of the molecules being removed.[43] Filtration plasmapheresis involves the passage of whole blood through a filter to separate the plasma components from the larger cellular components, namely red blood cells, white blood cells, and platelets. This is typically performed by nephrologists or

intensivists, and a large filter can be easily added to an existing continuous veno-venous hemodialysis circuit without interrupting patient care. The size of the molecules removed is limited by the size of the pore of the filter.[43]

Therapeutic plasma exchange is used in septic shock to remove pro-inflammatory mediators and antifibrinolytic mediators that are potentiating MODS and TAMOF and replenish anticoagulant proteins and ADAMTS-13. Several case series in pediatric and adult patients have reported survival benefit in patients with MODS and TAMOF.[24,44–46] A recent single-center case series of three neonates with sepsis on ECMO showed improvement in organ failure scores and a significant decrease in lactate levels. The neonates tolerated the procedure fairly well with the only complication being hypocalcemia, which was anticipated and treated. In this case series, two neonates survived to discharge.[24] In 2010, the American Society of Apheresis recommended the utilization of blood purification techniques such as TPE be individualized due to lack of an optimum role in patients with sepsis and MODS.[23] Thus, the use of TPE must be made on a case-by-case basis. In neonates with septic shock, MODS, and TAMOF on ECMO, TPE may be a reasonable therapy to offer to improve outcomes.

Neonatal septic shock remains a leading cause of morbidity and mortality. The majority of neonates recover from sepsis with supportive therapy and treatment with antibiotics. Few neonates require escalation in support to ECMO due to progressively worsening distributive shock or respiratory failure due to PPHN. Extracorporeal therapies such as CRRT and TPE may provide some benefit in neonatal patients with septic shock on ECMO.

CONCLUSIONS

- Neonates with septic shock can be supported with ECMO.
- The survival rate in neonates with septic shock managed on ECMO is high (~50%–70%).
- Early initiation of CRRT in neonates with septic shock may help improve fluid overload and clear serum lactate.
- Therapeutic plasma exchange should be used in critically ill neonates with septic shock on ECMO on a case-by-case basis.

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REVIEW QUESTIONS

1. A term infant presents with respiratory distress at birth following urgent cesarean section to a gravida 1, para 0→1, with chorioamnionitis, fever, and prolonged rupture of membranes. What is the likely diagnosis?

A. Sepsis
B. Respiratory distress syndrome
C. Pneumothorax
D. Transient tachypnea of the newborn

2. What is the most common pathogen to cause early-onset sepsis?

A. *Staphylococcus aureus*
B. *Listeria monocytogenes*
C. Group B *Streptococcus*
D. Coagulase-negative staphylococci

3. Which of the following should be the initial steps in management of neonatal sepsis?

A. Broad-spectrum antibiotics
B. Establish arterial and venous access
C. Inotropes
D. Airway, breathing, and circulation

4. What is the etiology of respiratory failure in neonatal sepsis?

A. Altered mental status
B. Pulmonary edema
C. Persistent pulmonary hypertension
D. All of the above

5. What are the preferred antibiotics to treat early-onset sepsis?

A. Ampicillin and gentamicin
B. Ampicillin and cefotaxime
C. Piperacillin-tazobactam
D. Clindamycin

6. What is the cause for coagulopathy leading to bleeding in neonatal sepsis?

A. Dysregulation of the immune cascade resulting in thrombotic microangiopathy
B. Therapeutic hypothermia for neonatal encephalopathy
C. Persistent hypocalcemia
D. All of the above

7. Which of the following statements is most accurate?

A. Neonates with septic shock receiving ECMO have a higher survival rate compared to pediatric and adult patients.
B. Neonates with septic shock receiving TPE are at risk for hypercalcemia.
C. Neonates typically present with warm septic shock.
D. Mortality is lower when neonates with septic shock on ECMO also require CRRT.

8. What are the potential benefits of CRRT?

A. Decrease fluid overload

B. Manage the abnormalities of acute kidney injury
C. Clear serum lactate
D. All of the above

9. Which of the following statements is incorrect?
A. ECMO is a viable therapy for distributive and cardiogenic shock.
B. Early initiation of CRRT in neonatal septic shock on ECMO may help improve fluid overload.
C. Therapeutic plasma exchange should be performed for blood purification in all neonatal septic shock patients on ECMO.
D. Airway, breathing, and circulation are first steps in initial resuscitation of neonates with sepsis.

10. Which of the following statements about TPE is incorrect?
A. Therapeutic plasma exchange helps filter the blood of pro-inflammatory mediators and antifibrinolytic mediators that potentiate MODS and TAMOF.
B. Therapeutic plasma exchange can be easily performed by adding a large filter to an existing continuous veno-venous hemodialysis circuit.
C. Therapeutic plasma exchange should be considered on a case-by-case basis due to lack of optimum role in patients with sepsis and MODS.
D. Therapeutic plasma exchange has shown clear survival benefit in neonates with septic shock.

ANSWERS

1A, 2C, 3D, 4D, 5A, 6D, 7A, 8D, 9C, 10D

24.

ECMO FOR THE PEDIATRIC PATIENT WITH STATUS ASTHMATICUS

Renee M. Potera and Lakshmi Raman

STEM CASE AND KEY QUESTIONS

A 10-year-old little girl (30 kg) with a history of mild persistent asthma presented to the emergency department (ED) with a 2-day history of cough, wheezing, and respiratory distress. Her home therapies consisted of an inhaled steroid and montelukast. Her mother reported that she had been using her albuterol inhaler every 3 hours for the last 12 hours without improvement in her symptoms. She had been admitted once in the last year for an asthma exacerbation but has never been admitted to the pediatric intensive care unit (PICU) and has never required mechanical ventilation.

On arrival to the ED, the patient was in obvious respiratory distress. Her respiratory rate was 50, and she was saturating 92% on room air. Clinical examination revealed poor air entry bilaterally with diffuse wheezing and marked retractions. She was treated with nebulized albuterol in three repeated doses with a total of 15 mg, 0.5 mg of ipratropium, 0.6 mg/kg dexamethasone, and 2 g of magnesium sulfate. Initial venous blood gas reveals a pH of 7.12 and PCO_2 of 72. The patient continued to demonstrate poor air entry and tachypnea and was placed on bilevel positive airway pressure (BiPAP) with an inspiratory positive airway pressure of 12 and expiratory positive airway pressure of 6. She received intravenous terbutaline and was started on a continuous terbutaline infusion, which was titrated to 2 μg/kg/min. She was admitted to the PICU for continued treatment.

On arrival to the PICU, the patient was noted to have declining mental status. An arterial blood gas revealed a pH of 6.9 and a PCO_2 of 98. She received 40 mL/kg of normal saline and was intubated using ketamine and rocuronium. The patient was continued on albuterol nebulization and terbutaline infusion and was sedated with a ketamine infusion. She had high airway pressures and no improvement in respiratory acidosis. Anesthesia was contacted, and she was started on inhaled sevoflurane. There was minimal improvement in her respiratory acidosis, and she was now requiring norepinephrine infusion due to hypotension and worsening lactic acidosis. The decision was made to support the patient with veno-venous (V-V) extracorporeal membrane oxygenation (ECMO).

Cannulation was performed using a 23 French (23F) double-lumen cannula in the internal jugular vein. Her ventilator settings were weaned, and the sevoflurane was discontinued. She remained on nebulized albuterol and methylprednisolone. Four days after cannulation, ECMO support was weaned off, and she was extubated to BiPAP 48 hours later. Her respiratory support was weaned over the next 48 hours, and she was transferred to the general pediatric floor 8 days after admission. She was discharged home with close outpatient follow-up with a pulmonologist.

WHAT IS THE INITIAL MANAGEMENT OF AN ACUTE ASTHMA EXACERBATION?

Expert guidelines from the National Institutes of Health (NIH) recommend correction of hypoxemia using supplemental oxygen and administration of a short-acting β-agonist (SABA) and systemic corticosteroids for all patients presenting with severe acute asthma exacerbations.[1] Reversal of airflow obstruction with a SABA remains first-line therapy for an acute asthma exacerbation.[2–5] Repeated doses may be safely administered in the ED, and continuous administration may be warranted.[2,6] The NIH guidelines recommend continuous nebulized albuterol at 0.5 mg/kg/h to a maximum of 15 mg/h.[1] This maximum dose is commonly exceeded with no evidence of benefit and increasing side effects, such as diastolic hypotension and tachycardia.[7,8]

In addition to a SABA, systemic corticosteroids should be administered to all patients presenting with severe acute exacerbations.[4,9,10] In patients presenting to the ED with acute asthma exacerbations, oral prednisolone or prednisone had historically been the corticosteroids of choice, administered at 1–2 mg/kg/d with a maximum of 60 mg. There may be poor adherence to oral therapy in pediatric patients due to the bitter taste of these medications. More recently, oral dexamethasone has been used in pediatric patients presenting to the ED with asthma exacerbations. A randomized controlled study comparing oral dexamethasone to oral prednisolone and showed equal efficacy and greater adherence.[11] Pediatric patients admitted to the hospital with mild-to-moderate asthma exacerbations receiving two doses of dexamethasone had shorter length of stay compared to patients receiving 3 to 10 days of prednisone, prednisolone, or methylprednisolone.[12] Patients admitted to the PICU were excluded from this study, and literature comparing

efficacy of different corticosteroids in the PICU setting are lacking.

For patients who do not respond to first-line therapies, inhaled ipratropium bromide and intravenous magnesium sulfate should be administered.[1] Inhaled ipratropium bromide, when used with a SABA, has been shown to reduce hospitalizations for asthma when administered in the ED.[13,14] Repeated doses in hospitalized patients, however, have not been shown to be beneficial.[15,16] Intravenous magnesium sulfate has also been shown to reduce hospitalizations when it is added to conventional therapies in the ED.[17,18] It is administered as an intravenous bolus of 25 mg/kg with a maximum dose of 2000 mg. Children who are ultimately admitted to the PICU and have received magnesium sulfate on presentation are less likely to require mechanical ventilation and have a less severe course.[19]

IF THE PATIENT DOES NOT DEMONSTRATE IMPROVEMENT, WHAT ADDITIONAL TREATMENTS MIGHT BE CONSIDERED?

Patients with status asthmaticus experience air trapping caused by increased resistance to exhalation. Noninvasive respiratory support, such as BiPAP, reduces the work of breathing by reducing the pressure gradient required to overcome the increased end-expiratory alveolar pressure caused by air trapping.[20] BiPAP is safe and generally well tolerated, although some pediatric patients require mild sedation.[21] Complications have been reported with this therapy, including the development of pneumothorax and pneumomediastinum[22]; therefore, careful monitoring is essential.

In patients with severe asthma exacerbations, the delivery of an inhaled SABA to distal airways may be impaired due to severe bronchoconstriction.[23] The use of intravenous β-agonists, such as terbutaline, may allow for delivery to distal airways. However, there are limited data to suggest that intravenous β-agonists offer any treatment benefit, and their use has been associated with increased cardiac toxicity.[24] Nonetheless, in the face of impending respiratory failure, it may be worth a trial of intravenous terbutaline with close monitoring for adverse effects.

Methylxanthines, such as theophylline and aminophylline, may be helpful in the treatment of severe asthma exacerbations as they induce bronchial smooth muscle relaxation through a separate receptor than β-agonists. Intravenous aminophylline is commonly used in the treatment of status asthmaticus. However, several randomized controlled trials failed to demonstrate improved outcomes in children treated with aminophylline.[25–27] The routine use of aminophylline in hospitalized patients is therefore not recommended by the expert panel due to lack of efficacy compared with a SABA alone and increased risk of adverse effects.[1,28] It is used on occasion in our institution in the patient with impending respiratory failure prior to intubation and mechanical ventilation. Due to the narrow therapeutic window, theophylline levels must be routinely monitored to avoid potential toxicities.

If the patient progresses to requiring intubation and mechanical ventilation, inhaled anesthetics may be offered. Isoflurane and sevoflurane have both been demonstrated to reduce bronchoconstriction through relaxation of bronchial smooth muscle.[29] Several case reports exist in the literature demonstrating the successful use of inhaled anesthetics in the treatment of status asthmaticus.[30–32] The most common adverse effect is hypotension, often requiring the initiation of vasopressor support. The use of inhaled anesthetics in the PICU setting requires scavenging equipment to avoid the release of anesthetic gas into the environment[33]; therefore, it is not available in all institutions.

WHAT ARE INDICATIONS FOR INTUBATION AND MECHANICAL VENTILATION IN PATIENTS WITH STATUS ASTHMATICUS? WHAT ARE THE POSSIBLE RISKS OF INTUBATING PATIENTS WITH STATUS ASTHMATICUS?

The timing of intubation for status asthmaticus is based primarily on clinical judgment. The only absolute indications for intubation are apnea and altered mental status.[1] Intubation can also be considered in patients with hypoxia and hypercarbia unresponsive to current therapies. Intubation of a patient with severe airway obstruction due to asthma is not without risk and should be attempted by the most experienced clinician. The introduction of invasive positive pressure ventilation may lead to worsening hyperinflation, increased intrathoracic pressure, and compromised venous return. Dynamic hyperinflation may also lead to an increase in the right ventricular afterload, and this coupled with the reduction of preload may lead to cardiovascular collapse. Intravascular volume should be replaced prior to intubation attempts, and code doses of epinephrine should be readily available.

The goal of mechanical ventilation is to improve gas exchange without causing additional lung injury. There is significant center variation regarding which ventilator mode is utilized for patients with status asthmaticus. A retrospective study of eight large PICUs demonstrated that the most common mode of ventilation in patients with status asthmaticus was pressure support with PEEP (36%), followed by pressure control (34%) and volume control (20%). Pressure-regulated volume control was the least utilized ventilator mode in this population (10%).[34] There are no reported differences in outcomes using a pressure mode of ventilation versus a volume mode[35]; however, volume modes have the advantage of allowing for monitoring of peak inspiratory and plateau pressures.[36] High peak inspiratory pressures are likely due to increased airway resistance; therefore, volumes can be titrated to maintain a plateau pressure less than 30 cm H_2O if possible.[36] Regardless of the mode of ventilation, time for exhalation should be maximized using low ventilator rates. When possible, the patient should be allowed to breathe spontaneously, therefore controlling their own expiratory time.

WHEN SHOULD THE USE OF EXTRACORPOREAL MEMBRANE OXYGENATION BE CONSIDERED?

The use of ECMO can be considered for a patient with a reversible disease process that is unresponsive to conventional medical therapies. Since status asthmaticus is a self-limited condition, it is an almost ideal disease to be supported on ECMO. While there are no absolute contraindications to ECMO, assessment of candidacy should be made on an individual patient basis.

Mechanical ventilation may lead to hyperinflation, barotrauma, and hemodynamic instability. Additionally, patients supported with mechanical ventilation are at risk of developing air-leak syndromes. ECMO provides adequate gas exchange and allows for reduction of ventilator settings, reducing the risk for further lung injury and reducing side effects from other therapies. In our center, we typically trial inhaled anesthetics prior to the initiation of ECMO. In centers that do not have the capability to administer inhaled anesthetics, ECMO may be considered earlier in the course.

Veno-venous ECMO is the preferred cannulation strategy, as these patients usually only require respiratory support. Cannulation is typically accomplished using a dual-lumen cannula in the right internal jugular vein in children. Other cannulation strategies include dual-site V-V ECMO, with the drainage cannula placed in a separate vessel than the return cannula (i.e., femoral-femoral or femoral-jugular). The drainage cannula should be of sufficient size to provide for complete respiratory support. As the oxygenator is extremely efficient at CO_2 removal, full support for status asthmaticus can typically be achieved with 50 mL/kg/min blood flows. Patients are generally cannulated at the bedside with either fluoroscopic or echocardiographic guidance, depending on site of cannulation and choice of cannula.

HOW IS THE PATIENT MANAGED ONCE ON ECMO?

In patients with severe hypercarbia at the time of initiation of ECMO, such as patients with status asthmaticus, carbon dioxide levels should be reduced gradually. Hypercarbia results in increased cerebral blood flow, and rapid correction of CO_2 levels have been associated with increased neurologic injury and cerebral hemorrhage.[37,38] In our practice, the circuit blood gas is adjusted to match the patients, and the sweep gas is gradually increased over time (4–8 hours) to slowly correct hypercarbia. This practice is consistent with recent literature.[39]

Once the patient is supported with ECMO, ventilator settings should be reduced. For patients with status asthmaticus, the patient should be allowed to breathe spontaneously as soon as possible and can be supported in a pressure support/PEEP mode of ventilation. Although pediatric patients will likely require sedation, the use of paralytics is not recommended. Anticoagulation is necessary for patients supported on ECMO and is typically achieved with a heparin infusion, although there is significant institutional variation.

As the patient's ventilation improves, the sweep gas and fraction of inspired oxygen (FiO_2) are gradually reduced on the ECMO circuit. Once these are at a minimum, the sweep gas is discontinued, and the oxygenator is capped. Serial blood gases are obtained to monitor the patient's native lung function. Once the patient demonstrates adequate ventilation and oxygenation with the oxygenator capped, ECMO may be discontinued and the cannula removed.

DISCUSSION

Asthma is a common childhood disease and is estimated to affect six million American children.[40] Factors known to increase the risk of death from asthma include history of prior intensive care unit admission or need for intubation, two or more hospitalizations or three or more ED visits due to asthma in the last year, and low socioeconomic status.[1,41–44] In a large retrospective study of pediatric patients with status asthmaticus who were intubated and mechanically ventilated, 4% died, with the most common cause of death being anoxic brain injury.[34] Importantly, 91% of the nonsurvivors suffered cardiac arrest prior to admission to the PICU.

The use of ECMO for respiratory failure secondary to the acute respiratory distress syndrome has been widely described in both adult and pediatric literature. The use of ECMO for status asthmaticus in the pediatric population is not as well described, consisting mainly of case reports and case series. This is likely due to the low use of ECMO for status asthmaticus, with 91 cases reported to the ELSO database from 2009 to 2015.[45]

Extracorporeal membrane oxygenation has been successfully used as a rescue strategy for adult patients with status asthmaticus.[46,47] A review of the ELSO Registry in 2017 identified 272 adult patients who were cannulated due to a primary diagnosis of asthma. Survival to hospital discharge was 83.5%. The most common cause of death was organ failure, which occurred in 37.8% of nonsurvivors. Complication rates were relatively high, with complications occurring in 65.1% of patients, with hemorrhagic complications being most common. There were four deaths that were attributed to hemorrhagic complications. Factors associated with in-hospital mortality included older age, bleeding, pre-ECMO PEEP, post-ECMO FiO_2, and post-ECMO driving pressure.[48]

The overall outcomes for pediatric patients with status asthmaticus supported with ECMO are also excellent, with 88% survival. This is compared with a 60% survival for all pediatric patients with respiratory failure.[45] One case series described 13 pediatric patients supported with ECMO due to status asthmaticus. The median arterial pH and PCO_2 prior to ECMO cannulation were 6.89 and 130, respectively. There were no deaths or significant neurologic complications in this series.[49] These results are similar to outcomes reported in the ELSO database. Of the 64 pediatric patients supported with ECMO due to status asthmaticus from 1986 to 2007, four patients died. The most commonly reported complications

were hemorrhagic (23%), cardiovascular (33%), and mechanical (23%).[49] Given the low mortality for patients with status asthmaticus supported on ECMO, it should be considered as a viable rescue therapy.

CONCLUSION

- Status asthmaticus is a common indication for admission to the PICU, and it has highly variable treatment strategies.
- The mortality rate for pediatric patients supported with ECMO for status asthmaticus are lower than for other causes of respiratory failure.
- ECMO should be considered for patients with status asthmaticus refractory to conventional therapies.

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REVIEW QUESTIONS

1. An 5-year-old little boy presents to the ED with wheezing and respiratory distress. Which of the following is the most appropriate initial treatment?

A. Albuterol
B. Ipatroprium bromide
C. Theophylline
D. Magnesium sulfate

2. Use of which of the following corticosteroids is associated with a decreased inpatient length of stay for pediatric patients with mild-to-moderate asthma exacerbations?

A. Prednisone
B. Prednisolone
C. Dexamethasone
D. Methylprednisolone

3. What is the most common side effect when using inhaled anesthetics for status asthmaticus?

A. Hypotension
B. Bradycardia
C. Tachypnea
D. Hypothermia

4. An 11-year-old girl presents to the ED with tachypnea, wheezing, and respiratory distress. A capillary blood gas reveals a pH of 7.2 and a PCO_2 of 67. During your examination, she becomes sleepy and difficult to arouse. Of the following, which feature of this patient's presentation would make you consider intubation?

A. Hypercarbia
B. Wheezing
C. Altered mental status
D. Tachypnea

5. Which of the following is an incorrect statement?

A. Spontaneous respirations are preferred for patients with status asthmaticus supported by ECMO.
B. Hypercarbia should be rapidly corrected once a patient is placed on ECMO.
C. Systemic corticosteroids should be administered to patients with status asthmaticus.
D. Intravenous magnesium sulfate reduces hospitalizations due to status asthmaticus when administered in the ED.

6. Which of the following statements about methylxanthines is incorrect?

A. They have a narrow therapeutic window.
B. They lead to bronchial smooth muscle relaxation.
C. They are recommended for routine use in all patients with status asthmaticus.
D. They have not been shown to improve outcomes in status asthmaticus.

7. Which of the following have not been associated with increased risk of death in asthma?

A. Low socioeconomic status
B. Prior intensive care unit admission
C. Three or more ED visits in the last year
D. Family history of asthma

8. Which of the following statements regarding ECMO cannulation for status asthmaticus is correct?

A. It must be performed in an operating room.
B. Veno-arterial ECMO is the preferred cannulation strategy.
C. A single dual-lumen V-V cannula may be used.
D. The drainage cannula should be as small as possible.

9. Which of the following treatments requires the use of a scavenging system?

A. Albuterol
B. Dexamethasone

C. Magnesium sulfate
D. Isoflurane

10. Which of the following statements regarding ECMO for status asthmaticus is incorrect?

A. It has a high mortality rate.
B. The use of anticoagulation is required.
C. The most commonly reported complications are hemorrhagic.
D. Ventilator settings can be reduced once the patient is supported on ECMO.

ANSWERS

1A, 2C, 3A, 4C, 5B, 6C, 7D, 8C, 9D, 10A

25.

ECMO FOR PEDIATRIC PNEUMONIA AND SEPSIS

Javier Rodriguez-Fanjul, Monica Balaguer Gargallo, and Iolanda Jordan Garcia

STEM CASE AND KEY QUESTIONS

A previously healthy 3-year-old girl presented to a local hospital emergency department with respiratory distress, 48 hours of fever and odynophagia, complaint of abdominal pain, vomiting, and joint pain.

The initial examination revealed poor capillary refill with a rash. She presented with fever (38.4°C), tachycardia (heart rate 160s), and low blood pressure (80/50 mm Hg). The initial laboratory data showed 3600 white cells ($\times 10^9$/L); a C-reactive protein of 113 (mg/L); a procalcitonin level of 275 ng/mL; and an arterial blood gas with pH 7.21, PO_2 95 mm Hg, HCO_3 16.5 mmol, base excess (BE) -8, CO_2 40 mm Hg, lactate 5.5 mmol/L, glucose 87 mg/dL, sodium 139 mEq/L, potassium 3.3 mEq/L, and calcium 8.1 mg/dL.

The patient was diagnosed with streptococcal shock, and fluid resuscitation (20 mL/kg) as well as empiric antibiotic treatment were commenced. The pediatric transport service was activated to transfer the patient to a pediatric intensive care unit (PICU), but on arrival of the team, the patient required endotracheal intubation and mechanical ventilation as well as inotropic/vasopressor support due to instability. The chest x-ray showed left lung pneumonia and pleural effusion.

Despite ventilation with high peak inspiratory pressure (PIP) of 40 cm H_20, positive end-expiratory pressure (PEEP) of 14 cm H_2O, and a fraction of inspired oxygen (FiO_2) 1.0, the patient was hypoxemic with a PaO_2/FiO_2 ratio of 90 and worsening hypercapnia, meeting criteria for severe acute respiratory distress syndrome (ARDS). Hemodynamically, despite high doses of vasopressors, the patient presented with poor perfusion and progressive lactic acidosis (pH 7.15, lactic acid 7.5 mmol/L).

At 24 hours from PICU admission, veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) was implemented. During the cannulation procedure, due to instability, the patient suffered a cardiac arrest of less than 5 minutes, requiring external cardiac massage. A 12 French (12F) access/drainage cannula was placed into the right jugular vein and a 12F arterial return cannula into the right carotid artery. Initial ECMO settings were 2 L/min flow, revolutions per minute (RPM) 3000, and a sweep gas of 1.5 L/min. Mechanical ventilation was reduced to lung rest settings (PIP 20 cm H_20, PEEP 10 cmH_20, respiratory rate 10 breaths/min, FiO_2 0.3).

Once on ECMO, the inotropic support was weaned, but the patient remained in hyperlactic metabolic acidosis with venous oxygen saturations (SpO_2) of 60%. It was decided to place another 12F venous drainage cannula in the right femoral vein to achieve higher flow rates and try to reverse shock. Once placed, ECMO flows were increased to 3 L/min and venous SpO_2 increased to 75%.

Over the next 24 hours, the patient developed acute renal failure. The initial oliguria progressed to anuria, requiring continuous renal replacement therapy.

On day 3 of ECMO support, the patient developed visible clots in the circuit. Hemolysis was determined by plasma-free hemoglobin of 1.5 g/L, and it was felt necessary to exchange the circuit.

The patient could be weaned and decannulated after 7 days of extracorporeal support and was weaned off mechanical ventilation on day 12 after PICU admission.

The only neurological deficit observed was poor right leg movement, where the venous femoral cannula was placed.

WHY IS THERE STILL CONTROVERSY ABOUT PLACING SEPTIC PATIENTS ON ECMO?

Sepsis has been historically a contraindication for ECMO due to high morbidity and mortality. Moreover, it was believed that the use of artificial circuits could contribute to uncontrolled infection,[1] as the presence of foreign membranes like the placement of central lines could potentially perpetuate bacteremia, enhance bleeding, and activate the inflammatory cascade. However, currently ECMO circuits have biocompatible surface coating, decreasing the risk of possible microorganism lodging in the ECMO circuit.

Over the last decade, the Melbourne group[2,3] has shown improved survival rates, and the American College of Critical Care Medicine recommended the use of ECMO in patients with septic shock unresponsive to all other measures.[4] The results from this group suggest the global survival of children placed on ECMO for septic shock is around 50%.[5,6]

However, these results have not yet been seen in the adult population, and although there have been a few manuscripts reporting experience with ECMO in adults with septic shock, experience remains limited.[7] This may be due to septic shock presenting differently in adults depending on hemodynamics and the microorganisms involved.

In newborn sepsis, the leading symptom is right ventricular dysfunction with persistent pulmonary hypertension, while in infants and younger children left ventricular dysfunction with

reduced cardiac output is commonly seen. In contrast, children and adults present in a hyperdynamic and hypotensive state. This distributive shock is characterized by increased cardiac output and relative hypovolemia secondary to hypotension from vasodilation.

Therefore, V-A ECMO may be beneficial for patients with ventricular dysfunction and not for those with profound vasodilation.[8] Flow-through peripheral cannulae require a minimum vasotone that can be achieved by the use of inotropes and vasopressors, such as epinephrine or vasopressin in pediatric septic shock.

The best flow can probably be achieved by central cannulation[3,9] or by adding another peripheral cannula, like in our case. Larger cannula diameters generate greater flow rates and potentially reverse shock and organ dysfunction earlier in patients with high oxygen demand.

More studies need to be performed to understand the outcome for septic patients requiring ECMO support, including which configuration, central or peripheral cannulation, may show better outcomes. Patient selection for ECMO support may be beneficial in the presence of associated myocardial dysfunction but not for distributive shock.[10] However, it is challenging to predict which patients in the context of profound septic shock have preserved systolic function to sustain the higher output required during that shock state.

Inotropic treatment depends mainly on identifying the hemodynamic pattern of each patient. For cardiogenic shock patients, dobutamine is the drug of choice, while in vasoplegic patients, vasopressin or epinephrine is recommended.[11] Therefore, ECMO support may be indicated in cardiogenic septic shock but not in vasoplegic shock. These different septic shock patterns may depend on the causative microorganism, although this is controversial.[8,12]

IS THE EVOLUTION OF PNEUMONIA PATIENTS WORSE THAN SEPTIC PATIENTS?

Extracorporeal membrane oxygenation is a well-established rescue therapy for refractory respiratory failure.[13] In fact, viral pneumonia is the most common condition leading to pediatric ECMO.[14]

Survival rates are higher than in septic shock, with a nearly 60% survival rate,[15] ranging between 40% and 90% in bacterial pneumonia and between 48% and 100% in viral pneumonia, being the syncytial virus with the highest post-ECMO survival rate.[16–22] An exception are children affected by *Bordetella pertussis*, who have the lowest survival rates, less than 40%.[23,24] Globally, there has been an increase in survival from 70% to nearly 80%.[25] These better outcomes may be due to better patient selection and based on the knowledge of a recent report of prolonged ECMO in patients with pneumonia due to influenza H1N1.[26] However, patients with bacterial pneumonia have higher mortality, especially cases due to pneumococcal pneumonia, probably because of higher global multiorgan dysfunction. Therefore, in patients with pneumonia, functional echocardiography should be done at the bedside to evaluate biventricular function before starting ECMO support.

If there is right ventricular dysfunction with preserved left ventricular function, the compromised hemodynamic situation may be restored with veno-venous (V-V) support, while if there is clear left ventricular dysfunction, V-A ECMO may be the support of first choice. This is extremely important as V-V ECMO decreases the risk of arterial embolization and avoids carotid artery ligation.[27] Moreover, V-V ECMO is more physiologic, avoiding the nonpulsatile blood flow generated by V-A ECMO, for which the pulse wave decreases. This leads to an alteration in different organs, especially the kidney, resulting in an antidiuretic effect and also stimulating carotid sinus receptors, releasing catecholamines, increasing the third-space leak sepsis phenomenon.[28] On the other hand, V-V ECMO requires a "healthy" heart to avoid cardiac failure.

While in the newborn population the only indication for ECMO is respiratory failure with a value exceeding 40 on the oxygenation index (OI),[29] there is not a clear indication for older children. This may be related to the fact that over the last decade different strategies have been included to avoid ARDS, one of the major complications of pneumonia in children. The clinical syndrome is characterized by bilateral infiltrates on chest radiography in the absence of left atrial hypertension and impaired oxygenation with a PaO_2/FiO_2 ratio less than 200.

The treatment strategies include lung-protective ventilation, inhaled nitric oxide, surfactant therapy, and high-frequency oscillation ventilation.[30] Local ECMO criteria to avoid acute lung injury differ between centers.[31] It is well known that in older children the OI may predict outcome, especially in the first 12–24 hours as it is an independent predictor of mortality.[32] In contrast to the neonatal population, as we have mentioned previously, there is no clear-cut threshold of the OI to predict mortality accurately; therefore, ECMO is indicated. Other ECMO indications may be PaO_2/FiO_2 ratio and Alevolar-arterial oxygen gradient ($AaDO_2$) in the setting of a PIP around 35 cm H_2O and PEEP between 10 and 12 cm H_2O to keep SpO_2 greater than 88%.[33]

Interestingly, most of the studies published have not found higher mortality in patients with pneumonia and septic shock, with survival rates higher than those patients with septic shock only.[34,35] Recent reports pointing out that although survival rates decrease with increasing ECMO duration, prolonged ECMO duration defined as longer than 14 days is increasingly being reported with lower mortality.[36] On the other hand, it may take longer than 2 weeks to see a complete recovery of the lung parenchyma.[37] Therefore, more studies are warranted to help elucidate outcomes and prognosis for long-run ECMO in the pediatric population.

WHY IS THERE A TENDENCY FOR CLOT FORMATION IN THE ECMO CIRCUIT?

Sepsis upregulates the synthesis of cytokines that have pro-inflammatory properties. At the same time, the coagulation cascade is also initiated by the active form of factor XII and by

soluble proteins along with monocyte tissue factor, leading to thrombin formation.

In this context, when ECMO support has been initiated, blood components come into contact with the foreign surface of the ECMO circuit, triggering these pathways, resulting in subsequent clot formation and in endothelial platelet adhesion.

Although the latest generation of ECMO devices has coating materials and increased system biocompatibility,[38,39] patients on ECMO experience some degree of sepsis-like inflammatory reaction and coagulation activation, leading to a third-space leak, which may lead to the necessity of ECMO circuit changes.[3,8]

In our case, also the placement of a second return cannula with consecutive decrease of flow through each ECMO cannula as well as time needed for connecting with the circuit may lead to clot formation. However, interruptions and flow stagnation during circuit changes can be counterbalanced by administration of heparin 5 minutes before the circuit change.

WHY DO NEWBORN SEPTIC PATIENTS PRESENT WITH BETTER OUTCOMES?

One suitable explanation that newborn septic patients present with better outcomes may be that septic patients undergo ECMO intervention because of right ventricular failure due to persistent pulmonary hypertension, triggered by the sepsis. To help the right ventricle by providing gas exchange through either partial or total V-V ECMO helps the right ventricular performance and correcting hypoxemia, acidosis, and pulmonary hyperinflation. It will also lead to hemodynamic improvement and reduction of pulmonary artery pressure, decreasing inotropic drug requirements, which in turn may decrease myocardial oxygen consumption and allow for lung-protective ventilator settings.[40] ECMO optimizes tissue perfusion in septic patients, allowing a "metabolic rest" during the septic "storm." If needed, hemodynamic support can also be provided by applying a V-A or veno-arterial-venous (V-AV) configuration.

Other contributing factors for better outcomes in newborn patients are well-established ECMO criteria, which may lead to earlier initiation of ECMO support[40]:

- Reversible cardiorespiratory failure
- Oxygenation index greater than 40 for more than 4 hours
- Oxygenation index greater than 20 despite maximal therapy
- Severe hypoxemic respiratory failure with acute decompensation (PaO_2 < 40 mm Hg)
- Progressive respiratory failure and/or pulmonary hypertension with evidence of right ventricular dysfunction or continued high inotropic requirement

Older children may require ECMO support in worse conditions, as there are no "strict" inclusion criteria.[41] Some of the patients may require cardiopulmonary resuscitation (CPR) before cannulation[2,8] or in the context of vasoplegic shock and not only of left ventricular dysfunction; this may explain the poor results in this population.

Gestational age is one of the major concerns and contraindication for newborns requiring ECMO. Historically, less than 34 weeks' gestation was a contraindication due to the increased risk of intracranial hemorrhage. However, recent reports have shown good results (even better than in children) in newborns with septic shock and pneumonia, with survival rates around 60%.[42] These numbers, although worse than the ones obtained in term newborns, with survival rates higher than 80%, are still better than in older children.[43]

DISCUSSION

Extracorporeal membrane oxygenation is not a treatment but an intervention that bridges septic shock patients with refractory cardiovascular dysfunction to organ function recovery. It may restore tissue perfusion and oxygenation, achieving a balanced oxygen extraction (O_2 ER) which is the ratio of VO_2 (oxygen uptake) over DO_2 (oxygen delivery) and increasing cardiac output while clinicians are able to decrease deleterious and aggressive invasive mechanical ventilation and inotropic support.

One of the major controversies in ECMO care are well-established indications for many different syndromes, which unfortunately are lacking in patients with septic shock.[41]

One suitable indication may be in those patients with persistent shock despite optimization of preload, vasoactive drug support, source control, appropriate antibiotics, and correlation of identifiable factors (intra-abdominal hypertension, pneumothorax or pericardial tamponade, and adrenal insufficiency).

MacLaren and Butt recommended its use when support meets the following criteria:

- There is greater than 1 μg/kg/min of epinephrine or equivalent.
- Resuscitation has followed the recommendations of the American College of Critical Care Medicine consensus statement.
- The patient continues to deteriorate with worsening hypotension and rising lactates or rapidly evolves in progressive multiorgan dysfunction although receiving the correct treatment.

While initial septic shock management is well established during the golden hour, the time to start ECMO depends on how quickly the patient may be transferred to a hospital with ECMO capability or the speed to mobilize the ECMO team if the patient is in a hospital able to provide it.

Once the golden hour has passed, there is a need in pediatric sepsis for validating surrogate outcome measures. It is well known that early aggressive resuscitation is associated

Table 25.1 SUMMARY OF MAIN STUDIES INVOLVING PEDIATRIC SEPTIC PATIENTS REQUIRING ECMO

	POPULATION	#	SURVIVAL	CPR PRIOR TO ECMO	ECMO RUNS (HOURS)	ETIOLOGY	HEMOFILTRATION
Schaibe et al. (2010)[43]	Newborn	42	69%		153 ± 105.91	No	Unknown
MacLaren et al. (2011)[3]	Children	23	78%	35%	93 (43–119)	Yes	Yes, 57%
MacLaren et al. (2007)[2]	Children	45	47%	40%	84 (32–135)	Yes	Yes, 62%
Tembo et al. (2009)[46]	Children	14	21%			Yes, 37.5% survival meningococcal	Unknown
Beca and Butt (1994)[47]	Children	9	56%		137 (57–231)		No
Goldman et al. (1997)[48]	Children	12	67%	41%	76 (20–263)	Yes, meningococcal	Yes, 41%
Solé et al. (2018)[8]	Children and newborn	21	33.3% pediatrics 50% newborns	52.4%	84 (24–120)	Yes, 0% survival pneumococcal	Yes, 71%
Hocker et al. (1992)[49]	Newborn	15	86% survival			Yes Group B streptococcal	
Horton et al. (2010)[9]	Children	47	47%, survival	38%	99 (38–165) 87 (23–119)		

CPR, cardiopulmonary resuscitation.

with improved outcomes and shock reversal,[44] as the indications for the use of V-A ECMO in children with septic shock are related to cardiocirculatory failure in the setting of cardiac arrest or refractory septic shock (Table 25.1).

Different groups[3] have found that patients with lower pre-ECMO arterial lactate levels had better survival. It is well known that institutions with an ECMO team on call and with ECMO circuits ready achieved better outcomes even or especially in CPR situations.[45]

Data suggest that patients supported by V-A ECMO in the early stages of their treatment are the ones who achieve better outcomes. Controversy remains which patients are the ones that will develop septic shock unresponsive to conventional management. These results also are similar in the neonatal population, with an increase in survival rates from 62% to 82% if patients are referred to an ECMO center during the first 24 hours compared to patients referred later.[43]

Extracorporeal membrane oxygenation remains controversial in children with distributive shock, the hemodynamic pattern with a high cardiac output state without cardiac dysfunction and without left ventricular dysfunction. Therefore, it is necessary to improve hemodynamic monitoring and differentiate patients with a

- Low cardiac output state with high systemic vascular resistance;
- Low cardiac output state with low systemic vascular resistance; and
- High cardiac output state associated with low systemic vascular resistance states.

The ECMO support may be supplied in children with (Figure 25.1) the following:

- Left ventricular failure
- Right ventricular failure
- Acute respiratory distress syndrome

When studies focus on ECMO survival, there are two major terms to be used, one is *survival of treatment*, and the other its *survival to discharge*. It is well reported in the adult population that if patients are able to be decannulated, the risk of death is highest during the first 3 months post-ECMO,[50] and these results are similar to the ones reported in children, with 5-year survival rates as high as 98%. It seems that compared to other ECMO indications, such as congenital diaphragmatic hernia, where there is an increase of long-term death, patients treated with ECMO for septic shock who receive adequate treatment and survive the acute "storm" phase have good outcomes.

Patients who have suffered from severe ARDS due to pneumonia may often have severe persistent lung pathology many years after their treatment; although survival in patients without comorbidities has steadily improved, a considerable number of patients with comorbid conditions treated with ECMO have increased during recent years.

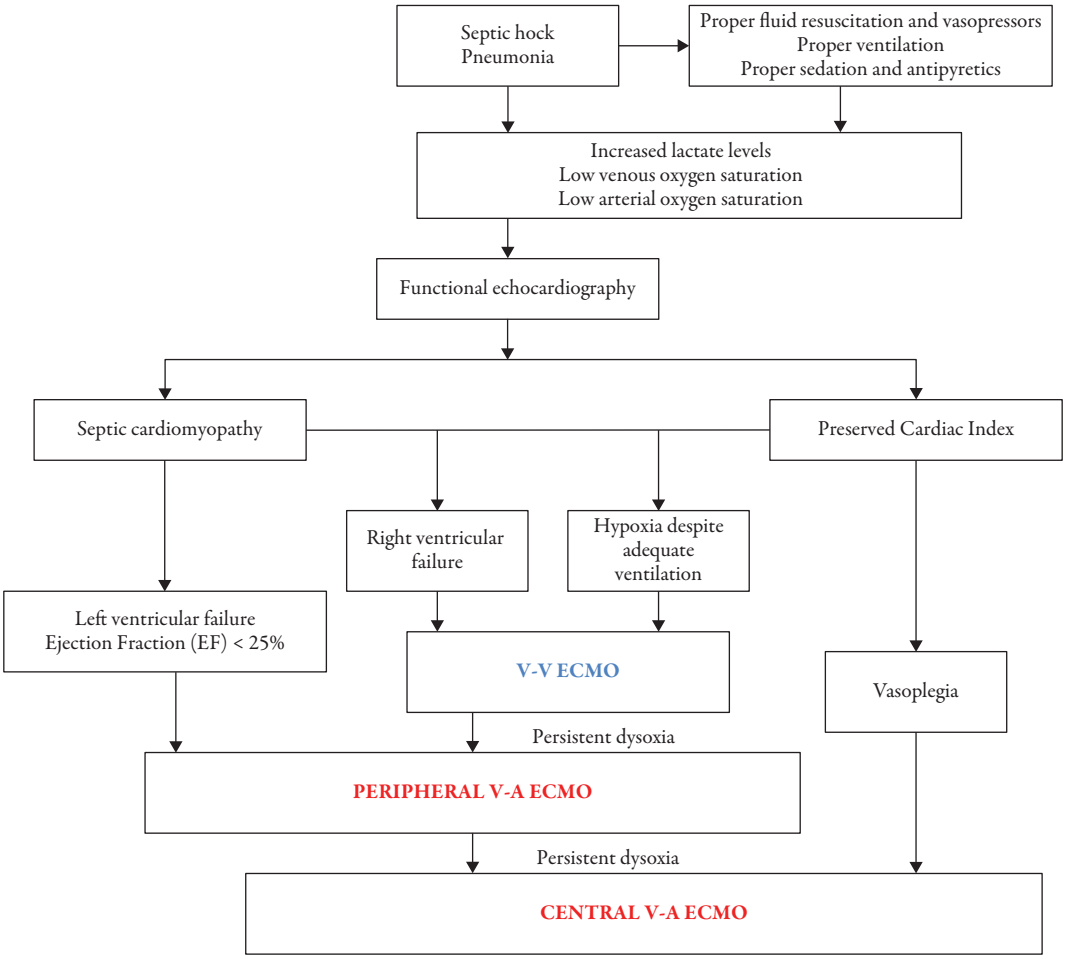


Figure 25.1 Algorithm for ECMO management in septic shock.

As mentioned, it seems that strategies with the aim to maximize flow rates in order to reverse shock and multiple-organ dysfunctions may improve outcomes. While recommendations in patients on V-A ECMO are to keep flows less than 110 mL/kg/min, different authors recommended increasing flow up to 150 mL/kg/min.

A recent multicenter study by Oberender et al.[51] found that reduction in mortality of pediatric patients with severe shock was seen with V-A ECMO flows greater than 150 mL/kg/min at 4 hours after implementation of ECMO. The authors stated that this need of higher flows in ECMO patients may explain why there is no survival increase in patients managed with conventional 110 mL/kg/min flows.

In contrast with the adult literature, when cardiac arrest before V-A ECMO increases mortality, this is not the case in the pediatric population as cardiac arrest has not been found a mortality predictor with survival rates higher than 40%.[3,8,48,52]

It is clear that in the setting of cardiogenic shock the configuration of choice should be V-A ECMO, which has the clear advantage of providing direct cardiac support, rapid hemodynamic stabilization, and good oxygen delivery. On the other hand, it has the disadvantage of nonpulsatile blood flow, increasing the third-space leak as well as the risk of potential hyper/hypoxia during cannulation in patients with low blood pressure and hypoxemia, lower myocardial oxygen delivery, and possible systemic circulatory emboli.[40]

Another piece in the puzzle may be the pathogen causing the septic process. It has been described that patients placed on ECMO with infections due to gram-positive cocci have better outcomes than those with gram-negative infection. These may be related to endotoxin released by gram-negative pathogens, leading to distributive shock with low systemic vascular resistance, while in gram-positive infections there is a predominant involvement of septic cardiomyopathy.[53–54]

In patients with pneumonia and acute respiratory failure without left ventricular dysfunction, V-V ECMO should be the ECMO configuration of choice since it has the advantage of maintaining pulsatile blood flow, normal pulmonary blood flow, and myocardial perfusion with oxygenated blood. However, if the patient develops cardiac insufficiency, it will not give direct cardiac support and lower oxygen delivery compared to V-A ECMO. In this case, it may become necessary to convert from V-V to V-A ECMO (Table 25.2).

In patients with septic shock from pneumonia, the etiology has importance in terms of prognosis. *Bordetella pertussis* or fungal pneumonia have significantly increased odds of mortality,[59] while patients with *respiratory syncytial virus* have

Table 25.2 SUMMARY OF MAIN STUDIES INVOLVING PEDIATRIC PATIENTS WITH PNEUMONIA REQUIRING ECMO

	POPULATION	PATIENT NUMBER	SURVIVAL RATE	ECMO TYPE	ECMO RUNS (HOURS)	ETIOLOGY
Ramanthan et al. (2019)[19]	Newborn and children	452	49% children 13.6% newborn	72% V-A vs. 28% V-V	254 ± 85.21	Adenovirus
Namachivaya et al. (2007)[55]	Newborn	4	0%	100% V-A	241.5	Pertussis
Minneci et al. (2013) [56]	Children	1489	67% RSV 53% influenza 50% adenovirus 45% MARSA 54% H. Influenza	65% V-A vs. 35% V-V	264 (168–432)	Viral and bacterial
Pathan et al. (2008)[57]	Children	81	75% RSV 42% Pertussis 50% Bacterial	63% V-A vs. 37% V-V	216 (120–408)	Viral and bacterial
Lihgow et al. (2014)[58]	Children	2	100%	100% V-A	295	A Streptococcal
Peng et al. (2012)[33]	Children	12	50% Streptococcus pneumoniae 100% Mycoplasma pneumoniae	58% V-A vs. 42% V-V	241.1 ± 194.9	Viral and bacterial

RSV, respiratory syncytial virus; MARSA, methicillin-aminoglycoside resistant Staphylococcus aureus.

decreased odds of death. This may be due to an inherent reversibility of the disease process or due to the absence of associated multiorgan failure. Patients with pertussis pneumonia are affected by the release of the toxin, accounting for different systemic manifestations of the disease and being correlated with lymphocytosis. The exact mechanism of pulmonary hypertension remains unknown, although it seems correlated with leukocytosis and high platelet counts; as ECMO therapy is associated with very poor outcome in this population, other factors may be related to it,[60] and other therapies such as leukodepletion may improve the results.[61]

Another challenging pneumonia is due to adenovirus, which may cause a rapidly progressive illness with multiple-organ failure. Despite ECMO improvements, a recent study[62] revealed no improvements in mortality, with a survival rate of only 40%, with these results even lower in the neonatal population (15%). ECMO intervention in this population should be chosen carefully as survival is unlikely.

Patients who have suffered from severe ARDS due to pneumonia may often have severe persistent lung pathology many years after the treatment, although survival of patients without comorbidities has steadily improved; however, the number of patients with a comorbid condition managed with ECMO has increased during recent years.

Newborns requiring ECMO support due to respiratory failure keep presenting with frequent respiratory symptoms when they are older than 10 years, once their lungs are completely developed after the treatment. These respiratory symptoms include wheezing during exercise or asthma. This may be explained by airway obstruction, hyperinflation, and hypoxia when these children are matched with other healthy children.[63]

The recent novel H1N1 pandemic helped to increase management of viral pneumonia with V-V-ECMO,[64] with ECMO durations similar to other viral pneumonias, with a mean duration of 10 days. Risk factors for increased life-threatening influenza include underlying chronic conditions and bacterial co-/superinfections with influenza.

Patients with respiratory failure due to pneumonia with immune deficiency or solid organ malignancy are the ones with lower survival.[65]

CONCLUSION

- In the pediatric septic shock population, V-A ECMO flows of 150 mL/kg/min appear to have better survival compared to conventional 100 mL/kg/min.
- ECMO treatment should be used with caution in patients with a vasoplegic shock pattern.
- Pediatric patients with septic shock should be transferred to ECMO centers as those supported in early states achieve better outcomes.
- Patients with pertussis or fungal pneumonia have increased odds of mortality despite ECMO treatment.

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REVIEW QUESTIONS

1. Which of the following scenarios represent criteria for exclusive V-A ECMO?

A. 5-year-old boy with pneumonia
B. 10-year-old girl with pneumonia in cardiac arrest
C. 3-day-old newborn with septic shock
D. 6-year-old girl with septic shock

2. An 8-year-old boy (body weight 30 kg) is placed on V-A ECMO due to refractory septic shock with a 14F access cannula into the right internal jugular vein and a 12F return cannula into the right carotid artery. ECMO settings were initially set for a flow of 2.5 L/min, RPM 3500, and sweep gas of 2 L/min. The premembrane pressure shows 450 mm Hg with postmembrane pressure of 430 mm Hg. The most likely situation is which of the following?

A. The problem is in the oxygenator.
B. V-A ECMO flows are too high for the cannula size.
C. Pressures are normal.
D. The problem is in the pump.

3. A 3-day-old girl (body weight 3.5 kg) is placed on V-A ECMO due to refractory septic shock with a 10F access cannula into the right internal jugular vein and a 10F return cannula. Initial ECMO settings are flow of 2.5 L/min, RPM 3500, and sweep gas of 2 L/min. The cannula is placed into the right carotid artery with a centrifugal pump. After 3 hours on ECMO, there is a sudden decrease in preload pressures with a decrease in the in pre- and postmembrane pressures. What is the problem?

A. The negative pressure generated will be restored with an increase in the pump flow.
B. The negative pressure generated by the pump is due to hypovolemia and will be restored with fluid volume.
C. The negative pressure generated will be restored with vasoactive agents.
D. The negative pressure will be restored only with decrease in the pump speed.

4. Which of the following situations is an absolute contraindication for ECMO in any patient?

A. 2-year-old girl with mild psychomotor delay
B. 5-day-old newborn boy with a right pneumothorax
C. 6-month-old girl with intracranial hemorrhage and mass effect
D. 6-year-old mechanically ventilated for 10 days

5. A 1-year-old boy is placed on ECMO due to septic shock secondary to meningococcal infection. Prior to ECMO cannulation, the child requires CPR for 8 minutes. Once placed on V-A ECMO, during the first 4 hours the patient requires the following settings: blood flow of 0.7 L/min and sweep gas

of 0.7 L/min. The premembrane pressure is 175 mm Hg, and postmembrane pressure is 160 mm Hg, with a preload pressure of 10 mm Hg. Systemic blood pressure is 110/75 on adrenaline (epinephrine) 0.1 μg/kg/min. The blood gas sample reveals a lactate increase of up to 8.5 mmol/L (previous of 6 mmol/L) and worsening metabolic acidosis. Venous SpO_2 is 50% with arterial SpO_2 of 100%. In addition, echocardiography reveals severe left ventricular dysfunction, with left ventricle and left atrium dilation. What do we think is happening?

A. The patient needs time to recover as main blood pressure is correct and oxygen saturation is 100%.
B. Veno-atrial ECMO is not effective; we need another type of ventricular assist device.
C. The patient is not adequately assisted, and we need to increase ECMO flows.
D. The patient is not adequately assisted, and we need to increase inotropic support without changing ECMO support.

6. A 24-hour-old boy (body weight 3.2 kg) is placed on V-A ECMO due to refractory septic shock by *Escherichia coli*. A 10F access cannula is placed in the right internal jugular vein and a 10F cannula into the right carotid artery. Initial ECMO settings are flow of 0.8 L/min, RPM 2000, and sweep gas of 0.8 L/min. At 48 hours after ECMO, we start seeing clots in the ECMO circuit, and suddenly there is an increase in the premembrane pressure of 255 mm Hg with a postmembrane pressure of 145 mm Hg and a preload pressure of -8 mm Hg. What do you think is happening?

A. The patient is awake and needs more sedation.
B. After 48 hours on ECMO, it is normal that premembrane pressures increase.
C. The ECMO membrane is clotting; we need to change the ECMO circuit quickly.
D. The patient is hypovolemic and needs extra volume.

7. Which of the following statements is incorrect?

A. Patients with respiratory syncytial virus pneumonia have increased odds of survival.
B. Patients with fungal pneumonia have increased odds of death.
C. Patients with pertussis pneumonia have increased odds of survival.
D. Newborn patients with adenovirus pneumonia have increased odds of death.

8. Which of the following statements for newborn ECMO criteria is incorrect?

A. Oxygenation index greater than 20 despite maximal therapy
B. Severe hypoxemic respiratory failure (PaO_2 < 20 mm Hg)
C. Reversible cardiorespiratory failure
D. Oxygenation index greater than 40 for more than 4 hours

9. Which of the following sentences is correct with respect to the central cannula placement for ECMO support in septic patients?

A. Central cannulation allows higher fluxes of volume, which helps to ensure adequate tissue oxygenation.
B. The cannula size in this context is usually bigger than with peripheral cannulation.
C. There is a greater exchange of blood, which leads to a higher blood product transfusion.
D. All options are correct.

10. The ECMO support in septic patients has particular difficulties; all of these complications but one are correct. Which is incorrect?

A. Capillary leak syndrome leads to major fluid replacement.
B. Coagulation parameters are difficult to manage not only because of ECMO but also because of the coagulation test impairment in sepsis itself.
C. In community sepsis, it does not matter which kind of antibiotic you indicate, or at what dose, because sepsis responds well to antibiotics.
D. It is important to adjust antibiotic treatment in septic ECMO patients due to the increased volume of distribution.

ANSWERS

1. B. A patient in cardiac arrest is an exclusive criterion for V-A ECMO. V-V ECMO support will not restore spontaneous cardiac circulation. Although V-A ECMO may be an indication in patients with septic shock or pneumonia, some may benefit from V-V ECMO.

2. B. A patient on ECMO due to septic shock may require high ECMO flows to restore systemic circulation; sometimes they will need to go for central cannulation or another extra peripheral cannula to achieve the target flow. If ECMO flows are too high for the cannula size, increased membrane pressures and circuit hemolysis are observed.

3. B. The patient is on ECMO due to septic shock and developed a third-space leak increased by ECMO, leading to a hypovolemic state. The negative pressure generated by the pump is due to hypovolemia and will be restored with fluid bolus administration and not with increasing ECMO flows or vasoactive agents.

4. C. The patient with intracranial hemorrhage and mass effect is an absolute contraindication for ECMO as once the patient is placed on ECMO, anticoagulation may be required and may increase the bleeding.

5. C. The increase of lactate levels and low venous saturation indicate poor perfusion, revealing inadequate cardiac output. The only way of restoring the homeostasis is increasing ECMO flows as the severe left ventricular dysfunction will not recover quickly.

6. C. One of the main problems intensivists face in septic patients on ECMO is the alteration of coagulation. During ECMO runs, patients may need multiple ECMO circuit changes. The increase in the premembrane pressure and not in the postmembrane pressure points out that the ECMO membrane is clotting, and the patient needs an urgent ECMO circuit change.

7. C. Patients with *B. pertussis* pneumonia due toxin release and lymphocytosis experience different systematic manifestations, with an increase on pulmonary hypertension. Although ECMO therapy is started, they achieve very poor outcomes, and other therapies such as leukodepeletion should be considered.

8. B. Thanks to strict ECMO criteria, newborn patients have better outcomes compared to pediatric patients. One of them is severe hypoxemic respiratory failure (PaO_2 < 40 mm Hg). It is important to remember that in the newborn population there may be a persistent fetal circulation thanks to persistent ductus arteriosus, leading to a decrease in oxygen levels in systemic circulation without right ventricular failure.

9. D. Patients with septic shock, like patients with cardiac failure, require bigger size cannulae to achieve higher target flows.

10. C. Although patients in septic shock are in a critical situation due to the systemic inflammatory response syndrome, the policy for antibiotic treatment is similar to that for community infections and not to nosocomial ones.

26.

ECMO IN PEDIATRIC LUNG TRANSPLANTATION

Suresh Keshavamurthy, Peter Rodgers-Fischl, Thomas A. Tribble, and Joseph B. Zwischenberger

STEM CASE AND KEY QUESTIONS

A previously healthy 11-year-old African American girl (38.5 kg) was transferred to our institution for extracorporeal membrane oxygenation (ECMO) management and potential lung transplantation. She was originally seen by her primary care physician approximately a month prior to transfer for presumed viral illness, which worsened to the point of requiring hospitalization. Following a chest x-ray (Figure 26.1), she was started on continuous positive airway pressure support on admission to the outside facility. Due to initial fevers and unclear etiology of her respiratory symptoms, the patient was initially placed on broad-spectrum antibiotics, including azithromycin for coverage of atypical pathogens such as *Legionella* and *Mycoplasma*. Over the course of the ensuing week, the patient continued to deteriorate. A computed tomogram (CT) of her chest noted diffuse ground-glass appearance and interlobular septal thickening (Figure 26.2). By the second week of hospitalization, she developed pneumomediastinum and subcutaneous emphysema. She was intubated and transferred to the pediatric intensive care unit (PICU) and placed on inhaled nitric oxide (NO) without significant improvement. A lung biopsy demonstrated acute interstitial pneumonitis, concerning for potential irreversible lung damage.

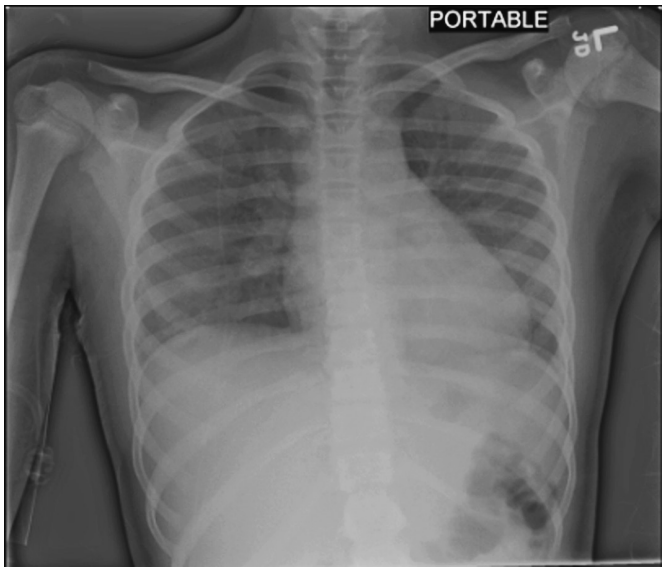


Figure 26.1 Patient chest x-ray performed approximately 2 weeks prior to initiation of ECMO.

IN THE SETTING OF WORSENING LUNG FAILURE AND IRREVERSIBLE LUNG DAMAGE, WHAT OTHER OPTIONS ARE AVAILABLE TO POTENTIALLY BRIDGE THE PATIENT TO TRANSPLANTATION OR DECISION?

Due to worsening respiratory failure in the setting of irreversible lung damage, the patient was placed on veno-venous (V-V) ECMO with a 31 French (31F) Avalon catheter (Maquet Medical Systems, Wayne, NJ) via the right internal jugular vein and was subsequently transferred to the University of Kentucky for further management (Figure 26.3). The Avalon catheter was utilized as a bridge due to its ability to potentially allow the patient to ambulate while on ECMO support.

WHAT PROBLEMS ASSOCIATED WITH AMBULATORY ECMO ARE ENCOUNTERED WITH THE AVALON CATHETER?

The Avalon double-lumen cannula had to be repositioned by echocardiogram (echo) guidance once at the outside facility, on ECMO day 3, due to inadequate flow across the tricuspid valve. On ECMO day 7, the patient was transferred to our facility, listed for transplant, and taken to the operating room OR the following day for cannula repositioning and tracheostomy.



Figure 26.2 Patient CT performed approximately 2 weeks prior to initiation of ECMO.



Figure 26.3 Patient chest x-ray performed on initiation of ECMO showing the Avalon dual-lumen cannula.

HOW IS DEAD-SPACE VENTILATION ABOLISHED WHILE ALSO AIDING PULMONARY TOILET IN A MECHANICALLY VENTILATED PATIENT?

Aggressive rehabilitation, including awake ambulation, optimization of nutritional status, and weaning of supplemental oxygen, occurred over the following month while the patient awaited donor availability. Of note, the Avalon catheter had to be repositioned an additional time in the OR on ECMO day 15 due to distal cannula migration into the hepatic vein while ambulating.

HOW IS LUNG TRANSPLANT PERFORMED IN PEDIATRIC PATIENTS ON V-V ECMO?

On ECMO day 40, the patient was taken to the OR for bilateral lung transplantation after a suitable donor was identified and accepted. Initially, we attempt to reroute the V-V ECMO circuit drainage limb to the cardiopulmonary bypass (CPB) circuit to avoid having to cannulate the right heart. This strategy affords excellent bicaval venous drainage; if ECMO is needed later, the same access and tubing can be converted back to V-V ECMO without having to cannulate alternate sites. This arrangement works best with preoperative dual-lumen V-V ECMO, but two-cannula V-V configuration can also be used.

WHAT ARE THE OPERATIVE STEPS FOR LUNG TRANSPLANTATION?

Bilateral anterior thoracotomy incisions through the fifth intercostal space exposed the right lung, which was profoundly fibrotic and consolidated. Likewise, the left hemithorax was completely obliterated with nonviable lung tissue and no viable planes. The operation proceeded first with left pneumonectomy by transecting the left superior and inferior pulmonary veins followed by transection of the left main pulmonary artery with a vascular stapler. The left lung was then explanted. Back-table preparation of the donor lungs was performed in standard fashion; the bronchus was cut to within one or two rings from the secondary carina.

The patient was then converted to CPB with drainage from the right atrium and return of blood through the ascending aorta. Just before going on CPB, the ECMO circuit was clamped; a purse-string suture was placed at the cannula insertion site in the neck, the cannula removed and the purse-string suture secured. Attention was returned to the left hemithorax. Proximal margins were established. The left donor lung was placed in the left hemothorax with end-to-end bronchial anastomosis performed with continuous 4-0 polydioxanone suture (PDS). The left atrial and left main pulmonary artery anastomoses were sewn with continuous 4-0 and 6-0 polypropylene sutures, respectively. The patient received intravenous Solu-Medrol before reperfusion of the left lung.

Attention was then turned to the right lung and hemithorax. Right pneumonectomy was performed in a similar fashion. The right lung bronchus was anastomosed with continuous 4-0 PDS suture. The left atrial and right main pulmonary artery anastomoses were completed once again with continuous polypropylene suture. After the anastomoses were completed the patient once again received intravenous Solu-Medrol before flow was reestablished with retrograde perfusion from the left atrium followed by slow progressive reperfusion from the right main pulmonary artery.

Both lungs were then ventilated with a total tidal volume of 400 mL (mL/kg) via the single-lumen endotracheal tube. The patient was weaned from CPB. Cannulae were removed. The patient received protamine to reverse the heparin. Due to significant bleeding and coagulopathy, the patient received multiple units of blood, fresh frozen plasma, and a single dose of factor VII. Despite apparent control of the bleeding, the decision was made to leave the chest open overnight. Chest tubes were inserted and a surgical sponge placed over the lungs. The sternum was loosely reapproximated. The next day, after hemostasis was confirmed, the sternum was closed, and the patient was taken to the PICU (Figure 26.4).

WHAT STRATEGIES ARE COMMONLY EMPLOYED TO ENSURE THE ANASTOMOSIS IS HEALING AND SECRETIONS ARE CLEARING?

Postoperatively, the patient had daily surveillance bronchoscopy to examine the anastomoses and pulmonary toilet. She was ambulating by transplant postoperative day 3. The patient was weaned from supplemental ventilation, and by postoperative day 9, her tracheostomy was downsized. She then underwent aggressive in-hospital rehabilitation and was subsequently discharged home approximately 1 month later.

DISCUSSION

Preoperative mechanical ventilation and hospitalization have previously been shown to be significant risk factors in lung transplantation.[1] Due to attrition while awaiting organs,

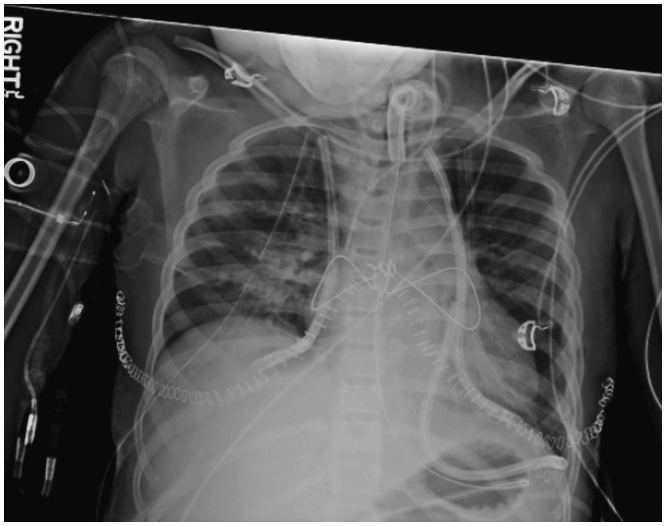


Figure 26.4 Patient chest x-ray performed transplant postoperative day 1.

strategies have become increasingly focused on extending the life of potential lung transplant candidates by means of ECMO as a "bridge" to transplantation.[2–4] Some transplant centers, however, consider mechanical ventilation and/or ECMO prior to lung transplant a contraindication, or relative contraindication, because of perceived postoperative complications, decreased 1-year survival, and concern for sensitization from increased blood transfusion requirements.[2,5,6] We focus on this controversy specifically related to lung transplantation in children.

Lung transplantation in children with end-stage or progressive lung or pulmonary vascular disease is always a delicate decision regarding risk of ongoing disease versus benefit of lung transplant.[7] While the progressive disease is a risky downward spiral, a lung transplant can provide greatly improved lung function at the price of a lifelong struggle with immunosuppression, rejection, and risk of infection. In adults, the most frequent primary indication for lung transplantation is chronic obstructive lung disease, followed by interstitial lung disease and cystic fibrosis. In children, the indications vary by age.[8] Pulmonary hypertension from any etiology is the commonest indication for lung transplant in children aged 1–5 years. Surfactant disorders represent the second commonest indication for transplantation in this age group. In older children and adolescents, end-stage lung disease secondary to cystic fibrosis is the commonest indication[9] (see Figure 26.5).

Referral for lung transplant is based on matching predictions of mortality with the anticipated waiting time for donor lungs. Before committing a child to transplantation, most pediatric centers carefully consider multiple additional factors, including trajectory of the underlying disease process, growth, nutritional status, frequency of hospitalizations, and psychosocial factors, including patient compliance and potential for improvement in overall quality of life.[10] The predicted life expectancy without lung transplantation should be balanced with the expected posttransplant survival, taking into account the potential time on the waiting list.[8]

Contraindications to pediatric lung transplant are driven primarily by conditions and circumstances that have historically been shown to demonstrate poor posttransplant outcomes. Absolute contraindications include multisystem organ failure, active malignancy, and chronic systemic infections such as HIV or tuberculosis.[8] Hepatitis C is no longer considered a systemic infection that would constitute an absolute

Diagnosis	<1		1-5		6-10		11-17	
Cystic Fibrosis	0		4	3.4%	116	48.1%	823	65.4%
Non CF-bronchiectasis	0		0		2	0.8%	25	2.0%
ILD	5	8.1%	6	5.2%	5	2.1%	39	3.1%
ILD Other Specify Cause	6	9.7	10	8.6%	21	8.7%	51	4.1%
IPAH	7	11.3%	31	26.7%	24	10.0%	112	8.9%
PH-not IPAH	16	25.8%	25	21.6%	7	2.9%	27	2.7%
Obiliterative Bronchiolitis (non-Retransplant)	0		10	8.6%	32	13.3%	60	4.8%
ABCA3 Transporter Multation	6	9.7%	6	5.2%	2	0.8%	1	0.1%
Bronchopulmonary Dysplasia	3	4.8%	4	3.4%	3	1.2%	3	0.2%
Surfactant Protein B Deficiency	14	22.6%	4	3.4%	3	1.2%	0	
Surfactant Protein C Deficiency	0		1	0.9%	0		2	0.2%
Retransplant (Obiliterative Bronchiolitis)	0		4	3.4%	7	2.9%	35	2.8%
Retransplant (not Obliterative Bronchiolitis)	0		5	4.3%	7	2.9%	43	3.4%
COPD, with or without A1ATD	2	3.2%	1	0.9%	3	1.2%	11	0.9%
Other	3	4.8%	5	4.3%	11	4.6%	26	2.1%

Figure 26.5 Number of lung transplants performed by age distribution in ISHLT registry.
Used with permission from ISHLT.

contraindication to lung transplantation.[11,12] Concomitant liver, renal, or heart failure are also absolute contraindications to bilateral lung transplantation. Patients with cystic fibrosis colonized by *Burkholderia cenocepacia* complex and related organisms are considered to have relative contraindications to transplantation.[13,14]

Patients can suffer sudden decompensation and develop acute decompensation on chronic respiratory failure, necessitating hospital admission and escalation of therapies. Strategies including noninvasive ventilation, intubation with mechanical ventilation, inhaled NO, paralytics, and prone positioning are often employed prior to ECMO. However, any patient with refractory hypoxemia or hypercapnia, despite maximal medical therapy and ventilator support, is a potential candidate for ECMO.[15] Likewise, patients who have previously been listed for lung transplant but develop an acute reversible process can be successfully bridged to transplant. In general, the indication for ECMO is determined by the patient's candidacy for transplantation. If the patient is not a candidate and has an irreversible process, ECMO is not indicated. If the patient is already on the wait list but has other irreversible end-organ damage, sepsis, or a contraindication to anticoagulation, then ECMO should be avoided.[15]

Much of the earliest use of ECMO as a bridge to lung transplantation was in adult patients with primary graft dysfunction (PGD) requiring retransplantation.[16] Over the last decade, improving outcomes have led to the use of ECMO bridging to primary transplantation, especially in adults.[16–19] Clinicians are encouraged to only bridge patients with a potential for good outcome in order to minimize the likelihood of unfairly disadvantaging other patients on the lung transplant waiting list.[20] Urgent exacerbation of lung failure is most likely to develop in patients with idiopathic pulmonary fibrosis or cystic fibrosis, but exacerbations can also develop in patients with pulmonary hypertension, bronchiolitis obliterans, or autoimmune diseases.[15] Anecdotal success has been reported in bridging previously healthy young patients to transplant when they suffer acute irreversible lung damage, such as from smoke inhalation, vaping, or aspiration of toxic chemicals.[21,22]

Kirshbom published one of the first retrospective case series regarding perioperative ECMO utilization in pediatric thoracic organ transplant in 2002.[23] A total of 65 patients under the age of 18 underwent perioperative ECMO for transplantation. Forty-five of the patients were supported with ECMO prior to transplant (31 heart, 8 lung, and 6 heart-lung), while 20 patients required ECMO support after transplantation.[23] Only 1 patient (7%) survived long enough to receive a simultaneous heart and lung transplant, while other lung transplant candidates were either withdrawn from the transplant list secondary to complications (12 patients) or had recovery of function (1 patient). Of the 8 patients requiring ECMO support after lung or heart-lung transplantation, 3 of 3 patients survived until discharge in the early post-transplant group, and 2 of 5 patients (40%) survived in the late posttransplant group. Shortly after this study was published, the lung allocation system (LAS) was implemented, and the number of patients receiving transplants increased.[23]

The LAS was implemented approximately 3 years after the review by Kirshbom for lung transplant candidates greater than or equal to 12 years of age.[23] The purpose was to shift lung allocation from a system based on accumulation of time to a system based on medical urgency. The LAS is not considered valid for candidates less than 12 years of age because of differences in diagnoses leading to inconsistent measures of medical urgency.[24] Key changes for children less than 12 years of age since LAS inception include broader geographic sharing and prioritized allocation of child donor lungs to child candidates, creation of a two-tier priority system based on medical urgency, and approval of an adolescent to participate in the LAS under special circumstances.[24–27]

Since the creation of the LAS in 2005, followed by the two-tier medical urgency priority system in 2010, many have reported their center's experience. In 2010, Puri et al. reported 344 pediatric patients undergoing lung transplantation from 1990 to 2008.[2] This study included patients both before and after implementation of the LAS. Fifteen patients (4.3%) required pretransplant ECMO support, and six (40% of the pretransplant ECMO group) were successfully weaned before transplantation.[2] Survival until discharge was higher in those weaned from ECMO before lung transplant (four of six, 66% vs. two of nine, 22%). Twenty-two patients also underwent postoperative ECMO, and five (23%) survived until discharge.[2] During the time frame that the study was performed, approximately 93 pediatric lung transplants and 8 heart-lung transplants were performed annually worldwide[28,29] (Figure 26.6). Survival after lung transplant was similar between children and adult recipients, with a 1-year survival of 83% and 4-year survival of 50%.[28,29]

A large retrospective study of 715 adult lung transplants was performed between May 2005 and September 2011. Of 31 patients receiving ECMO before transplant, 24 were eventually transplanted (3.3% of total transplants), with 83% of the pretransplant cohort surviving until discharge (30). Of the 31 patients placed on ECMO, 7 were deemed too sick for transplant and did not undergo transplantation. Of the remaining 24, there were 15 V-V and 9 veno-arterial (V-A) ECMOs who proceeded to transplantation. Postoperative ECMO support was used due to PGD in 54% of patients in the pretransplant ECMO group. Twenty patients (20/24, 83%) in the pretransplant ECMO group were discharged from the hospital, and 649 patients (91%) in the control group were discharged from the hospital. The actuarial survivals after lung transplantation at 12 and 24 months were 74% and 74%, respectively, in the pretransplant ECMO group and 83% and 74%, respectively, in the control group ($P = .787$).[30]

In 2015, Hayes et al. reported a query of the United Network for Organ Sharing (UNOS) database from 2000 to 2013 for pediatric lung transplant recipients less than 18 years of age.[31] Of the 587 pediatric patients who underwent lung transplantation in the United States, 24 patients were on ECMO at the time of transplantation, and 17 of those patients were transplanted after year 2000. No survival difference was seen between ECMO and non-ECMO patients with both univariate and multivariate Cox survival analysis.[31] In this retrospective review, only 2/17 appear to have survived

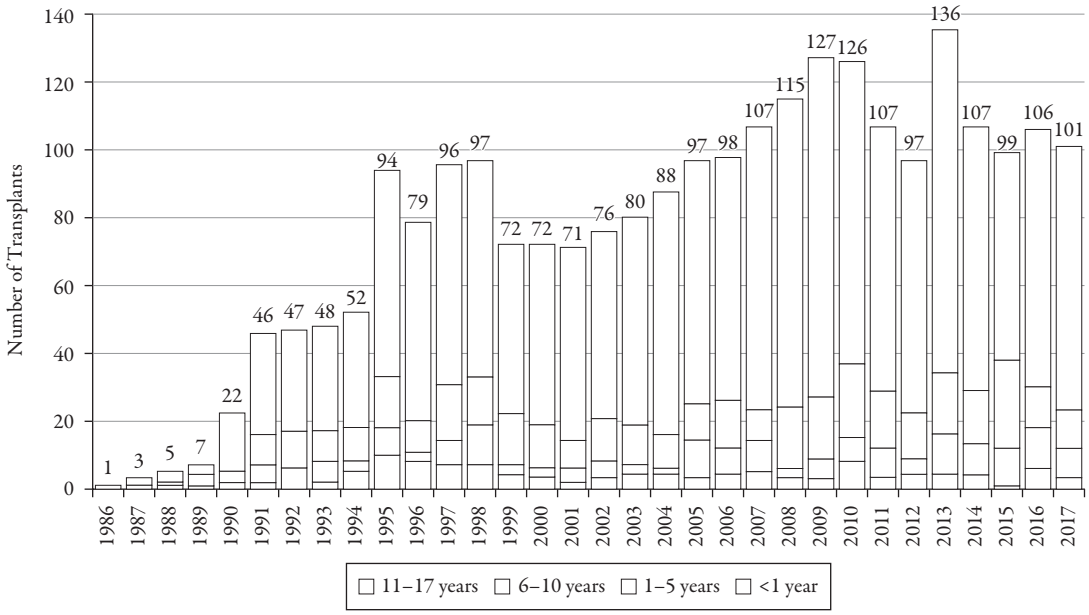


Figure 26.6 Diagnosis by age group.
Used with permission from ISHLT.

beyond 2 years. Propensity score-matching analysis, however, failed to demonstrate a significantly increased hazard ratio. In contrast, that same year, a questionnaire-based, international, multicenter review of 26 pediatric patients on pretransplant ECMO demonstrated approximately 85% of children on ECMO survived until transplant (median duration of 12 days), with an 86% 30-day survival.[32]

Utilization of ECMO for lung transplantation presents a complex set of management decisions, including volume shifts, impacts on lung water and compliance, extracorporeal circuit selection, staff availability, and challenges with conversion to CPB if necessary.[33] Compared to adult patients, children present with exaggerated challenges due to varying small size. The objective of any cannulation strategy is to provide cardiopulmonary support, facilitate early ambulation (if possible), while minimizing potential complications.

In cases of isolated respiratory failure, a V-V configuration utilizing a dual-lumen cannula (DLC) with internal jugular vein access is preferred to facilitate the possibility of ambulation and decrease recirculation.[34] With this configuration, some centers elect to perform early tracheostomy shortly after cannulation with the goal of quickly weaning the patient from pharmacological sedation and ventilation.[35] The Avalon cannula (Maquet) has been the mainstay of the efforts toward dual-cannula catheterization usage; however, its use has been limited in the pediatric population due to limited choices in cannula sizes.[36] Recently, the Crescent cannula (Medtronic, Minneapolis, MN) has become available. Both DLCs are position dependent to allow drainage from the superior vena cava and inferior vena cava, while reinfusing oxygenated blood toward the tricuspid valve. Both require image guidance for insertion and positioning. Another option is two cannulae, V-V ECMO to access the inferior vena cava (via the femoral vein) as well as the superior vena cava via internal jugular vein access. Two-cannula access does not require image guidance and is best for urgent or emergency cannulation. In patients with predominantly hypercapnic respiratory failure, lower ECMO flow rates may be effective, and hence a small-caliber DLC or peripheral cannula can be utilized.[34,37,38]

In patients with preexisting pulmonary hypertension and/or heart failure, V-V ECMO alone cannot assist low right or left cardiac output. In these cases, either peripheral V-A ECMO or central V-A ECMO may be considered.[34,39] In adult patients bridged with V-A versus V-V ECMO, neither technique has shown superiority.[2,20,40] For children requiring ECMO support, V-A configurations have traditionally dominated due to concerns about hemodynamic instability; however, small series supported the use of V-V configurations in the appropriate clinical setting.[2]

Central V-A ECMO is increasingly utilized for lung transplantation, including children. If hilar exposure is difficult, and the heart needs to be decompressed, then bicaval CPB is preferred. V-A ECMO has the added advantages of less coagulopathy and less PGD when compared to CPB.[41] CPB, however, is used more frequently due to size constraints and unavailable double-lumen endotracheal tubes in small sizes.[7,10,28,36] The majority of centers perform bilateral sequential lung transplants with the use of bilateral anterior thoracotomy with transsternal "clamshell-type" incisions through the fourth or fifth intercostal space.[7,10,28] Some centers perform sequential transplantation through a median sternotomy approach in pediatric patients in an attempt to minimize patient morbidity.[36] The donor bronchus is trimmed to within the first or second cartilaginous rings from the secondary carina and subsequently sewn in an end-to-end fashion utilizing continuous PDS for the membranous bronchial layer and interrupted sutures for the cartilaginous layer.[42] Absorbable suture is used to avoid hindrance to growth or granulomas

from nonabsorbable sutures. By contrast, polypropylene is generously used in adults for long-term strength. Telescoping the bronchial-to-bronchial anastomosis (recommended in the past for some adults) is avoided in order to reduce the likelihood of stenosis.[10] Some centers elect to cover the anastomosis with pericardial or peribronchial lymphatic tissue from either the donor or recipient in order to decrease the incidence of dehiscence.[10,43,44] Next, an end-to-end anastomosis of the donor to the recipient main pulmonary artery is completed, followed by the atrial anastomosis from the cuff of the donor atrium to the cuff of the recipient pulmonary veins with running polypropylene suture. The transplanted lung is then reinflated at room air fraction of inspired oxygen (FiO_2) with inflation pressures up to 30 cm H_2O, then ventilated with a tidal volume of 6–8 mL/kg.

En bloc double-lung transplantation is occasionally performed to overcome central airway and pulmonary artery abnormalities or anticipated difficulties with bronchial anastomotic healing and stenosis, especially for retransplant cases.[45] Many prefer sequential bilateral implantation due to the belief that donor collateral bronchial blood supply is improved with the sequential technique as was demonstrated in a small case series.[45] Some centers also utilize this technique preferentially for infant recipients due to purported advantages of a larger airway anastomosis (see discussion below).[46] Alternative surgical techniques include bronchial artery revascularization performed in either bilateral sequential or en bloc configuration with tracheal anastomosis. Airway ischemia and subsequent dehiscence is theoretically reduced due to the increased dual blood supply.[36] Guzman-Pruneda et al. reported evidence of fewer airway ischemic findings on routine bronchoscopy and a trend toward lower prevalence of bronchiolitis obliterans.[46]

When using ECMO during lung transplantation, conventional polymethyl pentene oxygenator membranes are impermeable to volatile anesthetics, so the oxygenator should be changed to a microporous membrane before surgery in order to use volatile gases for anesthesia.[33] One potential way to convert to CPB is to cannulate the aorta centrally and use the V-V limbs of the ECMO circuit with a Y connector for bicaval venous drainage. This obviates the need for separate venous cannulation. After the transplant has been completed, should the need arise, the option of leaving the patient on V-V ECMO can still be utilized.

Unlike adult patients with concomitant coronary or valvular heart disease, pediatric patients undergoing lung transplantation generally have normal hearts. Manipulation of the pediatric heart during the transplant is generally well tolerated. Smaller size chest tubes are generally used; we prefer Blake® silastic drains (Ethicon/Johnson & Johnson, Somerville NJ). These drains tend to remain from a few days to weeks depending on the drainage. We recommend less than 100 mL/24-h period for two consecutive days before removing drains.

No specific guidelines regarding size matching in pediatric patients currently exist, but centers generally consider a range of ±15% in height to be an acceptable size match.[36] Other measures are based on the ratio of donor to recipient total lung capacity (TLC). Adult data ISHLT donor acceptability guidelines suggest an acceptable donor size match of 75-125% of recipient TLC.[36,47] Current evidence demonstrates that transplanting undersized lungs carries increased risk for both early and late complications such as persistent pneumothorax, lung hyper-expansion, pulmonary hypertension, and or bronchiolitis obliterans syndrome.[48–51] Similarly, oversized grafts lead to atelectasis and bronchial distortion, which increases the risk of infection due to impaired airway clearance.[51,52]

Due to the ongoing shortage of suitable donor lungs, there has been debate regarding downsizing adult cadaveric donor lungs for pediatric patients.[48] In recent reports, perioperative and long-term outcomes are comparable to "full size" lung transplantation. Recommended techniques include stapled wedge resection for donor to recipient TLC ratio < 15%, back-table anatomic lobar resection greater than 15%, or bilateral lobar transplantation.[36,48,51,53] Increased procedural complexity and potential for complications highlight the importance of minimizing size mismatch for younger and smaller recipients.[36] To date, application of these techniques to smaller-sized children and infants remains undetermined.[36]

Another strategy to deal with the shortage of suitable donor lungs for pediatric candidates is by providing reduced sized allografts through the use of living-donor lobar resections.[36] In standard living donor lobar lung transplantation (LDLLT), right and left lower lobes are removed from two healthy donors and implanted into a recipient.[54] While the number of living donor lung transplants has declined in the US due to changes in the LAS, its use has continued in Japan.[54] In Japan, donor pulmonary function and anatomical size matching (through the use of three-dimensional tomography) is frequently utilized to ensure appropriate size match.[54]

The Novalung Interventional Lung Assist device (iLA; Novalung GmbH, Hechingen, Germany) is a pumpless V-V membrane ventilator designed as an efficient remover of carbon dioxide.[36] The device has previously been used in a child as young as two years of age.[55] A similar configuration using the Quadrox iD membrane oxygenator (Maquet) has also been used successfully as a bridge to transplant.[56] Disadvantages include continuous anticoagulation requirements normally required with ECMO and only partial gas exchange with no cardiac support.[36]

Additional areas of future study also include incorporation of ex vivo lung perfusion. This technology potentially enables the utilization of geographically remote donors for use in the pediatric population and simultaneously may reduce ischemia time. Currently, the technology is being employed in the adult population in Toronto and across multiple centers in the United States. While there is great potential for use in the pediatric population, data regarding its application have yet to be generated.[57]

Donation after circulatory death (DCD) is another category of nontraditional organ donation now under study to potentially increase the number of lungs available for transplantation.[36] Recently, a retrospective review of nine successful controlled DCD lung transplants in Melbourne, Australia, was published.[58] In brief, the authors described donor reintubation after 5 minutes of standoff time following cessation of circulation. Rapid sternotomy and pulmonary arterial cannulation were then performed for lung preservation infusion.

Postmortem donor ventilation was not initiated until 15 minutes after asystole in order to avoid cardiac reanimation. Lungs were implanted in the usual fashion. Two of the nine patients required pre–lung transplant ECMO, while post–lung transplant V-V ECMO was utilized in one patient. They found no statistical difference in 5-year mortality between DCD and brain dead cohorts.[58] Extrapolation of these data suggests that there is potential to increase availability of donor lungs.[59]

CONCLUSION

- The number of lung transplantations performed annually in the pediatric population was relatively flat over the previous three decades (Figure 26.5). ECMO is used only infrequently to bridge children to lung transplantation and has not shared in the growth of ECMO as a bridge to lung transplantation seen in the adult population.[60] ECMO utilization, as a bridge to transplant, perioperative support, or graft recovery, has mostly occurred over the last decade in the adult population. To date, utilization of ECMO for pediatric lung transplantation is limited, yet promising.
- The majority of pediatric patients undergo bilateral sequential lung transplantation via clamshell incision on CPB. Some centers are altering the way they perform the transplant and utilize central V-A ECMO and bilateral thoracotomy, thus avoiding the sternal division. V-A ECMO usage has less anticoagulation requirement, decreased utilization of blood products, and lower incidence of PGD.
- There are emerging technologies, including paracorporeal oxygenation, which still requires anticoagulation. As cohorts of pediatric patients emerge that were bridged to transplant, supported during transplant, or supported during recovery or graft failure, the analysis of these data subsets will allow better understanding and application of ECMO in this challenging clinical environment.

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REVIEW QUESTIONS

1. What is the commonest indication for lung transplant for adolescent children?

A. Surfactant deficiency
B. Pulmonary hypertension
C. Interstitial lung disease
D. Cystic fibrosis
E. Chronic obstructive pulmonary disease (COPD)

2. Which of these conditions is an absolute contraindication to lung transplantation?

A. Hepatitis C
B. Colonization with *B. cenocepacia*
C. Tuberculosis
D. Vaping
E. Aspiration of toxic chemicals

3. Bronchial anastomosis in pediatric lung transplantation is most commonly performed using

A. Telescoping anastomosis
B. Intussucepting anastomosis
C. End-to-end anastomosis with continuous PDS on the cartilaginous airway
D. End-to-end anastomosis with interrupted prolene on the cartilaginous airway
E. End-to-end anastomosis with continuous PDS for the membranous and interrupted PDS for the cartilaginous airway

4. Pediatric patients are commonly transplanted with the use of CPB because of which of the following?

A. Size constraints associated with double-lumen endotracheal tubes
B. Difficulty finding appropriate ECMO cannula sizes
C. To prevent clotting associated with arterial anastomosis
D. Due to difficulty associated with manipulating pediatric hearts
E. Because anticoagulation can be stopped with protamine

5. Which cannulation strategy enables "awake ECMO with ambulation"?

A. Central V-A ECMO with right atrial and aortic cannulation
B. Peripheral V-V ECMO via right internal jugular double-lumen cannula (Avalon dual lumen)
C. Peripheral V-V ECMO with bifemoral cannulation
D. Peripheral V-A ECMO with bifemoral cannulation
E. Left atrial-VA ECMO employed with drainage through the trans-atrial septum

6. Which cannulation strategy should be employed for patients with pulmonary hypertension or heart failure as a bridge to transplant?

A. Peripheral V-V ECMO via right internal jugular double-lumen cannula
B. Peripheral V-V ECMO via bifemoral cannulation
C. Central V-A ECMO via right atrial and aortic cannulation
D. Peripheral V-A ECMO including subclavian artery and internal jugular vein
E. Either/or question 6 answers C and D

ANSWERS

1. D
2. C
3. E
4. A
5. B
6. E

27.

WEANING AND DECANNULATION OF NEONATAL AND PEDIATRIC RESPIRATORY ECMO SUPPORT

Malaika Mendonca, Mark G. Davidson, and Peter P. Roeleveld

STEM CASE AND KEY QUESTIONS

A 7-month-old boy who was born prematurely at 30 weeks' gestation and now weighs 6 kg presented to the local pediatric hospital with increased respiratory effort. He was diagnosed with respiratory syncytial virus (RSV) bronchiolitis. Medical support escalated from nasal cannula oxygen to high-flow oxygen therapy to nasal continuous positive airway pressure (CPAP) before requiring intubation and mechanical ventilation on day 5 of the hospital admission. His clinical status further deteriorated despite appropriate sedation, muscle paralysis, proning, a trial of high-frequency oscillation ventilation, and inhaled nitric oxide. Clinical and echocardiographic assessment of the patient showed no structural heart disease or pulmonary hypertension. Inhaled nitric oxide had no clinical or echocardiographic impact. The patient was treated with empiric antibiotics as per local guidelines for community-acquired pneumonia. However, because of ongoing severe hypoxemia, hypercarbia, and acidosis, on day 6 the regional pediatric extracorporeal membrane oxygenation (ECMO) center was contacted to consider the role of ECMO. The patient was transferred on conventional ventilation to the ECMO center. On arrival at the ECMO center, ventilator settings were a rate of 45 breaths per minute (breaths/min), a peak inspiratory pressure (PIP) of 38 cm H_2O, a positive end-expiratory pressure (PEEP) of 15 cm H_2O and fraction of inspired oxygen (FiO_2) of 1.0 with oxygen saturation by pulse oximetry (SpO_2) of 78%. One hour after arrival, the patient was cannulated onto veno-venous (V-V) ECMO via the right internal jugular vein using a 15 French (15F) double-lumen Avalon cannula.

ECMO Day 1: Once supported on ECMO, SpO2 was 80%–85%, and the inhaled nitric oxide and epinephrine was quickly weaned off and muscle paralysis ceased. Enteral nutrition was commenced, and sedation was weaned with a focus on maintaining day and night circadian rhythm. Modest ventilation or "rest settings" (e.g., 10 breaths/min, PIP 20 cm H_2O, PEEP 10 cm H_2O, FiO_2 0.3) were employed to reduce secondary lung injury, and a diagnostic bronchoscopy with bronchoalveolar lavage (BAL) was undertaken to exclude an underlying airway abnormality and a secondary infection.

ECMO Day 2: The patient's arterial oxygen saturation level gradually dropped to around 65%, despite similar ECMO blood flow, sweep gas flow, and oxygen delivery to the membrane lung. During assessment of the circuit, it was noted that the ECMO circuit venous saturation had increased significantly to 90%. Chest x-ray and echocardiography confirmed the bicaval cannula tip had migrated further down into the inferior vena cava. After repositioning of the cannula under echocardiography guidance, the patient's saturations returned to the mid-80s.

ECMO Day 3: With no rapid improvement in lung function, gentle chest physiotherapy and proning were implemented. Antibiotics were stopped once the negative microbiology screen was confirmed on day 3 of the ECMO run. Anticoagulation was unremarkable to manage. Renal function was acceptable, and fluid balance was maintained on low-dose intravenous diuretics.

ECMO Day 7: The pediatric intensive care (PIC) fellow assessed the patient's chest x-ray overnight, which showed no aeration. This concerned him, and he subsequently attempted to assess lung compliance and recruit the lungs with Ayers T-piece and manual inflation. Ventilation pressures were then increased significantly to a PIP of 34 cm H_2O and a PEEP of 10 cm H_2O with a rate of 28 breaths/min. Four hours later the bed-side specialist alerted the PIC fellow the patient had become hemodynamically unstable, the oxygen saturation was lower again, the blood flow had dropped, and the right chest was not moving as well as previously. A chest x-ray was undertaken, which showed a large right-sided pneumothorax and the endotracheal tube (ETT) misplaced in the right mainstem bronchus. On review by the duty pediatric intensivist, a chest tube was placed with a Seldinger technique and connected to suction of -10 mm Hg with intermittent bubbling, the ETT was repositioned and the ventilator settings returned to 10 breaths/min, PIP 20 cm H_2O, and PEEP 10 cm H_2O. The chest x-ray afterward showed resolution of the pneumothorax and a well-positioned ETT.

ECMO Day 9: Tidal volumes on the rest setting had slowly improved over the last 2 days and were now between 5 and 6 mL/kg, and the chest x-ray showed some aeration of both lungs. During the day, the ventilator settings were mildly increased to a rate of 25 breaths/min with a PIP of 24 cm H_2O, PEEP of 10 cm H_2O, and an FiO_2 of 0.5. This led to tidal volumes of 8 mL/kg, and more active physiotherapy was instituted.

ECMO Day 10: Because of further improvement of tidal volumes and oxygen saturation, a weaning trial was commenced. Ventilator settings were adjusted to 30 breaths/min with a PIP of 24 cm H_2O, PEEP of 8 cm H_2O, and an FiO_2 of 0.6. The sweep flow on the ECMO membrane was weaned at 2:00 PM over the course of 4 hours and stopped; the gas line was then disconnected. There were no adjustments made to the blood flow. The child remained stable for 4 hours before ECMO sweep flow was recommenced and ventilation weaned to a PIP of 20, PEEP of 8, and 20 breaths/min as it was 9:00 PM, and the patient was supported on ECMO overnight. The members of the duty surgical team were contacted to coordinate the decannulation for the following morning.

ECMO Day 11: In the morning of day 11, the ECMO sweep flow was once again weaned to off, ventilation was increased as guided by arterial blood gases and end-tidal carbon dioxide levels, and the child was decannulated by noon. The patient was decannulated by simply removing the Avalon cannula in head-down position and compression of the insertion point. Heparin infusion was stopped at the moment of decannulation.

Day 14 Post–ECMO Initiation: Mechanical ventilation was gradually weaned, and the child was extubated onto high-flow oxygen support.

WHY WAS THIS CHILD CANNULATED ON V-V ECMO AND NOT V-A ECMO?

Support with ECMO for respiratory failure has been possible using either the V- V or V- A routes. The V-V ECMO cannulation route offers multiple benefits to the patient compared to veno-arterial (V-A) ECMO, where often the right carotid artery is used, impacting cerebral blood flow, increasing risk of systemic microemboli during the ECMO run, and may need to be ligated or removed with vascular repair after the procedure.[1,2]

V-V ECMO can be undertaken by either a single dual-lumen cannula or two-cannula, dual-site technique. The dual-lumen cannulae have been used extensively and gained popularity due to the need for only one surgical procedure; however the cannula has to sit in either the right atrium or a bicaval position, with drainage ports siting in the inferior and superior venae cavae with the return ports sitting in the right atrium. The latter can be challenging to achieve in patients with a low body weight. Furthermore, these cannulae can also have issues of obstruction to drainage flow due to the negative pressures that are created by the commonly used centrifugal pumps. Some centers internationally have moved away from the dual-lumen cannulation approach due to issues of atrial perforation.[3] Alternatively, the two-cannula, dual-site technique has been successfully used in patients with a low body weight and involves siting a drainage cannula in the right internal jugular, tip in the right atrium and a return cannula in the femoral vein.[4]

Most commonly, V-A ECMO is used in cardiac surgical patients but can also be used to support patients with respiratory failure. The skills of the team who site the ECMO cannulae may be a determining factor to use V-A ECMO instead of V-V-ECMO.

For V-V ECMO, cannulae may be sited by Seldinger or open techniques. Guidance of V-V ECMO cannulation is just as essential as in V-A ECMO cannulation to ensure appropriate positioning of the tip of the venous cannula, whether it be a dual-lumen cannula, which may be required to sit in either the right atrial cavity or a bicaval position or a two-cannula technique whereby the return cannula should sit either in or just above the right atrium. In pediatric patients, this guidance is most commonly undertaken by transthoracic echocardiography, whereas in adults it is also often done with fluoroscopy. Pediatric V-V ECMO cannulation is most commonly undertaken by either cardiac or noncardiac surgical teams; however, some centers do have intensivists skilled in this area.

ONCE ON ECMO, WHAT ARE THE OPTIONS FOR LUNG MANAGEMENT?

The generally accepted intention of respiratory ECMO is to rest the lungs and allow them to heal while ECMO provides adequate gas exchange. However, although lung rest is recommended to prevent further lung injury, there is no evidence to support the so-called "rest settings" improve outcomes. It is unknown what the best lung protective strategy actually is, and there is wide practice variation with regard to ventilator settings.[5,6] There are multiple aspects that play an important role in lung-protective ventilation, such as but not limited to ventilator settings, spontaneous breathing, ventilator-induced lung injury (VILI), respiratory muscle weakness, and the underlying lung disease itself.

Once established on ECMO, the neonatal Extracorporeal Life Support Organization (ELSO) guidelines advise slowly weaning ventilator settings to allow the lungs to rest during the acute inflammatory phase of the illness, commonly referred to as rest settings.[7] This reduces the ventilator-related aspects of VILI. Typical rest settings would be a PIP of 15–20 cm H_2O, a PEEP of 5–10 cm H_2O, a respiratory rate of 12–20 breaths/min, an inspiratory time of 0.5–1.0 seconds, and an FiO_2 of 0.21–0.30. This approach typically leads to complete lung collapse and limited native gas exchange.[6] As mentioned, however, there is discussion regarding what the best ventilator setting could or should be. This also depends on the phase of the illness, so let us start with the acute phase of acute respiratory distress syndrome (ARDS) and the early stages of ECMO.

Firstly, PEEP is an integral part of mechanical ventilation and is used in a variety of ways across ECMO centers to protect against lung collapse. In an ELSO study of over 3000 neonates, use of mid- to higher PEEP (7–12 cm H_2O) was associated with shortened duration of ECMO (5–20 hours), but increased duration of mechanical ventilation (20 hours) after decannulation from ECMO compared to lower PEEP strategies. There was no difference in survival.[5]

Secondly, apart from PEEP, PIP and driving pressure also play an important role in ventilator-induced baro- and volutrauma. In adult ECMO patients with ARDS, ultraprotective ventilation (low PEEP, low driving pressure) has been shown to reduce barotrauma.[8] And in an animal model of ARDS and ECMO, reducing ventilator settings to the lowest tolerable

settings (near-apneic ventilation) has been shown to reduce lung injury scores and the fibroproliferative response compared to conventional protective ventilation (6 mL/kg tidal volume) and nonprotective ventilation (10 mL/kg tidal volume).[9] However, in adults and children, mechanical ventilator settings did not impact the prognosis of the patients.[6,10] Furthermore, there may be risks involved in letting the lung collapse completely and fully depend on ECMO, as ECMO flow may be inadvertently interrupted in case of mechanical failure. Lung collapse may increase pulmonary vascular resistance, which may lead to or contribute to right heart failure. In children on V-V ECMO, especially neonates, it may be difficult to achieve adequate ECMO flows to fully support gas exchange, and some degree of mechanical ventilation may be necessary.

Thirdly, generally the FiO_2 is kept as low as possible to decrease one contributor to VILI and to decrease the likelihood of reabsorption atelectasis. Ventilator FiO_2 may contribute to mortality in children on V-V ECMO.[6] However, in some patients with peripheral cannulation (V-A ECMO), it may be necessary to ventilate and oxygenate the lungs to ensure adequate oxygen delivery to the brain.

Fourthly, regarding low respiratory rate, in the acute phase of the illness and ECMO run it is probably better not to promote spontaneous ventilation because vigorous spontaneous breathing could be harmful as it can cause injury to the diaphragm and also lead to large pleural pressure swings.[11,12] A low respiratory rate is often maintained to minimize movement of the lung.[5]

Finally, there is no compelling evidence that specific ventilator modes are superior to others. Controlled modes are most commonly used during the initial phase of disease. Our advice is to ventilate ECMO patients with the same mode and equipment as used in non-ECMO patients. The use of neurally adjusted ventilation has been shown to be safe and feasible in a small case series of six children on V-V ECMO.[13]

Other modalities in lung management during ECMO may include proning as it improves ventilation-perfusion mismatch, improves lung recruitment, reduces lung inhomogeneities without increasing PEEP, and decreases driving pressures.[14,15] Proning is safe in well-sedated patients and can also improve PaO_2 in situations where oxygenation is insufficient and V-V ECMO flow cannot be optimised further.[16,17] Other modalities to clear the lungs from secretions, such as physiotherapy, percussive ventilation, or cough assist, may be beneficial but are not supported with evidence in children at this time.[18] In adult ECMO patients, physical therapy has been shown to be feasible, safe, and potentially beneficial.[19,20] In children with RSV bronchiolitis, the use of antiviral therapy is not routine. There is also no evidence for use of bronchodilators, hypertonic saline nebulization, or corticosteroids in children with bronchiolitis, such as our stem case.[21]

Recruitment maneuvers (RMs) could be a part of lung-protective ventilation, but there is no evidence when or how to perform RM in neonates or children on ECMO. In treatment of adult ARDS, RMs are not routinely recommended.[22] It is probably reasonable to perform RMs after disconnection of ventilator tubing and/or after suctioning to diminish decruitment. Because of the risk of pneumothorax, one should be cautious not to use high pressures and to use the ventilator in order to exactly achieve the desired pressures.

Extubation during ECMO may have important benefits with regard to lung recovery in selected patients who are fully supported with ECMO. Active diaphragmatic contraction reduces atrophy, there can be improvement in ventilation-perfusion mismatch, and there is better lymphatic drainage and a reduced risk of ventilator-associated pneumonia. General benefits include reduced sedation requirements, reduced withdrawal and delirium, and the possibility of interaction with family and caregivers.[23] Awake ECMO in extubated neonates requires significant team preparation and careful consideration of risks versus benefit, but has been safely and effectively used.[24] However, there is risk of cannula dislocation, and some argue that extubation during ECMO should probably be reserved for after the acute phase of lung disease, such as for children awaiting lung transplantation.[12,25,26]

In ECMO patients with acute on chronic respiratory failure or entering the chronic phase of ARDS, ventilator management requires a different approach compared to acute respiratory failure described above. In these patients, it is probably wise to aim for extubation and spontaneous breathing in order to maintain a cough reflex and avoid the negative effects of positive pressure ventilation, such as barotrauma, ventilator dyssynchrony, and muscle weakness.

WHAT IS RECIRCULATION, AND HOW IS IT DEALT WITH?

Recirculation is a phenomenon, exclusive to V-V ECMO, in which reinfused oxygenated blood is withdrawn through the drainage cannula without passing through the systemic circulation (Figure 27.1).[27] Because recirculated blood does not contribute to systemic oxygen delivery, its presence decreases the efficiency with which ECMO provides oxygenation. Whether the amount of recirculation has clinical significance and whether it requires intervention depends on the degree to which the patient is dependent on ECMO for oxygenation.[28]

The percentage of recirculation can be quantified by the following equation:

$$\text{Recirculation (\%)} = (S_{pre}O_2 - SvO_2)/(S_{post}O_2 - SvO_2) \times 100$$

The $S_{pre}O_2$ is the saturation of blood entering the membrane oxygenator, $S_{post}O_2$ is the saturation of blood leaving the oxygenator, and SvO_2 is the saturation of venous blood returning to the vena cava. SvO_2 is difficult to measure and often estimated by measuring venous saturation of blood from the superior or inferior vena cava via a central venous catheter.

WHAT FACTORS AFFECT RECIRCULATION?

Cannula Position

In a double-lumen cannula, recirculation occurs when the position is not correct. For example, the reinfusion jet is situated in either the superior or inferior vena cava, leading to

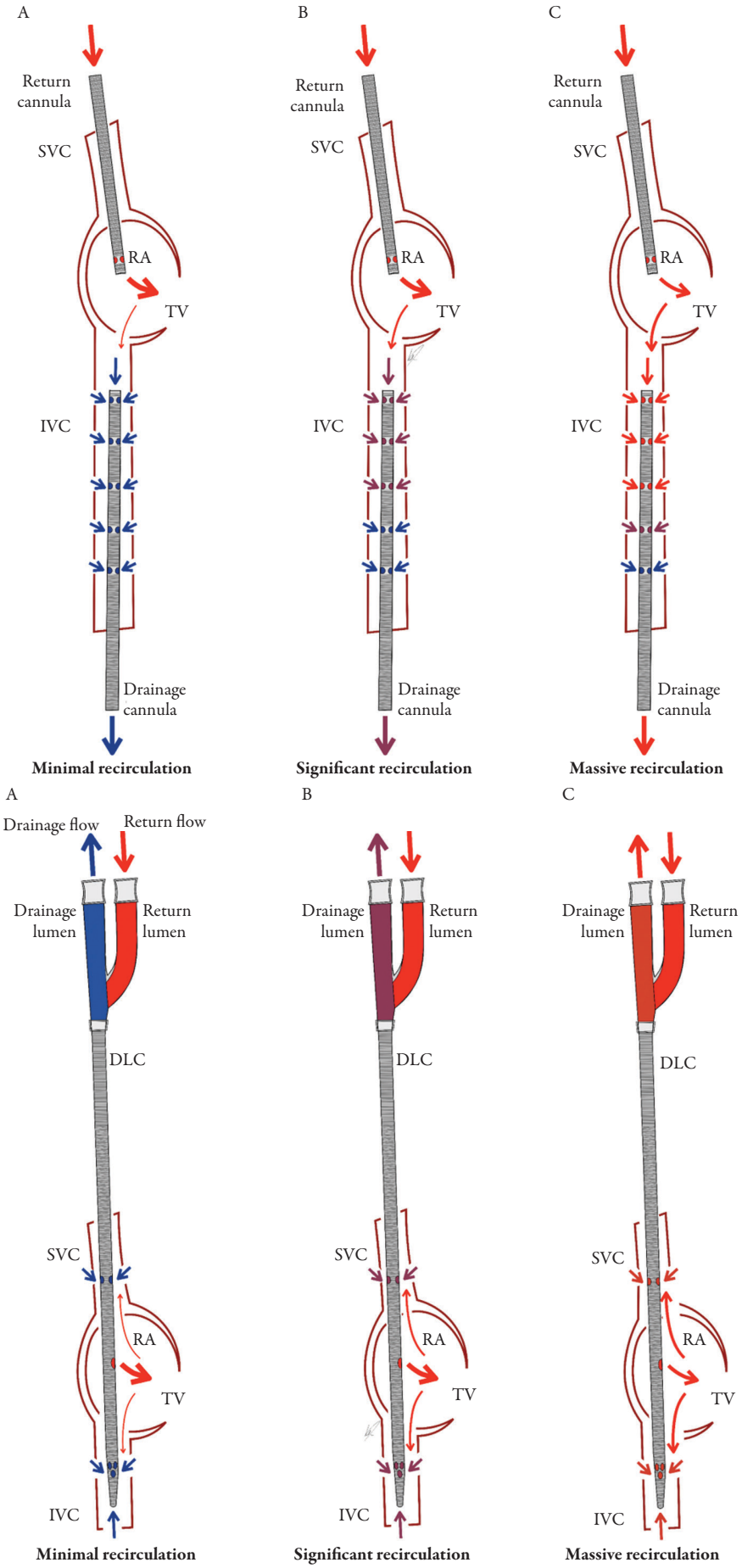


Figure 27.1 Recirculation in a (A) two-cannula approach and (B) a double-lumen cannula (DLC). Recirculation worsens from A to B to C. IVC, inferior vena cava; RA, right atrium; SVC, superior vena cava; TV, tricuspid valve.

Drawings by Marta Velia Antonini.

drainage of oxygenated blood back into the drainage port or one of the drainage ports migrates into the atrium by cannula, thereby draining fully oxygenated or recirculating blood back into the ECMO circuit. The key to this diagnosis is an increase in ECMO venous saturation while the patient saturations stay the same or fall, as seen in our case.

This can occur when the patient's intrathoracic volume reduces. When rest settings are instituted, the cannulae can migrate further down the inferior vena cava, as seen in our case, resulting in recirculation from the inferior drainage port. The cannula should be marginally withdrawn under echocardiographic guidance to resolve the issue. The cannula can also migrate up the superior vena cava, associated with increasing fluid overload and edema of the patient, thereby pulling the cannula in a cephalad direction due to being sutured to the skin at the insertion point, which also results in recirculation via the superior drainage port. The cannula should be marginally advanced to resolve this issue again under echocardiographic guidance.

In two-cannula V-V ECMO with femoral and internal jugular cannulation, the reinfusion jet is directed toward the drainage port (Figure 27.1). When the drainage and reinfusion cannulae are in closer proximity, one can expect more recirculation.

ECMO-Flow

Increasing the RPM (revolutions per minute) and the ECMO blood flow in an atrial cannulation with a dual lumen V-V ECMO cannula also can result in higher recirculation because of the higher amount of blood flow draining into the drainage port.

Changes in Intrathoracic, Intracardiac, and Intra-abdominal Pressures

Increases in intrathoracic and intracardiac pressure (i.e., pneumothorax, pericardial tamponade) will compromise venous return to the heart, which might preferentially direct reinfused extracorporeal blood flow toward the drainage cannula and therefore increasing recirculation. Extreme elevations in these pressures can lead to cessation of extracorporeal blood flow altogether.[29–31] Effects on increased intra-abdominal pressure are less well defined.

Identifying the cause for recirculation is crucial to tackle the problem. X-rays confirm the cannula positions and rule out pneumothorax or hemothorax. Echocardiography often shows the tip of the cannula better than x-rays, especially as not all cannulae are x-ray detectable, and some venous cannulae only have a small radiopaque marker at the end, which can be missed. Echocardiography can be helpful for assessing the flow direction of infusion cannulae, especially in bicaval, double-lumen cannulae to confirm correct positioning in the atrium. A cardiac tamponade can also be seen during the echocardiography.

HOW IS RECIRCULATION MANAGED?

When the underlying cause of recirculation is identified, intervention can then be directed as required.

Cannula Position

In a malrotated double-lumen cannula, an echo-guided attempt to turn the cannula should be performed to redirect the flow toward the tricuspid valve.[32] A deep cannula can be pulled back under guidance as undertaken in the stem case, but a cranially migrated double-lumen cannula (Figure 27.2), which is supposed to be in the IVC, is more challenging. Because of the angled inlet of the IVC into the atrium, the cannula is not likely to move spontaneously back into the IVC, but rather bears the risk of atrial perforation. The cannula will have to be advanced back into the IVC using a guide wire under echocardiographic or fluoroscopic guidance. One must keep in mind the higher risk of a bloodstream infection when pushing back the dislocated cannula from the skin toward the vessel. Before manipulating the cannula, one should consider if the patient might be ready to be separated from ECMO.

Increasing the distance between drainage and reinfusion ports in a double-cannula V-V ECMO configuration, by

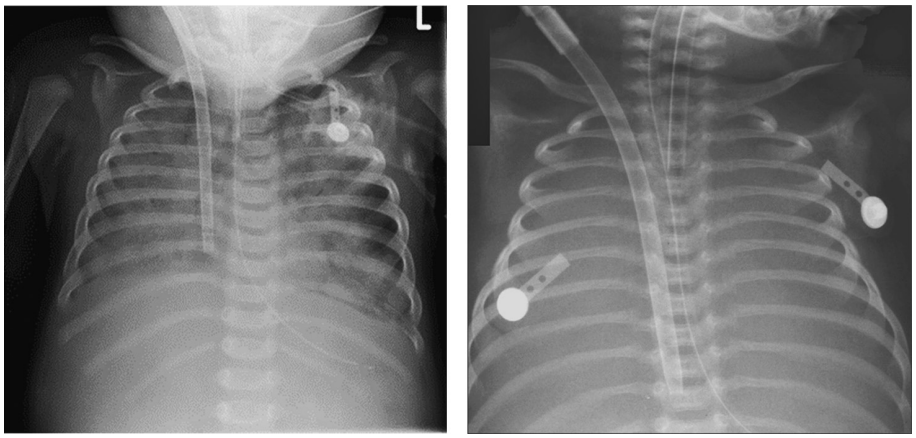


Figure 27.2 Bicaval, dual-lumen cannula position, which is sitting high (i.e., inferior port sited in the right atrium) and after (right) repositioning with tip in the inferior vena cava.

withdrawing one or both cannula(e), is the most direct way to reduce the amount of recirculation. However, there is no standard distance that should be maintained between ports. Chest radiography and ultrasonography should again be used to assess cannula positioning.

Flow

Reducing the flow, if possible, to achieve the desired oxygenation, is the easiest option. If that is not feasible, adding another drainage cannula may be considered in larger patients.

Given the relationship between pump speed, negative venous pressure, and recirculation, an additional drainage cannula may permit comparable blood flow rates to be achieved at lower pump speeds and at less negative pressure, thereby lowering the amount of recirculation.[33]

Changes in Intrathoracic, Intracardiac, and Intra-abdominal Pressures

Pneumothorax, hemothorax, or pericardial effusions must be addressed according to the compromise on the ECMO blood flow (see below for pneumothorax).

HOW CAN WE MONITOR RECOVERY?

As evidenced by data from the ELSO Registry, the length of time neonatal and pediatric V-V ECMO is required varies depending on the underlying respiratory pathology.[34,35] There are multiple ways to assess lung recovery, and as shown in a recent paper summarizing the weaning techniques from major European pediatric ECMO centers, there is little scientific evidence to back a specific method of weaning.[36,37] What is important is to have a consistent local approach that is responsive to the patient's physiological needs.

The resolution of chest x-ray appearances is the most commonly used indicator of lung recovery, along with improvement in lung compliance. The former means of assessment necessitate daily chest x-rays or at the least every second day, with the associated negligible risks of moving the patient on ECMO and exposing them to the minimal radiation. Many centers are reducing the number of chest x-rays on ECMO patients to reduce the burden of the associated risks. When assessing any chest x-ray of a patient on ECMO, it is essential to ensure that endotracheal tube placement is appropriate as well as ensure there is no migration of other aspects, such as chest drains, nasogastric tubes, or central lines. It is essential to ensure there is no pneumothorax or hemothorax on the chest x-ray, which would make any weaning from ECMO challenging and likely to fail.

The improvement in tidal volumes or lung compliance is the key method to guide the timing of a wean from ECMO in tandem with resolution of chest x-ray appearances. This can simply be undertaken by assessing the minute or tidal volume associated with pressure ventilation modes or the associated pressures needed to achieve the desired tidal volumes in a volume ventilation mode. Lung recovery, when it starts to occur, results in improved lung compliance. This may manifest as increasing tidal volumes on the ventilator when supported in a pressure control mode or in reducing PIPs required to deliver the same tidal volume when a volume control mode is utilized. The key is not to push the patient too early and thereby result in a secondary lung injury or VILI. Often, once a tidal volume of at least 3–4 mL/kg is seen on rest settings as previously detailed, then this is taken as the trigger to start to aggressively recruiting the lungs with physiotherapy, bronchoscopy, and increasing PIP and PEEP levels of support.

WHAT IS THE OXYGEN CHALLENGE TEST?

The oxygen challenge test is undertaken by some centers on a daily basis to chart potential lung recovery. This involves increasing the ventilator FiO_2 at 0.1 for at least 5 minutes, while not adjusting the ECMO support, and taking an arterial gas from the patient. The PaO_2 result will increase as lung recovery is seen. This test is confounded by the widespread use of rest settings on the ventilator and has the side effect of exposing the injured lungs to high levels of oxygen, which are known to be harmful. For these reasons, this has led to this guide to weaning not being used routinely.

Some centers have developed weaning algorithms to delineate a clear weaning strategy.[38] However, these are not commonplace, though physiologically exceedingly interesting proposals.

WHAT IS THE BENEFIT OF BRONCHOSCOPY, AND IS IT SAFE?

Bronchoscopy may possibly play a role in lung recruitment and aid in diagnosis of respiratory pathogens, but it is not routinely recommended. Bronchoscopy and BAL have been shown to be safe and of therapeutic benefit in three retrospective case series in children.[39–41] The risk of bleeding is minimal; however, it should be undertaken by an experienced team. It can be done without adjusting anticoagulation therapy. The timing of bronchoscopic intervention depends on the indication. In the case of inhaled foreign objects, mucus plugging in case of asthma, or burn injuries, early bronchoscopy with or without BAL is warranted. But, for children with ARDS, such as our stem case, it is probably wise to wait for some form of lung recovery before actively trying to recruit the lung, although there is no published scientific evidence to support this approach.

One of the advantages of performing bronchoscopy in smaller children while on ECMO is the option to extubate and use the oral route to introduce a bronchoscope with a larger suction channel via rigid bronchoscopy if oxygenation allows.[39] Some clinicians may use bronchoscopy to instill surfactant, but this is also not routinely recommended.[41] Beware of cannula position and impacting ECMO flow if the patient is cannulated in the neck and position of the head is manipulated during bronchoscopy. In conclusion, bronchoscopy is safe and a useful investigation in almost all ECMO patients.

HOW SHOULD WE MANAGE A PNEUMOTHORAX WHILE THE PATIENT IS ON ECMO?

Pneumothorax during V-V ECMO can cause obstruction to blood flow depending on cannula position and size of the pneumo-/hemothorax, as seen in the stem case. First, pressure on the right atrium can decrease its size, making inflow of blood into the ECMO circuit more difficult (leading to increased negative inlet pressure). Second, due to the increased intrathoracic pressure, outflow of oxygen-rich blood into the patient can be diminished (due to higher outlet pressure). And, third, recirculation can increase. Therefore, oxygen delivery to the patient can be in danger if the pneumothorax is large enough and depending on cannula position. Small pneumothoraces can often go clinically unnoticed. If, ECMO flow is impacted because of pneumothorax, two things can be done. Either, one decides to drain the pneumothorax, with the risk of bleeding complications,[42] or one decides to separate the patient from ECMO altogether, which is only possible if the child has sufficiently recovered and if the lung can be ventilated well enough. Bear in mind that it can be necessary to drain the pneumothorax to facilitate weaning from ECMO. Placement of a chest drain should be done by an experienced intensivist or surgeon and support team, prepared to deal with possible bleeding complications. The same approach applies to hemothorax or other pleural effusions.

WHAT IS THE ACTUAL WEANING PROCESS?

When weaning from ECMO, it is important to be clear on the need for a wean of blood flow and sweep gas flow. Routinely in V-A ECMO, both are weaned simultaneously. This is also the practice in weaning V-V ECMO in adult critical care and some pediatric centers. Most pediatric centers, however, do not adjust the blood flow during a wean and merely wean the gas flow to the membrane once ventilation has been optimized. This has the advantage of not necessitating an increase in anticoagulation. During the wean of the gas flow, it is essential to keep a keen eye on the patient's blood gases and end-tidal carbon dioxide and adjust ventilatory support as needed. Once the sweep gas flow is reduced to 0.1 lpm L/min and the sweep gas FiO_2 matches the ventilator settings, the sweep gas pipe may be disconnected from the membrane lung ("capped off"). The patient's lungs are then fully supporting the gas exchange and can be monitored for several hours in this situation.

If the patient does not cope with the planned wean from ECMO, then one needs to reattach the sweep gas to the oxygenator and put the sweep gas and the blender FiO_2 back to levels utilized prior to the wean. It may be necessary, if the patient's $PaCO_2$ does not reduce to previous levels, to "sigh the membrane" at this point. This is undertaken by increasing the sweep gas flow for no more than a minute to clear any moisture from the membrane lung that could have accumulated during the capped-off period. Once the patient is stable and back on V-V ECMO support, then one should reassess all potential reasons for the failure to wean. This may include repeat bronchoscopy, chest x-ray, echocardiography, chest computed tomography (CT), and screening for secondary infections.

If the patient does cope for several hours with the membrane capped off, one could proceed toward a decannulation from ECMO by removing the cannula(e). Many centers will paralyze and sedate patients for the wean from V-V ECMO similar to V-A ECMO weans, though this is less commonly practiced than previously. Prior to the actual decannulation, it is essential to be clear on criteria for a successful or unsuccessful wean in order that the whole team are aware and can reinstate ECMO in a timely fashion if needed.

SHOULD WE WEAN BLOOD FLOW WHEN WEANING ECMO?

The importance of flow in V-V ECMO and its relation to the native cardiac output to facilitate adequate oxygenation is very well described in "Physiology of Gas Exchange During ECMO for Respiratory Failure."[43] During weaning, in the adult population flow on V-V ECMO is often reduced, but it is differently done in many centers (1.5 L/min in Regensburg, Germany; 2.5–3 L/min in San Raffaele, Milan, Italy; and "reduced" in Karolinska, Stockholm).[36] Which flow, PaO_2, or saturations to aim for remains a topic of discussion.[37]

In practice, it makes sense to reduce blood flow to minimize shear stress on the blood components and hemolysis. However, for neonates to achieve a target goal of SpO_2 80%–90% and a PaO_2 40–60 mm Hg, a blood flow around 300 mL/min is required initially.[44] Taking into account the limitations of the currently available ECLS devices, the recommended minimal flow by companies is about 150–200 mL/min depending on the product used, and weaning the flow to the degree it is done in the adult population is not possible. Furthermore, such low flow settings increase the risks of clots in the circuit. Hence, reducing the flow during V-V respiratory ECMO in neonates is not common practice.[44]

For pediatrics, especially bigger children, the same general pathophysiological thoughts and practical approaches as in adults concerning reducing the flow can be applied.

Weaning blood flow during V-A ECMO for respiratory failure is of course necessary to determine readiness for decannulation. V-A ECMO is weaned as described for cardiac reasons and is described elsewhere in this book. It is worth mentioning the 'retrograde trial off' from V-A ECMO for respiratory failure that has been previously described.[45,46] With this method, which only works with centrifugal pumps, the flow probe is reversed and the RPM of the centrifugal pump are reduced until the systemic blood pressure exceeds the pressure generated by the pump. Blood then flows from the arterial cannula through the membrane and the pump, through the venous cannula, back to the patient. At that stage, pulmonary function can be assessed with the cannulae still in place, offering a way back if the lungs have not recovered enough.[46] Clots on the venous site of the oxygenator are well proven, and therefore a concern is that thrombotic material may be flushed into the arterial circulation during this

retrograde weaning trial.[47,48] The retrograde weaning off trial is not common practice.

WHAT IS THE PROCESS FOR DECANNULATION FROM V-V ECMO?

Decannulation is most often done in the intensive care unit and should be carefully planned. Risk factors should be mitigated, and the team should be briefed during a "time-out" procedure. Parents should be made aware of the risks of the procedure and the plan if decannulation should fail. Clotting factors, especially platelet and fibrinogen levels, should be optimized prior to the decannulation whether it is V-V or V-A decannulation.

Decannulation for percutaneous/semiopen V-V ECMO is straightforward, simply requiring the cannula to be withdrawn after discontinuation of ECMO. To avoid air embolism, the patient is put in head-down position, and a brief inspiration hold is applied if still intubated, sedated, and in some centers paralyzed, during the actual removal process. Pressure is applied to the exit side, and many people recommend a single suture to close the skin.[46,49]

Extubation during neonatal/pediatric ECMO runs is still less common than in the adult population, but the question occurs if and how the decannulation process differs when a patient is extubated. A single-center study reported 16 extubated neonatal/pediatric patients (at least for 24 hours) of 511. Of the 16, only 2 had reached decannulation criteria while extubated, and the group opted to secure the airway with laryngeal mask/intubation for the decannulation procedure.[23] For cooperative older patients, the approach from the adults with head down and deep breath holding on command might be an option.

Once decannulation is complete, it is important to assess for the potential development of a hemothorax, both clinically and radiographically. It is also essential to agree on an escalation plan for support in the coming hours among the team at this point, so all are on the same page.

Decannulation in V-A ECMO and the discussion whether to ligate or reconstruct the vessel is described elsewhere.

HOW TO ESTABLISH FUTILITY?

Establishing medical futility can be extremely difficult, especially when the patient is supported by ECMO as medical futility is not readily definable and subject to subjectivity.[50] A full discussion of the ethics involved are beyond the scope of this chapter. Historically, ECMO was considered futile after more than 2–3 weeks of mechanical support in non–lung transplant candidates (e.g., the stem case). However, over the last few years much longer ECMO runs have been published with good outcomes.[51] Complications of ECMO and/or the underlying disease can also contribute to the decision to withdraw ECMO treatment, such as intracerebral hemorrhage, multiorgan failure, and/or hypoxic brain injury.[52] The decision to withdraw ECMO should be made in the same multidisciplinary fashion as for any other child in intensive care, including input from the treating medical and nursing team, the parents, ethicists, and other support staff as needed.

If and when the decision is made to withdraw medical treatment, this does not mean that care is stopped. Providing end-of-life care is an extremely important part of the responsibilities of the medical team, nursing team, and support staff such as social work and spiritual care services. An empathic way of stopping ECMO treatment is first to extubate the child and remove the gastric feeding tube, then place the child in a parent's lap, giving the parents some time with their child while still supported on V-V ECMO. The next step would be to clamp and cut the ECMO cannulae. ECMO cannulae can be removed after the child has passed away so any unnecessary discomfort is not inflicted to the child just before death.

DISCUSSION

Achieving adequate weaning from ECMO depends fully on the recovery of the lungs. If the lungs do not heal, there are only three possibilities. First, one could reassess and give the patient more time on ECMO. Second, the patient is listed for lung transplant, which is available to only a very limited number of children. Or, third, ECMO is withdrawn. Therefore, it is essential that when ECMO is initiated in children with respiratory failure every attempt is made to rest the lungs, prevent secondary injury, and give enough time to heal. The big question remains: What is "enough"?

The ideal rest settings have not been established and remain a topic of discussion and research, but it is probably appropriate to use a medium PEEP (5–8 cm H_2O) and a low driving pressure or PIP with minimal FiO_2, as per the ELSO guidelines, especially in the acute phase of lung disease as described in the stem case.[7,44] In a more chronic phase of ECMO, let us say more than 2 weeks, extubation and spontaneous ventilation may be considered, although some centers have good experience when doing this earlier. Supportive measures such as physiotherapy, bronchoscopy, and prone positioning are a logical approach to actively facilitate lung recovery; however, the timing when best to start with these measures is also unknown, and no evidence exists that these interventions actually improve outcomes. The general approach is to let the lungs collapse and simply wait for tidal volumes to slowly improve. Once tidal volumes of 2–4 mL/kg are achieved on rest settings, a more active approach can be considered.

In our stem case, bronchoscopy was undertaken early for diagnostic purposes. If a lot of secretions had been present, it might have been advantageous to repeat the bronchoscopies every few days, but that was not the case. On day 3, we would usually not expect significant improvement in lung compliance and would choose to facilitate recovery with physiotherapy and prone positioning to recruit the lungs, though some centers might choose a more aggressive approach.

While the child is on ECMO, it is our duty to provide adequate tissue oxygenation and prevent complications. One of those complications is cannula dislocation/migration, which can be caused by movement of the patient during chest radiography, physiotherapy, nursing care, movement of the patient, and/or suture dehiscence. Migration of the cannula tip can also regularly be seen when ventilation is weaned on initiation

of ECMO, resulting in reduced thoracic volume, which in turn may result in the venous cannula moving further down the cava. Movement of the cannula can exacerbate recirculation, which is always present to some degree, to a level where it may cause desaturation, as seen in our stem case. When desaturation does occur, one should consider all possible causes, recirculation being just one of them. Careful repositioning of the cannula(e) when indicated will reduce recirculation and reestablish adequate tissue oxygenation.

Other complications include pneumothorax, as also seen in the described case. The most important lesson on day 7 was actually that it is very important to educate all involved in patient care as much as possible. Clearly, this fellow was not aware of the earlier chest x-rays of the patient and the risks involved with manual recruitment. Despite the best intentions, this RM failed. This is not to say it should never be done, but when it is done it should only be undertaken when there are some signs of recovery (increasing tidal volume) and then with lower peak pressure and by using the ventilator. The chest drain had to be inserted because the blood flow was impacted, and the child was not ready to come off ECMO. Fortunately, no hemothorax occurred when the chest drain was inserted.

For the stem case, a young child with RSV bronchiolitis, we would estimate ECMO would be required anywhere from 7 to 21 days. Fortunately, she recovered relatively quickly between day 7 and day 10 and was decannulated on day 11 of the ECMO run.

CONCLUSIONS

- Establishing the right time to initiate weaning is one of the most difficult aspects of ECMO as there are neither hard criteria nor scientific evidence available to guide us other than all of our collective experiences.
- Over the years, experience has taught us that patience is a virtue, and long V-V ECMO runs can be sustained to good effect.
- Weaning V-V ECMO is relatively easy compared to V-A ECMO, as lung function can be fully assessed while the patient is still cannulated.

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REVIEW QUESTIONS

More than one answer is possible unless otherwise indicated:

1. Which of the following are key exclusion criteria for the appropriateness of ECMO support for respiratory failure (more than one answer possible)?

   A. History of prematurity but no evidence of chronic lung disease
   B. Weight less than 2 kg
   C. Grade 1 intraventricular hemorrhage
   D. Associated liver and renal failure

2. What length of injurious ventilation management as seen on arrival at the ECMO center on day 6 of the patient's illness precludes the use of ECMO support?

   A. 1 day
   B. 5 days
   C. 10 days
   D. 20 days

3. Which of the following are recognized complications of bicaval, dual-lumen cannulation onto V-V ECMO (more than one answer possible)?

   A. Atrial wall perforation
   B. Hemothorax
   C. Intracerebral hemorrhage
   D. Surgical site infection

4. ECMO support for respiratory failure may be provided by the following modes:

   A. Ventricular assist device
   B. Veno-venous, single-cannula, bicaval approach

C. Veno-venous dual-cannula approach
D. Veno-arterial ECMO

5. Once supported on V-V ECMO, the ventilator settings should be

A. Increased to get the patient off ECMO as quickly as possible
B. Changed to CPAP
C. Reduced to a rate of between 12 and 20 breaths/min, a PIP of 15–20 cm H_2O, and a PEEP of 5–10 cm H_2O
D. Weaned rapidly and then the patient should be extubated

6. The following factors can affect "recirculation" in V-V ECMO:

A. Hematocrit levels
B. Low sweep gas flow
C. Cannula position
D. High blood flow

7. Lung recovery can be judged by the following means:

A. Chest CT every 2 days
B. Improved lung compliance
C. Bronchoscopy
D. Chest x-ray changes

8. The oxygen challenge test is

A. Practiced widely as a means of deciding readiness for decannulation
B. Undertaken by weaning the oxygen in the sweep gas flow to 21% to assess readiness for decannulation
C. Describes the increase in PaO_2 when 100% oxygen is given on the ventilator to a patient supported on ECMO
D. Is undertaken by the ECMO physician to see how long the patient can hold his or her breath

9. Which answer(s) are true? More than one answer is possible. Bronchoscopy on an ECMO patient

A. Has a high risk of bleeding complication
B. Has a low yield of positive findings
C. Should only be undertaken by trained and experienced personnel
D. Should be considered in every ECMO patient

10. Pneumothoraces are

A. Rarely seen in patients on ECMO
B. Never impact ECMO support or blood flow
C. Can be drained by a careful ultrasound-guided Seldinger approach
D. Should not be treated until the patient is off ECMO support and heparin is reversed

11. Weaning V-V ECMO (more than one answer possible)

A. Is undertaken by weaning ventilation and sweep gas flow concurrently
B. Necessitates optimization of ventilation prior to initiation
C. Is undertaken by weaning sweep gas flow and blender FiO_2 concurrently
D. Is undertaken by weaning blood flow

12. Decannulation from V-V ECMO (more than one answer possible)

A. Should be undertaken at any time of the day or night
B. Should be undertaken with the patient in the head-down position
C. May simply involve removing the cannula(e) and applying pressure to the cannulation site
D. Should be followed by a chest x-ray to confirm the absence of hemothorax

13. ECMO should cease and care reoriented if

A. ECMO support is needed for more than 14 days.
B. The multidisciplinary team sees no realistic opportunity for lung recovery or progression to lung transplantation.
C. The parents request this to be undertaken.
D. There is evidence of a severe neurological injury.

14. Extubating a patient while on V-V ECMO (more than one answer possible)

A. Is the gold standard in all V-V ECMO cases
B. Should only be undertaken in specific cases and after training of the team to ensure cannula safety at all times
C. May be useful in patients bridging to lung transplantation
D. Precludes decannulating from V-V ECMO

15. Once the patient is decannulated from ECMO (more than one answer possible),

A. They should not be weaned from respiratory support for several days.
B. The patient is not in any danger, and parents can be fully reassured.
C. Ventilation should be weaned as soon as possible and physiologic stability allows.
D. Ongoing neuromuscular and psychological rehabilitation should be a key target.

ANSWERS

1. B and D are true. Key exclusion criteria have reduced in number over recent years with a greater understanding of coagulation and other management strategies. Small size and existing severe multi-system or specific neurological or genetic abnormalities remain key exclusion criteria. All such decisions to not proceed to ECMO support should be taken as part of a multidisciplinary team.

2. D is true. Most centers use the published evidence of 14 days of injurious ventilation as the arbitrary cutoff for appropriate time for ECMO support to be initiated. There is increasing evidence, as in adults, that earlier institution of ECMO results in better results due to a reduction in VILI and secondary complications.

3. A, B, C, and D are true. All of the above are well-recognized complications of cannulation onto V-V ECMO.

4. B, C, and D are true. The method of support is often decided by the clinical skills of the cannulator as well as patient size, underlying pathology, and physiological derangement.

5. C is true. The ventilation settings detailed in C are known as rest settings and are undertaken with the aim of reducing any VILI. CPAP may be of use but only if there is a continuous air leak or severe pulmonary hemorrhage. Extubation has its place in V-V ECMO but tends to be reserved for potential lung transplant patients or in adults. There are only small published case series where this has been undertaken successfully in respiratory ECMO with these settings.

6. C and D are true. Recirculation is indicated by an increase in ECMO venous saturations and should trigger an assessment of cannula position first.

7. A, B, and C are true. Serial chest CT can be used but usually necessitate a patient move to the CT suite unless a portable CT scanner is available, and the CT images are usually not required. Bedside assessment of ventilation parameters and chest x-rays are often enough to guide lung recovery.

8. C is true. This test can be used to assess lung recovery and may be used as part of monitoring lung recovery. Weaning the blender FiO_2 to 21% in V-V ECMO should not be undertaken at any time as it may result in the patient significantly desaturating.

9. C and D are true. Bronchoscopy on ECMO has a high yield of positive findings and is very safe for ECMO patients but should only be undertaken by skilled personnel, and particular care should be taken of the ECMO cannulae and equipment.

10. C is true. It is important to treat any clinically significant pneumothoraces on any patient on ECMO. This is best undertaken by an ultrasound-guided Seldinger technique to minimize bleeding risk, but one must ensure the ability to step in surgically to control bleeding if it occurs secondary to the drain insertion. Clotting factors, especially platelet and fibrinogen function, should be optimized prior to drain insertion.

11. B and C are true. V-V ECMO weaning may be undertaken purely by weaning the sweep gas flow and blender FiO_2 once there is adequate lung recovery. There is no need to wean blood flow, and this means that there is no need to increase anticoagulation at this stage of the ECMO run. This is useful as these ECMO runs may be prolonged and therefore have increased risk of circuit clots.

12. B, C, and D are true. Decannulation from V-V ECMO is an elective procedure and ideally should be undertaken during daylight hours in a planned fashion. There is a very small risk of retrograde air embolization to the brain; hence, this necessitates undertaking it in a head-down fashion. It is important to exclude ongoing bleeding from the insertion site, which may manifest as a hemothorax by undertaking a postdecannulation chest x-ray.

13. B and D are true. Many V-V ECMO runs last significantly longer than 14 days and still have a positive outcome. It is important that the whole team is part of the decision-making process at all steps in an ECMO journey. The family's voices and thoughts are essential as part of this team, but the clinical team's duty is to the patient and to use their clinical judgment to support the family in the decision-making process.

14. B and C are true. Extubating a V-V ECMO case should only be undertaken in specific cases and with wide team training and awareness of the associated risks. It is easier to achieve in older patients and can be especially useful in potential lung transplant candidates given that it reduces the risk of ventilator-associated complications and enables enhanced neuromuscular rehabilitation.

15. C and D are true. It is important to wean the patient from respiratory support as able once decannulated from ECMO to minimize the likelihood of the complications of ongoing intensive care support. Neurorehabilitation and psychological support after ECMO support are a key part of the recovery process that the whole team and family should focus on. The journey does not stop at decannulation from ECMO.

ECMO IN NEONATAL AND PEDIATRIC CARDIAC DISEASE

28.

ECMO IN PEDIATRIC PATIENTS WITH UNIVENTRICULAR PHYSIOLOGY

Lee D. Murphy, David S. Cooper, and Kenneth E. Mah

STEM CASE AND KEY QUESTIONS

A 2.4-kg male was born at 36 weeks' gestation via vaginal delivery with a prenatal diagnosis of hypoplastic left heart syndrome (HLHS). Apgars were 6 and 8. Prenatal echocardiogram at 26 weeks' gestation revealed mitral stenosis and aortic valve atresia with an ascending aorta measuring 1.9 mm. A secundum atrial septal defect was present with left-to-right shunting without obstruction. There was no right ventricular outflow tract obstruction, and the right-sided atrioventricular valve was competent and normally formed. Postnatal echocardiogram later confirmed the prenatal diagnosis. Umbilical artery and vein catheters were placed, and the child was started on prostaglandin E_2 at 0.02 μg/kg/min to maintain ductal patency. The baby was then admitted to the cardiac intensive care unit (CICU). Four days later, the patient's saturations increased into the high 90% range, and the chest radiograph became progressively hazy, suggestive of increasing pulmonary edema and pulmonary overcirculation. The baby was taken to the operating room on day of life 7.

A Norwood procedure was performed, and a 3.5-mm modified Blalock-Taussig (mBT) shunt was placed. Cardiopulmonary bypass (CPB) time was 210 minutes. Cross-clamp time was 166 minutes. There were no rhythm issues during the case. The transesophageal echocardiogram showed an unobstructed atrial septum, trivial tricuspid valve regurgitation, a right ventricle with moderately diminished systolic function, unobstructed flow through the Damus-Kaye-Stansel anastomosis, and a widely patent 3.5-mm mBT shunt.

The patient returned to the CICU with an open sternum on infusions of epinephrine 0.05 μg/kg/min, milrinone 0.5 μg/kg/min, and calcium chloride 10 mg/kg/h. The mediastinal and pleural chest tubes were cumulatively putting out approximately 5 mL/kg every 30 minutes. Over the next 2 hours, packed red blood cells, platelets, cryoprecipitate, and fresh frozen plasma were administered to control the bleeding. Although the postoperative bleeding began to subside, the patient's blood pressure (BP) remained marginal, with systolic BPs in the range of 55–59 mm Hg and diastolic BPs in the range of 24–29 mm Hg, his common atrial pressure was elevated to 18 mm Hg. There was no urine output, his lactate rose to the 14 mmol/L range, and oxygen saturation and arterial partial pressure of oxygen were low.

Vasoactive infusions were escalated to address low cardiac output, without improvement. Given the refractory low cardiac output and the high potential for cardiac arrest, the surgeon was called to place the child on central veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) support.

The surgeon placed a venous cannula in the common atrium and an arterial cannula in the aorta. During the cannulation, the BP continued to drift down, and a 10th of a code dose of epinephrine was given to temporize the hemodynamics. An ECMO circuit with a centrifugal pump was used, and flow was initiated, then maintained at 180 mL/kg/min. Postmembrane pressures were high and consistent with elevated systemic vascular resistance, so the intensivist discontinued the epinephrine and calcium infusions, continued the milrinone infusion, and ordered a sodium nitroprusside infusion. Mean arterial pressures (MAPs) of 40–45 mm Hg were targeted, with ECMO flow also adjusted based on cerebral and somatic near-infrared spectroscopy and normalization of lactate.

Over the next 4 hours, the circuit was running well, lactate trends down, and the patient started to produce urine. Packed red blood cells were transfused to keep the hematocrit greater than 36 mg/dL. The arterial line read only a MAP value but would occasionally read a systolic and diastolic pressure with a very narrow pulse pressure. The next morning, clot started to develop in some of the ECMO circuit tubing connectors and in the venous cannula. A continuous infusion of heparin was started after taking into account clot burden of the circuit, the patient having an open chest, the presence of an mBT shunt, and bleeding from the chest tubes. Two days later, an echocardiogram was obtained showing adequate decompression of the right ventricle, trivial tricuspid valve regurgitation, and an unobstructed atrial communication. Adequate echocardiographic views clearly demonstrating flow in the mBT shunt were difficult to obtain due to the ECMO cannula in place and an open chest.

Three days later, a systolic and diastolic pressure were registering on the arterial line, with a pulse pressure of 15–20 mm Hg. The sodium nitroprusside infusion was able to be weaned off the day prior. Epinephrine was restarted at 0.03 μg/kg/min; milrinone, which had remained on since the operating room, was at 0.5 μg/kg/min; and calcium chloride was restarted at

5 mg/kg/h. Echocardiography was used to assess right ventricular systolic function while the flow on the ECMO circuit was weaned, followed by a trial off ECMO. The systolic BP on the arterial line ranged from 68–74 mm Hg and diastolic ranged from 38–45 mm Hg off ECMO. An echocardiogram demonstrated mildly depressed right ventricular systolic function. The oxygen saturation on the monitor read 35%, and the end-tidal carbon dioxide ($EtCO_2$) monitor read 15 mm Hg. An arterial blood gas was obtained with a partial pressure of carbon dioxide level that was 85 mm Hg and an oxygen saturation that was 40%. The ventilator appeared to be working effectively, and the settings were adequate. The fraction of inspired oxygen (FiO_2) was increased to 1.0, but there was minimal to no response on the oxygen saturation monitor.

The physician auscultated and did not appreciate a shunt murmur. There was concern for mBT shunt occlusion, so full ECMO support was resumed. A bolus of heparin was not given due to the recent bleeding, but the heparin infusion was resumed. The decision was made to urgently take the patient to the cardiac catheterization laboratory. An angiogram was obtained of the mBT shunt, which revealed it was occluded.

The patient is taken back to the operating room, and a new 3.5-mm mBT shunt was placed. The patient was subsequently able to be weaned from ECMO over the next 2 days, and the cannulae were removed. The chest was closed 2 days after decannulation without any complications.

WHAT IS THE ANATOMIC DEFINITION OF A PATIENT WITH A SINGLE VENTRICLE?

Hearts with univentricular anatomy have been referred to by several terms: cor triloculare biatriatum, single or common ventricle, primitive ventricle, double-inlet ventricle, univentricular heart, and univentricular AV connection.[1] There has been much debate over the years on how to correctly describe the relationship between the atria and ventricle, or the atrioventricular valve and the ventricle, or even if there is truly only a single ventricle in these patients. The true incidence of only one ventricle being present is low.[2–4] Single-ventricle patients can also be defined by an obstruction of blood flow to either the pulmonary or systemic system. This results in only one ventricle functioning to supply blood to both the pulmonary and systemic circuits. These lesions are also uncommon. For example, although HLHS is one of the more common single-ventricle etiologies, HLHS has an estimated occurrence of 2.3 per 10,000 live births or about 960 babies born per year in the United States.[5] Examples of lesions with systemic outflow obstruction include but are not limited to HLHS, critical aortic stenosis, critical coarctation of the aorta, interrupted aortic arch, and some variations of double-outlet right ventricle. Examples of lesions with pulmonary outflow obstruction include but are not limited to variants of tricuspid atresia, critical pulmonary stenosis, pulmonary atresia with intact ventricular septum, tetralogy of Fallot with pulmonary atresia, severe Ebstein anomaly, and some variations of double-outlet right ventricle. Although some of these lesions functionally have a single ventricle, it does not mean that they only have one anatomic ventricle.[6] Such is the case in the HLHS example used above in which there is typically a diminutive left ventricle and a normal size right ventricle that serves as the single functioning ventricle.

Irrespective of the underlying phenotype, the more important concept, especially in the clinical management of these patients, is to understand the physiology of a patient with a functional single ventricle.

WHAT IS THE PHYSIOLOGY OF A PATIENT WITH A SINGLE-VENTRICLE ANATOMY?

In the case above, the HLHS patient was born with systemic outflow obstruction. The left atrioventricular valve was stenotic, leading to a diminutive left ventricle with no outlet since the aortic valve was atretic. This means that there was complete mixing of the pulmonary and systemic venous return within the heart. In order for adequate decompression of the left atrium to occur, an unrestrictive atrial septal defect or patent foramen ovale must be present to allow left-to-right shunting of the pulmonary venous return.[6] Approximately 6% of all HLHS patients will be born with an intact atrial septum, and up to 22% of patients will have a restrictive atrial septal defect.[7] If a sufficient atrial communication is not present, then the patient will likely require a balloon atrial septostomy to prevent left atrial hypertension, which can lead to pulmonary venous congestion and severe cyanosis.[8] The entire blood volume (stroke volume) that is ejected out of the heart will be directed through the main pulmonary artery via the pulmonary valve. The pulmonary blood flow Qp comprises the blood volume that transits from the main pulmonary artery into the bilateral pulmonary arteries en route to the pulmonary bed. The systemic blood flow Qs will be provided through a right-to-left shunt through the ductus arteriosus into the aorta.

The balance of Qp and Qs will primarily be determined by the pulmonary and systemic vascular resistances.[5,9] Initially after birth, the pulmonary vascular resistance (PVR) will be high and will help to balance the Qp:Qs ratio. Over the next several days, PVR will decrease, which can lead to pulmonary overcirculation and inadequate systemic perfusion if total cardiac output is insufficient.[10] Signs of inadequate systemic perfusion can include hypotension, poor capillary refill, decreased urine output, tachycardia, laboratory evidence of end-organ dysfunction, and lactic acidosis.

WHICH ANATOMIC FEATURES NEED TO BE DELINEATED SHORTLY AFTER BIRTH OF A PATIENT BORN WITH HLHS?

The adequacy of the communication between the right and left atria will need to be determined. This can be assessed with echocardiography via two-dimensional imaging and looking for and quantifying a gradient across the atrial septum via spectral Doppler. However, this gradient must be interpreted in the setting of the patient's clinical signs and symptoms. Therefore, the child's respiratory rate, comfort of breathing, oxygen saturation, and chest radiograph will also be of valuable importance to assess pulmonary overcirculation versus venous congestion. The ductus arteriosus, which is normally

patent at birth, will start to constrict and become physiologically nonfunctional approximately 24–72 hours after birth in most patients. It is standard of care to use prostaglandin E_2 as a continuous infusion to maintain ductal patency and thus maintain systemic perfusion until an operation can be performed.[11,12] The goal is to maintain adequate ductal size at the lowest possible prostaglandin E_2 dose to avoid side effects of therapy.

WHAT ARE THE SURGICAL STRATEGIES FOR PATIENTS BORN WITH SINGLE-VENTRICLE ANATOMY/PHYSIOLOGY?

The goal of surgical intervention in these patients is to provide unobstructed systemic blood flow and unobstructed pulmonary venous return and provide a source of regulated pulmonary blood flow.[12] Surgical options that are available for treating a patient with HLHS include the Norwood procedure with an mBT shunt or right ventricle–pulmonary artery (RV-PA) conduit (Sano) and the hybrid and the modified hybrid procedures (bilateral pulmonary artery bands, balloon atrial septostomy and maintenance of a patent ductus arteriosus via stenting or prostaglandin E_2, respectively); and pulmonary artery banding plus arch augmentation.[13–15]

The patient in our example had a Norwood procedure. A neoaorta was created by transecting the pulmonary artery and combining it with the small ascending aorta in Damus-Kaye-Stansel fashion. An mBT shunt was placed between a branch of the aorta (normally the subclavian artery) and the central pulmonary arteries. The sizing of the mBT shunt is critical to ensure adequate regulation of pulmonary blood flow to balance Qp:Qs. Finally, an atrial septectomy was performed to create a common atrium for unobstructed pulmonary venous blood return and to afford atrial admixture. After the Norwood with mBT shunt operation, the systemic and pulmonary circulations were now in parallel instead of in series. The single pumping chamber has to supply blood to both the pulmonary and systemic circulations, compared to a two-ventricle heart in which one ventricle supplies blood to the pulmonary circulation and one ventricle supplies blood to the systemic circulation. Additionally, in a shunted patient, there needs to be a balance between the amount of blood going through the shunt to the pulmonary circulation and the amount of blood going systemically. In a perfect scenario, the flow would be perfectly balanced between the systems, and the Qp:Qs ratio would equal one. Scenarios are rarely perfect, and the Qp:Qs will primarily be based on the shunt size, PVR, and systemic vascular resistance.

WHAT RISK FACTORS PLACE A NEONATE WITH UNIVENTRICULAR PHYSIOLOGY UNDERGOING STAGE 1 (NORWOOD PLUS MBT SHUNT OR SANO) PALLIATION AT HIGH RISK FOR THE NEED FOR ECMO?

The neonatal myocardium compared to mature myocardium is at a structural disadvantage to tolerate the stress of a cardiac operation. The myocardial fibers are short, more rounded, and not in parallel, with an overall decreased amount of contractile proteins. This results in a heart that prior to undergoing any operation already has the potential for decreased contractility and comprises a myocardium that has difficulty relaxing.[16–18] A study by Friedland-Litte et al. specifically looked for risk factors for ECMO after the Norwood operation. On multivariate analysis, weight less than 2.5 kg and longer CPB times were independently associated with the need for ECMO.[19] Analysis of the Pediatric Heart Network Single Ventricle Reconstruction (SVR) trial also identified patients with weight less than 2.5 kg as well as the need for additional operations after the Norwood procedure as patients that were more likely to require ECMO. Additionally, neonates with mitral stenosis and aortic atresia were more likely to require ECMO compared to other anatomic variants of HLHS.[20] Of these three risk factors, only CPB duration is modifiable.

WHAT ARE THE SURGICAL CANNULATION STRATEGIES FOR PATIENTS WITH UNIVENTRICULAR PHYSIOLOGY?

Patients with univentricular physiology can be cannulated either peripherally or centrally. This will likely depend on the underlying anatomy, location of cannulation (operating room vs. CICU), surgeon cannulating (cardiothoracic vs. general surgery), and whether the patient already has an open or recently opened sternum. In the example above, the sternum is open, and the patient is status post-Norwood with mBT shunt. The surgeon places the venous cannula through the right atrial appendage into the common atrium. The arterial cannula is placed in the transverse aortic arch, often proximal to the mBT shunt. A similar cannulation strategy could be employed for stage 1 palliation patients who have undergone Norwood with RV-PA conduit.

The second stage of palliation for a patient with HLHS is the bidirectional Glenn operation. This type of operation entails superior cavopulmonary anastomosis and results in passive pulmonary blood flow from the superior vena cava (SVC) to the pulmonary arteries. For a patient who is status post-Glenn, placement of the venous cannula will depend on the physiology. If there is no obstruction (pulmonary artery obstruction, elevated PVR, pulmonary vein stenosis, elevated end-diastolic pressure resulting in left atrial hypertension) to passive pulmonary blood flow, then technically an inferior vena cava (IVC) catheter could be placed.[21] However, adequate decompression must be accomplished to allow sufficient cerebral perfusion pressure.[22] Therefore, most often, both SVC/Glenn and IVC cannulae will be placed to preclude venous congestion of both the upper and lower body compartments. The arterial cannula can still be placed in the innominate artery if cannulating peripherally or in the aorta if cannulating centrally.

The Fontan procedure is the third palliative operation for children with HLHS. This operation entails the IVC being joined to the pulmonary arteries, usually through an extracardiac conduit. This results in separation of the pulmonary and systemic circulations and places them in series.[16,22] A single venous cannula will occasionally accomplish the goal although

most of the time one venous cannula needs to be used to drain venous blood from the SVC, and an additional venous cannula needs to be used to drain blood from the IVC.[22–24] Depending on whether the patient is being cannulated peripherally or centrally, the arterial cannula can be placed in the innominate artery or aorta, respectively.

WHY DOES THE NORWOOD PATIENT NEED HIGHER ECMO FLOWS?

There are a couple of variables that need to be taken into account in order to understand why a patient following a Norwood with a mBT shunt operation needs a higher ECMO flow rate. A patient with an mBT shunt will most likely require increased ECMO flows of 180–200 mL/kg/min due to the flow through the shunt to the low-resistance pulmonary system[25,26] and the parallel systemic and pulmonary circulations. In scenarios when this pulmonary flow may compromise systemic perfusion despite increased ECMO flow, some institutions partially band the mBT shunt, whether prophylactically when ECMO is initiated or as needed based on clinical necessity.

While the aforementioned increased flow requirement is typically true for patients who are status post-Norwood with mBT shunt, the flow requirements are different for those having undergone a Norwood with RV-PA conduit. The difference between a Norwood with a Sano and a Norwood with an mBT shunt is that in the Norwood with a Sano an RV-PA conduit is placed from the right ventricle to the central pulmonary arteries. Thus, when on ECMO, only systemic blood flow needs to be provided, and the need to supply both Qp and Qs via the aortic cannula is eliminated. Understanding the differences between mBT shunt and Sano physiology on ECMO is important due to the clinical equipoise nationally between the two stage 1 palliations given the results of the ongoing SVR trial[20] showing no mortality difference at 6 years.

WHAT IS THE ANTICOAGULATION STRATEGY FOR POSTOPERATIVE CONGENITAL HEART DISEASE PATIENTS ON ECMO?

Anticoagulation strategy will be dependent on your local institution's practice. Heparin continues to be the primary medication used for anticoagulation on ECMO. Cannulation strategy, time from operation, and postoperative bleeding will all have to be taken into account when deciding when to initiate heparin therapy and goals for anticoagulation. The parameters employed to monitor and titrate anticoagulation are institution specific. While many institutions use heparin activity level (anti–factor Xa [anti-Xa]), others use a thromboelastogram, partial thromboplastin time, activated clotting time, or a combination of the aforementioned metrics. In addition to monitoring anticoagulation with laboratory values, physical examination of the ECMO circuit and patient is warranted. The venous and arterial cannulae, tubing connectors, and membrane should be inspected on a regular basis. Thrombus detection within the oxygenator can only be done on the visually exposed ends of the membrane. One way to monitor for unseen thrombus formation within the oxygenator is to monitor the efficiency of the membrane. This can be done by looking at pre- and postmembrane blood gases and determining whether the partial pressures of oxygen and carbon dioxide on the postoxygenator gas are anticipated given the current carbon dioxide sweep and FiO_2 settings. If the sweep and FiO_2 need to be uptitrated to maintain similar postoxygenator gas levels, this may be an indication of intramembrane thrombus accumulation.

In one of our institutions, approximately 12–18 hours after returning from the operating room, a heparin infusion is typically initiated, depending on the degree of bleeding. The patient is then put on a high-risk or low-risk bleeding protocol depending on patient factors. A patient who is status post-Norwood operation and is centrally cannulated would be in the high-risk protocol. Anticoagulation goals would include an anti-Xa from 0.3 to 0.5 international units (IU)/mL, platelets greater than 100,000/microliter, fibrinogen greater than 150 mg/dL, and hematocrit greater than 40%. This is just one example.

WHAT COMPLICATIONS CAN PATIENTS WITH SINGLE-VENTRICLE PHYSIOLOGY EXPERIENCE ON ECMO?

Complications for patients with single-ventricle physiology are not dissimilar from those experienced by other patients on ECMO. Emboli from thrombosis on the arterial side of the circuit can travel unimpeded to the patient, whereas on the venous limb of the circuit the oxygenator membrane acts a physical barrier to embolization. A thrombus that becomes a systemic embolus carries the risk of stroke. Tamponade physiology can occur due to blood or thrombus formation in the chest that limits circuit venous return. A chest reexploration and washout may need to be performed to relieve the pressure, resulting in tamponade physiology. Patients with open chests due to central cannulation are at a higher risk for infection. Depending on your local institution's practice, the patient will normally be treated with broad-spectrum antibiotics until decannulation and sternal closure.

DISCUSSION

In 1970, Baffes et al. were one of the first to describe having an extracorporeal perfusion apparatus and using it in pediatric congenital heart disease lesions that were previously unsurvivable.[27] Since then, the equipment, techniques, and settings used to deploy ECMO have been refined and expanded to serve as viable rescue therapy in pediatric cardiology as well as intensive care pediatric and adult populations. In the current era of congenital heart disease, many cardiologists and surgeons argue that having the ability to provide ECMO should be standard of care across institutions[28–30] that are performing congenital heart surgery. This discussion reviews the indications, modes, and importance of determining the etiology of decompensation requiring ECMO, incidence, outcomes associated with ECMO, and potential for recovery. When

possible, specific data and commentary on patients with univentricular physiology are provided.

Indications for V-A ECMO in patients with univentricular physiology are not dissimilar to the general indications for ECMO support. These indications include preoperative stabilization for low cardiac output, inability to separate from CBP, postoperative low cardiac output syndrome, intractable arrhythmias, and cardiac arrest. An indication specific to this patient population is shunt thrombosis if an mBT shunt is present.[25]

The etiology of decompensation, its potential for reversibility, and the indications for separation from ECMO need to be considered carefully prior to placing a patient on ECMO. ECMO is not a destination therapy, and while not ideal, it can occasionally be employed as a bridge to decision as it may be difficult to ascertain why a patient requires ECMO prior to cannulation. A key consideration is whether there are residual anatomic issues that led to the decompensation that need to be addressed in a timely fashion. Cardiac catheterization should strongly be considered once the patient is stabilized on ECMO support. In study of a 7-year period, Agarwal et al. described 119 patients who required postoperative ECMO support. Of the 119 patients, 28% of them were found to have hemodynamically significant lesions, predominantly involving the branch pulmonary arteries, shunts, and ventricular outflow tracts, requiring surgical intervention. Echocardiography is a useful tool but only identified 20% of the lesions, while cardiac catheterization identified 80% of the lesions.[31] Studies by Howard et al. and Abraham et al. described that the earlier residual lesions can be identified and treated after cannulation onto ECMO, the more likely the patient is to be a survivor.[32,33] Identifying the etiology for decompensation can also help one inform the family about potential reversibility and likely outcomes. Identification of etiology prior to or soon after ECMO initiation is essential.

The use of ECMO and extracorporeal cardiopulmonary resuscitation (ECPR) has experienced a steady increase over the past 30 years. The July 2019 Extracorporeal Life Support Organization (ELSO) international summary reported that there has been a total of 8498 neonatal cardiac and 11,839 pediatric cardiac ECMO runs since 1989. As a subset of ECMO patients, ECPR has become routine and is well described. Neonates and pediatric patients with single-ventricle lesions accounted for 46% and 40%, respectively, of the patients receiving ECPR in the ELSO database.[25,34,35] Furthermore, ECPR has a higher incidence in the CICU and is often performed on patients with univentricular physiology. Gupta et al. described the incidence of ECPR as 17% in the CICU compared to 3% and 4% in the neonatal and pediatric intensive care units, respectively.[36] In the SVR trial, 8.9% of patients were placed on V-A ECMO, and 6.6% required ECPR.[20] In Norwood patients, the use of ECMO can range from 13% to 20%.[34,37,38] For example, in a study by Mascio et al.,[39] 17% of the patients that underwent the Norwood procedure required postoperative mechanical support.

Despite improvements in technique and time to reach full ECMO flows, neonatal and pediatric outcomes after ECMO have not experienced similar advancement. As of January 2019, the ELSO experience notes neonatal survival to decannulation is 69% and survival to discharge or transfer is 43%. Similarly, pediatric survival to decannulation is 71%, and survival to discharge or transfer is 52%.[40] An individual patient's survival likelihood can be viewed in light of overall outcome statistics but is influenced by that patient's etiology of decompensation and indication for ECMO. To delineate these differences, Walters et al. divided patients into three cohorts: those who required ECMO support preoperatively, those who were unable to be weaned from CPB, and those who were able to be separated from CPB postoperatively but subsequently required ECMO. Overall hospital survival was 58%. However, of the patients who were unable to be weaned from CPB, only 23.5% survived to discharge compared to 69.4% who were cannulated after separating from CPB.[29]

The survival rate of single-ventricle physiology patients supported with ECMO appears to be similar to ELSO neonatal survival rate.[41] For example, Mascio et al. examined the Society of Thoracic Surgeons database and observed that patients who had undergone the Norwood procedure and required ECMO had a survival rate of 43%.[39] While outcomes in the univentricular physiology population are similar, the unique indication of shunt thrombosis appears to confer a survival advantage, likely due to its reversible nature. Allan et al.[42] observed that patients requiring ECMO for shunt thrombosis had a higher likelihood of survival compared to those who required ECMO due to either cardiovascular collapse or hypotension. Ravishankar et al. reported that all neonates with shunt thrombosis survived to discharge.[43] However, outside of shunt thrombosis, univentricular physiology patients appear to be similar to the neonatal and pediatric populations in terms of etiologies associated with poor outcomes. For example, inability to wean from CPB is associated with increased mortality in both populations.[44]

The outcomes in patients who have undergone the bidirectional Glenn procedure or the Fontan operation and subsequently require ECMO are similar to univentricular physiology patients who have undergone stage 1 palliation. For the Glenn/hemi-Fontan population requiring ECMO, Mascio et al. and Jolley et al. observed a 56% mortality rate in the society of thoracic surgeons (STS) database and a 58% mortality rate in the ELSO database, respectively.[39,45] For Fontan patients requiring ECMO, Rood et al. found a 65% mortality rate in the ELSO Registry.[46] The challenge in both these populations is achieving adequate decompression of both the SVC and IVC in the low-flow, passive Glenn or Fontan circuits. Elevated venous pressure can preclude sufficient cerebral perfusion pressure. This can ultimately lead to neurological injury and likely contributes to poor outcomes.

Despite the aforementioned outcomes in both the overall and univentricular physiology populations, it is possible for a patient to experience recovery from the inciting etiology and be successfully decannulated. This may occur spontaneously or via catheter-based or surgical intervention. In postcardiotomy patients requiring ECMO due to low cardiac output secondary to transiently depressed ventricular function after CPB, it is possible to have return of ventricular function within 48–72 hours.[28] Return and widening of the pulse pressure can be one

of the signs of returning ventricular function, as can normalization of lactic acidosis, improved clinical indices of perfusion on physical examination, return and increase in urine output, decreased tachycardia, improved central venous pressures, and improved cerebral and somatic near-infrared spectroscopy. Decreasing ECMO flow and monitoring of central venous pressure while using echocardiography can also help to determine the extent of myocardial recovery. If early diagnostic catheterization is unrevealing, there are no identifiable surgical targets, and ventricular function does not return in over a multiple-day period, withdrawal of care and durable mechanical support, such as a ventricular assist device (VAD), should be considered simultaneously. Should the latter be entertained, it must be in the context of VAD as a bridge to orthotopic heart transplantation as there are currently no destination devices in the pediatric population. Conversion to a durable device is likely warranted because pediatric patients waiting for heart transplantation on a VAD compared to ECMO have lower mortality and survive longer posttransplant.[47] Discerning the family's goals of care while thoughtfully counseling with data surrounding outcomes after ECMO, VAD, and heart transplantation is paramount.

CONCLUSIONS

- Patients with univentricular physiology are unique and present additional challenges when utilizing ECMO support compared to other pediatric populations.
- Use of ECMO has increased since its inception to the point that it is now considered standard of care.
- ECMO is indicated for similar etiologies of decompensation in both univentricular physiology patients and the general population to provide full cardiorespiratory support while a reversible cause is pursued.
- In single-ventricle physiology patients, it is important to be cognizant of the unique etiology of mBT shunt thrombosis.
- Survival to discharge for all stages of single-ventricle palliation remains less than 50%.

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REVIEW QUESTIONS

1. What therapeutic regimen is employed to provide myocardial rest while on V-A ECMO?

A. Epinephrine, calcium, milrinone
B. Epinephrine, calcium, milrinone, vasopressin
C. Milrinone
D. Epinephrine
E. Vasopressin

2. What typically is the first sign of complete shunt occlusion in a Norwood with mBT shunt patient who is not on ECMO?

A. Reduction in $EtCO_2$
B. Decreased oxygen saturation
C. Decreased BP
D. Tachycardia
E. Loss of flow-volume loops

3. What ECMO flows are typical for Norwood with mBT shunt patients?

A. 100 mL/kg/min
B. 120 mL/kg/min
C. 140 mL/kg/min
D. 160 mL/kg/min
E. 180 mL/kg/min

4. What means are used to maintain an unrestrictive atrial septum and a patent ductus arteriosus in an unrepaired HLHS patient prior to surgical intervention?

A. Rashkind procedure
B. Prostaglandin
C. Balloon atrial septostomy
D. Patent ductus arteriosus stent
E. Rashkind plus prostaglandin

5. What is the best sequence of interventions for acute mBT shunt thrombosis?

A. ECMO cannulation
B. Volume, epinephrine bolus, heparin bolus, ECMO cannulation
C. Heparin bolus and heparin infusion
D. Volume, heparin bolus, ECMO cannulation
E. Epinephrine bolus, ECMO cannulation

ANSWERS

1. Answer: C. Milrinone. Myocardial rest is optimized by minimizing myocardial oxygen consumption. To do this, afterload reduction is provided, and inotropic support and vasoconstrictive agents are avoided. Afterload reduction and lusitropy are provided with milrinone. Occasionally, direction vasodilatory agents, such as nitroprusside, are employed if

the patient remains hypertensive to further provide afterload reduction. Exogenous catecholamines increase myocardial work and are detrimental to recovery, so inotropic support, such as epinephrine, dopamine, and calcium, is discontinued once adequate ECMO flows are established. Similarly, vasoconstrictive agents increase afterload and thus myocardial work, so agents, such as vasopressin, phenylephrine, and norepinephrine, are avoided.

2. Answer: A. Reduction in $EtCO_2$. The mBT shunt provides Qp. If the mBT shunt is occluded, there is no pathway for blood to reach the pulmonary vasculature for gas exchange. As such, with no Qp, carbon dioxide remains in the blood and is not transferred to the alveolus to be exhaled. Because $EtCO_2$ is a measurement of carbon dioxide in each exhaled breath, $EtCO_2$ will be reduced without a change in ventilation. While oxygen is also exchanged via Qp, decreased oxygen saturation is often delayed compared to $EtCO_2$.

3. Answer: E. 180 mL/kg/min. Single-ventricle physiology patients palliated to stage 1 with an mBT shunt continue to have parallel circulations on ECMO so require additional flow to compensate for both Qs and Qp. With a Sano, additional flow is not required if adequate venous decompression is achieved. In this scenario, the pulmonary circuit does not receive significant blood flow because it is captured by the venous limb of the ECMO circuit.

4. Answer: E. Rashkind plus prostaglandin. Adequate intra-atrial mixing is required and is limited in the setting of a restrictive atrial septum. A Rashkind procedure, or a balloon atrial septostomy, is a catheter-based procedure employed to tear the restrictive atrial septum to afford obligatory atrial mixing and preclude left atrial hypertension and pulmonary congestion. A patent ductus arteriosus is required to maintain systemic blood flow. A continuous prostaglandin E_2 infusion is used to maintain ductal patency.

5. Answer: B. Volume, epinephrine bolus, heparin bolus, ECMO cannulation. Volume is readily accessible at the bedside and can be the first-line agent to provide adequate intravascular volume to fully distend the shunt or dislodge the thrombus within the shunt. An epinephrine bolus, not infusion, increases BP and pulsatility and may provide adequate driving pressure to open the shunt or dislodge the thrombus from the shunt. A heparin bolus often takes time to arrive at bedside but is the intervention of choice once it is available. Heparin may serve to dissolve the thrombus or dislodge the thrombus similar to volume or epinephrine. ECMO is an option should the mBT shunt remain occluded.

29.

ECMO IN PEDIATRIC PATIENTS WITH CONGENITAL HEART DISEASE

Ajay Desai and J. Andreas Hoschtitzky

STEM CASE AND KEY CONSIDERATIONS

A 14-month-old girl was admitted to the pediatric intensive care unit (PICU) from another hospital with presumed diagnosis of cardiomyopathy. Past history included term delivery with uneventful pregnancy with birth weight of 3.1 kg. There were no neonatal concerns. She was fully immunized. During her infancy, she was seen by the general practitioner (GP) on a few occasions due to poor growth and weight below the 0.4 centile. She was diagnosed with a nut allergy and possibly a sesame allergy. She could crawl but was unable to stand or walk. One week prior to admission, her parents noticed swelling of her face and labored breathing; they took her to the GP, who admitted her to the local hospital. Her admission weight was 6.4 kg. A chest x-ray (CXR) showed cardiomegaly and echocardiography showed a dilated heart with poor ventricular function. She was transferred to the PICU with a presumed diagnosis of dilated cardiomyopathy.

On admission, she was in a profoundly low cardiac output (CO) state. She was tachycardic and peripherally cold with very poor peripheral pulses with a noninvasive blood pressure of 75/60 mmHg. With the extracorporeal membrane oxygenation (ECMO) team on standby, she was intubated, and femoral venous and arterial catheters were inserted. The first arterial blood gas showed a pH of 6.8 with a lactate of 16 mmol/L. She was started on an adrenaline infusion. Admission echo showed a severely dilated left ventricle (LV) with very poor systolic function, global akinesis with an ejection fraction (EF) of 14% and shortening fraction of 9%. There was moderate mitral regurgitation with a dilated left atrium (A). The right ventricle (RV) function was normal, with no pulmonary stenosis and moderate pulmonary regurgitation. Pulmonary venous return was normal. The left main coronary artery arose from the proximal pulmonary artery and divided into two main branches. The right coronary artery (RCA) arose from the right coronary sinus. A diagnosis of anomalous left coronary artery from pulmonary artery (ALCAPA) was made. The B-type natriuretic peptide and troponin values were raised (4900 pg/mL and 15,450 ng/mL, respectively) on admission.

In view of the unstable hemodynamic, she was cannulated onto veno-arterial (V-A) ECMO via the right common carotid artery (Medtronic 8 French [8F]) and right internal jugular vein (Medtronic 16F). The cannulation position was confirmed on echocardiogram. An ECMO flow of 0.9 L/min (cardiac index of 2.5 L/min/m^2) was achieved. Adrenaline was weaned off. The CXR showed cannulae in good position, massive cardiomegaly, and severe pulmonary edema. In the next few hours, to decompress the left heart, she was taken to the cardiac catheterization laboratory, and a balloon atrial septostomy was performed.

A multidisciplinary team meeting was held, and the decision to go ahead with ALCAPA repair was made. Approximately 10 hours later, the patient underwent ALCAPA repair. The repair was performed with reimplantation of the left coronary artery (LCA) from the pulmonary root to the left coronary sinus of the aorta. A defect in the pulmonary artery was reconstructed with pericardium. The improved LV myocardial perfusion was observed promptly. Following surgery, the chest was left open, and she was electively placed on V-A ECMO (using the previous neck cannulae) again and returned to the PICU.

Severe coagulopathy was a major challenge in the first 48 hours postsurgery. She suffered bleeding from the mouth, nose, gastrointestinal tract, and mediastinum. The chest was reexplored; heparin was stopped for 24 hours, and during this period she received tranexamic acid and multiple blood products following hematology team advice. The ear, nose, and throat team performed nasal and posterior nasopharyngeal packing to control the bleeding. Heparin was restarted, and anticoagulation was maintained with target anti–factor Xa (anti-Xa) levels between 0.3 and 0.7 IU/mL. She remained in sinus rhythm, but cardiac function remained poor. She was started on milrinone infusion (0.3–0.5 μg/kg/min). Delayed chest closure was performed 9 days after the operation. She was successfully decannulated from ECMO on Day 10 on low dose adrenaline (0.05 μg/kg/min) and milrinone support. The right carotid artery and internal jugular vein were reconstructed. During the ECMO course, her neurology was monitored with electroencephalography, cranial ultrasound, and head computed tomographic scan, and was had no significant abnormal findings. She did not require renal replacement therapy during the ECMO run.

She was successfully extubated 2 weeks after ECMO decannulation. Eventually, she made a good clinical recovery and was discharged home after a total 6-week hospital stay. Discharge medications included captopril, diuretics,

digoxin, and aspirin. An echocardiogram at the time of discharge showed small interatrial communication shunting left to right, moderate mitral regurgitation, mild tricuspid regurgitation, no evidence of pulmonary hypertension, mild pulmonary regurgitation, relatively preserved RV function, persistent significant dilation of the LV, with severe dysfunction and global hypokinesia and no thrombus in the cardiac chambers or the valves.

HOW ARE CHILDREN WITH ALCAPA MANAGED?

The pathophysiology of ALCAPA revolves around changes in pulmonary artery pressure, intercoronary anastomoses the between LCA and RCA, myocardial steal and myocardial ischemia. With fall in pulmonary vascular resistance (PVR) in the postnatal period the pulmonary artery pressure (PAP) decreases resulting in reduced perfusion of LCA. The LCA oxygen content is reduced and LV myocardium being perfused by relatively desaturated blood under low pressure, leading to myocardial ischemia. Collateral vessels develop between the RCA and LCA and may provide adequate perfusion to the left myocardium. When LCA pressure falls further below RCA pressure, blood flows from the RCA to the LCA into the pulmonary artery (retrograde flow) rather than into the high-resistance myocardial blood vessels. Effectively, a coronary artery steal develops from the myocardium to the pulmonary artery (creating a left-to-right shunt). This steal phenomenon further worsens myocardial ischemia and causes infarction of the anterolateral LV free wall. Over time, this leads to LV dysfunction and congestive cardiac failure.

The goal of medical management is to stabilize the patient awaiting surgery. Ischemic injury in ALCAPA can be reversible, at least partially. Hence, an aggressive approach should be taken when the patient presents with severe cardiogenic shock. Critical care management should focus on optimizing myocardial oxygen delivery and minimizing oxygen demand. Intubation and mechanical ventilation (LV afterload reduction, reduced oxygen demand); sedation and analgesia (reduce anginal pain, reduce tachycardia, improve myocardial oxygen supply/demand ratio); diuretics if blood pressure allows (reduce myocardial wall tension and improve oxygen consumption/supply ratio, reduce pulmonary edema and improve oxygenation); and finally judicious use of systemic vasoconstrictors (e.g., phenylephrine) to raise diastolic blood pressure to improve myocardial perfusion without causing increased afterload or contractility of heart should be considered.

WHAT IS THE ROLE OF ECMO IN CHILDREN WITH ALCAPA?

Veno-arterial ECMO should be considered if the patient continues to deteriorate on medical therapy prior to surgical repair. When a child presents with a profound low CO state at admission, while medical management is initiated the preparation for ECMO should continue in parallel. Some children require ECMO support following surgery if weaning off cardiopulmonary bypass (CPB) is unsuccessful or if the ventricular function remains poor.

WHAT IS THE ROLE OF ECMO IN CHILDREN WITH CONGENITAL HEART DISEASE?

In neonates and children with congenital heart disease (CHD), ECMO can be used for preoperative stabilization (e.g., obstructed infracardiac total anomalous pulmonary venous connection); failure to wean from CPB (ventricular dysfunction, undiagnosed residual lesions); or low CO syndrome in the postoperative period. Following congenital heart surgery, ECMO is utilized in 1%–8.4% of operations. In a smaller proportion of patients in whom adequate functional recovery is not achieved, ECMO can be used to support the circulation until alternatives are instituted, including a ventricular assist device (VAD), orthotopic heart transplant (OHT), or end-of-life care. Cardiac arrest as an indication for ECMO is called extracorporeal cardiopulmonary resuscitation and described elsewhere in this book.[1,2]

WHAT ARE CANNULATION CONSIDERATIONS IN PEDIATRIC V-A ECMO?

Veno-arterial ECMO after open cardiac surgery can be a complex and laborious task and will very much depend on the etiology of the postoperative cardiac dysfunction, the vascular anatomy, and the intracardiac anatomical considerations, potential valvular prostheses, and the size and weight of the patient. As far as the cardiac function is considered, it is important to understand what the preexisting cardiac function is and understand if this is related to myocardial protection and bypass time only or also due to short- or long-standing dysfunction, such as due to chronic valvular disease.

In general, if patients are unable to wean off cardiopulmonary bypass, the bypass cannulae are used, and the patient is transferred from a bypass circuit to an ECMO circuit by briefly interrupting flow and changing the circuit. It will depend on the decompression of the systemic ventricle and the amount of ejection, as demonstrated on the arterial pressure waveform if the LV is rested enough. In case this is not the case, then an additional LA vent will be required or an atrial septostomy (in the catheter laboratory) or a patent foramen ovale or surgically left behind atrial septal defect to allow decompression of blood returning through the pulmonary veins into the LA. The chest wound will have to be stented and covered with a sterile silastic membrane until such time that the patient is off ECMO support, and the chest can be closed. The cannulae will come through this membrane out of the wound.

If the patient requires ECMO prior to bypass due to cardiogenic shock, cannulation can be done by using access in the neck for the internal jugular vein and right carotid artery. In young children, this can often be done without major complications, but in older children this is best done with a side graft on the artery to prevent the risk of strokes as it is often unknown if the circle of Willis is complete. If the calculated flow requirements are too high, then it is often necessary to add additional venous drainage from the femoral vein for older

children and teenagers; a small, multistage venous cannula can then be positioned through the femoral vein into the inferior vena cava–right atrial junction or further into the superior vena cava depending on the operation performed. In this scenario, it is also then best to use the femoral artery for arterial return and again use a side graft with the cannula into this to be able to have enough return with low enough line pressures. This will also facilitate potentially not having cannulae coming through the chest wound, and with peripheral cannulation, the chest wound could conceivably be closed if an atrial communication is used and the patient then gradually weaned of ECMO through this route. The choice between peripheral cannulation and central cannulation will depend on the surgeon's choice and center's preference. In case mechanical prostheses are present in the heart, it is best not to decompress the heart completely with a vent due to clot formation on the prosthesis and either the valve suddenly stopping to function or thromboembolism occurring. Therefore, some ejection with inotropes would be preferential.

It is important, though, that for any of these circumstances that the team is satisfied that the operative results are optimal for the anatomy and that the coronary patency is confirmed. This is best done with coronary angiography in the catheter laboratory and in combination with echocardiography as soon as practical after surgery. This will allow for optimal rest of the myocardium for recovery.

HOW IS BLEEDING MANAGED IN ECMO PATIENTS?

Bleeding is the most frequent complication in patients receiving V-A or veno-venous (V-V) ECMO. Hemorrhagic complications and the requirement for greater red blood cell (RBC) transfusion volumes are associated with increased mortality in both cardiac and noncardiac extracorporeal life support. Achieving hemostasis without causing thrombosis is a challenge due to complex hemostatic and inflammatory responses associated with the underlying conditions, which include infection, sepsis, surgery, and/or traumatic injury.[3]

Mild-to-moderate (5–10 mL/kg/h) bleeding should be anticipated, especially in the early postcardiotomy ECMO setting. Aggressive correction of coagulopathy with blood products is required. If the bleeding is local (central venous line insertion sites, ECMO cannulation site if via neck or groin, etc.), topical pressure application might help stop bleeding. The anticoagulation strategy needs to be revised (e.g., aiming for lower activated clotting time [ACT] target of around 150–170 seconds).

If the bleeding is severe (10–20 mL/kg/h or more) despite ongoing medical management, surgeons should be informed promptly. In the case of central cannulation, surgeons might consider chest reexploration. Running ECMO free of heparin for a limited duration should be considered in consultation with perfusionists. If the ECMO is run via central cannulation with an open chest and bleeding into the mediastinum continues with the above measures, conversion to neck cannulation and closing the chest might help. In extreme situations, weaning the patient off ECMO can be considered.

IS RECOMBINANT FACTOR VIIA USEFUL?

Despite multiple randomized studies of its use in varied clinical settings, meta-analyses have shown that effects of recombinant factor VIIa (rFVIIa) on transfusion requirements are modest at best, and that this is counterbalanced by a significant increase in the rate of arterial thrombosis, including fatal cerebral stroke. Significant clotting within the ECMO circuit is a risk in this setting. Therefore, use of rFVIIa should be considered only in exceptional circumstances of severe bleeding unresponsive to ongoing management and in discussion with the hematologist.[4]

WHAT ABOUT ANTIFIBRINOLYTIC AGENTS?

Excessive fibrinolysis (hyperfibrinolysis) leading to bleeding should be suspected if associated with high d-dimer levels with relatively normal platelet counts. A thromboelastogram can be used to determine if there is increased fibrinolysis as an indication for antifibrinolytic therapy such as tranexamic acid. It is important to note that active intravascular coagulation (disseminated intravascular coagulation) is a contraindication for use of antifibrinolytic agents. Always discuss with the hematologist prior to starting antifibrinolyitics.[5]

HOW ARE CHILDREN WITH CONGENITAL CONDITIONS ON V-A ECMO VENTILATED?

The majority of patients with cardiac ECMO have normal lung function and compliance. However, pulmonary edema—both cardiac and noncardiac in origin—can develop due to LA hypertension, reperfusion injury, systemic inflammatory response syndrome, transfusion-related lung injury, especially in the post-CPB setting.[6,7]

In general, the ventilation strategies in children on V-A or V-V ECMO include having an open lung approach and good physiotherapy to optimize lung function throughout the ECMO duration. However, in the setting of V-A ECMO the cardiovascular effects (RV function, PVR, and systemic afterload) of mechanical ventilation can be especially relevant. Because V-A ECMO reduces blood flow through the lungs, the optimal amount of alveolar ventilation may be different compared with patients requiring V-V ECMO. In addition, many patients on V-A ECMO for acute lung injury have significant RV dysfunction and may benefit from optimized RV preload and afterload by closely attending to intrathoracic pressures and pulmonary lung volumes.

There is no clear evidence for optimal positive end-expiratory pressure (PEEP) in V-A ECMO. Patients with preload-dependent CO may benefit from lower PEEP, and patients with afterload-dependent CO might benefit from higher PEEP. No single ventilation strategy is universally practiced, and the suggested target may be inappropriate in patients with an open sternum, poor lung compliance, pulmonary hemorrhage, or intrathoracic abnormalities such as hematoma.

In general, a PEEP of 7–10 cm H_2O, tidal volumes of 4–6 mL/kg, and low ventilation rates (10 breaths/min) can be considered at the start of a V-A ECMO run. It is important to reassess the settings at regular intervals. When cardiac

function has recovered and an ECMO wean is contemplated, it is important that lungs also are in good condition.[8–11]

WHAT DO WE GAIN FROM BLOOD GAS ANALYSIS?

Arterial blood gas on V-A ECMO may provide more information about the patient's native cardiac function than native pulmonary function. As native CO improves in patients on V-A ECMO, one should anticipate a worsening PaO_2 on arterial blood gas measurement because contribution from mechanical ventilation may not be optimal. At this point, the ventilation settings need readjusting. On the other hand, if arterial PaO_2 is similar to the PaO_2 of the arterial limb (return cannula) of ECMO, it may indicate worsening cardiac function rather than improving lung function.

HOW LONG DO WE CONTINUE V-A ECMO?

The duration of ECMO is a strong determinant not only of death on ECMO but also after weaning from ECMO. Longer duration of extracorporeal bypass has a deleterious influence on organ systems, including the immune system, which may contribute to later mortality. An ECMO support time of 10 days or more is a significant risk factor for failure to wean ECMO support as well as failure of hospital discharge despite successful decannulation.[12,13]

HOW DO WE ASSESS READINESS TO WEAN FROM ECMO?

Clinical course of myocardial dysfunction is a major determinant of the ECMO wean in terms of expected timing of both recovery and decannulation.

Recovery from primary myocardial dysfunction (ALCAPA, late repair of transposition of the great arteries—TGA) is quite different from myocardial injury after cardiac surgery and CPB. In the former, the expected duration of recovery can be much longer (weeks to months), well after ECMO decannulation, and in some patients the function may not recover at all.

In the postcardiotomy ECMO setting, the patient is usually supported for at least 48–72 hours allowing an inflammatory process to heal, maintain adequate tissue oxygen delivery, and identify and correct any underlying residual lesions.

Evidence of myocardial recovery is suggested by increasing pulse pressure, increasing end-tidal CO_2 (may not correlate well in children with systemic-to-pulmonary shunts) and improving function on echocardiography. Myocardial function measured by echocardiography while on full ECMO flow does not predict myocardial performance because of altered loading conditions. Some of the specific echocardiographic parameters commonly used to assess "readiness" to wean under low ECMO flows include aortic velocity time integral, improving EF, and lateral mitral/tricuspid annulus peak systolic velocity.[14,15]

In children who have atrial septostomy or LA vent, myocardial function recovery may be indicated by reduction in vent flow or reduction in ECMO circuit mixed-venous saturations. For weaning during V-A ECMO, decompression efforts must be ceased (e.g., clamping LA vent) to allow adequate filling of the LV.

It is always good practice to have a multidisciplinary team discussion prior to ECMO wean. Key challenges should be anticipated, a clear strategy should be agreed in advance (e.g., one-way ECMO wean, recannulation) and discussed with parents or carers.

Key preparations prior to actual ECMO flow wean include the following:

- Ensure stable airway (endotracheal tube position).
- Assess respiratory conditions (e.g., rule out major effusions, lung collapse).
- Assess need for pulmonary vasodilators (risk of pulmonary hypertension).
- Optimize filling conditions (monitor central venous pressure).
- Assess arterial line and end-tidal CO_2 monitoring.
- Assess adequate central venous access.
- Assess need for any external cardiac pacing (pacing wires checked and connected to pacing box).
- Optimize electrolyte (K, Ca, Mg) abnormalities if any.
- Assess need for increased anticoagulation during low flows (increased risk of clot formation).

Low-dose inotropes with or without vasopressors are usually started several hours prior to ECMO flow wean. Our first-line approach in postcardiotomy ECMO wean is a combination of low-dose adrenaline and milrinone. Use of a checklist is highly recommended in order to minimize human errors. Levosimendan has a potential role in improving survival in pediatric postcardiac surgery with poor ventricular function during weaning of ECMO. Further research is required to better identify patients who would benefit most.

Once assessment is complete and key preparations are addressed, the ECMO flow is slowly weaned from full flow to approximately 30%–40% of flow (not below 200 mL/min to minimize risk of clot formation) over several hours while paying attention to regular hemodynamic assessment (pH, lactate, mixed venous oxygen saturation—MVO_2, echocardiography) and management. Other strategies include clamping of the cannula proximal to the patient and circulating the circuit slowly through the bridge between arterial-venous cannulae (allowing complete separation from ECMO flow for a brief period); pump-controlled retrograde trial (detailed description is beyond the scope of this chapter).

Unless it is a case of "one-way" ECMO wean, inotrope dose should be kept as low as possible (i.e., one should not wean from ECMO on maximum inotropic support). This is because patients usually require more inotropic/vasopressor support hours after decannulation. Ventilation needs to be adjusted with increased pulmonary blood flow.

For peripheral cannulation, vascular reconstruction may be required. For central cannulation, the preferred approach would be to leave the chest open and opt for delayed chest closure.[16–18]

DISCUSSION

Although ECMO flow provides adequate CO, the afterload for the LV increases. Increased LV afterload created by extracorporeal blood flow leads to excessive myocardial wall tension, increased oxygen demand, decreased coronary blood flow, and impaired ventricular performance and recovery. The LV may not be able to eject blood to decompress the LA, a so-called myocardial stun. It may also result in LV subendocardial ischemia, which is highly undesirable in the ALCAPA background. Moreover, bronchial and Thebesian venous blood (that is not drained by the ECMO access cannula) gradually fills the left heart and contributes to further increases in LA pressure. Intracavitary thrombus formation and pulmonary edema will occur when LA pressure exceeds 25–30 mm Hg. Echocardiography is essential to assess LV distension and the presence of "spontaneous contrast."[19–22]

Some features in the post-ECMO cannulation phase (first hours) might help in deciding whether to consider LV or LA decompression—pulmonary edema on CXR, LA and/or LV dilation on echocardiography, nonpulsatile arterial waveform, aortic valve not opening during systole, and pulmonary hemorrhage. The decision to address LA decompression needs to be taken soon after ECMO initiation. Late LA decompression (18 hours or more) has been associated with longer duration of ECMO support and mechanical ventilation. It is important to note that echocardiographic findings can be misleading and may underestimate the LA pressure. Hence, some centers routinely undertake early left heart decompression.[23–25]

There are medical, interventional, or surgical strategies that can help "decompress" the left heart. A combination of systemic vasodilators (e.g., sodium nitroprusside or milrinone) and/or low-dose inotropes can help reduce systemic vascular resistance and improve LV ejection and aortic valve opening. However, this approach alone may not be sufficient in all patients. Additional interventions for LA decompression include septostomy using a balloon or blade to dilate or perforate the interatrial septum in the cardiac catheterization laboratory under echocardiography and fluoroscopy guidance. In the setting of postcardiotomy V-A ECMO, surgeons may insert an LA "vent"—a small drain (usually 8F–15F) to help decompress the LA, which is then connected to the venous limb (access cannula) of the ECMO circuit. Other surgical options include insertion of a drain into the LV. An intra-aortic balloon pump is not suitable in small children.

CORONARY CIRCULATION

The CO is decreased in inverse proportion to the ECMO flow; that is, high-flow ECMO results in decreased RV and LV output. During V-A ECMO, coronary perfusion is derived only from blood ejected by the LV (i.e., blood coming via the lungs from the RV as well as Thebesian and bronchial veins that are desaturated). Hence, supplemental oxygen via the ventilator (e.g., setting the fraction of inspired oxygen on the mechanical ventilator at around 40%) would improve pulmonary venous saturations, which translates into improved coronary perfusion.[26,27]

UNDERLYING CONDITION

An underlying cardiac condition is one of the important factors that determines the ECMO outcomes. In general, nonsurgical cardiac disease has a better prognosis compared to surgical CHD. For example, published reports suggested up to 70% survival to hospital discharge rates in children with acute viral myocarditis who required ECMO. Within cardiac surgical ECMO, certain lesions/procedures carry higher risk compared to others. According to a recent Society of Thoracic Surgeons database study, mortality for ECMO following Ross-Konno repair or truncus repair is approximately 70%, whereas that following ALCAPA repair is 14%. Factors such as preoperative physiologic compromise, intraoperative myocardial ischemia and reperfusion, and the technical complexity of the operations (e.g., restoration of adequate coronary artery anatomy and perfusion and the potential for residual defects and hemodynamic burdens) constitute a complex field of variables that determine eventual ECMO outcomes.[28]

RESIDUAL LESIONS

Residual lesions are present in approximately 25% of postoperative cardiac surgery patients requiring ECMO support. All postoperative pediatric cardiac surgery patients unable to be weaned off ECMO successfully should be evaluated actively for residual lesions, preferably by cardiac catheterization, as echocardiography detects approximately only 20% of all residual lesions. Earlier detection, preferably within the first 24–48 hours, of residual lesions and reintervention is associated with improved survival rates. Cardiac catheterization can be safely performed on patients supported by ECMO and is a critical tool in the early recognition, diagnosis, and direct treatment of hemodynamic and/or anatomic abnormalities.[29–31]

PH AND LACTATE LEVELS

The effects of both pH and lactate levels on ECMO mortality have been analyzed in multiple studies. Low pH (<7.35) after 24 hours of an ECMO run is predictive of death on ECMO. A high lactate level prior to ECMO has not been consistently shown to be a risk factor for ECMO mortality; however, the lactate levels at 24 and 48 hours are predictive of death on ECMO. Abnormal values of these indicators of tissue perfusion reflect either the overall hypoperfusion before deployment of ECMO or problems in oxygen delivery and/or extraction after deployment of ECMO.[32,33]

URINE OUTPUT, RENAL FAILURE, AND FLUID OVERLOAD

Urine output in the first 24 hours of the ECMO run, a surrogate marker of organ perfusion, is an independent factor influencing death on ECMO. A low urine output in the first 24 hours reflects either the ischemic insult to the kidneys sustained during the pre-ECMO period or continued organ perfusion abnormalities despite extracorporeal support.[34]

The presence of renal failure and/or fluid overload is a significant risk factor for both death on ECMO and overall hospital mortality. Acute kidney injury is probably a reflection of pre-ECMO injury but could also be due to insufficient ECMO flow. Fluid overload, with or without renal failure, may impact respiratory mechanics and myocardial recovery. Studies have shown an association between fluid overload at continuous renal replacement therapy initiation and mortality in pediatric patients receiving ECMO.

Intervening prior to the development of significant fluid overload may be more clinically effective than attempting fluid removal after significant fluid overload has developed. Renal impairment has been shown to have an adverse influence on the various organ systems and significantly decreases chances of recovery. A higher amount of blood transfusion as a significant factor for renal failure is well established.[35,36]

TRANSFUSIONS

Bleeding is the most frequent complication in patients receiving ECMO therapy. The requirement for greater RBC transfusion volumes is associated with increased mortality in both cardiac and noncardiac ECMO patients.

Red blood cell transfusion is an independent risk factor for higher mortality, longer stay in the hospital, sepsis, organ failure, and increased costs. RBC transfusion is associated with risks of alloimmunization, transfusion-related immunomodulation, transfusion-related acute lung injury, and microcirculatory dysfunction. Blood transfusion has been shown to be associated with increased incidence of infections.[37–39]

Better ECMO circuit designs, careful management of heparinization at the time of deployment of ECMO, meticulous surgical hemostasis, and cell salvage can all help reduce the amount of blood exposure. Newer oxygenators that require smaller priming volumes (Quadrox oxygenator; Maquet) might help reduce exposure to blood.

There is evidence that having a blood transfusion policy in the intensive care unit and a method of ensuring its implementation has an impact in reducing the number of red cell transfusions.[40,41]

ECMO DURATION

A large multi-institutional database analysis by Gupta et al. showed that the longer the duration of ECMO, the higher the mortality. After adjusting for patient and center characteristics, there was a 12% increase in the odds of mortality for every 24-hour increase in ECMO duration (odds ratio 1.12, 95% CI 1.07–1.18, $P < .001$).[42]

In their study, Chaturvedi et al. evaluated the predictors of hospital survival in children with biventricular physiology supported with V-A ECMO after open heart surgery. The median duration of ECMO was 6 days. The density curve for survivors was close to a normal distribution. There were two prominent modes in the distribution of deaths. The early peak was due to withdrawal of support from patients in whom brain death became apparent early in the ECMO run.

An Extracorporeal Life Support Organization Registry study showed that overall ECMO survival is 45% in children with cardiac disease and drops down to 23%–25% survival for ECMO between 14 and 28 days and 13% for ECMO runs longer than 28 days.[43,44]

In summary, the average duration of V-A ECMO post–cardiac surgery is around 3–7 days. Survival rates decline significantly beyond 10 days. Reversibility of ventricular function is key. Any residual lesions must be diagnosed and treated early in the ECMO run. Children with superimposed lung injury may need longer ECMO runs even if cardiac function recovers.[45–47]

CONCLUSIONS

- In children with CHD, V-A ECMO is used to stabilize the hemodynamics prior to and postsurgery.
- ECMO aims to provide CO while "resting" the heart following the operative insult to allow time for recovery of function.
- Due to the heterogeneity of conditions and patient factors, the indications and timing of V-A ECMO in postcardiotomy patients are based on empirical clinical judgment.
- Any underlying residual lesions must be identified and corrected promptly.
- Reversibility of the underlying etiology of circulation failure is crucial to a successful outcome.
- Exit strategies include bridge to recovery/surgery, bridge to VAD, OHT, or end-of-life care.
- Key factors for improved ECMO outcomes include having a structured ECMO program, multidisciplinary team approach, anticipation, protocolized approach, continuing education and training of ECMO staff, and research.

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REVIEW QUESTIONS

1. Cardiac index in a neonate is approximately

   A. 1.8 L/m^2/min
   B. 2.8 L/m^2/min
   C. 3.8 L/m^2/min
   D. 4.8 L/m^2/min

2. Which of the following is least important in DO_2 (oxygen delivery)?

   A. Cardiac output
   B. Hemoglobin concentration
   C. Hemoglobin saturation
   D. Dissolved plasma oxygen

3. Cardiovascular effects of V-A ECMO include all of the following except

   A. Decreased preload
   B. Increased afterload
   C. Decreased pulse pressure
   D. Increased stroke volume

4. Increasing ECMO flow in V-A mode results in all of the following except

   A. Increased LV end-diastolic pressure
   B. Increased mean arterial blood pressure
   C. Increased PaO_2
   D. Increased CO

5. Which of the following statements is false regarding anticoagulation on ECMO?

   A. ACT is the most commonly used test to monitor anticoagulation.
   B. ACT correlates well with anti-Xa activity.
   C. ACT is affected by temperature, platelet count, and anemia.
   D. Anti-Xa levels indicate heparin activity rather than actual heparin level.

6. Which of the following is true regarding hemolysis on V-A ECMO?

   A. Red or dark urine indicates hemolysis.
   B. Clots in the circuit are the most common reason.
   C. Plasma free hemoglobin is a useful diagnostic test.
   D. Morbidity arises from its byproducts, specifically plasma free hemoglobin (pfHb).
   E. Circuit change should be considered if hemolysis is significant.
   F. All of the above.

7. For Harlequin syndrome, which of the following statements is false?

   A. It is not a feature of V-V ECMO.
   B. It is due to a dual source of oxygen content—native lung and ECMO.
   C. It can happen at the aortic root, causing coronary insufficiency.
   D. As the LV ejection improves, the watershed area (mixing point) moves proximally toward the proximal aorta.

8. Improving mixed venous oxygen saturation (SVO_2) and lactate clearance are considered to indicate adequacy of ECMO support. If this is not observed, which of the following statements is true?

   A. Inadequate ECMO flow could be the reason.
   B. Septic shock (increased oxygen consumption—VO_2), rather than poor ventricular function, could be the reason for ECMO.
   C. Localized ischemia (bowel) or infarction should be considered.
   D. All of the above.

ANSWERS

1. B
2. D
3. D
4. C
5. B
6. F
7. D
8. D

30.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION IN CHILDREN

Juan M. Lehoux and Giles J. Peek

STEM CASE AND KEY QUESTIONS

A 3-year-old, 13-kg female was taken to the emergency department (ED) by her parents; she had symptoms of lethargy, nausea, and vomiting. The child was diagnosed with influenza and was treated with over-the-counter medications, and oral hydration and sent home after a period of observation in the ED.

A day after the initial encounter, the patient's brother was brought to the same ED with similar symptoms. Further questioning by the ED staff revealed that the family had used aluminum phosphide pellets against a bedbug infestation. The family was advised to bring the sister back to the ED for emergent evaluation. On arrival to the ED, the patient was lethargic and difficult to arouse. The child was afebrile, and her blood pressure was 60/40 mm Hg with a heart rate of 155 beats/min.

The 3-year-old female was admitted to the pediatric intensive care unit (PICU), where an echocardiogram revealed an ejection fraction (EF) of less than 20%. The patient was started on a dopamine infusion and transferred to a tertiary care center for management of significant cardiotoxicity. The child's hemodynamics continued to deteriorate after arrival to the referral hospital's PICU despite the use of inotropic medication (dopamine 10 μg/kg/min), prompting urgent intubation and extracorporeal membrane oxygenation (ECMO) team consultation.

Shortly after the ECMO team activation, the child went into cardiac arrest, and cardiopulmonary resuscitation (CPR) was started. The surgical team arrived 10 minutes after the start of the resuscitation.

The child was cannulated during external cardiac massage via cutdown on the right cervical vessels. The right carotid artery was cannulated with a 14 French (14F) Biomedicus cannula (Medtronic, Minneapolis, MN) and the right jugular vein using a 17F Biomedicus NextGen (Medtronic). ECMO support was started on full flow (100 mL/kg/min). Flow was adequate per our protocol and not limited by our choice of cannulae.

Despite adequate veno-arterial (V-A) ECMO support, significant metabolic acidosis remained. The child was started on continuous renal replacement therapy via the ECMO circuit, with normalization of her pH after 12 hours of initiation of support. The temperature was set at 34°C on the ECMO circuit as a neuroprotective measure for the first 24 hours.

Early in the ECMO course, the child had evidence of severe multiorgan dysfunction. The patient was anuric and had an alanine aminotransferase of 2800 U/L, consistent with significant kidney and liver injury. The neurologic examination was normal despite over 1 hour of CPR.

After 4 days of V-A ECMO support, there was no detectable pulsatility on the arterial line trace. The child had worsening pulmonary edema due to severe left ventricular (LV) dysfunction and distention. The patient was taken to the catheterization laboratory for a balloon atrial septostomy. The initial left atrial pressure was 33 mm Hg with a right atrial pressure of 16 mm Hg. After the septostomy, the atrial pressures equalized, and the pulmonary edema resolved over the course of several days.

After 15 days of support, her cardiac function recovered. A pump-controlled retrograde trial off (PCRTO) ECMO was performed, during which the EF was 46% with adequate hemodynamics.

The child was decannulated from the V-A ECMO circuit without difficulty and the vessels repaired.

The patient was weaned from the ventilator 4 days after decannulation and discharged after several weeks. The child made a complete recovery.[1] The brother recovered from his mild symptoms without requiring intervention.

DOES THIS CHILD MEET CURRENT INDICATIONS FOR EXTRACORPOREAL CPR?

Extracorporeal membrane oxygenation was first successfully used by Bartlett in the 1970s for children undergoing cardiac surgery with subsequent inability to wean off cardiopulmonary bypass (CPB) and later in neonatal respiratory failure.[2] Outcomes in the cardiac surgical patient has prompted the expansion of indications for mechanical circulatory support to other etiologies of hemodynamic compromise, including sepsis and, more recently, in-hospital cardiac arrest.[3–5] The etiology of this child's heart failure is cardiomyopathy secondary to intoxication with phosphine gas. Many case reports have described the use of extracorporeal life support (ECLS)

in cases of acute intoxication in patients not expected to survive otherwise.[6–8] The studies describing extracorporeal CPR (ECPR) in cardiogenic shock of toxic etiology described a survival between 24% and 71% despite CPR times of over 60 minutes.[9,10]

Phosphine gas is a mitochondrial poison that inhibits the oxidative capacity of the cell and has no known antidote.[11] Despite our concern that end-organ function would continue to deteriorate despite adequate V-A ECMO support, the child made a full recovery. This result supports our strategy of offering ECPR to children in shock unless a known contraindication exists.

WHAT WAS THE CANNULATION STRATEGY FOR THIS CHILD?

Children that need ECPR have great variation in their size and weight. Available cannulation sites include the cervical vessels, the femoral vessels, and central cannulation. In children who are not yet walking, femoral cannulation is rarely an option due to the inadequate size of the femoral artery and vein. Once the child's weight is more than 10 kg, femoral cannulation is possible. For ECPR, maintaining uninterrupted, quality CPR is essential for good neurologic outcomes.[12,13] Despite femoral cannulation being technically possible in this patient, performing a femoral cutdown would hinder ongoing CPR. Cervical cannulation allows the surgeon to stand over the head of the child, leaving space for chest compressions to continue. Cervical cannulation is also technically easy in a child and allows fast institution of flow. An intact circle of Willis is usually present in children. The management of the cervical vessels at the time of decannulation varies between institutions. Some will ligate the vessels out of concern for post-decannulation embolization into the cerebral circulation. It is our practice to attempt to repair the cervical vessels if technically feasible. The neurologic fate of children after V-A ECMO decannulation remains under study. Currently, few data exist to support one strategy over the other.[14–16]

Central cannulation is usually reserved for the post–cardiac surgery patient. Any child who has recently undergone cardiac surgery and later arrests in the cardiac intensive care unit should have their chest opened as soon as possible.[17] If there is no return to spontaneous circulation with chest opening, then V-A ECMO cannulation can be performed using the aorta and right atrium. Central cannulation is advantageous because large cannulae can be used to support supraphysiologic flow rates if the patient so requires. A major disadvantage in the setting of ECPR without recent cardiac surgery is that CPR must be interrupted in order to perform the sternotomy, potentially compromising neurologic outcomes.

WHY DID THIS CHILD DEVELOP PULMONARY EDEMA ON ECMO SUPPORT?

Patients cannulated for ECPR secondary to cardiogenic shock have, by definition, extremely compromised LV function. In addition to the underlying dysfunction, the arterial cannula flowing at full flow (100 mL/kg/min) adds significant afterload to an already dysfunctional ventricle. Despite full flow, rarely does the venous cannula capture 100% of the systemic blood returning to the right atrium. That volume, in addition the bronchial artery flow, returns to the left side of the heart, causing progressive distention of the LV with resulting increase in pressure. The elevated left ventricular end-diastolic pressure (LVEDP) subsequently elevates the pressures in the pulmonary vasculature, resulting in pulmonary edema.

In children, this problem is usually managed by performing a balloon atrial septostomy, as was done in this case. This allows the V-A ECMO circuit to decompress the left side of the heart via the venous cannula. In adolescents, the atrial septum is usually as thick as in adults, making balloon septostomy ineffective. Several strategies have been described to deal with LV distention in adults and older children, including septal puncture and placement of a left atrial venting cannula, LV apical venting, and Impella device decompression. Preferred strategies vary by institution.[18–20]

HOW IS V-A ECMO WEANED AFTER ECPR?

After the patient is on V-A ECMO, the etiology of the arrest must be determined. Any residual structural lesions must be addressed in the catheterization laboratory if feasible or in the operating room if necessary. Any metabolic causes must be corrected. In cases of intoxication, the end organs must be given sufficient time to recover. Time of support will vary depending on the etiology.

Pulsatility of the arterial line trace is usually a good indicator of recovery. Echocardiographic evaluation of the LV on full flow usually underestimates the degree of recovery given the significant afterload caused by the arterial cannula flow.

The V-A ECMO weaning strategies vary between institutions. The most common method is to decrease flows and clamp off the circuit, allowing circulation via the bridge between the arterial and venous cannulae. Maintaining circulation in the ECMO circuit prevents clot formation in the oxygenator. Using this method, the V-A ECMO cannulae are briefly unclamped every 10 minutes to prevent clot formation in the tubing.

Our method of choice is the PCRTO strategy.[21] This method allows trial off V-A ECMO without clamping the circuit. In PCRTO, a bridge between the limbs of the circuit is not necessary; this simplifies the circuit and reduces the needed connectors, which contribute to stagnant flow and clot formation in the circuit.[22]

After optimization of mechanical ventilation, the V-A ECMO flows are slowly reduced to zero. Once no flow is measured in the circuit, pump revolutions per minute are decreased further until a retrograde flow of approximately 10% of full flow is established, and the circuit gas sweep is disconnected.

Echocardiographic evaluation is performed while the trial off is ongoing. Once the patient has demonstrated ventricular recovery and the ability to maintain adequate hemodynamics, decannulation is performed.

WHAT DO YOU DO IF THERE IS A CATASTROPHIC COMPLICATION WHILE ON SUPPORT OR LACK OF MEANINGFUL RECOVERY AFTER ECPR?

Despite our best efforts, fewer than half of the patients afforded ECPR will live to hospital discharge.[3] ECLS provides hope of recovery where there was once minimal chance of survival. As with many technological advances in medicine, our ability to sustain life often leaves us in the unenviable situation of caring for patients who are technically alive, but that have no realistic chance of recovery.

Clear and open communication with family members is of utmost importance. The decision to terminate support is often the hardest that a family will ever make. This is especially true in the case of a child. Termination of support in the face of family resistance despite no chance of recovery remains one of the more difficult issues associated with ECPR. Cultural, religious, moral, and legal concerns vary widely between countries. ECMO centers benefit from a predetermined strategy devised with contribution from a multidisciplinary team to facilitate termination of support when indicated.[23]

DISCUSSION

The use of ECPR continues to increase as the indications expand. Due to the similarity of ECMO to CPB and the familiarity that cardiac surgeons have with extracorporeal support, ECPR was initially used exclusively for postcardiotomy shock. Refinements in the ECMO circuits and increased understanding of the technology has yielded improved management protocols that have simplified the care of these patients and provided opportunity for survival where there was once none.

Improved survival using ECPR in the post–cardiac surgery patient has allowed us to consider ECPR in many patients that suffer in-hospital cardiac arrest. The decision to offer ECPR to the noncardiac patient must be made at a moment's notice. Only patients with an expectation of meaningful recovery should be offered mechanical support. Patients with advanced malignancies, significant chromosomal abnormalities, and severe neurological injury should not be offered ECMO.

Once the decision to cannulate the patient is made, time is of the essence. Establishment of adequate circulation in the shortest amount of time improves outcomes. Prolonged CPR duration before V-A ECMO is a significant risk factor for death.[24] That being said, given the complexities of mobilizing a team, in reality, most patients receive more than 60 minutes of CPR before V-A ECMO support can be established.[25] No one measure of hypoperfusion such as lactic acidosis or low pH should be used as a reason not to continue efforts to cannulate the patient. Once the decision is made and the team has been activated, the priority of the treatment team should be to continue quality CPR with minimal interruption while the team arrives and cannulation is performed.[26]

Cardiac arrest in a pediatric patient is a high-stress situation for all members of the healthcare team. It is not uncommon for the resuscitation to be hindered by members of the healthcare team not directly involved in caring for the patient, who are drawn to the site of the arrest with the best intention but are providing no actual assistance to the code team.

Best efforts should be made by the leader of the resuscitation to clear the room of unnecessary staff. Space is often limited, and the ECMO team will need room not only the circuit, but also to establish a sterile field expeditiously. Cardiac arrest simulations are common in high-functioning children's hospitals. These simulations are familiar to all staff caring for critically ill children and have traditionally only included Pediatric Advanced Life Support protocols and the like. Including ECPR into the algorithm and practicing setting up for V-A ECMO cannulation can potentially decrease the time to full support, contributing to improved neurologic outcomes.[27–29]

Current recommendations only include ECPR in witnessed in-hospital arrests; however, patients suffering witnessed out-of-hospital cardiac arrest who have received prompt, continuous, high-quality CPR are increasingly offered ECPR with varying degrees of success.[30–32]

Adults undergoing ECPR are usually cannulated femorally. Since children range from neonates to adult-size adolescents, cannulation techniques vary among age groups and indications.

In the post–cardiac surgery patient who has had a recent sternotomy, opening the sternum urgently is usually part of the resuscitation algorithms. If the patient remains in cardiac arrest, V-A ECMO support is easily established via central cannulation. This holds true in most cardiac surgery patients regardless of age. In children who suffer in-hospital cardiac arrest who have not had a sternotomy, the decision between femoral and cervical cannulation is made considering the patient's size and suitability of the vessels for adequate cannulation.

In children who are not yet of walking age, cervical cannulation is universal due to the inadequate size of the femoral artery and vein for adequate support.

In children who are over 10 kg, femoral cannulation is usually possible; however, in the setting of ECPR, it is, in our opinion, rarely feasible in younger children. Cervical cannulation in infants and larger children not yet of adult size allows the implanting team to work while external chest compressions continue uninterrupted. The cervical vessels are easily and quickly dissected free of surrounding tissue. Cannulation is usually easily accomplished, thereby decreasing the time to establishment of circulation.

In adolescents of adult size, the femoral route is usually chosen for ECPR. Both percutaneous and cutdown techniques may be used. Although cutdown can be performed efficiently in a slim adolescent in cardiac arrest, on occasion the child will be obese, making dissection of the femoral vessels with active CPR challenging. For this reason, percutaneous cannulation is our method of choice in adolescents. Establishment of vascular access while the child is in cardiac arrest can be quite challenging. Trying to distinguish if the guide wire is in an artery or vein can be a challenge with no difference in pulsatility or color of the blood. Transesophageal echocardiography guidance allows visualization of the wire

in the vasculature and aids in appropriate cannulation. Once femorally cannulated and on V-A ECMO support, attention must be paid to the distal limb perfusion. Management strategies vary among centers, from an expectant approach that provides revascularization via a distal perfusion cannula connected to the ECMO circuit only of the lower extremity shows signs of compromised perfusion versus universal placement of a distal perfusion cannula soon after cannulation, which is our preferred approach. Whatever method is chosen, close attention must be paid to the lower extremity distal to the site of cannulation in order to avoid significant morbidity and possible limb loss.[33–35]

After circulatory support is established, inotropic and pressor medications should be weaned off to allow vasodilation and improved tissue perfusion if blood pressure allows. Higher flow rates are preferred to pressor medications in the management of arterial blood pressure.

Pulmonary edema on V-A ECMO support is a common complication after ECPR. LV dysfunction plus the afterload provided by the circuit prevents ventricular emptying and frequently causes LV distention. The increased end-diastolic pressure is transmitted via the left atrium and pulmonary veins to the pulmonary vasculature, causing increased hydrostatic pressure and fluid extravasation, leading to severe pulmonary edema. In addition to pulmonary dysfunction, high ventricular pressures lead to endocardial ischemia and impedes possible cardiac recovery. Decompression of the distended LV is of utmost importance.[18–20]

Several methods of LV decompression have been described in the pediatric population. In neonates, infants, and small children, the atrial septum is thin enough to allow for an atrial balloon septostomy in the cardiac catheterization laboratory. As children age, the atrial septum becomes much less compliant, making septostomy unfeasible. In older children as well as in adults, LV decompression has been accomplished via transcatheter septal puncture. After the septum is punctured, a cannula can be placed across the septum with fluoroscopy guidance. This left atrial "vent" is then connected to the venous limb of the V-A ECMO circuit, allowing for decompression.[18] Alternative strategies include transapical vent placement via a left anterior thoracotomy, a retrograde trans–aortic valve pigtail catheter, and an Impella device have all been used with varying levels of success.[20]

Once on support, an anticoagulation strategy that simplifies management should be devised. The commonest protocols in use today use heparin given its wide use in clinical practice. Despite its wide use in children, all heparin protocols are derived from adult practice and are often inadequate, especially in neonates. Heparin depends on antithrombin III for its antithrombotic activity. In neonates with immature coagulation systems, the levels of antithrombin can be quite variable, causing significant variation in levels of anticoagulation. This, in conjunction with the lower flow rates used in small children, predisposes to increased incidence of circuit thrombus or overanticoagulation, causing bleeding complications.

Routine use of direct thrombin inhibitors (DTIs) obviates the need for antithrombin III. Bivalirudin is a DTI in common use in the Berlin Heart left ventricular assist device (LVAD) patient.[36–38] Use of a DTI in ventricular assist device patients has reduced complications related to ventricular assist devices (VADs) in recent years. Given the success of this anticoagulation strategy in VADs, we have adopted bivalirudin as our first-line anticoagulant in neonates and infants, reducing our need for circuit exchanges and reducing our incidence of neurologic and bleeding complications.[39]

If the child on V-A ECMO shows evidence of cardiac recovery, a weaning trial is usually performed to determine if the patient can maintain adequate hemodynamics without mechanical assistance.

Several methods exist, as described in the section above. PCRTO is our preferred method for several reasons. Retrograde flow through the circuit minimizes clot formation and therefore allows for a longer trial off, minimizing the risk of losing the circuit in the eventuality that the patient is not yet ready to be decannulated.

The retrograde trial off causes a left-to-right shunt that represents a mild volume load to the ventricle. It stands to reason that if the child tolerates the trial off with the slight volume load of the retrograde flow through the circuit, then he or she should easily tolerate decannulation.

Survival after ECPR is approximately 40% in neonates and in children with some degree of variation (29%–43%) depending on the age of the child and the location of the cardiac arrest.[3] This stands in contrast to the often-dismal results of conventional CPR. We predict that ECPR use will continue to expand as familiarity with cannulation techniques and ECMO continues to improve. Every effort should be made to expand the availability of this potentially life-saving technology.

CONCLUSION

- Extracorporeal CPR provides superior outcomes when compared to traditional CPR in children.
- A team approach is critical to successful outcomes.
- High-quality CPR must be performed while resources are mobilized.
- Cardiopulmonary resuscitation times of less than 60 minutes before the start of mechanical support are key.
- Evidence-based protocols facilitate ECMO management after ECPR.

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REVIEW QUESTIONS

1. You are called to the bedside of a 1-year-old boy who sustained a VF cardiac arrest after sticking a metal object into an electrical outlet. The incident was witnessed by the mother,

who started External Cardiac Massage. Paramedics inserted an Laryngeal Mask Airway and an intraosseous needle; duration of cardiac arrest was 40 minutes. What is your opinion?

A. Extracorporeal CPR is not indicated as the arrest has been over 30 minutes.
B. Extracorporeal CPR is not indicated as the patient is too young.
C. Extracorporeal CPR should be initiated via percutaneous femoral cannulation.
D. Extracorporeal CPR should be initiated by open cannulation of the right neck vessels.

2. You are called on a satellite phone by the ski patrol; a teenager has been recovered from an avalanche. He was buried for around 2 hours. When he was found there was a good air pocket and a clear airway; he appeared to be in asystole. His core temperature was 18°C. CPR was started as soon as he was extricated. He has an obvious femoral fracture but no other injuries. A helicopter is inbound to the casualty equipped with Lund University Cardiopulmonary Assist System (LUCAS). Flying time to your institution is 1 hour. What do you advise?

A. Stop CPR and declare death as the patient is too cold, has a femoral fracture, was buried for too long, and will take too long to arrive.
B. Start LUCAS, confirm the airway is secure and ventilation is effective, and transfer the patient for consideration of ECPR.
C. Start LUCAS, start external warming measures, and bring the patient to your institution. ECPR can only be considered if the core temperature rises above 25°C.
D. Do not start LUCAS as it can cause rib fractures; do not perform ventilation but bring the patient for ECPR.

3. You are called to the oncology floor. A 72-year-old woman undergoing chemotherapy for stage 4 colonic cancer and brain metastases has had a cardiac arrest. The team started cardiac massage half an hour ago. They were going to stop resuscitation but the patient's family said that they "wanted everything done," and they had seen an article on the news about a teenager saved from an avalanche by a "miracle heart machine." What action should you take?

A. Initiate ECPR via the femoral vessels as quickly as possible.
B. Refuse to attend as the patient is not a candidate for ECPR.
C. Initiate ECPR via the neck vessels to obtain higher flow.
D. Attend the floor to examine the patient, confirm the history, and then explain to the family why their relative is not a candidate for ECPR.

4. A 4-year-old suffered a cardiac arrest following 75% total body surface area, full-thickness burn injury; she was cannulated for ECPR via the neck vessels in the ED a week ago. Unfortunately, she suffered hypoxic brain injury during the fire and subsequent cardiac arrest and has now been declared brainstem dead on ECMO. The parents have asked if she can be an organ donor. What is your advice?

A. She cannot be an organ donor because she is on ECMO.
B. She cannot be a heart donor because she had a cardiac arrest.
C. She cannot be a lung donor because she was in a fire.
D. None of the above.

5. A 5-day-old baby is postoperative day 1 following an arterial switch operation. The surgery was challenging, and the patient had to go back on CPB to revise the coronary artery buttons. The patient has had several runs of ventricular tachycardia and has been treated with amiodarone. The sternum is splinted open, and a Gore-Tex membrane has been sewn to the skin edges. While you are rounding, the patient suffers a cardiac arrest with ventricular tachycardia rapidly progressing to asystole. External cardiac massage is started; the end-tidal CO_2 trace is normal. What is the best course of action?

A. Open the chest, initiate ECPR draining from the right atrium and returning to the aorta, stabilize the patient overnight, and then reassess.
B. Open the chest, initiate ECPR draining from the right atrium and returning to the aorta, stabilize the patient, and then go to the catheterization laboratory.
C. Start ECPR via the neck vessels as this is the best thing to do in a baby.
D. Do not attempt ECPR, which is contraindicated because the operation has been unsuccessful.

ANSWERS

1D. There is no absolute cutoff for a witnessed arrest with good resuscitation in terms of duration when ECPR becomes contraindicated. There is consensus that if ECMO flow can be started in under approximately 1 hour that outcomes are acceptable. Age/weight cutoffs for ECPR are based on those used for neonatal ECMO (i.e., 2 kg and 34 weeks' estimated gestational age). Femoral cannulation is inadvisable in patients who have not begun walking as the vessels are too small to insert adequate size cannulae. The neck is the best access for this patient; a median sternotomy is also a viable option if it can be done quickly enough.

2 B. The patient was alive when buried, as evidenced by the air pocket and clear airway; he had a hypothermic cardiac arrest. Hypothermic patients may be resuscitated after long periods of arrest, particularly if good CPR is given once they are rescued. A mechanical CPR machine such as the LUCAS can provide much improved cardiac output compared to manual compressions; while rib fractures can occur, the benefit outweighs the risk. Ensuring adequate ventilation is important during a long transfer; this can be done by any method (i.e., bag/valve/mask, laryngeal mask airway, or endotracheal tube), but must be confirmed to be effective, ideally by positive end-tidal CO_2 tracing. The femoral fracture is only a relative contraindication to ECMO and should be manageable with low-dose anticoagulation and traction. Cannulation should

be via the contralateral groin vessels. Attempts to actively warm the patient during transfer are unlikely to be effective and will probably be counterproductive as the hypothermia is neuroprotective.

3D. Over the age of 65, the chance of a successful neurological outcome reduces markedly, and ECPR should only be offered to elderly patients in very exceptional circumstances. In addition, ECMO outcomes are very poor in patients with disseminated cancer, which can legitimately be seen as a contraindication. Just because something can be done does not mean it should be done. Patients' families will often take great solace from the fact that their relative was carefully considered for ECPR but that nothing more could be done.

4D. All of her organs are potentially usable, and ECMO is not a contraindication. Each organ will need to be assessed individually to deem suitability. The ECMO circuit can be used to support the donation process by cooling the donor and maintaining organ perfusion. Brainstem testing while on ECMO support must follow a specific apnea protocol to ensure an adequate $PaCO_2$ is obtained.

5B. Ventricular arrhythmias are rare in children even after heart surgery and are usually related to myocardial ischemia. It is likely that there is a problem with the coronary arteries that was not fixed during the second run on bypass. Rapid initiation of ECPR via chest cannulation will allow organ function to be preserved while a treatable cause is sought. Cardiac catheterization and coronary angiography will determine if the coronary arteries are remediable or not. If they are not or if the myocardium does not recover, the patient may be a candidate for longer term support with bridge to transplantation.

31.

ECMO AS BRIDGE TO PEDIATRIC HEART TRANSPLANTATION

Marissa A. Brunetti, Christopher E. Mascio, and Matthew J. O'Connor

STEM CASE AND KEY QUESTIONS

A 14-year-old, previously healthy, female presented to the emergency room of her local children's hospital with a 2-week history of nonproductive cough, shortness of breath, and tachypnea. She denied rhinorrhea, congestion, or fevers. She reported nausea and loss of appetite but no emesis or diarrhea. She also reported decreased energy and easy fatigability. She was seen by her primary pediatrician 1 week prior and given a diagnosis of a viral syndrome. She re-presented to her primary pediatrician 3 days ago for worsening symptoms and was prescribed amoxicillin for presumed pneumonia. Her parents brought her to the emergency room for ongoing work of breathing. She lives with her parents and 2 siblings, who are all healthy, with no known sick contacts.

In the emergency room, her heart rate was 130 beats/min, respiratory rate 40 breaths/min, blood pressure 95/50 mm Hg, and oxygen saturation 90% on room air. Physical examination revealed a well-nourished female with moderate respiratory distress with tachypnea and retractions. Cardiac examination revealed a tachycardic, regular rhythm with a gallop but no murmur. Lungs had audible crackles, and the abdominal examination was nontender with liver edge palpable 3 cm below the right costal margin. The extremities were cool, with diminished distal pulses in all four extremities. There was no clubbing or edema in her extremities. A chest x-ray was obtained, which showed cardiomegaly and pulmonary edema without infiltrate or effusions. Her white blood cell count was 10 K/μL, hemoglobin 12.5 g/dL, platelet count 210 K/μL. Electrolytes were normal, blood urea nitrogen (BUN) 30 mg/dL, and creatinine 0.6 mg/dL. Given her symptoms with cardiomegaly and pulmonary edema on chest x-ray, an echocardiogram was obtained, which showed a structurally normal heart, mild right and severe left heart dilation, moderate right and severe left ventricular (LV) dysfunction with a LV ejection fraction of 26%, mild tricuspid regurgitation, and moderate mitral regurgitation (MR). Given her echocardiogram findings, she was admitted to the cardiac intensive care unit (CICU) for management of decompensated heart failure (HF) in the setting of presumed dilated cardiomyopathy (DCM).

HOW IS DILATED CARDIOMYOPATHY DIAGNOSED?

Her B-type natriuretic peptide (BNP) was elevated at 2500 pg/mL. Serum troponin was sent to evaluate for myocarditis and was low at 0.02 ng/mL. Also, a sample was collected for a viral panel to further evaluate for viruses associated with myocarditis; the panel was negative. Electrocardiogram showed sinus tachycardia with no signs of ischemia. On her second hospital day, cardiac magnetic resonance imaging (MRI) was performed, which showed severe LV dilation, severely decreased biventricular ejection (LV ejection fraction 24%, right ventricular (RV) ejection fraction 22%), moderate MR, no evidence of focal or diffuse fibrosis, no criteria for myocarditis, and low Qs by velocity mapping at 1.9 L/min/m^2, all consistent with a diagnosis of DCM.

HOW IS DECOMPENSATED HEART FAILURE MANAGED?

On admission to the CICU, the patient was started on high-flow nasal cannula (HFNC), a low-dose milrinone infusion at 0.25 μg/kg/min, and intravenous furosemide for management of HF. Her respiratory status improved on HFNC and intravenous furosemide. Milrinone was increased for inotropic support of severe biventricular dysfunction. On her second hospital day, after uneventful MRI, her creatinine was noted to be elevated to 1.0 mg/dL. She had increased nausea with intermittent emesis. She then developed hypotension requiring initiation and titration of dopamine. Hypotension continued, and the decision was made to intubate with extracorporeal membrane oxygenation (ECMO) standby.

HOW IS MECHANICAL SUPPORT USED IN DECOMPENSATED HEART FAILURE?

The patient was intubated without cardiac arrest; however, with ongoing hypotension requiring escalating vasopressor support, a mixed venous saturation of 40%, and signs of inadequate organ perfusion (elevated creatinine and emesis prior to intubation), she was urgently placed on ECMO via cervical

cannulation. She was maintained on ECMO flows of 130 mL/kg/min, which provided adequate blood pressure and a mixed venous saturation of 65%–70%. The patient had no patent foramen ovale seen on echocardiogram, and lung fields developed significant pulmonary edema on chest x-ray, so she was taken urgently for balloon atrial septostomy in the catheterization laboratory to decompress the left heart. Heparin infusion was started with cannulation, and coagulation laboratory values were maintained at appropriate levels. The ventilator was set to maintain open lungs.

Over the ensuing 5 days, her creatinine decreased to her baseline of 0.6 mg/dL. Urine output remained adequate on ongoing furosemide therapy. Liver function test results initially increased due to low cardiac output but then returned to baseline. She was maintained on sedation with the ability to answer questions and follow commands. Enteral feeds were begun and advanced via a nasogastric tube. She remained without signs of infection. Milrinone was increased to a maximal dose of 1 μg/kg/min, and dopamine was weaned and maintained at 3 μg/kg/min, both for inotropic support of HF. Echo imaging continued to show a dilated heart with severe biventricular dysfunction. With attempts to wean ECMO flows, she developed recurrence of hypotension. Given the low likelihood of myocardial recovery, she was evaluated for heart transplant (HT), and plans were made for conversion to a ventricular assist device (VAD) for long-term mechanical support as a bridge to transplant. On her seventh hospital day, she underwent uneventful left VAD placement and ECMO decannulation. She recovered from VAD placement and was able to be discharged home with good end-organ function and baseline neurologic examination 3 weeks after VAD placement. A suitable donor became available, and she underwent orthotopic HT 3 months after initial presentation.

DISCUSSION

HEART FAILURE BACKGROUND

Heart failure, defined by the American Heart Association as a complex clinical syndrome characterized by impairment in the ventricular filling or ejection of blood, is uncommon in children.[1] It can be challenging to diagnose since many symptoms of HF, particularly early in the course of illness, are encountered in common childhood illnesses and because many children are unable to verbalize classic symptoms of HF, such as dyspnea or palpitations. For example, in a study of children presenting to the emergency department with HF, the most common presenting complaint was abdominal pain; it is not uncommon for children with HF to have multiple medical evaluations for symptomatic complaints before the correct diagnosis is achieved.[2] Therefore, a high index of suspicion coupled with careful physical examination are necessary to prevent delays in diagnosis and initiation of appropriate HF therapy.

The differential diagnosis of HF in children is broad, and a full discussion of all possible causes is beyond the scope of this chapter. However, a list of potential causes is provided in Box 31.1. Primary cardiomyopathies (dilated, hypertrophic, restrictive, noncompaction, and arrhythmogenic RV dysplasia) all occur in children, with DCM the most common, with an incidence of approximately 0.6 cases per 100,000 children

Box 31.1 **ETIOLOGY OF HEART FAILURE IN CHILDREN**

Primary cardiomyopathies
Dilated[a]
Hypertrophic
Restrictive
Left ventricular noncompaction
Arrhythmogenic RV dysplasia-cardiomyopathy

Cardiomyopathy related to neuromuscular disease
Duchenne muscular dystrophy
Becker muscular dystrophy
Friedreich ataxia

Inflammatory
Myocarditis
Systemic lupus erythematosus

Acquired heart disease
Kawasaki disease
Rheumatic fever
Endocarditis
Uncontrolled hypertension

Toxic
Global hypoxemic-ischemic injury
Sepsis-related myocardial dysfunction
Anthracycline chemotherapy
Chest radiation
Ethanol

Metabolic
Hyperthyroidism
Hypothyroidism
Inborn errors of metabolism
Disorders of mitochondrial metabolism

Congenital heart disease
Preoperative
- Coarctation of aorta
- Severe aortic stenosis
- Hypoplastic left heart syndrome
- Congenital mitral regurgitation
- Anomalous origin of the left coronary artery from the pulmonary artery

Postoperative
- Single-ventricle congenital heart disease
- Residual atrioventricular valve regurgitation
- Residual semilunar valve regurgitation or stenosis
- Residual left-sided obstruction

Cardiac rhythm related
Arrhythmia induced from chronic atrial or ventricular arrhythmias
Chronic ventricular pacing
Congenital complete heart block

[a]Includes idiopathic and familial subtypes.

per year.[3] DCM may be encountered in familial and idiopathic forms or may result secondary to an external insult to the heart, such as the sequelae of myocarditis or exposure to toxins (e.g., anthracycline chemotherapy.)

Myocarditis is an important cause of HF in children and, in developed countries, is most commonly associated with viral infection; parvovirus B19, adenovirus, and human herpesvirus 6 are examples of causative viral agents. Myocarditis is frequently subclinical in nature, but can occasionally have a fulminant presentation characterized by rapid (<24 hours) development of HF symptoms, leading to cardiovascular collapse. Myocarditis may also have a more indolent course and can be difficult to distinguish clinically from idiopathic DCM.

Several etiologies of HF distinct to children warrant special mention. Although ischemic cardiomyopathy (CM) is substantially less common in children than adults, it may be encountered in children with Kawasaki disease (KD), in which coronary artery aneurysms formed as a result of a generalized small- and medium-vessel vasculitis characteristic of KD undergo thrombosis and/or stenosis; in addition, ischemic CM can be seen in children with an anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). In ALCAPA, the anomalous left coronary artery origin creates a coronary steal phenomenon due to the left coronary artery being connected to the low-pressure pulmonary artery, leading to myocardial ischemia in portions of the LV supplied by the left coronary artery and its tributaries. ALCAPA is classically encountered in young infants with failure to thrive, feeding intolerance, and a left-sided infarct pattern on electrocardiogram (Figure 31.1). Disorders of metabolism may also manifest as HF in children, particularly infants. A classic example is disorders of fatty acid oxidation, but other metabolic derangements, such as mitochondrial disorders, can result in HF.

DIAGNOSIS OF HEART FAILURE

The diagnosis of HF starts with a thorough history and physical examination, with laboratory testing and imaging studies driven by findings in the history and physical examination. There is no single diagnostic test for HF. With respect to the history, questions appropriate to the child's developmental state may reveal HF symptoms; for example, investigation into feeding in an infant may reveal clues to the diagnosis of HF, whereas questions regarding physical activity may be more appropriate for adolescents. Many of the classic physical examination findings in HF in adults (tachycardia, soft heart tones, gallop on auscultation, hepatomegaly) are present in children; however, jugular venous distension may be difficult to elicit, particularly in infants, and peripheral edema is less common in children with HF relative to adults.

An electrocardiogram should be obtained early in the diagnostic process and examined carefully to confirm the presence of sinus rhythm; patients with chronic atrial arrhythmias (e.g., ectopic atrial tachycardia, supraventricular tachycardia) may have HF from arrhythmia-induced CM. In addition, clues to the presence of myocardial ischemia (pathological Q waves, ST segment elevation and/or depression) should be investigated. Patients with myocarditis may have dramatic and diffuse ST segment changes that mimic ischemia (Figure 31.2).

Echocardiography is central to the diagnosis of HF owing to its portability, noninvasive nature, widespread availability, and no requirement for sedation. Echocardiography can rapidly assess ventricular systolic function, exclude anatomic abnormalities found in congenital heart disease (CHD), and determine the presence of valvular regurgitation and pericardial effusion. Echocardiography may be used serially to follow response to HF therapy, although typically patients exhibit symptomatic improvement in HF well before improvements in ventricular function are observed on imaging.

Cardiac MRI is being increasingly used in children for the diagnosis of HF; it is regarded as the gold standard imaging modality for assessing ventricular systolic function and provides tissue characterization that can be used to exclude the presence of myocardial inflammation (myocarditis). Cardiac MRI, however, has more limited availability, and its benefits need to be weighed against the need for sedation in young children. Finally, laboratory diagnosis of HF focuses on

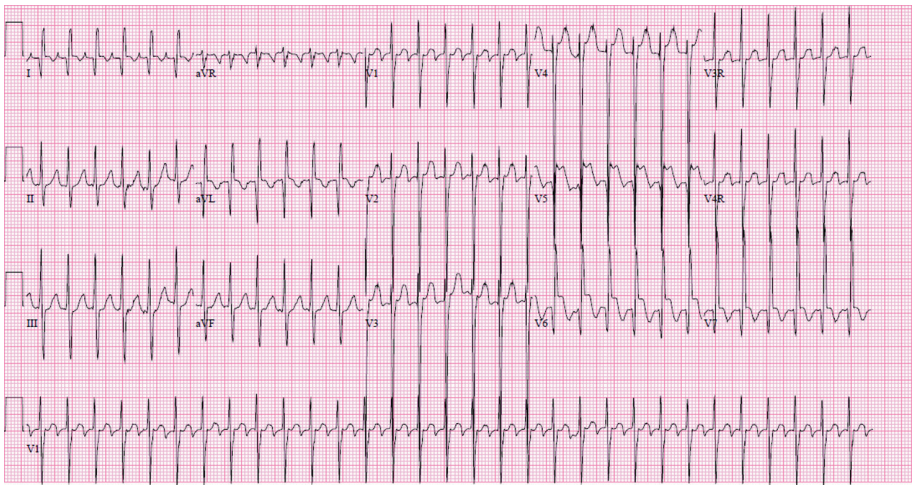


Figure 31.1 Ischemic changes seen in ALCAPA. Note T-wave inversions and Q waves in I and AVL and ST segment elevations in V5 and V6.

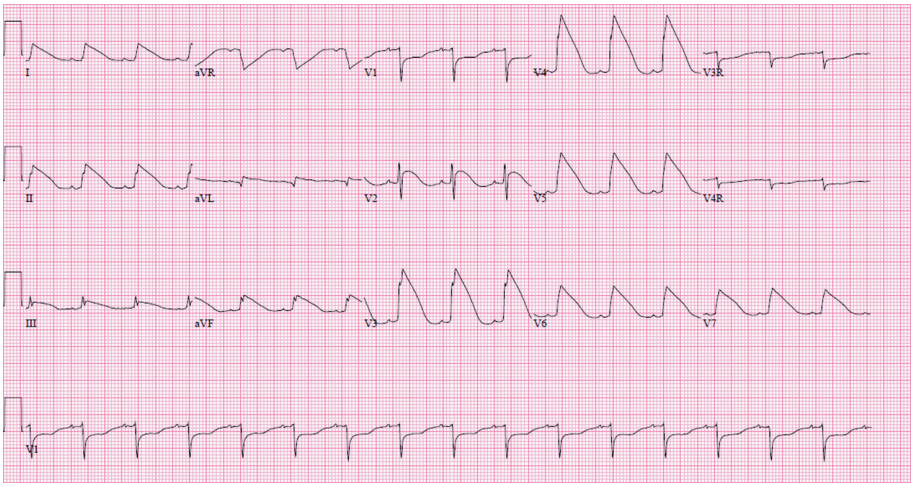


Figure 31.2 Electrocardiogram showing ST segment changes commonly seen in myocarditis patients.

assessment of end-organ function (renal function, liver function, coagulation parameters).

In addition, a number of biomarkers may be detectable in HF with high specificity and sensitivity. The most commonly utilized biomarker in children with HF is BNP; this is a hormone released by the ventricular myocardium in response to wall stress and can be used in conjunction with physical examination and imaging findings to confirm the diagnosis of HF and track response to therapy.

MEDICAL MANAGEMENT

The medical management of HF in children can be divided into three phases: stabilization of the patient in acute HF, chronic medical management, and advanced HF therapy. For a child in acute HF, therapy rests on supporting cardiac output, preventing and/or reversing end-organ dysfunction, and minimizing myocardial oxygen demand. Provision of cardiopulmonary monitoring, reliable intravenous access, and supplemental oxygen are essential. A chest x-ray should be obtained early in the clinical course in order to assess heart size and the degree of pulmonary vascular congestion. In the acute setting, medical management mainly rests on the administration of diuretics to ease pulmonary vascular congestion and respiratory distress and use of inotropic medications such as milrinone, dopamine, or epinephrine to augment cardiac output. Diuretics should be administered with caution in patients who are volume depleted or who have hypertrophic CM, and the benefit of inotropic medications should be weighed against potential adverse side effects, such as increased arrhythmia potential and increase in myocardial oxygen demand, which may be counterproductive to myocardial recovery. While endotracheal intubation and mechanical ventilation may be necessary in some patients with acute HF, this should be performed with extreme caution as pharmacologic induction, manipulation of the airway, and the change to positive pressure ventilation may result in hemodynamic instability and/or cardiac arrest.

Once stabilized through the above measures, many patients with HF can be transitioned to medication regimens administered orally as part of a chronic outpatient regimen. In this chronic medical management phase, a number of medications are used in a strategy of "reverse remodeling." Remodeling encompasses a broad array of processes initiated at the myocyte level following myocardial injury.[4] These processes are maladaptive and include myocyte loss and replacement of healthy myocytes with fibrosis, which in turn can lead to ventricular dysfunction and dilation. Chronic HF medical therapy is aimed at halting or reversing the remodeling process. The composition of reverse remodeling therapy for HF in children (and adults) typically includes a β-blocker, an angiotensin-converting enzyme inhibitor (ACEi), *or* an angiotensin receptor blocker (ARB), and a mineralocorticoid receptor antagonist (MRA). All of these classes of medications have been shown to improve survival in adults with chronic HF; while similar benefit has, in general, not clearly been demonstrated in children, their proven effectiveness in adults has led to extrapolation of these findings in children with HF.[5] Commonly used reverse remodeling medications for HF in children, owing to readily available liquid formulations, include carvedilol (β-blocker), captopril or enalapril (ACEi) *or* losartan (ARB), and spironolactone (MRA). Some patients with chronic HF may also benefit from oral diuretics as well as digoxin, but use of these medications chronically in HF is less common.

An important aspect of chronic medical management of HF in children includes assessment of sudden death risk, with mitigation of this risk as appropriate. Children with chronic HF may be at increased risk of life-threatening ventricular arrhythmias, such as ventricular tachycardia and/or ventricular fibrillation, although the overall incidence of sudden cardiac death in children with CM appears to be less than that seen in adults.[6] For selected patients with chronic symptomatic HF and LV ejection fraction less than 35%, implantation of an automated implantable cardioverter-defibrillator may be considered, but for technical reasons owing to small patient size, this is often not possible in infants and small children.

Patients with HF who exhibit symptoms despite adequate chronic therapy described above may be considered for

advanced HF therapies, including long-term inotrope use, durable mechanical circulatory support (MCS) with a VAD, and HT.

ECMO USE AND MANAGEMENT

Indications and Timing of Cannulation

Indications for ECMO in HF patients include low cardiac output with escalating vasoactive support and/or signs of end-organ dysfunction, such as rising lactate, liver function tests, including bilirubin, and creatinine. Hypoxia from worsening pulmonary edema and recalcitrant arrhythmias are also indications. If a patient has end-organ dysfunction, ECMO is used as a mode of emergent support as it can be deployed faster than a VAD can be placed. Additionally, a VAD should not be placed until the status of the end organs is clear since organ dysfunction affects transplant listing, and VAD support provides cardiac output only. Respiratory support and renal support cannot be provided with a VAD as they can be with ECMO. For HF, veno-arterial (V-A) ECMO is always used. V-A ECMO is ideally used as a bridge to recovery or a bridge to VAD placement.

Cannulation for ECMO would ideally happen before end-organ dysfunction occurs; however, it can be difficult to ascertain when patients are failing medical therapy alone until signs of organ dysfunction occur. In our study of ECMO use across U.S. CICUs, we found that the mortality rate for medical cardiac patients, such as those with CM, on ECMO was 63.3% but mortality rose to 82.7% when medical cardiac patients were placed onto ECMO while undergoing cardiopulmonary resuscitation (CPR).[7] Almond et al. performed a study of ECMO as a bridge to HT, which found that CPR before ECMO cannulation was an independent risk factor for wait-list mortality.[8] Given the rise in mortality rate with cardiac arrest, we aim to cannulate before a patient approaches cardiovascular collapse.

Anatomic and Physiologic/Functional Concerns of ECMO Cannulation

The primary goals of ECMO for cardiopulmonary support include adequate drainage of both systemic venous and pulmonary venous return and providing appropriate cardiac output to the patient. To this end, when planning ECMO cannulation, an imperative initial consideration is patient anatomy.[9] Single-ventricle patients and biventricular patients have fundamental anatomic differences related to cannulation, drainage, and weaning ECMO.

Two-Ventricle ECMO

Biventricular patients requiring ECMO are at risk of left heart distension with drainage of only systemic venous return. The pulmonary venous blood returning to the left atrium (LA) will cause distension and impair recovery of a poorly functioning LV. Approaches to achieving decompression of the left heart are discussed below.

Single-Ventricle ECMO

Most single-ventricle patients have an unrestrictive atrial septum and therefore drainage of the anatomic right atrium (RA) will provide excellent decompression of systemic venous and pulmonary venous return in those that have not undergone cavopulmonary connection. There are rare exceptions, but in general, complete drainage of the anatomic RA will decompress the entire univentricular heart. For patients who are at the superior cavopulmonary connection stage (Glenn or hemi-Fontan), ECMO can be challenging as the superior vena cava (SVC) and inferior vena cava (IVC) do not drain to the same chamber.[10] For those patients at the Fontan stage, the SVC and IVC once again drain to the same location and therefore can usually be drained simultaneously. The pulmonary venous return is separated from the systemic venous return at the Fontan stage, and therefore the ventricle is still at risk for distension and nonrecovery unless the common atrium or single ventricle is drained via a fenestration or vent.

Cannulation

Cannulation for ECMO is performed one of two ways—peripheral or central. The chosen approach is largely institution and surgeon dependent, but some patients necessitate one approach over another due to occluded peripheral arteries and/or veins and other anatomic issues. Critically ill patients should have a patency ultrasound to assess the carotid arteries, jugular veins, and femoral arteries and veins. Peripheral cannulation is advantageous for those receiving chest compressions as the interruption to CPR is minimized. Central cannulation is often associated with bloody drainage around the open sternal dressing as the cannulae exiting the mediastinum prevent a proper seal of the dressing to the skin edges. This drainage has been associated with increased risk of mediastinitis in those cannulated for long periods of time.

Cannulation of the Single Ventricle After Stage 1 Palliation

A neonate who has undergone stage 1 palliation and requires ECMO is most easily cannulated via the right carotid artery and right jugular vein. A properly placed venous cannula will completely decompress the heart. The arterial cannula should be inserted a short distance (2 cm). The venous cannula is inserted such that the side holes of the cannula are in the RA. Cannula position should be confirmed by chest radiography. A quick rule of thumb for the venous cannula insertion depth is to place the cannula over the neck incision with the tip of the cannula at the right costal margin. That distance will generally place the venous cannula in the proper location. A poorly positioned cannula is easily adjusted after chest radiography. Those patients with a systemic-to-pulmonary shunt anastomosed to the innominate artery will have flow through the shunt even if the cannula bridges the origin of the innominate artery. It is possible to "test" the performance of a

systemic artery–to–pulmonary artery shunt while on ECMO by removing the oxygenator from the circuit.[11] This works because the arterial cannula provides blood flow through the shunt and lungs. The venous return to the ECMO circuit is a mix of deoxygenated systemic venous blood and oxygenated blood from the pulmonary veins. It is not possible to test a shunt from the RV to the pulmonary artery in this fashion as the venous cannula is decompressing the heart and the shunt has minimal flow through it. As a result, the venous return to the ECMO circuit is completely deoxygenated blood due to the lack of shunt flow.

Cannulation of the Single Ventricle After Superior Cavopulmonary Anastomosis (Bidirectional Glenn or Hemi-Fontan)

An infant with a superior cavopulmonary anastomosis that requires ECMO presents challenges. It is the toughest stage to support with ECMO in the single-ventricle pathway. Cervical cannulation will provide limited venous drainage and circuit flow as only the SVC blood is able to be drained. Blood from the IVC empties into the heart and is not anatomically accessible by the jugular venous cannula. The amount of flow provided by the SVC might be enough to support the infant, but if the ventricle is poorly functioning and distended, recovery will be hindered. In these cases, femoral cannulation is unlikely to decompress the heart as the small size of the femoral vessels significantly limits the cannula size that is able to be utilized. This leaves central cannulation as the only other option. This is not always practical as cannulation requires a redo sternotomy and possibly a prolonged period of time with an open sternum.

Cannulation of the Single-Ventricle After Fontan

Fontan patients in need of ECMO support come in a variety of ages and sizes. The patient can be as young as 2–3 years or as old as 20–30 years. For younger patients with either an extracardiac conduit or a lateral tunnel, cervical cannulation is usually possible, and the venous cannula is generally able to be advanced into the Fontan such that it bridges the SVC and IVC and provides excellent drainage. If a fenestration is present, the common atrium and therefore the single ventricle are usually able to be decompressed. Those without a fenestration (or a small one that is not effective) are not able to properly decompress the systemic ventricle and often need a fenestration created (or enlarged) in the cardiac catheterization laboratory. If a fenestration is unable to be created in the cardiac catheterization laboratory, discussions of risk/benefit of repeat sternotomy to add additional cannulae are necessary.[12] Although experience is very limited, using an Impella device in an appropriate size patient might help decompress the single ventricle in those without a fenestration struggling with distension. For older Fontan patients who are unable to achieve adequate ECMO flow with one cannula (cervical or femoral), an additional venous cannula (cervical or femoral) will augment venous return and improve flow. Femoral cannulation is challenging and not always effective in patients less than 20 kg due to small femoral vessel size and the subsequent limitation on cannula size.

Left Heart Decompression in Two-Ventricle Patients

In patients with two-ventricle circulation and LV dysfunction on ECMO, the left heart can become dilated, leading to LV wall stress, which can prevent myocardial recovery, and myocardial ischemia due to high end-diastolic pressures. Additionally, high LA pressure leads to elevated pulmonary pressures, which can cause pulmonary edema and pulmonary hemorrhage. Both of these issues can prevent or delay recovery; thus, many institutions utilize left heart decompression to facilitate recovery. Indications for decompression include left heart dilation on echocardiogram while on ECMO, which can impair venous drainage to the circuit, worsening pulmonary edema on chest x-ray, or pulmonary edema or hemorrhage out of the endotracheal tube.

Various techniques have been reported for left heart decompression, including blade septostomy, adjustable/fenestrated atrial septal defects, static balloon atrial septostomy, dynamic balloon atrial septostomy, atrial septal stent placement, or a surgically placed LA or LV vent.[13–16] LA and LV vents drain into the venous side of the ECMO circuit, whereas the remaining techniques allow the LA to drain into the RA, which is then drained into the ECMO circuit. There are adult reports of using the Impella device in conjunction with V-A ECMO to decompress the left heart.[17,18] In adult literature, this has been labeled Ecpella. Although some pediatric centers have experience with this approach, there are thus far no published pediatric studies of outcomes with this approach.[19,20]

Outcomes of left heart decompression show mixed results. Kotani et al. reported a single-center study of patients placed on ECMO, with approximately 13% undergoing LA decompression in their series.[13] Most were postoperative patients. All patients were decompressed within 12 hours of ECMO cannulation. There was no correlation between timing of LA decompression and length of ECMO support, LV recovery, or survival. Sample size was small, and LA decompression was rapid in all cases, making it difficult to draw conclusions. There was no comparison between those who were decompressed and those who were not.

Eastaugh et al. reported their single-center experience in which left heart decompression was undertaken in approximately 10% of ECMO patients.[14] Fifty percent of patients had myocarditis. Although they found a reduction in LA pressure and improvement in pulmonary edema on chest x-ray, time to decompression did not affect survival to hospital discharge.

Hacking et al. reported their single-center experience where they compared those who were decompressed electively at cannulation versus emergently for left heart dilation or pulmonary edema.[15] Mean time to emergency venting was 31.4 hours after ECMO cannulation. On multivariate analysis, elective decompression significantly decreased ECMO duration; however, there was no difference in ventilator days, intensive care unit (ICU) length of stay (LOS), ECMO survival, or survival to ICU discharge between the elective and emergency decompression groups.

The largest study of left heart decompression was a multicenter cohort study that found that time to decompression varied within and across centers.[16] Decompression of 18 hours or longer was significantly associated with longer ECMO duration, longer mechanical ventilation duration, and ICU LOS; however, there was no difference in hospital LOS, in-hospital mortality, VAD utilization, HT, overall survival, or transplant-free survival between the groups.

ECMO Complications

Patients are at risk for the complications reported by the Extracorporeal Life Support Organization (ELSO), including circuit complications such as oxygenator failure and cannula issues and patient complications such as central nervous system events, bleeding, and tamponade.[21] In Almond's study of ECMO as a bridge to transplant, the most frequent complication was bleeding in 46% of the cohort.[8] Most of these episodes were surgical site bleeding. Arrhythmias, circuit thrombus, and circuit malfunction occurred in about 25% of the cohort. Most of the circuit issues involved oxygenator and cannula events. Renal dysfunction occurred in 19%, and central nervous system events occurred in 16% of the cohort.

MECHANICAL CIRCULATORY SUPPORT OPTIONS

Patients with poor ventricular function with no additional medical options available should be evaluated for MCS. The two broad categories are ECMO and long-term VADs. ECMO is the mechanical therapy of choice for patients who have had a cardiac arrest, near arrest, or multisystem organ failure. In these situations, ECMO can be used as a bridge to decision: it provides adequate cardiac output to evaluate the brain, liver, kidney, lungs, and/or heart for recovery. ECMO is rapidly deployable and available at most institutions. With the advent of ECMO transport teams, patients put on ECMO at smaller hospitals are able to be transferred to tertiary care centers for further treatment. Once on ECMO, it is advisable to make a long-term plan—decannulation, transition to a longer term/durable assist device, or withdrawal of care—within 1–2 weeks. Complications from ECMO start to accumulate after that period, and patients rapidly become noncandidates for additional intervention. Patients with poor ventricular function and no further medical options who are stable should be considered for a long-term VAD. There are a variety of devices available depending on patient size, including relatively newer pumps that are fully implantable (save a driveline exiting the skin) and have smaller, portable batteries that permit discharge from the hospital with improved quality of life over the previous generations of devices.

TRANSITION TO VENTRICULAR ASSIST DEVICE

As mentioned above, the transition to a more durable, long-term device should be considered in the first 1–2 weeks of ECMO.[22] Important patient considerations include extracardiac organ function; presence of infection; long-term plan (bridge to decision, bridge to transplant, or destination therapy); and patient anatomy. ECMO is generally able to resuscitate end organs that are marginal, especially the liver and kidneys. If ECMO was instituted during a cardiac arrest or near arrest, evaluation of the brain is necessary for overall prognosis. Active infection is a contraindication to VAD placement. Blood cultures should be negative, and other markers of infection, including white blood cell count and C-reactive protein, should be downtrending. Historically, long-term mechanical devices were implanted in pediatric patients for bridge to decision or bridge to transplant. With improvement in device size, performance, and complication profile, certain patient populations, such as those with muscular dystrophy, are being considered for destination therapy.

There have been poor outcomes with current devices in those that are shunted single ventricles and those at the superior cavopulmonary stage. As such, long-term durable devices are not generally offered to these patients. Fontan patients with poor ventricular function are candidates for VAD placement. Failing Fontan patients with preserved ventricular function will not be improved with a VAD. The Fontan population does present challenges, primarily due to size. In smaller patients, techniques to overcome space issues include excision of the atrioventricular valve, placement of the device in the common atrium, and use of spacers on the sewing ring. In biventricular patients undergoing placement of a left VAD, there are a few important operative considerations. First, any intracardiac communications should be closed. This includes a patent foramen ovale, atrial septal defect, and ventricular septal defect. Second, the RV needs to be supported when weaning from cardiopulmonary bypass (CPB). This includes the use of inotropes and inhaled nitric oxide (iNO). Preparations should be made to place a right VAD in all patients undergoing left VAD placement if needed.

HEART TRANSPLANT

Heart transplantation (HT) is the definitive therapy for end-stage HF in children and adults and can restore a normal quality of life for many patients. The effectiveness of HT is constrained, however, by limited donor availability, a finite life span of the transplanted heart, ongoing risk for rejection, and comorbidities that accompany the need for lifelong immune suppression following HT. Children with chronic HF being considered for HT must undergo a rigorous evaluation to ensure that they will derive benefit from HT. This evaluation includes laboratory testing for blood type, HLA (human leukocyte antigen) antibody status, exposure to infectious agents, and careful evaluation of end-organ function to ensure that no irreversible damage has occurred. Patients being considered for HT also undergo careful assessment of family support structures to ensure that compliance with complex medical regimens and need for careful long-term follow-up are ensured.

There are several important and unique considerations for children undergoing HT evaluation. For children with CHD

and end-stage HF, careful attention must be paid to the underlying cardiac anatomy as this may influence the conduct of the transplant operation. For example, abnormal systemic or pulmonary venous connections and abnormal position of the heart in the chest may necessitate creative surgical approaches to the transplant. CHD patients undergoing HT should have cross-sectional imaging and/or cardiac catheterization for anatomic evaluation of all structures. Children with CHD may have developed antibodies against non-self HLA antigens on account of multiple blood transfusions and exposure to non-self homograft tissue during prior surgical reconstructions and any prior course of ECMO; the presence of HLA antibodies, also known as sensitization, increases the risk of rejection postoperatively and therefore may prolong wait times until an HLA-compatible organ can be found.[23] Finally, children with complex CHD are at risk for increased posttransplant mortality, when compared to patients with CM and structurally normal hearts.[24] This is largely related to a higher hazard of early posttransplant (within first year) mortality, which is in turn related to increased operative complexity and preoperative recipient comorbidities.

The technique of HT—biatrial (BA) or bicaval (BC)—is surgeon and institution dependent. The BA technique has been associated with increased incidence of atrial dysrhythmias, tricuspid regurgitation, and permanent pacemaker placement. Criticisms of the BC technique point to stenoses of the systemic venous anastomoses. There should be no hesitation in using the BC technique in even the smallest patients as the superior cavopulmonary anastomosis is generally done at a weight of 4–5 kg. When weaning from CPB after HT, care should be taken to support the RV as the transplanted heart is likely pumping into lungs that were exposed to elevated LA/common atrial pressure due to the failing systemic ventricle. Routine use of inotropes and iNO, along with isoproterenol for the bradycardia associated with the denervated heart, is advisable.

OUTCOMES

According to the 2016 pediatric ELSO report, survival to hospital discharge for pediatric patients requiring ECMO for CM or cardiogenic shock is in the 60%–65% range.[21] Survival for those with acute myocarditis is higher at 76%. Survival for neonates with CM is the same at 60%, but survival for cardiogenic shock and acute myocarditis in neonates is lower, at 39%–50%. As mentioned above, in an analysis of ECMO use across U.S. CICUs, our group found that for medical patients, which included those with acute HF, chronic HF, pulmonary hypertension, and transplant rejection, survival to hospital discharge was only 37%, and if a patient was cannulated onto ECMO during active CPR, survival decreased to 15%–20%.[7]

In the past decade, several studies have shown superior survival in patients bridged to HT with a VAD rather than ECMO. Almond et al. merged data from two databases for pediatric patients bridged to HT with ECMO.[8] In this large study, 64% had CHD, and 28% had CM. Thirty-eight percent had bridge to transplant listed as the primary indication for ECMO. Survival to transplant was only 45%. Twenty-eight percent died on the wait list, and 11% were removed from the wait list for clinical deterioration. Survival to hospital discharge was 47%. Those with myocarditis had the best survival at 61%.

In a follow-up study, Almond et al. looked at Berlin Heart VAD outcomes in patients from 47 transplant centers.[25] They found 75% 12-month survival, including 64% who survived to HT. Mortality on VAD support was 25%. Weight less than 5 kg and renal dysfunction were associated with the worst survival rates. Dipchand et al. looked at the effect of ECMO at the time of transplant listing and the time of transplant on outcomes over a 20-year period.[26] Those on ECMO were younger, smaller, sicker, and more likely to have renal insufficiency than those not on ECMO at listing or the time of transplant. Those on ECMO had worse wait-list, posttransplant, and overall survival up to 20 years compared to those on VADs and those not on MCS. By 12 months posttransplant listing, 49% of those listed on ECMO were transplanted compared to 79% of VAD patients. Of note, they found that if a patient was on ECMO at transplant listing but weaned off ECMO or transitioned to a VAD by the time of transplant, their outcomes improved to those of the non-ECMO groups. For patients on ECMO at the time of transplant, lower weight, higher creatinine, and underlying CHD or myocarditis were associated with worse survival after transplant.

In a more recent study by the same group, they looked at an international, multicenter cohort of VAD patients and examined the effect of ECMO prior to VAD on outcomes.[27] They again found that those on ECMO were younger, smaller, and sicker. For those bridged to transplant with ECMO then a VAD, 51% reached transplant, and 36% died at some point during their course. For those bridged to transplant with a VAD only, 77% reached transplant, and 14% died at some point during their course. They again found differences in outcomes out to 20 years for those on ECMO closest to transplant compared to those on VAD or no MCS (Figure 31.3). Eighty-four percent of CM patients reached transplant.

Yarlagadda et al. also studied survival for ECMO only versus VAD only before HT.[28] VAD patients had significantly longer wait-list survival and overall survival compared to ECMO patients. They did not find a significant difference in posttransplant survival between the two groups. Wehman et al. compared outcomes for those bridged to transplant with ECMO or a VAD to those who underwent direct transplantation.[29] Posttransplant survival was similar in the direct transplantation and VAD groups, with the ECMO group having significantly lower survival. Four months posttransplant was found to be the critical time at which differences in outcomes were seen. When outcomes for the first 4 months after transplant were excluded, long-term survival up to 5 years was similar across the three groups. They additionally looked at outcomes for patients placed on ECMO then converted to VAD for bridge to transplantation. In this group, they found that short-term and long-term posttransplant

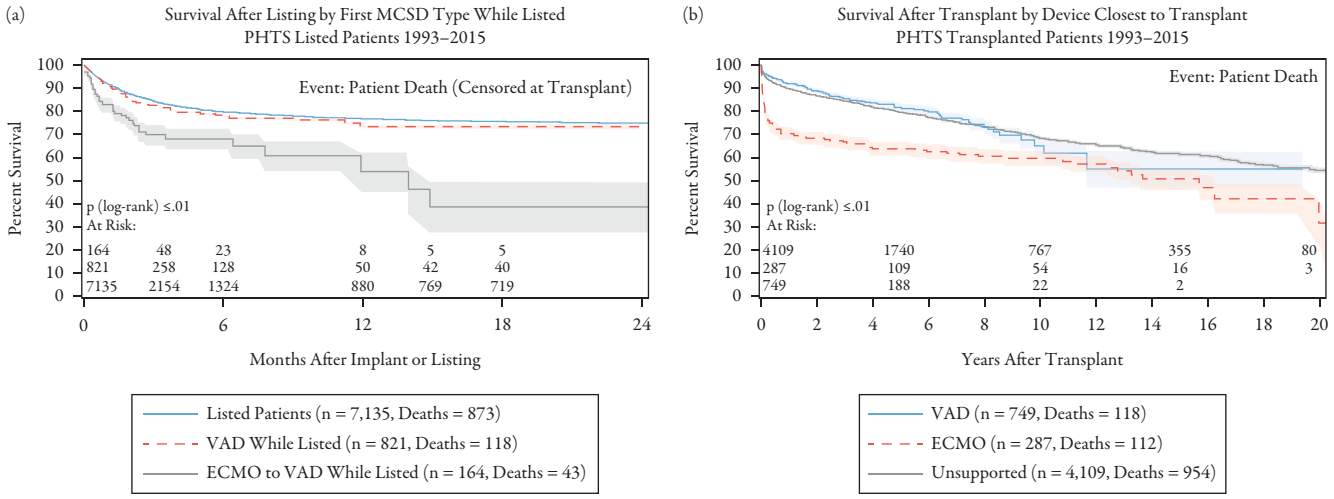


Figure 31.3 Overall survival by mechanical circulatory support device (MCSD) type: (A) Postlisting survival by first MCSD type while listed. (B) Posttransplantation survival by MCSD type closest to transplantation.

survival approximated the VAD and direct transplantation groups.

Given the data showing higher likelihood of survival to transplant with VADs compared to ECMO, our practice is to preferentially bridge with a VAD. If a patient has ongoing signs and symptoms of HF on intravenous medications but without signs of end-organ dysfunction, we prefer to place a VAD as the first source of MCS. If a patient needs emergent stabilization for end-organ dysfunction or suffers a cardiac arrest, we use ECMO to stabilize the patient with a plan for conversion to VAD as soon as the end organs are functioning well, preferably within days.

SPECIAL CONSIDERATIONS IN CONGENITAL HEART DISEASE PATIENTS

Congenital heart disease may be associated with HF, both in patients who are in the unrepaired state and in those who have undergone surgical procedures for repair or palliation of complex CHD. Patients who have undergone surgery for CHD are at risk for developing HF at any point postoperatively, with some patients not manifesting HF until many years after surgery. While the wide variety of CHD lesions and associated surgical procedures prevents a full discussion of the multiple etiologies of HF in this population, several groups of patients should be considered at high risk. These include patients with single-ventricle CHD in whom the RV serves as the systemic ventricle, patients who have undergone a Fontan operation, and patients with complete congenital heart block requiring long-term ventricular pacing.

Several studies have shown worse outcomes in patients with CHD bridged to transplant with MCS. In the study by Almond et al. of ECMO as a bridge to transplant, those with two-ventricle CHD had 39% survival to hospital discharge after HT, while those with single-ventricle CHD had the worst survival to discharge at 27%.[8] They found that two-ventricle and one-ventricle CHD were both independent risk factors for wait-list mortality and posttransplant mortality compared to myocarditis and CM patients. In Almond et al.'s study of Berlin Heart VAD outcomes, for infants less than 5 kg with CHD, 93% died.[25] In Dipchand's study of ECMO versus VAD as bridge to transplant, patients with CHD on ECMO had the worst wait-list survival and worst posttransplant survival.[26] In Dipchand's study of VAD patients, only 57% of those with CHD reached transplant.[27]

CONCLUSIONS

- Heart failure in children is uncommon but a complex disease process with many causes.
- The diagnosis of HF requires a thorough history, physical examination, and a series of tests.
- The treatment of HF is done with several complementary acute and chronic medications.
- Patients with refractory HF, including persistent symptoms of low cardiac output and end-organ dysfunction, require MCS.
- ECMO is a mode of emergent support that can provide hemodynamic, respiratory, and renal support.
- The patient's underlying cardiac anatomy must be taken into account when planning cannulation.
- Survival for HF patients on ECMO varies based on the underlying age, diagnosis, and mode of MCS while awaiting HT.
- Outcomes are superior with VAD support, so ECMO patients should be converted to a VAD if they do not have recovery of cardiac function.
- Heart transplant is the definitive therapy for end-stage HF.

- Patients with CHD require special considerations in the management of HF and ECMO.

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REVIEW QUESTIONS

1. Tests used to diagnose HF include all except

   a. Echocardiogram
   b. Cardiac computed tomographic scan
   c. B-type natriuretic peptide
   d. Cardiac MRI

2. The most common type of CM in children is

   a. Hypertrophic
   b. Dilated
   c. Restrictive
   d. Noncompaction

3. A previously healthy 5-year-old male presents with acute myocarditis and decompensated HF requiring intubation, dopamine,

and epinephrine with ongoing hypotension, lactic acidosis, and rising BUN and creatinine. The appropriate next step is

a. Ventricular assist device placement
b. Continue medical therapy by adding vasopressin
c. Cannulation for V-A ECMO
d. No changes in management are required

4. Complications for HF patients on ECMO include

a. Bleeding
b. Thrombosis
c. Tamponade
d. All of the above

5. The worst outcomes for HF patients requiring ECMO are seen in

a. Cardiomyopathy patients
b. Myocarditis patients
c. Adolescents
d. Congenital heart disease patients

ANSWERS

1B, 2B, 3C, 4D, 5D

32.

WEANING AND DECANNULATION OF PEDIATRIC CARDIAC ECMO

Bonnie A. Brooks and John T. Berger

STEM CASES AND KEY QUESTIONS

CASE 1

A 16-month-old, previously healthy, female presented to her local emergency room (ER) with tachypnea and increased work of breathing. Over the past week, she was noted to have decreased energy, fever, diarrhea, and vomiting. She was diagnosed with a urinary tract infection and prescribed antibiotics. The following day, she developed respiratory distress and returned to the same ER, where a chest x-ray was concerning for cardiomegaly and pulmonary edema. An electrocardiogram showed diffuse ST changes with low voltages in all leads, and a blood test revealed a mildly elevated troponin level. After rapidly decompensating, she was intubated for respiratory failure and transferred to a facility with a higher level of care.

She developed sustained pulseless ventricular tachycardia. She was defibrillated and started on a lidocaine infusion with return of spontaneous circulation. She was then rapidly cannulated onto veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO). She was maintained on flows 80 mL/kg/h and a cardiac index of 3 L/min/m^2. Approximately 8 hours after cannulation, she had a mean arterial blood pressure of 70 mm Hg and absent pulsatility on the arterial waveform tracing.

WHAT IS THE MOST LIKELY CAUSE FOR THIS PATIENT'S CARDIOMEGALY ON CHEST X-RAY?

An echocardiogram was performed and confirmed severe biventricular systolic dysfunction. Given this patient's constellation of symptoms, as well as echocardiographic and electrocardiographic findings, a working diagnosis of viral myocarditis was made. Other possible causes of severe myocardial dysfunction include left-sided obstructive lesions (e.g., aortic stenosis or coarctation of the aorta); coronary anomalies (e.g., anomalous origin of left coronary artery from pulmonary artery); Chagas' disease; toxins; dilated cardiomyopathies (including idiopathic, familial, neuromuscular disease related; and metabolic); and arrhythmias.[1] Though it is not a sensitive screen, an enlarged cardiac silhouette on chest x-ray can be specific, with a high positive predictive value, for enlarged heart size in children.[2]

WHAT IS THE DIFFERENTIAL DIAGNOSIS OF ABSENT ARTERIAL LINE PULSATILITY?

Absence of an arterial waveform or pulse pressure on arterial line monitoring while on ECMO suggests that either the systemic (typically, left ventricle (LV)) has little or no ejection or the arterial line is dysfunctional. Lack of pulsatility may be due to poor myocardial contractility, inadequate ventricular filling, severe aortic insufficiency, increased afterload on the systemic ventricle, or cannula malposition.[3,4]

HOW CAN THE CAUSE OF ABSENT PULSATILITY BE DETERMINED?

Echocardiography can be useful in confirming cannula position, determining the presence of aortic insufficiency, determining ventricular volume status, and evaluating the LV function. An M mode through the aortic valve can determine degree of opening. Echocardiography can also assess for new mitral insufficiency or LV thrombus formation.[5]

One important question is difficult to answer by echocardiogram: whether there is significant left atrial (LA) hypertension and pathologic LV distention. The finding of LV distention on echocardiography does not always correlate with elevated LV end-diastolic pressures on cardiac catheterization.[6] It is therefore important to perform a comprehensive evaluation and rapidly investigate a drop in pulse pressure or new absence in pulsatility.

WHAT ARE THE CONSEQUENCES OF ABSENT PULSATILITY?

The cardiovascular consequences of V-A ECMO include increased LV afterload and variable effects on LV preload depending on whether the LV is ejecting. Even at high flows, there is persistent blood flow to the LA from pulmonary, Thebesian, and bronchial veins. If the LV is unable to eject against the increased afterload, the LV distends, resulting in

increased wall stress and myocardial oxygen consumption. The LV end-diastolic pressure, and consequently LA pressure, also rises, limiting coronary perfusion pressure and resulting in subendocardial ischemia. The mismatch between oxygen delivery and consumption can compromise myocardial recovery. Another potentially life-threatening complication is pulmonary hemorrhage due to LA hypertension, which can be exacerbated by mitral valve regurgitation. Finally, there is a risk of thrombus and emboli formation in the noncontractile ventricle.[5,7,8]

WHEN IS CARDIAC ECMO UTILIZED IN CHILDREN?

Cardiac ECMO in children is utilized in two distinct populations: those who have primary myocardial disease, including myocarditis and cardiomyopathies, and those children who have undergone repair of congenital heart disease. The approaches to weaning support and intervening on those who fail to wean differs between these two populations.

ON DAY 2 OF ECMO, BLOOD-TINGED, FROTHY SECRETIONS WERE NOTED ON SUCTIONING THE PATIENT'S ENDOTRACHEAL TUBE. WHAT IS THE LIKELY ETIOLOGY OF THIS? WHAT SHOULD BE DONE?

The patient is experiencing pulmonary hemorrhage secondary to increased LA pressure. In the face of pulmonary hemorrhage or severe pulmonary edema, atrial decompression with placement of a LA cannula or creation of an atrial communication is warranted. Other temporary measures include altering ECMO flows, vasodilators, and inotropes. While weaning ECMO flows effectively decreases afterload, it may also result in inadequate systemic oxygen delivery if the native LV output does not increase. Vasoactive agents (inotropes and vasodilators) may be titrated to promote contractility and reduce afterload; however, inotropes have the side effect of increasing myocardial demand, while vasodilators may be of limited use in the setting of a patient with low systemic vascular resistance, such as in the setting of septic shock.[5,8]

If the patient does not improve with reduced flows and medical management, LA decompression should be considered early and can be pursued via balloon or blade atrial septostomy, transseptal stent, or surgical LA or LV vent.[9,10] Another option with increasing use in larger patients is a transcatheter microaxial ventricular assist device (VAD) such as the Impella® device.[11] Some centers promote early, and even prophylactic, decompression of the LA via balloon atrial septostomy, particularly in neonates, in order to prevent the vicious cycle resulting in pulmonary hemorrhage as described above.[12] Whether early atrial decompression improves survival remains uncertain; although, early decompression has been associated with shorter duration of ECMO and mechanical ventilation.[13,14] In the absence of severe pulmonary edema or pulmonary hemorrhage, the decision should be made on a case-by-case basis with frequent echocardiographic assessments.

WHAT CLINICAL SIGNS CAN ONE FOLLOW TO DETERMINE A PATIENT'S READINESS TO WEAN?

Readiness to wean and weaning strategies remain an area of active research in the pediatric ECMO population, and formulated guidelines remain lacking. Generally, the overall patient clinical picture should be improved for at least 24 hours, as evidenced by improved pulse pressure and adequate systemic oxygen delivery while requiring minimal inotropic medications. The indication for initiation of ECMO support should be reversed.[15] Finally, the patient should successfully tolerate a weaning trial. There is considerable variation in how quickly institutions decrease flows and the duration over which this is performed.

WHAT ECHOCARDIOGRAPHIC VALUES CAN ONE FOLLOW TO PREDICT WEANING SUCCESS?

Echocardiography has been used both to assess weaning readiness (i.e., before a weaning trial) and to predict success of decannulation. While there are no absolute cutoff values, higher ejection fraction and aortic velocity-time integrals (VTI) are associated with successful weaning in adults.[16] In an adult study, echocardiographic measurements were obtained during incremental flow weans. The values that were predictive of a successful wean included an aortic VTI greater than 10 cm, LV ejection fraction greater than 20%–25%, lateral mitral annulus peak systolic velocity (TDSa) greater than 6 cm/s, and the absence of LV dilation on minimal ECMO flow support.[17] Diastolic function parameters (mitral E and tissue Doppler Ea velocities and E/Ea ratio) were not as valuable in differentiating those patients who were successfully weaned. In the neonatal population, weaning to low flows is precluded by the minimal flow requirements of the circuit itself,[10] and these measurements are less likely to be useful.

WHAT ARE IMPORTANT CONSIDERATIONS IN THE DECANNULATION PROCESS?

The patient's heart was noted to be ejecting with a pulse pressure on 50-mL/kg/min flows on day 6 of ECMO, and she was successfully decannulated. Decannulation requires full medical and surgical teams as well as appropriate equipment. The team should discuss possible complications from decannulation and whether to reinstitute ECMO for failed separation. The team should include providers responsible for monitoring the patient condition during the decannulation. Special care should be taken during the physical removal of the cannula to prevent air embolism. The Extracorporeal Life Support Organization (ELSO) guidelines provide a helpful

decannulation checklist that can be used as a resource and tailored to each institution and patient.[15]

IN THE SETTING OF ACUTE FULMINANT MYOCARDITIS, WHEN SHOULD ONE CONSIDER TRANSITION TO A VENTRICULAR ASSIST DEVICE? WHAT ABOUT OTHER CONDITIONS?

Duration of ECMO support is often determined by the underlying disease process and indication for support. The majority of patients will not gain further myocardial improvement after 2 weeks on ECMO.[18] In order to prevent the negative neurologic, hematologic, and overall deconditioning consequences of prolonged ECMO support, children with cardiac disease unable to wean from ECMO for longer than 10–14 days should be transitioned to another type of support.[18–20] A multicenter review of the Pediatric Health Information System database found a median duration of ECMO of 4 days (interquartile range 1, 7), and also noted a 12% increase in the odds of mortality for every additional 24 hours on ECMO (odds ratio 1.12, 95% CI 1.07–1.18, $P < .001$). In a large review of the ELSO database, there was a markedly decreased survival of 13% (17/135 children) in pediatric patients who required prolonged cardiac ECMO, defined as longer than 28 days.[19,20] In eligible children with primary myocardial disease, transition to a VAD is the next step as a bridge to heart transplantation.

CASE 2

A 5-day-old with hypoplastic left heart syndrome underwent a Norwood operation with a 3.5-mm modified Blalock-Taussig (BT) shunt. He returned to the intensive care unit (ICU) intubated and on low-dose vasoactive support. Three hours after his arrival to the ICU, he had a hypoxic arrest and was cannulated onto V-A ECMO via central cannulation.

WHAT IS THE LIKELY MECHANISM FOR THIS PATIENT'S HYPOXEMIA LEADING TO A CARDIAC ARREST?

The differential diagnosis for early postoperative arrest in this patient includes shunt occlusion, elevated pulmonary vascular resistance, lung disease, or profound low cardiac output. Prior to the arrest, the patient experienced significant hypoxia despite increasing fraction of inspired oxygen (FiO_2) to 100% and inhaled nitric oxide (iNO) of 20 ppm. End-tidal CO_2 was noted to be low and then undetectable during extracorporeal cardiopulmonary resuscitation despite judicious bag-mask ventilation. A 100-U/kg bolus of heparin for shunt obstruction was given due to the suspicion of an occluded BT shunt. The patient was maintained on systemic heparinization during the ECMO run. Shortly after cannulation, the heart was noted to be ejecting with robust blood pressure on the arterial line in the right radial artery.

WHAT CONSIDERATIONS MUST BE ACCOUNTED FOR IN PATIENTS WITH RIGHT VENTRICLE–TO–PULMONARY ARTERY CONDUITS COMPARED TO THOSE WITH AORTOPULMONARY SHUNTS ON V-A ECMO?

In patients with an aortopulmonary shunt, a portion of the ECMO flow will "run off" into the pulmonary vasculature due to the lower pulmonary vascular resistance compared to higher systemic vascular resistance. In the early days of ECMO for patients with systemic-to-pulmonary shunts, a typical solution would be to "clip" the shunt. This was associated with higher rates of mortality, and more institutions have adopted a practice of increasing ECMO flows (up to 200 mL/kg/min) and accepting the potential for increased shunt flow, and in turn pulmonary blood flow and left atrial return, to allow for adequate systemic and myocardial perfusion.[21]

WHEN SHOULD THE POSTOPERATIVE CARDIAC PATIENT BE WEANED FROM ECMO?

When ECMO is utilized in the postoperative period, myocardial recovery is thought to improve more rapidly as compared to patients with myocarditis. Typically, patients are cannulated for low cardiac output or inability to separate from cardiopulmonary bypass. Once the clinical situation is stabilized and the myocardium has recovered from the acute insult from bypass itself, patients can undergo weaning and decannulation. This usually takes place in less than 72 hours.

ON DAY 3 OF ECMO, THE PATIENT REMAINED ON FLOWS OF 120 ML/KG/MIN AND WAS NOTED TO HAVE A NARROWED PULSE PRESSURE OF 50/45 MM HG AND A DECREASE IN END-TIDAL PCO_2 TO 20 MM HG. FURTHER WEANING OF ECMO WAS NOT TOLERATED. WHAT ARE THE NEXT STEPS?

Early assessment for residual surgical lesions is essential for postoperative patients requiring ECMO. Residual lesions should be evaluated with transthoracic echocardiography and cardiac catheterization if necessary. Early detection and intervention of residual surgical lesions is associated with higher rates of ECMO decannulation and survival to hospital discharge.

An echocardiogram was performed, and the systemic-to-pulmonary shunt could not be visualized. Due to concern for recurrent shunt obstruction, the patient was taken to the cardiac catheterization lab, where he was noted to have a discrete area of shunt stenosis at the distal insertion site. Other components of the cardiac repair were acceptable, including absence of aortic arch obstruction and atrial restriction. Balloon angioplasty of the BT shunt was performed with improved visualization of the shunt and flow into the pulmonary arteries. The patient was successfully weaned from ECMO and decannulated over the next 12 hours.

DISCUSSION

EXPECTED DURATION OF CARDIAC ECMO

The strategy to separate a patient from ECMO must be developed early in the ECMO course and as early as the time of cannulation. The indication for ECMO support is an important determinant in considering duration of therapy and projecting a date for weaning and decannulation. While general goals of ECMO weaning have been described, strategies vary by institution, and research in this area is lacking, particularly in pediatrics. There are also specific patient and anatomic conditions that should be considered. Finally, there should be investigative and alternative management strategies for patients who do not wean successfully.

The majority of patients with primary myocardial dysfunction will not gain further myocardial improvement after 2 weeks of support.[15] If recovery has not occurred within this time frame, transition to an assist device, transplant, or redirection of care should occur. Most centers begin transition within 10 days due to an increased mortality for each additional day on ECMO support.[15,17–19] Some centers have recommended transition to assist device earlier in the course of myocarditis, specifically by performing an echocardiographic assessment of function every 8 hours after cannulation. If signs of recovery are not observed within the first 72 hours of cannulation, bridge to VAD is initiated within the first 7 days of support.[22] Early transition to a VAD, however, may complicated by inability to cannulate the ventricle, increased morbidity due to VAD complications, or long-term dysfunction from ventricular cannulation in patients who do recover. Patient and provider-specific considerations may also influence timing for weaning and transitioning to an assist device, for example, a center's capability for listing a patient for heart transplant or for ECMO transport.

When ECMO is utilized in the postoperative cardiac period, myocardial recovery is expected to occur more rapidly than in those patients with primary myocardial dysfunction. Usually, this will take place within the first 72 hours. Common indications for pediatric ECMO support following cardiac surgery are an inability to separate from bypass and low cardiac output states.[23,24] Frequently, the etiology of low cardiac output is thought to be secondary to bypass-induced inflammation and ischemia-reperfusion injury; however, early identification of residual surgical disease is of paramount importance in successful decannulation and stability off ECMO support. If surgical disease is excluded, allowing these patients at least 48 hours of myocardial rest and adequate oxygen delivery to end organs is reasonable.[15] Preparations for weaning and decannulation should be discussed within the first 72 hours.

ASSESSING WEANING READINESS

In general, signs of myocardial recovery, adequate pulmonary function, and resolution of major metabolic disturbances should be present before the weaning process is started. Specifically, arterial pulsatility should be present for at least 24 hours on minimal vasoactive support.[17,25] Echocardiography has been shown in adults to be predictive of successful ECMO weaning and decannulation and is utilized by many pediatric centers.[17] Systolic function as assessed by echocardiogram does not need to be completely normal but should be adequate to support systemic oxygen delivery.

WEANING TRIALS

Weaning trials, though variable in protocol by institution, provide an assessment of how myocardial function will respond to the increased preload and decreased afterload once separation takes place. Many centers perform some version of weaning and/or clamping trial. In pediatrics, weaning trials can be accomplished by decreasing flows incrementally while measurements of myocardial performance are made via echocardiography, serial blood gas, and markers of end-organ perfusion (e.g., lactate, near-infrared spectroscopy). Practitioners are advised not to decrease flows to less than the rated minimum flow of the oxygenator due to risk for thrombus formation. Adequate volume, inotrope, and ventilatory support should be provided during this time. This can be followed by, or supplemented with, a clamping trial where flow is circulated through an A-V bridge. In this state, the ECMO and patient circulations are effectively separate from each other. The patient is systemically heparinized as the bridge can be a site for thrombus formation. It is advised to flush the cannulae every 10 minutes during this process to prevent thrombi. Otherwise, intermittent recirculation should be done to eliminate stasis, which requires repeated pauses in the trial.[10,15]

Alternatively, "pump controlled retrograde flow trial off" is a strategy that does not require increased stasis in the circuit. In a centrifugal pump system, the revolutions per minute can be decreased until the level of the patient's arterial blood pressure is higher than the postoxygenator pressure, driving the blood retrograde through the circuit.[22] Pump-controlled retrograde trial off was found to shorten periods off the circuit while allowing providers to evaluate a patient's hemodynamics. The technique is limited by patient size, however. In one study, two patients less than 3 kg required conversion to a weaning trial utilizing an A-V bridge.[25,26]

Direct decannulation or clamp trials without a weaning trial may be the only option for those patients who underwent clipping of systemic-to- pulmonary shunts during the ECMO course. Weaning flows may result in acute hypoxemia and sometimes cannot be tolerated.

Echocardiography is often utilized during a weaning trial. Data regarding specific parameters and cutoffs are limited primarily to adult studies. In adult patients undergoing an incremental weaning trial, echocardiographic parameters that were predictive of a successful wean included LV ejection fraction greater than 20%–25%, aortic VTI 10 cm or greater, and TDSa 6 cm/s or greater on minimal support. These parameters were also coupled with increasing arterial systolic and pulse pressures through the trial.[17] Another trial utilized continuous transesophageal echocardiography to assess whether a patient could be decannulated or transitioned to a VAD.[27]

A single prospective study compared six echocardiographic variables between pediatric patients who died or required heart transplant and those who weaned from ECMO, including shortening/ejection fraction; outflow tract Doppler-derived stroke distance (VTI); degree of atrioventricular valve regurgitation; longitudinal strain, and circumferential strain. Failure to augment VTI was the only parameter associated with poorer outcomes. The other variables were not different between the two groups.[28] Clearly, additional studies need to be performed in the pediatric population.

While echocardiographic measurements are important in monitoring a patient during a weaning trial, other clinical parameters and the level of vasoactive support should be assessed to provide a comprehensive assessment of the patient. An increasing systolic pressure, rising end-tidal CO_2, clearance of lactate, and normalization of end-organ markers are all suggestive of ability to decannulate.

TROUBLESHOOTING FAILURE TO WEAN

In the event a patient fails to have myocardial recovery or is unable to wean from ECMO support, the team should undertake early investigations to assess for residual surgical disease, secondary cardiac dysfunction related to ECMO, infection, or lung disease. Investigatory methods to consider include echocardiograms, cardiac catheterization, chest ultrasound, and chest computed tomography (CT).

In our first stem case, the patient with myocarditis underwent LA decompression to treat LA hypertension, which manifested as pulmonary hemorrhage on ECMO. LA decompression by LA cannulation or creation of an atrial communication by static balloon dilation or stent placement reduces pulmonary venous congestion, minimizes LV distention, and may allow for improved coronary blood flow by lowering LV intracavitary pressure. In a pediatric study, percutaneous LA decompression was performed in 44 of 419 pediatric cases and was frequently utilized in the setting of myocarditis (22 of 44 cases).[9] Pulmonary venous congestion on chest x-ray and LA pressures improved. Another complication of ECMO that may inhibit myocardial recovery is aortic valve insufficiency due to an arterial cannula in the ascending aorta. Cannula malpositioning should be adjusted promptly.

In the postoperative cardiac patient, the possibility of a residual cardiac lesion should be thoroughly investigated prior to weaning and decannulation and requires intervention prior to weaning. In a single-center series from the 2000s, 35 of 119 postoperative patients placed on ECMO had residual lesions requiring intervention. In patients who had both catheterization and an echocardiogram, catheterization revealed a residual lesion not seen by echocardiogram in 88% of patients. Diagnostic tests for this evaluation can include catheterization, echocardiography or CT angiography.

DECANNULATION

Similar to cannulation, decannulation requires careful planning and coordination. Important supplies, including medications (inotropes and vasopressors, anesthetics, volume); blood products; and a temporary pacemaker, should be available and prepared.[15] Lung recruitment strategies should be performed, and mechanical ventilation should be optimized. A decannulation checklist is helpful in ensuring that all the pieces are in place for a successful procedure. The team should be prepared for the development of low cardiac output, pulmonary hypertension, bleeding, and arrhythmia. The timing of decannulation should account for the availability of personnel if ECMO needs to be reinstituted. After the cannulation sites are carefully examined, the heparin infusion is stopped. Recommendations to observe from 20 to 60 minutes at low flows have been suggested. In scenarios where the circuit may be reused, blood is recirculated immediately after the cannulae are removed. In contrast to adult ECMO, pediatric patients are often centrally cannulated following cardiac surgery. The chest is frequently left open after decannulation until hemodynamics are stable and there is confidence that recannulation will not be necessary. If a patient is peripherally cannulated, vessel reconstruction can be required. There are new techniques to remove peripheral cannulae in adult patients, including closure devices that are currently being investigated for safety.[23,24] After decannulation, the heart will be under different loading conditions: the preload rapidly increases and the afterload of the ECMO circuit is removed.[15] Extracorporeal life support survival in pediatric cardiac ECMO was 71% in the July 2019 ELSO Registry report. Survival to discharge or transfer, however, was only 52%.[26] In addition to investigating best strategies for weaning and decannulation, we need to investigate further and tailor our post-ECMO rehabilitation strategies.

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REVIEW QUESTIONS

1. All of the following may be required when weaning V-A ECMO EXCEPT

A. Increasing ventilator support
B. Discontinuing paralytic drugs
C. Circulating through ECMO bridge during clamping
D. Providing volume expanders

2. Which of the following has not been suggested as an echocardiographic parameter that may predict successful wean?

A. Left ventricular outflow tract VTI greater than 10 cm
B. Lateral mitral annulus peak systolic velocity greater than 6 cm/s
C. Left ventricular ejection fraction greater than 20%–25%
D. Ventricular interdependence

3. A newborn with pulmonary atresia undergoes placement of a systemic-to–pulmonary artery shunt. He returns from the operating room on ECMO for low cardiac output. On postoperative days 2 and 3, the lactate increases, and the patient requires increasing doses of vasoactive support. Weaning trials are aborted. All of the following are appropriate next steps EXCEPT

A. Initiation of milrinone infusion
B. Cardiac catheterization to evaluate for residual disease
C. Transthoracic echocardiography
D. Head ultrasound

4. All of the following are recommended during a weaning trial EXCEPT which of the following?

A. The patient and circuit should be kept anticoagulated with heparin during the weaning trial.
B. The circuit can be flushed periodically.
C. The flows should be decreased as low as possible to avoid a clamping trial.

D. Transthoracic or transesophageal echocardiography assessment should be made of cardiac function at different levels of support.

5. A 6-year-old patient was placed on ECMO for acute fulminant myocarditis 2 weeks ago. She was taken to the catheterization laboratory for a LA vent placement that resulted in adequate LA decompression. Several weaning trials have been attempted without improvement in cardiac function despite the addition of epinephrine and milrinone and clamping the LA cannula. Which of the following is the most appropriate next step?

A. Weaning the ECMO circuit on maximum vasoactives and iNO
B. Changing out the ECMO circuit
C. Discussing VAD placement versus redirection of care
D. Repeat percutaneous LA vent placement

ANSWERS

1. B
2. D
3. A
4. C
5. C

ECMO IN ADULT RESPIRATORY DISEASE

33.

VENO-VENOUS ECMO FOR ACUTE RESPIRATORY DISTRESS SYNDROME

John P. Skendelas, William A. Jakobleff, and Giles J. Peek

STEM CASE AND KEY QUESTIONS

A 21-year-old male presented to the emergency department with a 3-day history of worsening shortness of breath and fever. Serum testing was positive for influenza B, and the patient was admitted for observation and oseltamivir therapy. Overnight he developed respiratory distress, which required prompt intubation. Portable chest x-ray showed complete pulmonary consolidation bilaterally, while repeat laboratory analysis demonstrated new hypercapnia, hypoxemia, and acute kidney injury consistent with septic shock and multiorgan dysfunction. His respiratory function failed to improve in the next 6 hours, and the extracorporeal membrane oxygenation (ECMO) team was consulted for recommendations.

WHAT FACTORS SUPPORT THE USE OF ECMO FOR TREATMENT OF ACUTE RESPIRATORY DISTRESS SYNDROME IN THIS PATIENT?

The ECMO team arrived and assessed the situation. The latest arterial blood gas (ABG) demonstrated a serum pH of 7.05 with $PaCO_2$, PaO_2, and base excess of 56.3 mm Hg, 77.1 mm Hg, and -19.0 mmol/L, respectively, on the following ventilator settings: positive end-expiratory pressure (PEEP) of 15 cm H_2O, fraction of inspired oxygen (FiO_2) of 1.0, and estimated lung compliance of 30 mL/cm H_2O tidal volume V_T/[peak inspiratory pressure (PIP)-PEEP]. This resulted in a Murray score of 3.8. Calculated age, PaO_2/FiO_2, and plateau pressure score (APPS) and age-adjusted oxygenation index (AOI) were consistent with anticipated mortality of 80% or greater. The ECMO team determined veno-venous (V-V) ECMO support was indicated for acute respiratory distress syndrome (ARDS) management. The patient's mother was informed of the risks and benefits of intervention and consented to ECMO cannulation.

HOW CAN VASCULAR ACCESS BE OBTAINED, AND WHAT ARE THE TECHNICAL CONSIDERATIONS WHEN PLACING A PATIENT ON ECMO FOR ARDS?

The patient's right neck, right groin, and heart were examined using ultrasound. His left ventricular systolic function was adequate; however, the right ventricle was dilated, and the interventricular septum was deviated. The decision was made to proceed with V-V access because the right ventricular dysfunction often improves after initiation of V-V ECMO and concomitant reduction in ventilator pressures. The patient was provided a weight-based bolus of unfractionated heparin, and the right internal jugular vein was cannulated under ultrasound guidance using a 27-French (27F), dual-lumen (bicaval) catheter with flow at 4.5 L/min. The mean arterial pressure maintained at 70 mm Hg and repeat bedside echocardiography demonstrated improved right heart function. The patient was then transitioned to a continuous bivalirudin infusion to maintain an partial thromboplastin time (PTT) 1.5–2.5 times the control.

HOW SHOULD A VENTILATED PATIENT ON ECMO SUPPORT BE MANAGED IN THE INTENSIVE CARE UNIT?

The patient remained in the intensive care unit (ICU) on V-V ECMO support. His ideal body weight (IBW) on admission was 60 kg, which was used to estimate ventilator parameters. ECMO blood flow was maintained at 4.5 L/min (~75 mL/kg/min) with 1:1 sweep flow using 100% oxygen (sweep oxygen concentration [FsO_2] 100%) to maintain arterial oxygenation ($PaO_2 \geq 45$ mm Hg, $SaO_2 \geq 80\%$), and ensure adequate CO_2 clearance. Over the next 72 hours, the patient remained paralyzed, sedated, and ventilated using a lung-protection protocol of resting ventilation (pressure control 25/15, rate of 10 breaths/min, FiO_2 30%) and prone positioning for 16 hours per day.

WHAT ARE SOME OTHER MANAGEMENT CONSIDERATIONS FOR A PATIENT ON V-V ECMO?

The patient's comprehensive diagnostic workup revealed no underlying autoimmune, hematologic, rheumatologic, or other etiology of his rapid respiratory failure. He completed a course of oseltamivir for treatment of influenza B pneumonia. The patient demonstrated no evidence of renal recovery and required continuous veno-venous hemofiltration (CVVH) to maintain dry weight and prevent

pulmonary edema in the setting of intermittent blood product transfusion requirements: hemoglobin greater than 10 g/dL, platelets greater than 80 k/μL, and fibrinogen within 250–300 mg/dL.

WHAT ARE THE CRITERIA FOR WEANING AND DECANNULATION OF VENTILATION AND ECMO SUPPORT?

Serial ABG measurements demonstrated normalization of serum pH, base deficit, and hypercapnia by 12 hours. The pH was corrected slowly to prevent sudden swings in cerebral blood flow that can occur with precipitous correction of hypercapnia. The patient was kept sedated and paralyzed for 72 hours to reduce transalveolar sheer stress and facilitate prone positioning. Sedation was held every 24 hours to allow for neurologic assessment. Following this period, the paralysis was stopped, and the sedation changed to the lowest dose of dexmedetomidine to encourage mobilization and spontaneous breathing. The pressure control level and PEEP were weaned during this interval to 20 and 10 cm H_2O, respectively, to maximize patient comfort. As spontaneous breathing improved, the ventilator was changed from pressure control to pressure control/pressure support and the synchronized intermittent mandatory ventilation (SIMV) rate was set to 10; pressure support was set to PEEP plus 10 to match the SIMV breaths and keep the PIP well under 30 cm H_2O. The FiO_2 was left at 30%. Moreover, the ECMO team was able to reduce flow and sweep flow in a stepwise fashion, alternating with ventilator parameter changes, without detrimental effects to oxygenation or CO_2 elimination. On ECMO day 6, the patient's chest x-ray demonstrated improvement in aeration as he achieved larger and larger spontaneous V_T, in excess of 300 mL (>4 mL/kg IBW), on an ECMO flow of 1.0 and sweep of 2.5 L/min, respectively. The ventilation was adjusted to give an FiO2 of 60% and pressures of 28/8; the sweep gas on the V-V circuit was turned off to assess his native lung recovery. Unfortunately, during the trial off ECMO his $PaCO_2$ increased to 58 mm Hg. The patient was therefore placed back on ECMO support, and the ventilation was again reduced to rest settings. Over the next few days, the sedation was further weaned, and the patient continued to improve. By ECMO day 9, the patient was able to tolerate 12 continuous hours of minimal pressure support and underwent uncomplicated extubation. On ECMO day 12, the patient tolerated an overnight trial off ECMO when the sweep gas was discontinued, and the blood flow was maintained allowing CVVH and drug delivery to continue via the circuit. The next morning the circuit was turned off, local anesthetic was injected around the cannula, and a mattress suture was placed in the skin. The patient was then instructed to perform a Valsalva maneuver, and the cannula was removed by an assistant while the suture was tied. A CVVH cannula was immediately inserted in the right jugular vein with a puncture above the cannulation site. CVVH was continued for 6 days until renal function returned. The patient remained under observation in the ICU for the next 48 hours until transferred to a step-down unit for ongoing hospital care and rehabilitation.

DISCUSSION

After decades of biomedical research, in 1972 the first case report using extracorporeal oxygenation for adult respiratory failure emerged.[1] Contemporary ECMO practices reflect a cumulative effort to advance understanding of appropriate patient selection, extracorporeal physiology, lung-protective ventilation strategies, and intensivist care. The purpose of this discussion is to review practice guidelines for ECMO utilization in ARDS in the adult population.

ACUTE RESPIRATORY DISTRESS SYNDROME

Acute respiratory distress syndrome is characterized by a constellation of pathologic cellular and inflammatory changes within the lung parenchyma, causing significant alveolar injury and impaired gas exchange due to pneumonia, aspiration, or trauma or secondary to underlying sepsis.[2] The "Berlin classification" and its "Kigali modification" serve as the standard diagnostic framework for the establishment of ARDS, as defined by: respiratory failure of 7 days or less, bilateral pulmonary opacities observed on thoracic imaging, PaO_2/FiO_2 ratio 300 mm Hg or less with PEEP 5 cm H_2O or more, and no clinical evidence of cardiac failure or hypervolemia. ARDS severity is further defined by PaO_2/FiO_2 ratio ranges: mild ($200 < PaO_2/FiO_2 \leq 300$), moderate ($100 < PaO_2/FiO_2 \leq 200$), and severe ($PaO_2/FiO_2 \leq 100$).[3,4] Using this classification, ARDS has been diagnosed in 10.4% of ICU patients worldwide and required ECMO utilization in 0.2%, 2.4%, and 6.6% of mild, moderate, and severe cases, respectively.[5]

APPRAISAL OF THE LITERATURE AND QUALITY OF EVIDENCE

In the contemporary era, there have been two major randomized controlled trials (RCTs) that have evaluated the use of ECMO in the management of ARDS. CESAR, or the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure, trial was published in 2009 and reported a 16% difference in mortality between patients who were referred for ECMO (63%) compared to the control group (47%; relative risk 0.69, 95% CI [0.05–0.97], $P = .03$).[6] Although a survival benefit was observed, 22 patients (25%) of the ECMO group did not receive ECMO, and no standardized management protocol in the control group was used. These shortcomings were addressed with the 2018 release of a second RCT, the EOLIA, or ECMO to Rescue Lung Injury in Severe ARDS, trial.[7] Unfortunately, the crossover design meant that 35 patients received rescue ECMO, which complicated analysis and limited external validity. Nevertheless, 60-day mortality

was lower in the ECMO group (35%) compared to the control group (46%; relative risk 0.76; 95% CI [0.55–1.04], P = .09). Analysis of the secondary outcome, death or crossover to ECMO, did demonstrate higher mortality in the control (58%) compared to ECMO (35%; relative risk 0.62, CI [0.47–0.82], P < .001). While imperfect, these trials provided the strongest quality of evidence favoring ECMO utilization in ARDS.

Between the CESAR and EOLIA trials, there have been several studies that evaluated use of ECMO during H1N1 influenza outbreaks in the 2000s. In a propensity-matched case control study from this population, in-hospital mortality was 24.0% among the ECMO group compared to 46.7% (relative risk 0.51, CI [0.31–0.81], P = .008) in the conventional ventilation group.[8] A pooled meta-analysis of eight studies published between 2010 and 2011 identified a similar mortality risk of 27.5% (95% CI [18.4–37.7]).[9,10] Overall, over 21,000 patients internationally have received ECMO for adult respiratory failure since 1990 per the Extracorporeal Life Support Organization (ELSO).[11]

A summary of these studies and others is presented in Table 33.1.

INDICATIONS, CONTRAINDICATIONS, AND CONSIDERATIONS FOR EXTRACORPOREAL LIFE SUPPORT

Judicious patient selection is integral to successful ECMO application. The indications and contraindications presented in this section reflect a combination of recommendations from ELSO[12,13] and criteria from CESAR and EOLIA.

Indications

Referral for ECMO should be considered in patients with potentially reversible respiratory failure and hypoxemia or hypercapnia refractory to optimized mechanical ventilation. These include patients younger than 65 years who are likely not to survive and are without irreversible neurologic injury or disability.[6,7,12] Survival can be estimated by the APPS[14] or AOI[15] scores.[12] Other commonly employed and validated risk calculators can be used to a similar effect. Another approach uses the "Murray score," an independently developed and prospectively validated tool to calculate need for ECMO referral.[16] Scores 3.0 or greater suggest ECMO is

Table 33.1 EXTRACORPOREAL OXYGENATION FOR ARDS: MAJOR STUDIES AND FINDINGS

STUDY	DATE	TYPE	# PATIENTS[a]	FINDINGS[b]	LIMITATIONS
ELSO[11]	2019	REG	>21,000	Cumulative registry with 69% and 59% survival after ECMO and to hospital discharge/transfer, respectively, for *overall adult pulmonary failure*[2]	1. Retrospective analysis 2. No control group
EOLIA[7] (Combes et al.)	2018	RCT	124	1. Lower mortality at 60 days in ECMO (35%) compared to control group (46%) 2. Composite treatment failure, death or crossover to ECMO, at 60 days in control group (58%)	1. Results difficult to interpret due to 28% control group crossover into ECMO group 2. Trial was stopped prematurely at 75% maximum calculated sample size due to ethical concerns of futility
H1N1[10] (Zangrillo et al.)	2013	MAA	266	1. Majority (94%) received V-V access 2. Mortality in hospital and to 90 days after discharge ranged from 8% to 65%; overall estimated pooled in-hospital mortality 28%	1. Retrospective analysis 2) No studies with control group or randomization included
ANZ-ECMO[9] influenze investigators, Davies, et al.	2009	COH	68	1. Majority (93%) received V-V access 2. Mortality in-hospital 23% in the ECMO group compared to 13% in the control group	1. Retrospective analysis 2. No randomization, criteria for ECMO initiation not reviewed 3. ECMO cohort more likely to have vasopressor requirements
CESAR[6] (Peek et al.)	2009	RCT	68	Six-month survival without disability higher in the ECMO referral (63%) compared to the control group (47%)	No standardized management in control group

ANZ-ECMO, Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome study; ARDS, acute respiratory distress syndrome; CESAR, Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial; COH, observational cohort study; ECMO, extracorporeal membrane oxygenation; ELSO, Extracorporeal Life Support Organization; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS trial; H1N1, Extracorporeal Membrane Oxygenation (ECMO) in Patients with H1N1 Influenza Infection systematic review and meta-analysis; MAA, meta-analysis; RCT, randomized controlled trial; REG, registry data.

[a]Number of patients enrolled who received ECMO.

[b]Composite of all patients with adult respiratory failure, not specific to ARDS.

indicated, whereas a score of 2.5 or greater was used in the CESAR trial to identify high-risk patients. ECMO is indicated in patients who have received mechanical ventilation for less than 7 days and have refractory hypoxemia or hypercapnia as determined by a PaO_2/FiO_2 ratio less than 80 mm Hg for more than 6 hours (or PaO_2/FiO_2 ratio < 50 mm Hg for 3 hours) or uncompensated pH less than 7.25 and $PaCO_2$ of 60 mm Hg.[6,7,12]

Contraindications

There are no absolute contraindications to ECMO.[12] Recommended contraindications have been established explicitly or extrapolated from RCTs. Patients with moribund functional status, irreversible neurologic injuries, or otherwise unexpected to have meaningful recovery are not considered for ECMO referral. This also includes patients with active malignancy and less than 5-year expected survival. Furthermore, patient factors associated with worse outcomes, including age greater than 65 years and mechanical ventilation for 7 days or more, are considered relative contraindications. Less commonly, patients who cannot receive systemic anticoagulation or must be pharmacologically immunosuppressed, with absolute neutrophil count (ANC) less than 400/mm^3), may not be considered eligible.[6,7,12] Although body mass index (BMI) 45 kg/m^2 or more has been previously cited as a relative contraindication to V-V ECMO utilization, patients with BMI 40 kg/m^2 or greater may have superior outcomes compared to nonobese patients.[17] Duration of pre-ECMO ventilation does seem to have an effect on the duration of ECMO support required before the lung recovers. As a rule of thumb, patients may require an additional week of ECMO for each day of ventilation in excess of 9 days.

Other Considerations

Referral for and utilization of ECMO are ultimately at the discretion of the supervising physician. There are numerous case reports in the literature where ECMO use in extenuating circumstances has been described. However, the decision to place a patient on ECMO must be accompanied by discussion with an appointed healthcare surrogate and anticipated pathway for its eventual removal or bridge to another life-sustaining modality (Table 33.2).[12]

EVALUATION OF THE HEART: IS VENO-ARTERIAL ACCESS OR TRIPLE CANNULATION REQUIRED?

Once the decision has been made to initiate ECMO, the patient should be evaluated to determine the most appropriate mode and access. This assessment can be performed quickly at the bedside with echocardiography. Although the knee-jerk reaction is that patients with hemodynamically significant left ventricular dysfunction should receive veno-arterial (V-A) access rather than V-V, it is essential to remember that V-A ECMO is rather poor at offloading the left ventricle, and better hemodynamics can often be obtained with V-V ECMO through improved myocardial oxygenation and a reduction of ventilator pressure. Except in cases of near cardiac arrest, it is usually better to establish V-V ECMO and reevaluate. In patients who do not improve on V-V ECMO with reduced airway pressure, the femoral artery can be cannulated and connected to the V-V circuit to establish a veno-veno-arterial (V-VA) configuration.[18,19]

VENO-VENOUS ACCESS

Vascular access may be obtained via cutdown, percutaneously, or during open surgery and with imaging guidance (i.e., ultrasound or fluoroscopy). Placement can be done with two large (23F–31F) venous cannulae in a femoral and internal jugular vessel, or a double-lumen catheter in an internal jugular vein. ECMO flow rate is limited by the overall diameter of the catheter per Poiseuille's law; therefore, the appropriate size must be used in order to maintain adequate flow rates. However, larger (e.g., 31F) double-lumen cannulae are associated with a higher risk of intracranial hemorrhage due to venous obstruction.[20] The advantages of bicaval, double-lumen, V-V cannulation are reduced recirculation and improved ability for the patient to ambulate; however, they are more difficult to place, and imaging is mandatory. Systemic anticoagulation should be administered prior to cannulation. Appropriate positioning is important to reduce risk of recirculation, whereby oxygenated blood is recycled through the venous drainage to the ECMO circuit rather than into the venous circulation.[12,19,21]

INITIAL EXTRACORPOREAL SUPPORT MANAGEMENT

For V-V ECMO, the flow rate must be titrated to approximate the metabolic demands of the body. For adult patients, the rate can be initiated at 60–80 mL/kg/min and adjusted to sustain a ratio of maximum oxygen delivery DO_2 to oxygen consumption, VO_2 greater than 3. DO_2 is determined by the oxygenation capacity of the ECMO circuit, and contribution of the native lung. ECMO circuit oxygen transfer can be estimated by the differential in outlet and inlet oxygen saturation and the circuit flow velocity. Inlet oxygen saturation greater than 75% may suggest recirculation or cannula malposition. A DO_2/VO_2 ratio less than 2 may indicate the need to increase the ECMO flow or improve the oxygen capacity of the blood (i.e., blood product transfusion) (see Other Management Considerations). Adequate oxygen delivery can usually be obtained with a PaO_2 of 45 mm Hg or greater or SaO_2 of more than 80% assuming adequacy of both cardiac output and hemoglobin concentration. Initial sweep gas flow rates can be independently titrated up to 15 L/min to maintain $PaCO_2$ below 50 mm Hg.[12] Care should be exercised not to reduce the $PaCO_2$ too quickly in patients who are severely hypercarbic; therefore it is preferable to restore the pH to normal over a 12- to 24-hour period.

Table 33.2 EXTRACORPOREAL OXYGENATION REFERRAL FOR ARDS: ADAPTED SELECTION CRITERIA PER RANDOMIZED CONTROLLED TRIALS AND CONSENSUS GUIDELINES

INDICATIONS	SOURCE
Age < 65 years	CESAR[6]
Reversible respiratory failure	CESAR
Calculated mortality risk ≥ 80%[a]	ELSO[12]
Endotracheal intubation and mechanical ventilation < 7 days	EOLIA[7]
Optimized mechanical ventilation, adjunct therapies,[b] and PaO_2/FiO_2 ratio < 50 mm Hg for 3 hours, or PaO_2/FiO_2 ratio < 80 mm Hg for > 6 hours Uncompensated hypercapnia, $PaCO_2$ ≥ 60 mm Hg, with serum pH < 7.25	EOLIA ELSO, CESAR, EOLIA
Murray score ≥ 3.0	CESAR
Need for intubation in a patient on lung transplant list	ELSO
Relative Contraindications[c]	**Source**
Age > 65 years	CESAR
Optimized mechanical ventilation ≥ 7 days	ELSO, CESAR, EOLIA
Moribund, irreversible neurologic injury or terminal malignancy (life expectancy < 5 years)	ELSO, CESAR, EOLIA
Unable to receive systemic anticoagulation or history of heparin-induced thrombocytopenia	CESAR, EOLIA
Major pharmacologic immunosuppression (absolute neutrophil count < 400/mm^3)	ELSO

AOI, age-adjusted oxygenation index; APPS, age, PaO_2/FiO_2, and plateau pressure score; CESAR, Conventional Ventilation or ECMO for Severe Adult Respiratory Failure trial; ELSO, Extracorporeal Life Support Organization; EOLIA, ECMO to Rescue Lung Injury in Severe ARDS trial; FiO_2, fraction of inspired oxygen; NO, nitric oxide; PEEP, positive end-expiratory pressure.

[a]Risk determined by Murray score, AOI, or APSS; ECMO should be considered if mortality ≥ 50%.

[b]Ventilation (defined by EOLIA): FiO_2 ≥ 0.8, V_T 6 mL/kg, and PEEP ≥ 10 cm H_2O; adjuncts: inhaled NO, recruitment maneuvers, prone positioning, and almitrine infusion.

[c]There are no absolute contraindications to ECMO referral.

INITIAL MECHANICAL VENTILATOR MANAGEMENT

The practices used to improve outcomes in patients with ARDS have been driven by lung-protective strategies. The EOLIA trial was the first to establish a standardized ventilation protocol for both the ECMO and control groups, based on the EXPRESS, or Positive End Expiratory Pressure in Adults with Acute Lung Injury and Acute Respiratory Distress Syndrome, trial parameters.[22] Similar parameters must be optimized prior to ECMO initiation. These include V_T less than 6 mL/kg, FiO_2 less than 0.40, PEEP below 15 cm H_2O, respiratory rate less than 5 breaths/min, and plateau pressure less than 30 cm H_2O.[12] In addition, steroids,[23] prone positioning,[24] neuromuscular blockade,[25,26] and other practices have been employed with mixed results (see Adjuncts and Recruitment Trials).

OTHER MANAGEMENT CONSIDERATIONS

In the course of ECMO, careful attention must be paid to all other aspects of daily ICU management to improve outcomes. Complications reported during the EOLIA trial included bleeding that required blood transfusion (46%); thrombocytopenia (count < 50 k/μL, 40%); ventilator-associated pneumonia (39%); arrhythmia (31%); hypothermia (23%); cardiac arrest (19%); pneumothorax (15%); and stroke (2%).[7] Sedation should be kept to a minimum. Renal replacement therapy may be required to maintain dry weight and prevent complications of fluid overload. Enteral or parenteral nutrition should be provided.

Anticoagulation is required to prevent thromboembolic and circuit complications, but ECMO without its use has been reported.[27] Unfractionated heparin is the standard option for

anticoagulation, but experienced centers may increasingly use direct thrombin inhibitors (e.g., argatroban, bivalirudin, and lepirudin) or direct factor Xa inhibitors (e.g., rivaroxaban). Bivalirudin in particular has emerged as a potential first-line or viable option for anticoagulation in patients with contraindications to heparin therapy or to obviate the risk of heparin-induced thrombocytopenia. Moreover, bivalirudin may be more cost-effective and reduce major bleeding events in adults compared to heparin.[28–30]

Anticoagulation and hematologic parameters should be diligently monitored multiple times per day via a protocol-driven approach. Common tests include ACT, anti–factor Xa level, activated PTT, or use of thromboelastography or thromboelastometry. Blood product transfusion is required to maintain normal hematocrit (>40%), fibrinogen greater than 100–150 mg/dL, platelets greater than 80,000/μL, and antithrombin activity more than 30% in absence of severe complications or other pathologic states. However, there are no strict, established guidelines that can be used in all situations and across all centers.[12,31,32]

DE-ESCALATION OF CARE: WEANING MECHANICAL VENTILATION AND EXTRACORPOREAL SUPPORT

Once ECMO has been initiated, the aim of ICU care is to wean the patient to ECMO decannulation and extubation. Extended mechanical ventilation and ECMO placement both confer significant risks and complications with long-term consequences, yet there is no consensus on de-escalation. A few general practices based on ELSO guidelines, recent reports, and expert opinion can be considered.

Neurologic Examination and Mental Status

Patients with deep sedation and, if used, neuromuscular blockade are unable to provide a reliable neurologic examination, but sedation can be weaned within 12–36 hours. If there are any concerns for localized neurologic deficits or altered mental status, cross-sectional imaging of the head should be obtained. Bleeding or other intracranial pathology may indicate irreversible neurologic injury and complicate ongoing care (see Ethical Considerations: Deferring Initiation, Withdrawal of Care, and Referral to Lung Transplant).[12]

Preservation of Lung-Protective Mechanical Ventilation

Lung-protective mechanical ventilation remains essential to preventing ventilator-induced lung injury on top of widespread parenchymal injury and impaired gas exchange secondary to ARDS. ECMO flow can be increased in response to worsening hypoxemia or hypercapnia in order to preserve lung-protective ventilation parameters and weaned over the ensuing hours or days as tolerated. Once support measures peak, de-escalation procedures should be initiated following a previously established outcome. These may include a target V_T with spontaneous breathing[12,33–35]; PIP,[34,35] PEEP,[34,35] or FiO_2 marker with positive Cilley test[12,34,35]; improvement in aeration on serial chest x-rays[12,35]; or after a prespecified time interval (e.g., 24 hours).[34] The Cilley test is performed by increasing the FiO_2 to 100%. If the SaO_2 increases to 100%, the test is positive, and this indicates that the native lung has regained partial respiratory function.[12]

Adjuncts and Recruitment Trials

Adjunct measures to treat severe ARDS have been commonly employed with ECMO. Adjuncts were frequently used in the EOLIA trial, including prone positioning (66%), glucocorticoids (65%), nitric oxide or prostacyclin (60%), and recruitment maneuvers (22%).[7] These modalities and others (e.g., neuromuscular blockade) have been used with some benefit, except high-frequency oscillation ventilation, and should be considered prior to ECMO referral.[36] Recruitment trials are recommended by ELSO once "significant aeration" on chest x-ray, V_T greater than 4 mL/kg, and a positive Cilley test are achieved. The recommended protocol uses CPAP with spontaneous breathing at 25 cm H_2O *or* pressure support ventilation at 25/10 cm H_2O, respiratory rate of 5 breaths/min, and inspiratory-to-expiratory ratio of 3:1 for 10 min/h. These measures are repeated until rest ventilation or ECMO flow rates can be decreased.[12]

Extracorporeal Flow Rate and Trialing Off ECMO

The optimal approach to concurrently wean mechanical ventilation and extracorporeal support is unclear once de-escalation criteria are met. Methods to first wean ECMO, mechanical ventilation, or some combination thereof have been described.[12,34,35] There is neither a consensus nor a simple way to assess the superiority of any single approach; however, "awake ECMO" after extubation or tracheostomy may confer unique benefit (see Extubation or Tracheostomy Placement). Nevertheless, lung-protective settings must be maintained. Adjustments to ECMO flow can occur more quickly than those for mechanical ventilation and can be used to adapt to sudden changes in pulmonary compliance if native lung function deteriorates. Weaning from mechanical ventilation can otherwise follow a protocol employed in conventional ICU care. Special attention should be paid to coordinating changes in ECMO flow, sweep gas, or mechanical ventilation to correctly interpret the patient's respiratory status, arterial oxygenation capacity, and ability to eliminate CO_2 regardless of the utilized approach.

Each ECMO weaning protocol uses a different threshold for blood and sweep gas flow rates to initiate trials off ECMO but follows a linear, stepwise reduction in flow over hours or days with routine assessment by ABG. For simplicity, only an adapted ELSO approach is described. In that protocol, ECMO weaning is indicated when flow rates of 1 L/min on a FSO_2 of 100% *or* 2 L/min flow with a decrease in FSO_2 to maintain SaO2 greater than 95% are tolerated. If met, the patient can be trialed off ECMO for 1–2 hours and reassessed. If arterial oxygenation (SaO_2 > 95%) and CO_2 clearance ($PaCO_2$ < 50 mm Hg) are maintained on reasonable levels of ventilation (FiO_2 60% and PIP < 30 cm H_2O) the anticoagulation and

can be turned off and the cannula removed.[12] The V-V trial off is accomplished by disconnecting the sweep gas and maintaining ECMO blood flow. A V-A trial off is more complex and can be achieved by the classical technique of recirculation via the bridge while clamping and intermittently flashing the cannulae or the more elegant pump-controlled retrograde trial-off technique.[37] Use of the phrase "clamping out" should be avoided as clamps are often not required or can be extremely dangerous. In addition, conducting a V-V ECMO trial off in a patient on V-A ECMO can be fatal. Access sites should be evaluated after decannulation with venous duplex studies due to high risk of deep vein thrombosis (DVT).[38] If failed, secondary causes of hypoxemia (e.g., anemia or ventilator-associated pneumonia) can be evaluated and another trial repeated. If $PaCO_2$ remains high during the trial off, extracorporeal CO_2 removal ($ECCO_2R$) may be considered (see Selective CO_2 Elimination), although it is usually simpler to achieve this using the ECMO circuit.

Extubation or Tracheostomy Placement

Extubation parameters are similar to those in conventional ICU protocols. In cases of prolonged or anticipated prolonged mechanical ventilation, a tracheostomy should be placed within 5 days.[12,39] Alternatively, ECMO support can be maintained after extubation or, increasingly, in place of mechanical ventilation at experienced centers.[40] Awake ECMO usage allows for more patient comfort, ambulation, and limited physical and occupational therapy without increased morbidity or mortality; however, its use remains limited.[33,41]

Selective CO_2 Elimination

Some patients may demonstrate persistent hypercapnia while trialing off ECMO. $ECCO_2R$ can be utilized through maintenance of low-flow ECMO rates (300–1500 mL/min) with sweep gas flow rates up to 15 L/min. This setup can also be used during awake ventilation or spontaneous breathing. Subsequent trials off can be pursued as previously described.[12,42,43] An alternative strategy is to see if the patient will develop metabolic compensation by performing a prolonged V-V ECMO trial off for 24–48 hours. If the pH stabilizes close to 7.3 and the patient remains stable with PIP less than 30 cm H_2O, they can often be decannulated safely.

POSTDECANNULATION MANAGEMENT

Following ECMO, patients often remain critically ill in the ICU with ongoing mechanical ventilation requirements or other forms of multiorgan dysfunction. Careful observation should be maintained to assess for short-term, delayed, or previously unrecognized sequelae after decannulation (e.g., respiratory failure, stroke, bleeding, renal failure, DVT, post-decannulation systemic inflammatory response syndrome, wounds, and secondary infections).[12,44] Physical and occupational therapy started during ECMO remain integral to patient recovery.

ETHICAL CONSIDERATIONS: DEFERRING INITIATION, WITHDRAWAL OF CARE, AND REFERRAL TO LUNG TRANSPLANT

The use of ECMO creates many challenging scenarios for healthcare teams. Use of advanced directives and informed family discussions can help direct management, even if ECMO is indicated. An international survey of ECMO providers revealed older age, multiorgan failure, extended mechanical ventilation, immunosuppression, and failure to utilize prone positioning were commonly cited factors associated with deferring ECMO initiation.[45]

Although ELSO recommends consideration of ECMO withdrawal if there are no indications of lung recovery in 2 weeks or if meaningful recovery is unexpected (e.g., in the presence of irreversible neurologic injury or moribund functional status),[12] there is increasing experience that the lungs can recover after several months, so most expert groups will usually wait much longer than 2 weeks to give the lungs a chance to recover in the absence of any other contraindication to continued treatment. Other factors associated with withdrawal include pulmonary fibrosis, multiorgan failure, and patient or healthcare surrogate decision.[45] In some cases, transition to V-A or VV-A ECMO may be necessary. Alternatively, patients without underlying end-stage lung disease or multiorgan failure may be eligible for lung transplant.[46] In situations in when care is withdrawn, decannulation or extubation can result in immediate patient expiration.

REVIEW OF THE STEM CASE AND KEY QUESTIONS

In the presented case, an otherwise-healthy 21-year-old male was admitted to the hospital with influenza B pneumonia and ARDS. The patient met established indications for ECMO referral: age less than 65, fewer than 7 days of mechanical ventilation, Murray score 3.8, PaO_2/FiO_2 ratio less than 80 for 6 hours, and mortality risk score of 80% or greater. ECMO flow and sweep flow parameters were empirically initiated with a weight-based calculation (60–80 mL/kg/min) and 1:1 sweep flow. These parameters were titrated based on serial ABG measurements to a PaO_2 of 45 mm Hg or greater and SaO_2 greater than 80%. A lung-protective strategy of mechanical ventilation was used with IBW-based V_T, low respiratory rate, and high PEEP. After a few days of ECMO treatment, de-escalation measures were performed, including recruitment trials and eventual extubation and successful decannulation from V-V ECMO.

CONCLUSION

- Veno-venous ECMO is best utilized in ARDS patients with reversible forms of respiratory failure who meet criteria including age less than 65 years, serum pH less than 7.25 with uncompensated hypercapnia, Murray score of 3.0 or more, and mechanical ventilation for less than 7 days.
- The core tenet of V-V ECMO utilization is to promote lung recovery using optimized lung-protective

mechanical ventilation strategies and correction of underlying ARDS.

- The ECMO flow and sweep gas flow can be titrated to increase oxygenation and CO_2 clearance, respectively, while maintaining minimal ventilator settings.
- Weaning from ECMO and mechanical ventilation should be coordinated using a protocol-driven approach to expedite decannulation, extubation, and overall recovery.
- Patient progress should be closely monitored to guide discussion related to withdrawal of care or referral to transplant as medically appropriate.

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REVIEW QUESTIONS

1. Which of the following patients with ARDS on V-V extracorporeal support is the most eligible for lung transplantation?

A. 19-year-old female with no medical history and acute inhalational injury after occupational accident managed for 2 weeks
B. 20-year-old female with asthma and influenza B pneumonia managed for 5 days
C. 51-year-old male with bilateral rib fractures, pulmonary contusions, ventilator-associated pneumonia, and kidney failure requiring continuous renal replacement therapy after a motor vehicle accident managed for 2 weeks
D. 65-year-old female with idiopathic pulmonary fibrosis and sepsis from a urinary tract infection managed for 7 days

2. A 54-year-old, 100-kg male is intubated and placed on V-V extracorporeal support for management of influenza B pneumonia and ARDS. His mechanical ventilation parameters are optimized. The most recent ABG shows a hematocrit of 42%, partial pressure of arterial oxygen and carbon dioxide of 35 and 45 mm Hg, respectively, with blood flow rate of 4.0 L/min and sweep gas rate of 6.0 L/min. The next best step in management is

A. Transfuse 1 unit of packed red blood cells
B. Increase blood flow rate to 6.0 L/min
C. Increase sweep gas rate to 8.0 L/min
D. Continue current management and repeat blood gas in 4 hours

3. Which of the following intubated patients with ARDS and optimized mechanical ventilation meet common criteria for V-V extracorporeal support?

A. 26-year-old female with no medical history in the surgical ICU with bilateral pulmonary contusions, grade II spleen laceration, and subarachnoid hemorrhage after a jet ski accident
B. 23-year-old male with uncontrolled HIV and bilateral chest tube placement for pleural effusion
C. 72-year-old male with BMI of 35 kg/m^2 and inhalational injury due to a malfunctioning electronic cigarette
D. 31-year-old male with newly diagnosed autoimmune pancreatitis and small pleural effusion

4. Which of the following patients with severe ARDS is most likely to meet criteria for V-V extracorporeal support?

A. 31-year-old female with bilateral necrotizing pneumonia and cystic fibrosis intubated 2 days ago for uncompensated hypercapnia
B. 22-year-old male recently immigrated from Southeast Asia with no past medical history, emergently intubated 1 hour ago and supported with norepinephrine in the emergency department; bilateral pulmonary consolidation and small pericardial effusion identified on chest x-ray
C. 55-year-old male with history of rectal cancer completely treated 6 years ago with neoadjuvant chemotherapy and abdominoperitoneal resection complicated by recurrent rectal bleeding intubated 4 days ago for community-acquired pneumonia
D. 19-year-old female with tracheostomy and anoxic brain injury sustained in motor vehicle accident 3 years ago admitted for fever secondary to infected decubitus ulcer and possible aspiration

5. A 55-year-old man with history of hypertension, type 2 diabetes complicated by end-stage renal disease, and chronic obstructive pulmonary disease presents to the emergency room with shortness of breath after receiving a blood transfusion during dialysis. The patient is intubated and placed on V-V extracorporeal support via right internal jugular and femoral vein cannulation. After 48 hours of treatment, he becomes hypotensive and requires maximal vasopressor and inotropic support. Repeat bedside echocardiography shows a mildly reduced ejection fraction. The next best step for management is

A. Increase V-V sweep gas rate to increase CO_2 clearance
B. Consider arterial cannulation to initiate VV-A support and referral for temporary mechanical circulatory support device placement

C. Emergent hemodialysis to relieve volume overload and correct electrolyte derangements
D. Increase V-V circuit flow rate to ensure arterial oxygenation

ANSWERS

1. A. The patient in A has no other medical problems, no other organ dysfunction, or no underlying end-stage lung disease. She has received ECMO for 2 weeks without recovery and may not survive without transplantation.[12,46] The patients in B and D can still be managed with ECMO for longer in anticipation of lung recovery. The patient in C has an active pulmonary infection and multiorgan dysfunction.

2. B. The patient remains hypoxemic despite optimal ventilation and use of V-V ECMO. The blood flow rate should be increased to meet the patient's metabolic demands, calculated initial settings (60–80 mL/kg/min)*(100 kg)*(1 L/1000 mL) = 6.0 to 8.0 L/min. The patient does not meet criteria for blood product transfusion with a hematocrit of 42% (A). CO_2 clearance is already adequate at the current rate (C). Waiting 4 hours for a repeat ABG would not be appropriate when the patient is already hypoxemic (D).

3. D. The 31-year-old male with autoimmune pancreatitis does not have any contraindications to ECMO. The patient in A has an intracranial hemorrhage, which likely precludes necessary anticoagulation.[27] The patient in B has uncontrolled HIV with pleural effusion suggestive of severe immunosuppression. Last, the patient in C is older than 65 years.[6,7,12]

4. A. The 31-year-old female with cystic fibrosis has been ventilated 7 days or less and has uncompensated hypercapnia with no provided contraindications. The patient in B is hemodynamically unstable with clinical and imaging findings concerning for a possible cardiac etiology (e.g., myocarditis) that is more amenable to V-A or temporary mechanical circulatory support.[18,19] The patient in C completed cancer treatment but may not be eligible for systemic anticoagulation due to recurrent rectal bleeding. Last, the patient in D has poor functional status and irreversible neurologic injury that prohibits invasive support measures.[6,7,12]

5. B. This patient is admitted due to complication from blood transfusion, a rare cause of ARDS,[5] and decompensates while on V-V ECMO secondary to an unknown cause. Bedside echocardiography findings are nonspecific but can indicate need for other interventions.[18] VV-A ECMO and possible mechanical circulatory support are appropriate to stabilize the patient, who is already on maximal pharmacologic support.[19] This would allow time to complete a more comprehensive workup and manage the patient more effectively. The other options would not improve the patient's hemodynamics.

34.

EXTRACORPOREAL CO_2 REMOVAL TO ENHANCE PROTECTIVE VENTILATION IN ARDS

Guillaume Franchineau and Matthieu Schmidt

STEM CASE AND KEY QUESTIONS

A 62-year-old man is hospitalized for acute respiratory failure associated with septic shock. His medical history includes a chronic obstructive pulmonary disease, Global Initiative for Chronic Obstructive Lung Disease 2, without recent hospitalization. The hypoxemia rapidly required orotracheal intubation with invasive mechanical ventilation. During the following 24 hours, the patient developed a moderate acute respiratory distress syndrome (ARDS), with PaO_2/FiO_2 (fraction of inspired oxygen) ratio of 130, despite protective ventilation with 6 mL/kg ideal body weight tidal volume V_T, and a positive end-expiratory pressure (PEEP) set at 12 cm H_2O, leading to a plateau pressure (Pplat) at 28 cm H_2O. Respiratory rate (RR) was set at 30 breaths/min to maintain $PaCO_2$ at 44 mm Hg and a normal pH. A bronchoalveolar lavage identified a 10^6 *Streptococcus pneumoniae* pneumonia. In addition, acute renal failure required renal replacement therapy (RRT) on a dialysis catheter inserted in the femoral position, associated with fluid administration and vasopressor for septic shock. Despite continuous neuromuscular blocker infusion and a 16-hour prone-positioning session, the PaO_2/FiO_2 ratio did not improve. To apply an ultraprotective ventilation strategy aiming to further reduce V_T and RR, an extracorporeal CO_2 removal device ($ECCO_2R$) was inserted in the jugular position without complications.

The $ECCO_2R$ blood flow was 1200 mL/min, whereas the sweep gas flow was set at 15 L/min. This support permitted decreasing V_T to 4 mL/kg, with an RR at 20 breaths/min, while increasing PEEP to 14 cm H_2O and maintaining Pplat at 24 cm H_2O. Associated with the CO_2 removal device, the targeted activated partial thromboplastin time (aPTT) for anticoagulation with unfractionated heparin was 60–75 seconds or anti–factor Xa (anti-Xa) activity was 0.3–0.5 IU/mL. Improvement of hemodynamic parameters led to stopping vasopressors and starting fluid removal with RRT.

Two days later, bleeding at the insertion site of the cannula and in the oropharyngeal sphere imposed a reduction of the anticoagulation target and the transfusion of 4 units of red blood cells. A few hours later, clot formation appeared in the oxygenator, and blood flow progressively decreased despite a similar pump speed. Biological data revealed hemolysis associated with hypofibrinogenemia. The decision was made to remove the CO_2 removal device, to limit $ECCO_2R$-related complications, after fibrinogen transfusion and correction of the hemostasis. Two days after $ECCO_2R$ device removal, the respiratory condition continued to improve, with normalization of the static lung compliance, PaO_2/FiO_2 ratio 250, and a normal $PaCO_2$ with a V_T set at 6 mL/kg ideal body weight and a RR at 22 breaths/min.

Sedation was rapidly stopped, and extubation was successful after 1 week of mechanical ventilation. Normalization of the kidney function led to intensive care unit (ICU) discharge, with the patient returning to home a few weeks later without any other complication.

WHAT IS THE RATIONALE FOR USING A CO_2 REMOVAL DEVICE?

Ventilator-induced lung injury (VILI) is a well-known complication of mechanical ventilation, favored by a high V_T and excessive airway pressures. Patients with ARDS will more likely have VILI due to their decreased functional lung volume, frequent atelectasis, and intense alveolar inflammation.[1–3] Moreover, refractory severe hypoxemia and hypercapnia could force clinicians to increase the RR and minute ventilation, leading to an increase of the mechanical power transmitted to the lung.[4] Physiological data suggest that hyperinflation could occur despite a low V_T set at 6 mL/kg as recommended.[2] Moreover, barotrauma may still be a threat despite limited Pplat in some patients,[5] reinforcing potential benefits for a more protective mechanical ventilation. Last, altered compliance in severe ARDS also leads to an increase of the driving pressure, which could impact the outcome.[1]

Extracorporeal CO2 removal was first developed in 1980 for severe ARDS.[6] Better knowledge of the harmful effects of mechanical ventilation and the investigation of the potential benefits of an ultraprotective ventilation[7] both led to regaining interest for this technique. $ECCO_2R$ allows further decrease in V_T and RR, therefore enhancing protective ventilation.[8] By doing so, the mechanical power transmitted to the lung decreases with a reduction of VILI.[4] In that context, recent data suggest that $ECCO_2R$ could be associated with a significant reduction of systemic and pulmonary inflammatory mediators.[9]

Additionally, few data highlight that severe hypercapnia (>50 mm Hg) during ARDS is associated with an increased

risk of mortality in the ICU.[10,11] Extrapulmonary effects of hypercapnia could explain this finding. Indeed, hypercapnia

- Increases cerebral blood flow and favors intracranial hypertension[12];
- Increases pulmonary arterial vasoconstriction associated with microvascular alteration;
- Increases right ventricular afterload; and
- Decreases myocardial contractility.

All of these effects contribute to hemodynamic dysfunction.[13,14]

WHAT ARE THE MAIN COMPONENTS OF $ECCO_2R$?

Extracorporeal CO_2 removal is composed of a drainage cannula, a pump, a membrane lung, and a return cannula.[15] In most cases, drainage and return cannula are associated in a dual-lumen catheter. Due to low blood flow (200 mL to 1500 mL/min, depending on devices and the lumen size of the catheter), oxygenation is minimal. However, the sweep gas flow allows significant CO_2 removal, which is approximately 20% of the metabolic CO_2 production.[16] The unique function of decarboxylation of $ECCO_2R$ devices could sometimes be assimilated into "carbon dioxide dialysis."[17] Because CO_2 diffusion is much more efficient than O_2 diffusion, only low blood flow is needed to extract CO_2 compared to those required for oxygenation. Consequently, 250 mL of CO_2 could be removed from less than 1 L of blood.[15] Besides, the greater solubility of CO_2 across extracorporeal membranes largely contributes to this point.[18]

The performance of the decarboxylation depends on three factors: the diffusion gradient, the membrane-blood contact time, and the membrane diffusion characteristics. The diffusion gradient is the difference between the blood concentration of CO_2 and the airflow. The higher the $PaCO_2$, the greater the CO_2 removal through the biocompatible membrane will be.[19] The membrane-blood contact time depends on the membrane geometry and the membrane surface area. Modern membranes vary between 1 and 3 m^2 and are made of nonmicroporous poly-4-methyl-1-pentene[20] and offer good biocompatibility. This last is enhanced by the heparin coating of the membrane.

Centrifugal and diagonal with radial rotating impellers are the two pump types currently used. They have been developed to provide enough power by limiting the stress on blood cells and the risk of hemolysis. Despite these technological improvements, the impact of shear stress remains significant, especially with low blood flow used during $ECCO_2R$.[21,22]

WHICH VASCULAR ACCESS SHOULD BE CHOSEN TO PERFORM $ECCO_2R$?

In the early 2000s, most of the $ECCO_2R$ devices were pumpless and used an arterio-venous (A-V) configuration.[23] The blood was drained from the femoral artery and reinfused in the femoral vein. Therefore, the $ECCO_2R$ blood flow fully depended on the cardiac output and the blood pressure. Also, vascular complications due to artery puncture were frequent. A veno-venous (V-V) setting, using a single dual-lumen venous catheter, is now the recommended vascular access for modern $ECCO_2R$,[16] allowing a unique puncture and reducing the risk of vascular damage. The lumen size of the catheter directly impacts the $ECCO_2R$ blood flow. Due to less need for high blood flow, the $ECCO_2R$ cannula is smaller than those used with extracorporeal membrane oxygenation (ECMO). These heparin-coated catheters, however, are larger than those used in dialysis, with a size ranging between 15- and 24-French (15F and 24F) cannulae.

HOW IS AN $ECCO_2R$ CATHETER INSERTED?

As for any central catheter insertion, the procedure should be ultrasonography guided[24] and performed by an experienced clinician. The distal tip of the catheter is positioned in the superior or inferior vena cava for an access site in the internal jugular vein or in the femoral vein, respectively. Unlike V-V ECMO, the distal tip of the cannula does not reach the right atrium, which makes it more sensitive to mobilization and displacement, with a higher risk of blood flow variation. Femoral and internal jugular access are both used. Femoral access has a higher infection risk; it may limit the patient's mobility, and its flow is highly dependent on body position.

HOW IS MECHANICAL VENTILATION WITH $ECCO_2R$ SET?

The main objective of $ECCO_2R$ in patients with moderate or severe ARDS is to maintain $PaCO_2$ and pH in an adequate range while applying an ultraprotective ventilation strategy. It is worth noting that other adjuvant therapies such as continuous neuromuscular blockade or prone positioning are applicable under $ECCO_2R$.

International recommendations suggest that patients with moderate-to-severe ARDS should be managed with low V_T (6 mL/kg ideal body weight) and high PEEP[25] while keeping Pplat lower than 30 cm H_2O. Due to the low lung compliance in some patients, a high Pplat despite the reduction of V_T and/or PEEP could lead to hypercapnic acidosis.[26] Moreover, a low tidal volume of 6 mL/kg could still cause tidal hyperinflammation, which could be reduced by a further decrease of the V_T.[27]

The rationale for $ECCO_2R$ is therefore to reduce VILI by decreasing Pplat and driving pressure,[1] V_T,[8,28] mean minute ventilation,[4,9] and increased PEEP. Recent studies suggested targeting a V_T at 4 mL/kg ideal body weight, 24 cm H_2O Pplat, and a maximal reduction of the RR. Recent feasibility studies have shown that these objectives could be achieved safely. The Strategy of UltraProtective Lung Ventilation With Extracorporeal CO2 Removal for New-Onset Moderate to seVere ARDS (SUPERNOVA) pilot study included 95 patients treated for moderate-to-severe ARDS in 23 ICUs. ECCO2R allowed a significant decrease of the Pplat (from 27 to 24 cm H2O), the VT (from 6 to 4 mL/kg), the RR (28

to 24 breaths/min), and the minute ventilation (from 10 to 6 L/min).29 Despite the significant reduction of the minute ventilation, pH and PaCO2 were maintained greater than 7.3, and with an increase less than 20% baseline PaCO2. Similar results were obtained with different devices,8,30 such as a combined CO2 removal device on a renal replacement platform (Prismalung®, Gambro-Baxter)31 or in other observational studies.32

WHICH ADJUVANT MEASURES COULD BE USED WITH $ECCO_2R$?

By allowing higher CO_2 clearance, $ECCO_2R$ could lead to better tolerance of very low V_T for these patients. Doing so, the sedative dose could potentially be reduced. To date, only two trials have evaluated the impact of $ECCO_2R$ on sedation, with a significant decrease in analgesic or hypnotic drugs needed.[28,33] If ultraprotective ventilation is achieved safely, with appropriate patient-ventilator synchrony, neuromuscular blockade could be discontinued.

To our knowledge, the combination of $ECCO_2R$ and prone positioning has not been thoroughly evaluated. As the blood flow is highly dependent on the catheter position, it could be misplaced during nursing care or mobilization. Caution is therefore warranted when prone positioning is combined with $ECCO_2R$.

WHICH ANTICOAGULATION STRATEGY SHOULD BE CHOSEN FOR $ECCO_2R$?

Despite the use of heparin-coated membrane and circuit, blood contact leads to an activation of the coagulation pathway and platelet activation, which favor clotting and vascular or circuit thrombosis. Consequently, systemic anticoagulation is crucial for these techniques, with close monitoring of the bleeding risks. The management of these patients is a difficult balance between bleeding and thrombosis risks. Notably, the clotting risk is directly related to the type of device, the $ECCO_2R$ blood flow, and the size of the cannula. The smaller the lumen of the cannula, the lower the $ECCO_2R$ blood flow will be and the higher the risk of thrombosis.

Studies on $ECCO_2R$ performance targeted a 1.5 to 2 aPTT ratio[29,31,32] using unfractionated heparin. Stopping anticoagulation should be urgently discussed in case of a bleeding event.

WHAT IS THE INCIDENCE AND IMPACT OF BLEEDINGS UNDER $ECCO_2R$?

Arterio-venous $ECCO_2R$ was associated with severe complications, such as limb ischemia or femoral artery pseudoaneurysm,[34] but these pumpless devices are not used anymore in routine. Modern V-V $ECCO_2R$ does not expose patients to these arterial complications, but severe complications due to venous vascular access are described, such as perforation of the iliac vein, with retroperitoneal bleeding and patient death[35]; vein perforation by the catheter and retroperitoneal hematoma[36]; or massive right frontal parenchymal hematoma and pneumothorax at cannula insertion.[29]

Due to the low blood flow of V-V $ECCO_2R$, the risk of catheter and/or membrane thrombosis is high. Systemic anticoagulation is required during $ECCO_2R$, but it also increases the risk of significant bleeding.[37] Hence, the management of $ECCO_2R$ requires a difficult balance between bleeding and thrombosis. Usually, bleeding does not impair the patient's hemodynamics because it is often minimal, but it increases the need for blood transfusion.[28,30,34] The incidence of $ECCO_2R$-related bleeding is not well known but affected 14% of patients in the recent SUPERNOVA pilot study.[29] Surprisingly, Braune et al. reported a higher rate of severe bleeding, with 11 episodes in nine patients (36%). This higher incidence could be explained by a longer $ECCO_2R$ duration, with these episodes starting after 5.3 days.[38] Besides, this study also enrolled nonintubated patients with chronic obstructive pulmonary disease exacerbation, which could explain the long duration of $ECCO_2R$, which is usually not observed in studies in ARDS. A recent observational study observed a similar incidence of bleeding (30%), but most of the patients had the Hemolung device (Alung Technologies, Pittsburgh, PA).[32] Of note, only 6% of bleeding was observed with the iLA activve device.[32]

WHAT IS THE INCIDENCE OF CLOTTING UNDER $ECCO_2R$?

Membrane clotting could reduce membrane CO_2 clearance, increase transmembrane pressure, and cause premature withdrawal of the device/treatment. Depending on the technology used, the incidence of this adverse event could vary widely. Schmidt et al. described an incidence of 50%, despite a high anticoagulation regimen with an aPTT time ratio at 1.8 and 230 IU/kg/h of continuous heparin infusion. Consequently, membrane clotting led to early withdrawal of $ECCO_2R$, after only 20 hours. It is worth noting that this feasibility study used a Prismalung device, which provides CO_2 removal through a classical dialysis catheter and lower blood flow (e.g., 425 mL/min). The SUPERNOVA pilot study used three different devices. One offered low CO_2 removal and low blood flow (300 to 500 mL/min), whereas the two others had higher CO_2 removal and greater blood flow (800 to 1000 mL/min). Consequently, a lower incidence of membrane clotting was reported with these last two devices (14%), with significantly higher rates of adverse events with low CO_2 removal devices, despite similar anticoagulation regimen.[29,39]

To reduce the risk of membrane clotting, physicians should pay attention to catheter placement and kinking. Indeed, kinking would reduce blood flow and promote membrane thrombosis despite adequate anticoagulation. Last, superior vena cava access should be preferred for patients with elevated intra-abdominal pressure or obesity.[30,40]

WHAT ARE THE OTHER EXPECTED COMPLICATIONS UNDER $ECCO_2R$?

Hemolysis is also a common $ECCO_2R$-related complication. Although few data are available, Fanelli et al. reported one case of severe hemolysis out of 15 patients that urgently required $ECCO_2R$ withdrawal.[30] Similarly, an incidence

of 12% hemolysis was reported in the SUPERNOVA pilot study.[29] The daily dosing of free hemoglobin and lactate dehydrogenase is warranted for patients under $ECCO_2R$ to detect hemolysis early and avoid acute kidney injury.

Thrombocytopenia is also a frequent complication. Interactions between the blood, the pump, and the artificial surfaces of the circuit and membrane generate blood trauma and activate the pathways of coagulation and fibrinolysis associated with an intense inflammatory response.[40–42]

Local infectious complications have been rarely reported. For instance, cannula infection occurred in only two patients in the SUPERNOVA pilot study,[39] while it was reported for 1.5% of patients by Augy et al.[32] The duration of $ECCO_2R$ for only a few days may have contributed to this low incidence.

Last, fatal adverse events reported are mainly related to bleeding. Augy et al. reported two intracranial bleeds and one tamponade out of 70 patients.[32] The SUPERNOVA pilot study had none.[39]

WHAT IS THE INCIDENCE OF HYPOXEMIA UNDER $ECCO_2R$?

Extracorporeal CO_2 removal exerts predominantly effective removal without a significant effect on oxygenation. However, worsening hypoxemia could be due to decreased mean airway pressure, lower ventilation-perfusion ratio, or lower partial pressure of alveolar oxygen.[43]

Also, the $ECCO_2R$ effect on oxygenation occurs predominantly in the native lungs, resulting in a decreased native lung respiratory quotient. The hypoxemia could, at least in part, reflect an $ECCO_2R$-induced modification of the alveolar gas content.[44] Fanelli et al. reported severe hypoxemia requiring prone positioning and/or ECMO in 40% of patients.[30]

An increase in the level of PEEP, to counteract the derecruitment induced by the V_T reduction,[29] could explain the low incidence of hypoxemia worsening in the SUPERNOVA pilot study. It also highlights the need to adjust the PEEP with an ultraprotective ventilation strategy.

WHAT IS THE DURATION OF $ECCO_2R$, AND WHAT ARE THE MAIN REASONS TO REMOVE THE DEVICE?

The duration of $ECCO_2R$ varies widely in the literature. Although $ECCO_2R$ weaning criteria are still unclear, the potential to wean off very low V_T ventilation with $ECCO_2R$ should be assessed daily when PaO_2/FiO_2 is greater than 200 with conventional ARDSnet settings (V_T = 6 mL/kg, PEEP = 5–10 cm H_2O, RR = 20–30 breaths/min, FiO_2 = 40%) and when the sweep gas flow is switched off. If under these conditions the patient remained stable for at least 12 hours with Pplat less than 25 cm H_2O and $PaCO_2$ less than 50 mm Hg (allowing a RR up to 30–35 breaths/min), the $ECCO_2R$ device and venous catheter could be removed.[29,31,32] By applying these criteria, $ECCO_2R$ was removed in 47% to 50% of patients.[31,32] In the largest cohorts published to date, the mean $ECCO_2R$ duration was 5 days.[29]

Last, a recent multicenter observational study identified that complications led to removing $ECCO_2R$ in 29% of mechanically ventilated patients.[32] It was even more frequent with low CO_2 removal devices, with 50% clotting after only 20 hours.[31]

WHAT IS THE OUTCOME OF ARDS PATIENTS ON $ECCO_2R$?

To date, no study using V-V $ECCO_2R$ has investigated the impact on the outcome of a strategy combining ultraprotective ventilation and $ECCO_2R$. Only physiological and feasibility studies are available, which precludes raising any conclusion in terms of outcome benefits with this strategy.

Combes et al. reported, in a cohort of 95 patients with moderate ARDS, 27% 28-day mortality, with a median of 17 days of mechanical ventilation,[29] whereas mortality was 47% in a smaller cohort of 15 patients with moderate ARDS.[30] Interestingly, the XTRAVENT study using A-V $ECCO_2R$ on a patient with moderate ARDS observed similar mortality between the interventional group (40 patients ventilated with 3 mL/kg ideal body weight and an A-V $ECCO_2R$) and the control group (39 patients ventilated with 6 mL/kg ideal body weight).[28]

WHICH CENTERS COULD PERFORM $ECCO_2R$ IN ARDS?

Beyond easier cannulation with smaller cannula than those used for V-V ECMO, experienced clinicians and nurses are still required for managing patients on $ECCO_2R$.[45] The relation between the outcome and the case volume has been well reported in the context of V-V ECMO[46,47] but warrants further investigation in the context of $ECCO_2R$. As previously reported for ECMO,[48] a program combining a regular review of the serious adverse events, patient outcome, regional accreditation of a specialized team, and a prospective registry seems promising for improving the safety and the efficiency of $ECCO_2R$.

WHAT IS THE AGENDA FOR RESEARCH FOR $ECCO_2R$ IN ARDS?

Materials that are more biocompatible should be developed to reduce potential hemorrhagic or thrombotic adverse events. Current pumps exhibit significant recirculation, shear stress, and hemolysis in physiological studies, suggesting the need to design an adapted pump for these devices with low blood flow.[22] For comparison, modern management of V-V ECMO allows marked reduction of anticoagulation. Some teams have even described success under prolonged V-V ECMO without anticoagulation.[49] Recent trials have highlighted the low risk of severe bleeding events under V-V ECMO.[50] For now, we cannot translate these promising findings to $ECCO_2R$, which still needs a full anticoagulation regimen.

Large clinical trials to investigate the impact of $ECCO_2R$ for ARDS on outcomes are urgently needed. Beyond the efficacy and the safety of the technique, the benefit of ultraprotective

Table 34.1 AVAILABLE $ECCO_2R$ DEVICES AND THEIR MAIN CHARACTERISTICS

DEVICE	COMPANY	FLOW RATE (ML/MIN)	CATHETER SIZE (FRENCH)	INSERTION SITE	MEMBRANE SIZE (M^2)
Prismalung	Baxter	<450	13–14	Internal jugular	0.32
ProLUNG	ESTOR	<450	13.5	Femoral, internal jugular	1.8
Hemolung Respiratory Assist Device	ALung	350–550	15.5	Femoral, internal jugular	0.59
iLa activve MiniLung petite kit	Novalung (Fresenius)	100–800	18	Internal jugular	0.32
iLA activve MiniLung kit and Novalung MiniLung kit	Novalung (Fresenius)	350–2400	18–24	Femoral, internal jugular	0.65
iLA activve iLA kit	Novalung (Fresenius)	500–4500	18–24	Femoral, internal jugular	1.3
Diapact	BBraun	200–500	13	Femoral, internal jugular	1.35–1.8

ventilation to enhance VILI prevention remains to be proven. The REST study (protective ventilation with V-V lung assist in respiratory failure, NCT02654327) is ongoing. It aims to compare V-V $ECCO_2R$, a V_T of 3 mL/kg or less, and a Pplat of 25 cm H_2O or less, versus standard protective ventilation. The primary outcome is 90-day mortality.

Future research should focus on the selection of the patients who will more likely benefit from this strategy. The lung-protective benefits of $ECCO_2R$ increase with higher alveolar dead space fraction, lower respiratory system compliance, and higher device performance. Patients with high alveolar dead space and low lung compliance are more likely to have better response to $ECCO_2R$[51] and should, therefore, be preferentially included in randomized controlled trials.

DISCUSSION

Two factors have contributed to the resurgence of $ECCO_2R$ in the last decade. First, the technology has markedly improved, switching from pumpless A-V access to V-V access, which is now recommended.[16] Moreover, devices use more biocompatible circuits, with less traumatic pumps, leading to a lower risk of hemolysis and clotting and better safety[20,22] (Table 34.1). Development of dual-lumen, heparin-coated catheters with a similar diameter than dialysis catheters,[31] ultrasonography-guided insertion,[24] have contributed to improve the safety of the technique. Recent platforms combining RRT and CO_2 removal with the same access appear promising but still need further investigations.[31] Second, some studies highlighted the physiological benefits of ultraprotective ventilation to reduce V_T, RR, and the energy transmitted to the lung by the mechanical ventilation.[52] This strategy may not benefit all patients but could be useful for the ones with most severe problems.[28,51]

Despite a growing number of studies on this topic, randomized controlled trials are still lacking to support the use of $ECCO_2R$ in routine practice for ARDS. For now, it seems mainly used for research purposes in referral centers. In an observational study conducted over 2 years in 10 French ICUs, the $ECCO_2R$ rate was 0.19 patients/month, with a maximum of 1.2 patients/month in the most experienced centers.[32] Other surveys reported consistent results.[53]

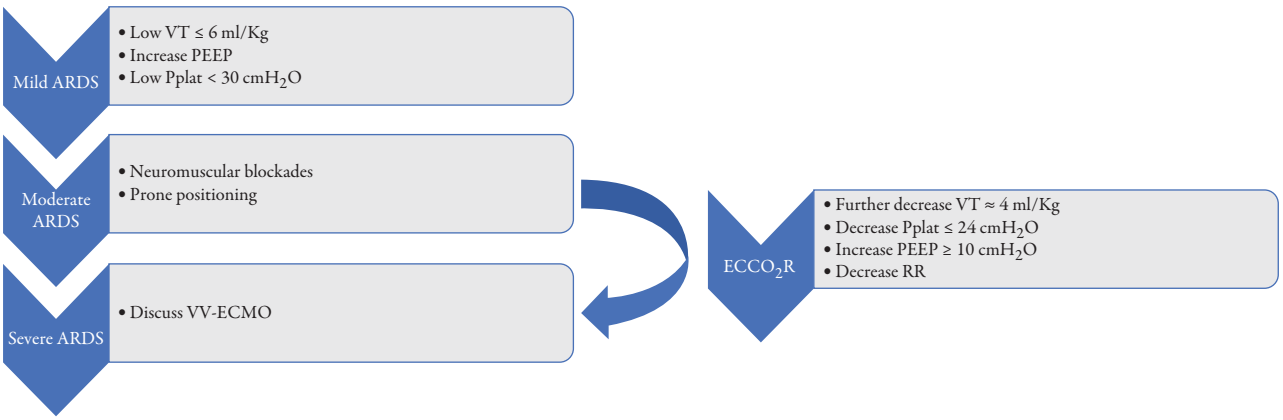


Figure 34.1 Potential place of $ECCO_2R$ in the ventilation management of ARDS. PEEP, positive end-expiratory pressure; Pplat, plateau pressure; RR, respiratory rate; VT, tidal volume.

In addition to the lack of experience in most centers, many questions remain unanswered. What is the place of $ECCO_2R$ in ARDS management? Which patients are more likely to benefit from an ultraprotective strategy with $ECCO_2R$? What is the optimal device to use and with which settings?

CONCLUSION

- $ECCO_2R$ is a resurgent adjuvant measure for moderate ARDS that could allow ultraprotective ventilation with a further decrease of V_T, Pplat, and driving pressure with a potential beneficial impact on VILI prevention.
- Beyond a physiological rationale to use ultraprotective ventilation, the benefit on clinically relevant outcomes is still unknown.
- Several ongoing randomized trials (REST, SUPERNOVA) could answer this question soon.

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REVIEW QUESTIONS

1. In a patient ventilated with 6 mL/kg tidal volume, PEEP set at 8 cm H_2O, Pplat at 29 cm H_2O, RR at 30 breaths/min for ARDS, blood gas results reveal pH at 7.38; $PaCO_2$ 44 mm Hg, PaO_2 80 mm Hg, with FiO_2 0.6. What are the correct answers related to the patient's management?

   A. $ECCO_2R$ could allow decreasing driving pressure.
   B. The PaO_2/FiO_2 ratio does not indicate utilization of $ECCO_2R$.
   C. Absence of hypercapnia is not in favor of $ECCO_2R$ insertion.
   D. These parameters protect the patient from VILI.

2. Concerning $ECCO_2R$ components, which answer(s) is (are) correct?

   A. Some V-V $ECCO_2R$ could be pumpless.
   B. Blood flow is driven by membrane surface area.
   C. Modern $ECCO_2R$ still exposes patients to blood trauma.
   D. Catheter lumen size varies between 19F and 26F catheters.

3. You choose to use an $ECCO_2R$ for a patient with moderate ARDS due to severe pancreatitis. Which vascular site do you prefer?

   A. Internal jugular vein with one double-lumen catheter
   B. Femoral
   C. Arterio-venous configuration
   D. One drainage cannula in femoral and reinjection in jugular vein

4. After $ECCO_2R$ insertion, $PaCO_2$ remains high. What could explain this phenomenon?

   A. Sweep gas flow is too high
   B. Membrane surface area is too large
   C. Clotting on membrane
   D. High blood flow

5. What should be your strategy for mechanical ventilation under $ECCO_2R$ in the context of ARDS?

   A. Increase RR
   B. Decrease PEEP to limit the mean airway pressure and prevent barotrauma
   C. Maintain Pplat around 28–30 cm H_2O
   D. Decrease tidal volume

6. After the correct implantation of an $ECCO_2R$ for ARDS, what could be your first strategy?

   A. Decrease sedation to let patient breath spontaneously
   B. Decrease the dose of neuromuscular blockade

C. Perform prone positioning
D. Try to wean mechanical ventilation

7. What should not be part of your daily management on $ECCO_2R$?

A. Daily monitoring of plasma free hemoglobin and lactate dehydrogenase
B. Anticoagulation with unfractionated heparin aiming for an aPTT ratio between 2.5 and 3
C. Daily monitoring of renal function
D. Daily monitoring of membrane aspect

8. Your patient under $ECCO_2R$ developed bleeding at the insertion site with a loss of 3 g/dL of hemoglobin. What could be your therapeutic strategy?

A. Remove $ECCO_2R$
B. Change heparin to citrate
C. Change insertion site
D. Decrease blood flow

9. What proposal could not explain a decrease in blood flow despite no therapeutic modification?

A. Kinking of cannula
B. Membrane clotting
C. Thrombosis in cannula
D. High blood pressure

10. What is the most common cause of premature interruption of $ECCO_2R$?

A. Therapeutic limitation
B. Infection
C. Clotting
D. Hemolysis

11. What biological abnormality is usually not explained by $ECCO_2R$?

A. Thrombocytopenia
B. Acute kidney injury
C. Elevated creatine kinase
D. Hypofibrinogenemia

12. What is the prognosis of patients on $ECCO_2R$?

A. They exhibit a better outcome than patients with conventional treatment.
B. Prognosis of these patients is still unknown.
C. They exhibit a shorter length of mechanical ventilation than patients treated with conventional treatment.
D. $ECCO_2R$ could not be performed safely in patients with moderate ARDS.

13. Which information was provided by feasibility studies?

A. Low-flow $ECCO_2R$ seems to be more efficient.
B. High-flow $ECCO_2R$ exhibits longer durability of the membrane.
C. Cannula infection is a common complication.
D. Ultraprotective ventilation is rarely achieved despite correct functioning of $ECCO_2R$.

14. Which of the following statements is (are) correct about randomized controlled trials on $ECCO_2R$?

A. There is no trial comparing management of moderate ARDS with $ECCO_2R$ to conventional treatment.
B. No trial has been designed to look for a mortality difference with $ECCO_2R$.
C. The REST study primary outcome is mortality at 60 days.
D. The SUPERNOVA trial will be a future randomized controlled trial in the field.

15. Which of the following statements is (are) correct?

A. Some ICUs exhibit a number of annual cases of $ECCO_2R$ superior to 50.
B. There is no correlation between the number of cases of ECMO per year and mortality.
C. Development of an expert center is not recommended.
D. Training of the medical team should be developed.

ANSWERS

1 A. Despite a correct mechanical ventilation setting, recent data show that we could not exclude the development of VILI. Moreover, this patient presents moderate ARDS, which is typical for patients included in feasibility studies, and the level of $PaCO_2$ is not a condition for an $ECCO_2R$ decision.

2 C. Only V-A $ECCO_2R$ could be pumpless because it uses the cardiac output to ensure blood flow. Blood flow is driven by the pump and catheter lumen size, which varies between 15F and 24F cannulae.

3 A. The internal jugular vein is the best choice because of the risk of elevated abdominal pressure. The A-V configuration or double catheter is no longer recommended.

4 C. Clotting, low sweep gas flow, low membrane surface area, and low blood flow could lead to a decrease in CO_2 removal performance.

5 D. Optimal strategy is to apply ultraprotective ventilation by decreasing V_T (and doing so driving pressure and Pplat) and RR to decrease mechanical power. PEEP could be increased to maintain oxygenation and recruitment-dependent regions.

6 B. Patients should be adapted to the ventilator to ensure ultraprotective ventilation, but it could be achieved safely without neuromuscular blockade.

7 B. Daily monitoring should focus on the potential complications of $ECCO_2R$, such as hemolysis (by searching for plasma free hemoglobin and lactate dehydrogenase in a blood sample) and its complications—acute kidney injury and clotting—by checking the membrane aspect. Recommended anticoagulation aims for an aPTT ratio between 1.5 and 2 or anti-Xa activity between 0.3 and 0.6 IU/mL.

8 A. In case of severe complications under ECCO2R, interruption should be discussed. Citrate has not been evaluated for $ECCO_2R$, and other proposals do not impact the risk of bleeding.

9 D. In that case, only high blood pressure could not explain a potential decrease in blood flow. The other proposals should be checked.

10 C. The commonest causes of premature interruption in different studies are clotting and bleeding. Hemolysis and infection are less frequent.

11 C. Due to the activation of coagulation and consumption of platelets by contact between blood and circuit, thrombocytopenia and hypofibrinogenemia could be observed. Acute kidney injury could be present in the case of hemolysis.

12 B. Actually, the outcome of these patients compared to conventional treatment in terms of mortality or length of mechanical ventilation is still unknown because only feasibility trials have been published so far. The REST trial may answer these crucial questions soon.

13 B. Results of feasibility studies suggested that high-flow $ECCO_2R$ is more efficient and could last longer. Ultraprotective ventilation seems to be easily achieved for these patients, and infection is a rare complication under $ECCO_2R$.

14 C. The REST study is an ongoing trial that compares $ECCO_2R$ to conventional treatment with a primary outcome of mortality at 60 days. The primary outcome of the SUPERNOVA pilot was the achievement of ultraprotective ventilation.

15 D. To date, utilization of $ECCO_2R$ in the ICU is rare, but experience with ECMO suggests the experience of the medical team impacts patients' outcomes.

35.

ECMO IN MIDDLE EASTERN RESPIRATORY SYNDROME (MERS-COV)

Ibrahim F. Hassan and Bishoy Zakhary

STEM CASE AND KEY QUESTIONS

A 45-year-old male with no significant past medical history presented with 2 days' history of fever, dry cough, and progressive shortness of breath. Review of systems was remarkable for diffuse body aches. He works with camels and has smoked 1 pack of cigarettes per day for the last 10 years.

On examination, the patient was in respiratory distress. He was diaphoretic. His temperature was 39°C, blood pressure was 120/60 mm Hg, and pulse oximetry was 89% on room air and 94% on 4 L nasal cannula. Clinical examination was remarkable for bilateral crackles at the lung bases with normal cardiac function and no evidence of peripheral edema.

The patient was placed on respiratory isolation in the emergency department. Two peripheral intravenous lines were established, and he was started on broad-spectrum antibiotics and an antiviral. A nasopharyngeal swab was sent for a viral panel. However, the patient continued to deteriorate, with drowsiness and a respiratory rate (RR) reaching 35 breaths/min. Oxygen by nasal cannula was switched to a nonrebreathing mask at 100% and 10 L/min to maintain SpO_2 90–92%. Arterial blood gas measurement showed pH 7.37, $PaCO_2$ 42, PaO_2 58, HCO_3 21.

The patient was intubated and placed on lung-protective ventilation. Results of a bronchoscopy with bronchoalveolar lavage came back positive for Middle Eastern respiratory syndrome coronavirus (MERS-CoV). The patient continued to decline and was initiated on veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) with a 25 French (25F) right femoral vein drainage cannula and a 21F right internal jugular vein return cannula. ECMO settings were blood flow 3.8 L/min and sweep gas flow 3 L/min. Gas exchange and hemodynamic status improved significantly, and mechanical ventilation settings were switched to achieve ultra–lung-protective ventilation.

Despite ECMO initiation, the patient remained hypoxemic, necessitating a second drainage cannula. Ventilator settings were subsequently reduced to lung rest settings with pressure control 10 cm H_2O, positive end-expiratory pressure (PEEP) 10 cm H_2O, RR 10 breaths/min, and fraction of inspired oxygen (FiO_2) 40%; tidal volume was 1 mL/kg on these settings. On day 2 of ECMO, recirculation with hypoxemia necessitated cannula repositioning. The patient had a tracheostomy placed and was then weaned off sedation and liberated from mechanical ventilation. Over the course of the next 16 days, there was improvement in chest x-ray opacities with reduction in ECMO settings. The patient was then trialed off ECMO and subsequently decannulated and discharged to a rehabilitation facility.

WHAT IS MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS?

Middle East respiratory syndrome coronavirus is a zoonotic viral respiratory illness caused by a novel coronavirus, first reported in 2012 in Saudi Arabia.[1] Since then, MERS-CoV cases have been reported across the Arabian peninsula, with occasional cases exported among travelers to other continents. Dromedary camels are a major reservoir host in which the virus causes negligible disease.[2] The virus can spread from dromedary camels to humans, through both direct and indirect contact, causing significant morbidity and mortality. The clinical spectrum ranges from asymptomatic illness to septic shock and multiorgan failure.

As of January 2019, a total of 2298 laboratory-confirmed human cases of MERS-CoV from 27 countries have been reported, including 811 associated deaths, giving a fatality rate of 35.2%.[3] Eighty percent of cases have been reported from countries in the World Health Organization (WHO) Eastern Mediterranean Region.

Human-to-human transmission of MERS-CoV has been described in several closed clusters of cases, including a small family cluster of mild disease. Two major healthcare-associated outbreaks due to superspreading events led to massive numbers of cases and excessive morbidity and mortality in several countries. Currently, there has been no evidence of sustained human-to-human transmission.

HOW IS THE DIAGNOSIS OF MERS-COV MADE?

Molecular tests are used to diagnose active infection (presence of MERS-CoV) in patients who are thought to be infected with MERS-CoV based on clinical symptoms and links to places where MERS has been reported. Serologic testing is used to detect prior infection (antibodies to MERS-CoV) in

people who may have been exposed to the virus. The presence of antibodies to MERS-CoV indicates that a person has been previously infected with the virus and developed an immune response.[4]

The WHO recommends sampling from the lower respiratory tract for MERS-CoV Reverse transcription polymerase chain reaction (RT-PCR) testing, especially when sampling is delayed by a week or more after onset of symptoms. Recommended sample types include bronchoalveolar lavage, tracheal/tracheobronchial aspirate, pleural fluid, and sputum. If available, lung biopsy or autopsy tissues can also be tested. An oropharyngeal and throat swab or a nasopharyngeal aspirate/wash are recommended first as they are less invasive than lower respiratory tract sampling. Paired sera, collected 2 to 3 weeks apart, are preferable for serological testing, while a single sample is sufficient if collected 2 weeks after disease onset or during the first 10–12 days if conducting RT-rtPCR. Human urine and stool have been found to contain MERS-CoV RNA 12 to 26 days after symptom onset and are listed as samples that should be considered.

WHAT IS THE TREATMENT FOR MERS-COV?

Once the diagnosis is made, treatment for MERS-CoV is primarily supportive. Hemodynamic support can include both vasopressor and inotropic support. Respiratory failure is a common feature, and mechanical ventilation is often necessary. Of note, lung-protective ventilation is a mainstay of management. Antiviral therapy is inconsistently used, and efficacy is unclear. For high risk or critically ill patients, a combination of ribavirin, interferon, and lopinavir/ritonavir is recommended.[5] For patients who fail antiviral therapy, convalescent plasma therapy is a consideration.

ONCE ON ECMO, WHAT MECHANICAL VENTILATION SETTINGS ARE APPROPRIATE TO ACHIEVE ULTRA–LUNG-PROTECTIVE VENTILATION?

Mechanical ventilation settings during ECMO are of fundamental importance, and the lack of standardized protocols likely contributes to variability in outcomes of patients undergoing V-V ECMO.

The optimal ventilator strategy during ECMO is debated,[6] with great variability among centers. Lung-protective ventilation is facilitated with extracorporeal support,[7] but the optimal targets and the timing to achieve and maintain these parameters are not clear. A number of ventilator strategies may potentially be used to avoid ventilator-induced lung injury. Based on available data, the most reasonable approach is reduction of inspiratory pressure to low plateau and driving pressures, reduction of RR to reasonable levels (5–15 breaths/min), and maintenance of moderate levels of PEEP with the goal of minimizing alveolar derecruitment and avoiding overdistention.

The Extracorporeal Life Support Organization (ELSO) guidelines suggest targeting ventilator settings of FiO_2 less than 0.4 and plateau pressure (Pplat) less than 25 cm H_2O.[8,9] It is recognized that lung collapse may occur, so that the use of "some inflation pressure as high pressures are decreased" is suggested. After 24–48 hours, lower levels of pressure (PEEP 10 and peak airway pressure of 20 cm H_2O) are recommended, and use of light sedation promoting spontaneous breathing is suggested. A common approach is implementation of the "10-10-10" setting: pressure control 10 cm H_2O, PEEP 10 cm H_2O, RR 10 breaths/min. Tidal volume is not a primary target and typically varies from 0.5 to 2.0 mL/kg, consistent with ultra–lung-protective ventilation.

WHY DID THE PATIENT REQUIRE A SECOND DRAINAGE CANNULA?

Hypoxemia on V-V ECMO can have a number of etiologies, and a systematic approach to diagnosis and therapy is important.[10] When evaluating a patient who is hypoxemic on V-V ECMO, comparison of the drainage and return tubing can be helpful; in a normally functioning circuit, there should be a color change from dark (deoxygenated) blood in the drainage tubing to bright (oxygenated) blood in the return tubing. If there is loss of this color change and both sets of tubing are dark, there is a problem with the oxygenator or with the gas source to the oxygenator; if both sets of tubing are bright, there is a high fraction of recirculation. Pre- and postoxygenator blood gases should also be sent to evaluate oxygenator function and recirculation fraction. If there is insignificant recirculation and the oxygenator is functioning well, it may be that the ECMO blood flow to native cardiac output ratio is too low (a high portion of blood is bypassing the ECMO circuit and shunting through the poorly functioning lung). In this case, increasing ECMO blood flow, or placing a second drainage cannula if blood drainage is already maximal, is needed. Another consideration if the preoxygenator saturation is low, is to institute measures to reduce oxygen consumption; these can include sedation, paralysis, or therapeutic hypothermia.

WHY DID THE ECMO CANNULAE REQUIRE REPOSITIONING?

Recirculation is a phenomenon seen in V-V ECMO where infused oxygenated blood exiting the return cannula is drawn into the drainage cannula without passing systemically to the patient's body. This fraction of blood does not participate in oxygen delivery and is thus wasted flow. Recirculation can be suspected when the preoxygenator blood gas shows an increasing oxygen saturation while the patient's saturation declines. The degree of recirculation is a function of three variables: pump speed, cannula configuration, and native cardiac output. Recirculation is ubiquitous on V-V ECMO—all patients exhibit a certain degree of the phenomenon. As pump speed is increased, the degree of recirculation increases. Cannula configuration is also an important determinant of recirculation fraction: The closer the cannula tips are to one another, the easier it is to recirculate. In this case, repositioning of the cannula, with gentle withdrawal of the drainage cannula a few centimeters, resolved the issue.

HOW WAS THE PATIENT WEANED FROM ECMO SUPPORT?

Weaning of V-V ECMO is a process whereby ECMO support is reduced as native lung function improves.[11] As oxygenation improves, ECMO blood flow and sweep gas inlet oxygen fraction (FsO_2) are titrated down; as ventilation improves, the sweep gas flow rate is titrated down. Once ECMO settings are sufficiently low, a "trial off" may be performed in which the gas flow is turned off. When this occurs, the patient is effectively off ECMO even though blood will still be flowing in the circuit. The trial off is typically performed for several hours to ensure the patient is able to maintain adequate gas exchange through the native lungs. If the patient does well, decannulation can then be performed. On V-V ECMO, trialing off does not require clamping the circuit as turning gas flow off is sufficient. For patients who are spontaneously breathing, trialing off and decannulation can (and should) be performed without placing them back on the ventilator.

DISCUSSION

Middle East respiratory syndrome (MERS), first described in 2012, is caused by a novel coronavirus (MERS-CoV).[12,13] Saudi Arabia has been the major hub for the virus, with 1567 cases reported in 2016 associated with a 41% mortality.

The clinical spectrum of MERS-CoV infection ranges from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and other life-threatening complications.[14] Mild symptoms are nonspecific and can include headache, fatigue, fever, mild cough, sore throat, and runny nose. Some patients may present with gastrointestinal symptoms, including diarrhea. The nonspecificity of MERS signs and symptoms poses several challenges, not only for the timely identification and isolation of infected patients, but also for reducing secondary transmission within the healthcare facility, particularly to healthcare workers and between patients.

Healthcare workers continue to constitute a substantial proportion of secondary MERS-CoV infections.[15] Among all cases of MERS-CoV reported to WHO as of June 2, 2018, healthcare workers accounted for 18.6% of all cases and 34.2% of secondary cases. This is similar to other respiratory pathogens: In the 2003 outbreak of severe acute respiratory syndrome, 23% of cases in Hong Kong, 40% in Canada, and 41% in Singapore were among healthcare workers.

While MERS-CoV appears to be inefficient at transmitting between humans in the general community, about half of the reported MERS-CoV infections have occurred in healthcare settings. Healthcare-associated transmission of MERS-CoV has been reported in France, Jordan, Saudi Arabia, United Arab Emirates, Republic of Korea, and the United Kingdom and has on occasion resulted in large outbreaks. Secondary transmission has occurred between patients, from patients to healthcare workers, and from patients to visitors at the hospital. To date, there has been limited evidence of transmission documented between healthcare workers in Saudi Arabia and anecdotal evidence from healthcare workers to patients in Saudi Arabia. Since healthcare workers have not routinely been tested for MERS-CoV infection and detailed outbreak investigations have not occurred within all hospital outbreaks, the role of healthcare workers in onward transmission remains unclear. Given the large number of infected healthcare workers to date, it is possible that healthcare workers can propagate an outbreak within a healthcare facility. Among reported secondary MERS cases in such outbreaks, a substantial proportion have been healthcare workers.

Preventing MERS-CoV infection in healthcare workers is critical because of their role in the clinical management of patients and in ensuring adequate infection prevention and control measures are implemented in healthcare facilities. Unnecessarily exposing healthcare workers to MERS-CoV affects the safety of both the healthcare workers and other patients in the healthcare facility, potentially propagating secondary transmission in healthcare-associated outbreaks. Understanding MERS-CoV infection in healthcare workers to date and the risk factors for adverse outcomes is important for preventing future infection of healthcare workers, for informing and updating infection prevention and control measures in healthcare facilities, and for reducing secondary MERS-CoV transmission within healthcare settings.

While coronaviruses typically cause a mild upper respiratory tract illness, this novel virus exhibits high virulence, with affected patients at risk of ARDS with severe hypoxemia, septic shock, and multiorgan failure.[13] Standard ARDS care with lung-protective ventilation and prone positioning may not be adequate in some patients, leading some centers to apply V-V ECMO in this setting.

Veno-venous ECMO has become increasingly accepted as a therapy for various etiologies of the ARDS, including viral pneumonitis. ECMO has been successfully applied in adults with ARDS since the early 1970s, but, until recently, was limited to small numbers of patients at selected ECMO centers. In the last decade, however, improvements in ECMO circuit components, encouraging results during the 2009 influenza A (H1N1) pandemic,[16–18] and publication of the "Efficacy and Economic Assessment of Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR)" trial,[19] ECMO use has markedly increased. While the most recent randomized trial ECMO to Rescue Lung Injury for Severe ARDS (EOLIA) concluded that among patients with very severe ARDS, 60-day mortality was not significantly lower with ECMO than with a strategy of conventional mechanical ventilation that included ECMO as rescue therapy,[20] the trial was limited by a 28% crossover from the control arm to the intervention arm, diluting the effect of ECMO observed in the intention-to-treat analysis. Mortality was considerably worse in the crossover group than in the conventionally managed cohort overall, and, notably, 33% of patients who crossed over to ECMO still survived.

Among patients with MERS-CoV, the application of V-V ECMO has been described with promising results. Observational data from centers in Saudi Arabia and from the Republic of Korea reported a 5.8% and a 7.1% incidence

of ECMO for MERS-CoV patients,[13,14] respectively. More recently, a retrospective cohort study compared patients with MERS-CoV ARDS and severe hypoxemia managed with ECMO or managed conventionally.[21] The study found a significant mortality benefit to ECMO (65% vs. 100% mortality, $P = .02$) as well as fewer organ failures. The study concluded that until randomized data are available, ECMO should be considered in select MERS-CoV patients.

Like other forms of ARDS, indications for ECMO initiation in MERS-CoV ARDS include severe hypoxemic respiratory failure (PaO_2/FiO_2 ratio < 80–100) or respiratory acidosis (pH < 7.1–7.2), requiring injurious mechanical ventilatory settings. Cannulation is typically percutaneous. Once on ECMO, patient management is supportive while awaiting lung recovery. Institution of ultra–lung-protective ventilation is of paramount importance, as discussed above. There has been a general trend toward less sedation and moving toward the awake patient in selected V-V ECMO patients[22,23] in an effort to facilitate mobilization and recovery.

While MERS-CoV outbreaks are difficult to predict, it is likely that novel viruses will present in a similar manner with severe respiratory failure and multiorgan dysfunction. The clinical experience and descriptive literature gained from applying ECMO to MERS will help form a framework to support patients with novel infections.

CONCLUSION

- MERS-CoV is a virulent novel coronavirus associated with severe ARDS.
- Management of MERS-CoV ARDS involves lung-protective ventilation, prone positioning, and V-V ECMO in select patients.
- Observational cohort data suggest that in patients with MERS-CoV, V-V ECMO can be a life-saving therapy.

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REVIEW QUESTIONS

1. A 35-year-old male patient is admitted with suspected MERS-CoV pneumonia. A nasopharyngeal swab resulted as

negative for MERS-CoV. Which statement below is accurate regarding the diagnostic accuracy of MERS-CoV testing?

A. The nasopharyngeal swab is the gold standard, and with a negative result, isolation can be safely discontinued.
B. A negative nasopharyngeal sample does not rule out MERS-CoV, and a lower airway sample is necessary to rule in or rule out the diagnosis.
C. Serological testing for MERS-CoV is the best method to detect active infection and should replace the molecular method of testing.
D. Bronchoscopy in patients intubated due to MERS-CoV carries a significant risk and should not be performed.
E. Human urine and stool have not been found to contain MERS-CoV and are not listed as samples that should be considered.

2. A 25-year-old-male is diagnosed with MERS-CoV pneumonia. The intensive care unit staff is very concerned regarding the risk of transmission of MERS-CoV to healthcare workers. All of the following are correct regarding the transmission of MERS-CoV to healthcare workers except

A. Approximately half of the reported laboratory-confirmed infections of MERS-CoV have occurred in healthcare settings.
B. Healthcare workers constitute over one-third of all secondary infections.
C. The fatality rate of MERS-CoV–infected healthcare workers is significantly higher than infected non-healthcare workers.
D. There are no documented cases of MERS-CoV transmission to healthcare workers.

3. A 44-year-old-male admitted with severe MERS-CoV infection required intubation and protective lung ventilation. Over the next 24 hours, the patient's respiratory status declined. Mechanical ventilation settings are volume cycle with tidal volume 5 mL/kg, PEEP 18 cm H_2O, RR 35 breaths/min, and FiO_2 1.0. Pplat is 38 cm H_2O, and static lung compliance is 18 mL/cmH_2O. Arterial blood gas shows pH 7.19, $PaCO_2$ 58, PaO_2 49, HCO_3 19, and SaO_2 80%. The chest x-ray shows the endotracheal tube is in good position and worsening infiltrate in all four quadrants with no evidence of pleural effusion. What is the best next step in this patient's management?

A. Start inhaled nitric oxide and switch to high-frequency oscillatory ventilation
B. Switch the ventilator mode to airway pressure release ventilation (APRV) with high PEEP 20 cm H_2O and low PEEP 5 cm H_2O
C. Put the patient in prone position ventilation for 16 hours and reassess
D. Preform another lung recruitment maneuver and increase the PEEP to 20 cm H_2O

4. A 42-year-old-female with severe MERS-CoV failed lung-protective ventilation and prone position ventilation and was placed on V-V ECMO at the bedside. Cannulation was with a 25F right femoral drainage cannula and a 21F right internal jugular return cannula. ECMO settings include blood flow 3.8 L/min, revolutions per minute 2800, access pressure -80 cm H_2O, sweep gas flow 3 L/min. Gas exchange improved on ECMO initiation. The patient was weaned from norepinephrine. Ventilator settings included volume control with tidal volume 280 mL, PEEP 12 cmH_2O, RR 20 breaths/min, and FiO_2 0.6. All of the following s statements regarding mechanical ventilation on V-V ECMO are true except

A. In retrospective analysis, Pplat less than 25 cm H_2O was associated with improved survival.
B. There is no prospective randomized controlled study regarding the best strategy to ventilate the lung during V-V ECMO.
C. In retrospective analysis, driving pressure less than 15 cm H_2O was associated with better survival.
D. Lung recruitment maneuvers and PEEP optimization should be used to facilitate weaning from ECMO.

REVIEW ANSWERS

1. B
2. D
3. C
4. D

36.

ECMO IN SARS-COV-2 (COVID-19) PATIENTS

Sebastiano M. Colombo, Gianluigi Li Bassi, Giacomo Grasselli,

Antonio M. Pesenti, and John F. Fraser

STEM CASE AND KEY QUESTIONS

A 46-year-old was admitted to the intensive care unit (ICU), Ospedale Maggiore Policlinico, in Milan, Italy, for severe acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, confirmed by real-time polymerase chain reaction (PCR) nose/throat swab. The patient did not present relevant comorbidities except for mild depression and obesity, with a body mass index of 32. After admission, the patient was mechanically ventilated for 8 days, but respiratory function did not improve despite use of advanced interventions such as prone positioning or inhaled nitric oxide (iNO). Notably, due to substantial impairment of respiratory system compliance, protective ventilation became unfeasible. Thus, veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) through femoro-femoral access was started by using an HLS 25 French (25F), 55-cm venous multistage cannula (Getinge) as drainage and a Bio-Medicus NexGen 23F, 60-cm venous cannula (Medtronic) as return in the inferior vena cava directed toward the right atrium.

Following ECMO commencement, ventilatory requirements substantially decreased. In particular, tidal volume (Vt) was reduced to achieve a driving pressure less than 14 cm H_2O, and respiratory rate was reduced to 10 breaths/min, while positive end-expiratory pressure (PEEP) was increased up to 15 cm H_2O. Ten days later, respiratory function further deteriorated due to superinfection and alveolar bleeding; a second ECMO system was added through a double-lumen 23F, 31-cm AVALON-ELITE cannula (Getinge), via the right jugular vein, to increase peripheral oxygen saturation to greater than 80%. Two ECMO circuits have been used simultaneously without major interferences between them, and no particular flow interactions were observed between the femoral return cannula and the tip of the jugular double-lumen cannula.

After 18 days of ECMO, the patient developed abdominal compartment syndrome, which resulted in acute kidney injury. Furthermore, after 42 days of ECMO, the patient developed refractory septic shock and died due to refractory severe vasoplegia associated with capillary leak syndrome and sepsis-induced myocardial dysfunction. Unfortunately, due to severe vasoplegia associated with capillary leak syndrome, a potential switch to any kind of veno-arterial (V-A) support was deemed futile.

WHAT IS SARS-COV-2?

Coronaviruses are a family of enveloped, single-stranded, positive-strand RNA viruses classified within the Nidovirales. In previous years, SARS-CoV[1,2] and Middle Eastern respiratory syndrome coronavirus (MERS-CoV[3,4]) have caused serious respiratory infections, with mortality rates of 10% for SARS-CoV[5] and up to 37% for MERS-CoV.[6] In late December 2019, in Wuhan, Hubei, China, a new respiratory syndrome emerged with clinical signs resembling viral pneumonia and person-to-person transmission.[7] Prompt diagnostic methods corroborated emergence of a novel coronavirus, namely the 2019 novel coronavirus (SARS-CoV-2),[8] and as shown in Figure 36.1, SARS-CoV-2 particles appeared spherical, between 60 and 140 nm in size, with distinctive spikes, characteristic of the Coronaviridae family, approximately 9 to 12 nm long.

WHAT IS COVID-19, AND WHAT IS THE PATHOPHYSIOLOGY DURING COVID-19?

The World Health Organization named the disease caused by SARS-CoV-2 COronaVIrus Disease-2019 (COVID-19). Currently, the pathophysiology and clinical manifestations of COVID-19 are not fully described, and patients present with highly heterogeneous signs and symptoms, with respiratory, cardiovascular, gastrointestinal, or central nervous system involvement as well as metabolic derangement. Clinicians have also emphasized coagulation disorders and prothrombotic state in patients with COVID-19 since many of those experience peripheral thromboembolism and pulmonary embolism.

To date, the COVID-19 pathophysiology remains largely unknown, irrespective of the reports from several authors on associated multiorgan injury. Thus, management of these patients is still imperfect, and personalized therapies are unavailable, likely causing excessive deaths during the first waves of the

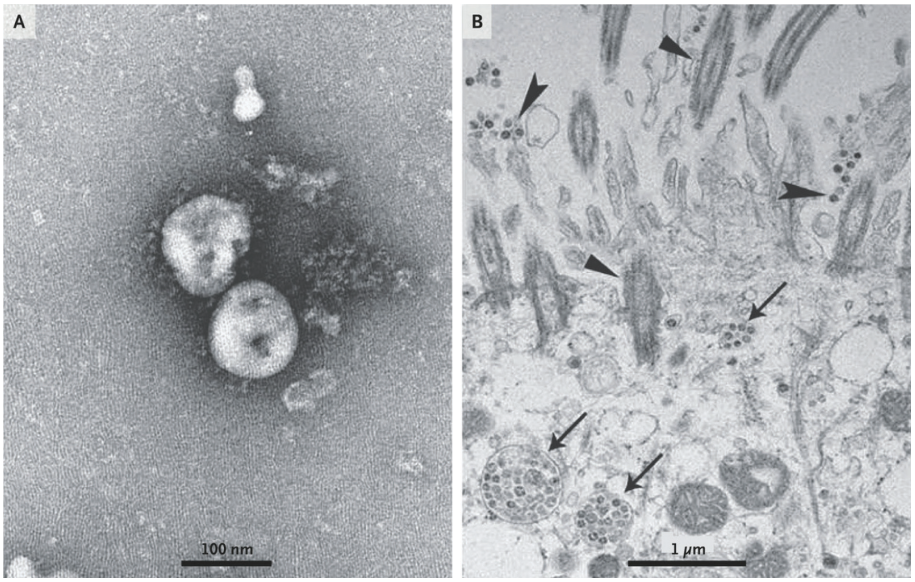


Figure 36.1 Visualization of 2019-nCoV with transmission electron microscopy. Negative-stained 2019-nCoV particles are shown in (A), and 2019-nCoV particles in the human airway epithelial cell ultrathin sections are shown in (B). Arrowheads indicate extracellular virus particles; arrows indicate inclusion bodies formed by virus components; and triangles indicate cilia.

Zhu N, et al., *N Engl J Med.* 2020;382:727–733.

pandemic. Generally, several antiviral treatments have been used since January 2019, and evidence in favor of remdesivir has been corroborated, specifically for severe cases.[9] Corticosteroids and immunomodulators have been widely administered to reduce the hyperinflammatory response, with beneficial effects associated with dexamethasone in a preliminary analysis.[10] Based on the limited therapeutic options, supportive measures (e.g., mechanical ventilation, prone position, or ECMO) remain the only valuable options to reduce mortality. This chapter provides a comprehensive account on the use of extracorporeal circulation in patients with COVID-19, reasoning its use in view of the currently available knowledge on the respiratory and cardiovascular pathophysiology of the disease.

LUNGS: IS COVID-19 ARDS SIMILAR TO ARDS FROM OTHER ETIOLOGIES?

There is consistent evidence that COVID-19 primarily results in severe hypoxemia with either relatively normal or severely deranged pulmonary mechanics. Gattinoni and colleagues suggested the existence of two potential different phenotypes of COVID-19 ARDS, based on pulmonary imaging findings, respiratory system compliance (C_{RS}) and response to PEEP.[11,12] The first COVID-19 phenotype is characterized by nearly normal compliance (>50 mL/cm H_2O), with extensive normally aerated lung regions; thus, likely in this case hypoxemia may be related to ventilation/perfusion (V_A/Q) mismatch due to the loss of hypoxic pulmonary vasoconstriction and impaired regulation of pulmonary blood flow. The intravascular pathology (i.e., pulmonary microthrombi or emboli) may play a crucial role in the increased dead space and severe hypoxemia reported in these patients. Conversely, in COVID-19 patients "conventional" ARDS is characterized by increased lung weight, reduction in normally inflated lung, and extensive areas of atelectasis. Several of these patients seem to respond to PEEP and/or prone positioning, likely due to redistribution of pulmonary perfusion and consequent improvement in V_A/Q mismatch. Conversely, in the second phenotype,[13] hypoxemia is associated with lower compliance, a more "classical" ARDS pattern at computed tomographic (CT) scan, with vast areas of gravity-dependent decruitment. At this stage, it is uncertain the burden of either phenotypes in the COVID-19 population, and no specific predictive markers are available to differentiate between these different clinical presentations. In addition, it is uncertain if these phenotypes are patient specific or may simply be different phases of COVID-19 clinical continuum.

Other small case series of critically ill COVID-19 patients have reported respiratory system compliance values between 20 and 40 mL/cm H_2O and provide valuable arguments on the possibility that COVID-19 ARDS does not significantly differ from ARDS caused by different etiologies.[14–18] Indeed, as Bos et al.[19] highlighted, pooling data from various publications, respiratory system compliance in COVID19 patients ranges between 30 and 50 mL/cm H_2O, which is similar to the figures reported by the international LUNG-SAFE observational study on ARDS prior to the rise of COVID-19.[20] In addition, it is important to emphasize that in recent years several investigators have already emphasized the existence of inflammatory or uninflamed ARDS subphenotypes,[19] and it is unknown whether subphenotypes identified in COVID-19 could share similar characteristic features.[21]

Due to the lack of substantial data that can characterize COVID-19 patients, our group has set up an international consortium of ICU physicians all around the world (COVID-19 Critical Care Consortium – CCCC) to study and define

the characteristics of patients affected by SARS-CoV-2 infection. Preliminary results on more than 600 patients suggested that there is no association between C_{RS} and days from onset of syntoms to commencement of mechanical ventilation, median C_{RS} within the 48h from intubation was 34.1 mL/cm H_2O. Interestingly females presented lower C_{RS} and higher body mass index than males. Mechanical characteristics seem also to get worse over the time with a slow reduction in C_{RS} during the first week of mechanical ventilation.[22]

HEART: DOES SARS-COV-2 CAUSE CARDIAC INJURY?

In addition to the substantial impact on the lungs, several studies reported cardiac injury in patients with COVID-19 and increased mortality in this subset of patients.[23] In a recently published meta-analysis, Santoso and colleagues pooled data from 13 studies to describe incidence and outcomes associated with cardiac injury, defined as elevation of highly sensitive cardiac troponin I greater than the 99th percentile, regardless of electrocardiographic and echocardiographic findings.[24] Cardiac injury was associated with higher mortality (risk ratio [RR] 7.95 [5.12, 12.34], $P < .001$); higher need for ICU care (RR 7.94 [1.51, 41.78], $P = .01$); and increased severity (RR 13.81 [5.52, 34.52], $P < .001$). Interestingly, the rise in troponin was concomitant to an increase in inflammatory biomarkers, which implies the primary role of COVID-19–related cytokine storm in multiorgan failure.[25] Nevertheless, cardiac injury caused by COVID-19 could also be related to direct myocardial injury by the virus. Indeed, in a small study, interstitial mononuclear cells were shown to infiltrate myocardium of patients who died from COVID-19.[26]

Shi et al. investigated 671 COVID-19 patients and found that myocardial injury occurred more frequently in nonsurvivors versus survivors (75.8% vs. 9.7%, respectively; $P < .001$).[27] In multivariable logistic regression, age, comorbidities (e.g., hypertension, coronary artery disease, chronic renal failure, and chronic obstructive pulmonary disease), and high level of C-reactive protein were predictors of myocardial injury.

In a case report, Tavazzi isolated SARS-CoV-2 from the myocardium of a 69-year-old patient with ARDS.[28] The patient rapidly developed cardiogenic shock requiring vasoactive support, intra-aortic balloon pump, and ultimately V-A ECMO. Electron microscopy from postmortem heart samples demonstrated single or small groups of viral particles with the morphology and size of coronaviruses. The viral particles were observed in cytopathic, structurally damaged, interstitial cells that demonstrated loss of cytoplasmic membrane integrity. Cardiac myocytes showed nonspecific damage, mainly characterized by focal myofibrillar lysis. This study adds evidence on the SARS-CoV-2 tropism beyond the respiratory tissue.[29–31] In patients with substantial cardiac impact, ECMO and in particular V-A ECMO, is a possible alternative to support the initial, most critical phase of the disease. In particular, the Extracorporeal Life Support Organization (ELSO) currently recommends the use of V-A ECMO in COVID-19 patients who are in refractory cardiogenic shock.[32]

COAGULATION AND INFLAMMATION: HOW DOES THE INFLAMMATORY RESPONSE TO SARS-COV-2 INTERPLAY WITH THE COAGULATION SYSTEM?

Early studies have suggested that elevated circulating D-dimer levels are associated with increased mortality, potentially suggestive of a prothrombotic coagulation disorder associated with COVID-19.[33] This hypothesis was demonstrated by autopsy studies that revealed the presence of fibrin thrombi within distended small vessels and capillaries and widespread extracellular fibrin deposition.[34,35] COVID-19 patients have also demonstrated abnormalities in coagulation tests, such as prolonged prothrombin time and reduced platelet count. These alterations reflect a generalized activation of coagulation, with thrombin generation and hyperfibrinolysis. Concomitantly, lung injury and hypoxia induce an hyperinflammatory state driven by macrophage and endothelial activation, resulting in the cytokine storm (interleukin [IL] 1, IL-6, IL-8, tumor necrosis factor alpha [TNF-α]) that dominates the second stage of COVID-19.[36] Pulmonary microvascular thrombosis likely contributes to the vicious cycle, ultimately resulting in extensive pulmonary embolism.[37–40]

It has been widely recognized that in a proportion of patients, the immune system overresponds to the invasion by SARS-CoV-2, as shown in Figure 36.2.[41] This hyperresponsiveness is key for clinical deterioration, increased thrombotic events, and mortality.[42–44] The hypercoagulation and prothrombotic state is distinctly noticeable in the lungs.[45] The proof for this lung-specific clot formation is supported by two clinical observations. First, acute-phase reactants, such as platelets and fibrinogen, C-reactive protein and ferritin are markedly increased during COVID-19. In particular, it seems that thrombocytosis is consistent in these patients,[46] which is only occasionally seen in critically ill patients with severe infections by other pathogens. Especially fibrinogen, which is a marker of hypercoagulability, is significantly increased in COVID-19 patients.[47] Second, postmortem examinations have found evidence of pulmonary microthrombi in patients with COVID-19.[48] There are suggestions that modifiable factors, such as different ventilatory patterns, could play a role in the formation of microthrombi and clinical deterioration.[13] Ranucci and colleagues recently reported comprehensive coagulation analyses including d-dimers, fibrinogen levels, and viscoelastic testing, in the COVID-19 patients with ARDS and reported a procoagulant profile on ICU admission.[49] Panigada and collaborators performed a similar analysis and also noted increased fibrinogen levels, enhanced platelet activation, and increased viscoelastic variables.[50]

HOW SHOULD I MANAGE A PATIENT WITH COVID-19 BEFORE INTENSIVE CARE IS REQUIRED?

As a consequence of the rapid pandemic spread of SARS-CoV-2 infection, and consequently of the exponential increase of patients with COVID-19, healthcare systems of affected countries are facing an increasing number of patients presenting to

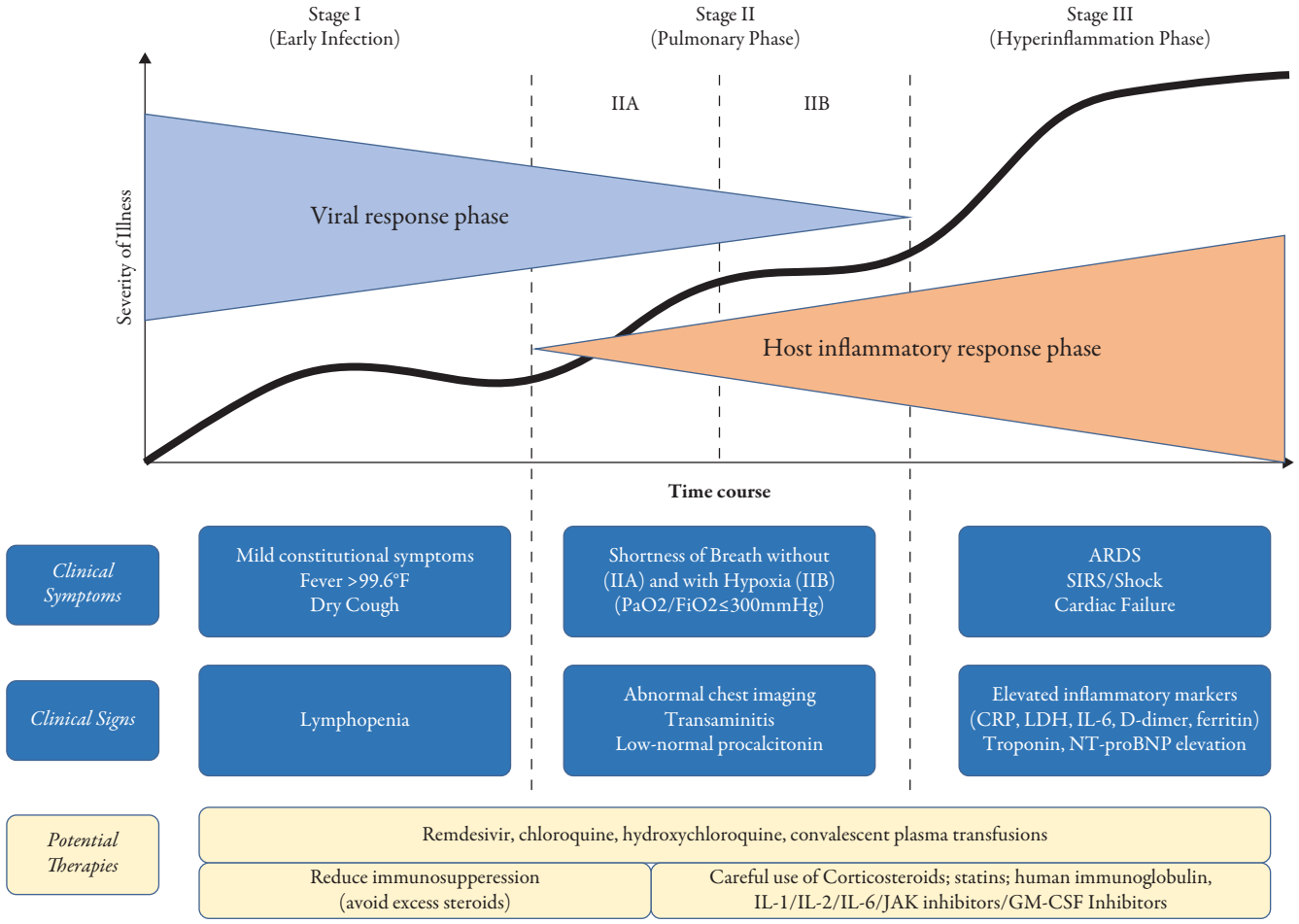


Figure 36.2 Classification of COVID-19 disease states and potential therapeutic targets. The figure illustrates three escalating phases of COVID-19 disease progression, with associated signs, symptoms, and potential phase-specific therapies. ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; GM-CSF, granulocyte macrophage colony-stimulating factor; IL-6, interleukin 6; JAK, janus kinase; LDH, lactate dehydrogenase; NT-proBNP, N-terminal pro B-type natriuretic peptide; SIRS, systemic inflammatory response syndrome. Please note that at the time of publication chloroquine and hydroxychloroquine were widely used; subsequent papers have then shown their ineffectiveness.

Siddiqi HK, Mehra MR. *J Heart Lung Transplant.* 2020;39(5):405–407. doi:10.1016/j.healun.2020.03.012

emergency departments with hypoxemic respiratory failure. Therefore, immediate supplemental oxygen therapy is mandatory when SpO_2 levels are low (<90%), with the aim to improve SpO_2. Noninvasive support for oxygenation and/or ventilation may offer a better outcome by lowering complications (i.e., ventilator-acquired pneumonia) and reducing the number of patients who need invasive support. This is fundamental in case of a shortage of mechanical ventilators and ICU beds during the COVID-19 pandemic.

In a good proportion of hospitalized COVID-19 patients, nearly 90% of patients admitted to the ICU with respiratory failure rapidly worsened, and mechanical ventilation was ultimately needed.[17] In the most severely ill patients, the clinical downfall is rapid, and management should be aimed to decrease complications prior to commencement of ECMO.[11] Herein, we provide a few practical recommendations on the pre-ECMO management of COVID-19 patients undergoing mechanical ventilation. These suggestions are based on our clinical experience and rapidly growing evidence; yet, it is important to emphasize that only careful research will confirm the best ventilatory approach in COVID-19 patients.

As previously described, patients with COVID-19 may have a relatively normal compliance of the respiratory system as in non-COVID-19 ones, especially in the first phases of the disease. This indicates well-preserved lung volume and relatively low work of breathing prior to intubation, in contrast with what is typically expected in severe ARDS. Due to preserved compliance, COVID-19 patients do not have excessively increased work of breathing and may develop "silent hypoxemia" with the risk of a rapid deterioration in the absence of severe symptoms. Due to progressive alveolar damage and infiltrates, progressive alveolar collapse can develop, with a gradual development of areas with atelectasis.

The application of PEEP may be useful for lung recruitment and to improve ventilation-perfusion mismatch. Due to the lack of randomized controlled trials, no specific recommendations are offered on noninvasive ventilatory support in these patients, but cautious trials of noninvasive respiratory support in selected patients in a protected environment and

experienced centers can be attempted.[51] A noninvasive positive pressure ventilation (NIPPV) trial could be attempted for a limited period of time, being aware that a prolonged NIPPV treatment can be harmful, delaying intubation and increasing the risk of patient self-inflicted lung injury.[52] During the ongoing COVID-19 pandemic, given the overwhelming number of patients requiring assistance, it may be impossible to monitor spontaneously breathing patients during noninvasive ventilation trials; for this reason it might be advisable to try NIPPV only in highly selected patients with close observation.

Because COVID-19 patients often have tolerable work of breathing related to high compliance, they may not need much mechanical inspiratory support but can simply benefit from continuous positive airway pressure (CPAP). CPAP is able to deliver a stable PEEP level and to provide alveolar recruitment, possibly avoiding excessive harmful tidal volumes and reducing a patient's high negative intrathoracic pressure swings, which can increase lung injury. The ideal indicator would be the measurement of esophageal pressure swings. If impossible, the clinical signs of inspiratory efforts should be carefully scrutinized. If respiratory distress is present, endotracheal intubation should be strongly considered to avoid/limit self-induced lung injury.

The lowest effective PEEP should be used to avoid severe hemodynamic impairment, fluid retention, gastric insufflation, and aspiration. CPAP delivered by head helmet has been shown as safe and effective as CPAP delivered by face mask and better tolerated for prolonged ventilation periods.[53] Moreover, with the use of a closed system and viral filters, the helmet may be superior to other interfaces regarding the risk of environmental contamination and viral transmission.[54]

In terms of recommendations on management of patients with acute hypoxemic respiratory failure, Privitera and colleagues suggested a flow chart of noninvasive ventilation support in COVID-19 patients.[55] Initial oxygen administration of 5 L/min through a face mask was suggested, with a respiratory target of a maximum of 28 breaths/min and a SpO_2 of at least 94%. If targets have been reached after 10–15 minutes, the patient should be observed every 30 minutes; otherwise, a step-up support should be initiated with helmet CPAP or non-invasive mask ventilation.

In conclusion, due to the enormous number of COVID-19 patients with acute respiratory failure and to the potential shortage of ICU beds and ventilators, helmet CPAP can be the perfect balance between life-saving resource and adequate noninvasive support.[56] In particular, in a scenario of a discrepancy between facilities and a large number of casualties, as with the COVID-19 pandemic, the application of helmet CPAP might be useful as an "easy-to-perform" supportive strategy. Prone position sessions may adjust pulmonary perfusion, diverting flow toward high Va/Q areas and allowing a redistribution to aerated and nonaerated areas whenever present.[57,58] Furthermore, as opposed to noninvasive intermittent positive pressure, helmet CPAP does not necessarily need a ventilator, and it is not affected by patient-ventilator asynchrony, a determinant of discomfort and treatment failure. Considering these factors, Longhini and collaborators suggested the use of prone position during helmet CPAP support in selected COVID-19 patients who may benefit from this combination in order to reduce the need for intubation and invasive mechanical ventilation and for "buying time" for clinical improvement.[59] Prone position during helmet CPAP requires some precautions in order to avoid discomfort, skin and eye lesions, and treatment failure.[60,61]

Several reports have shown the potential of helmet CPAP in COVID-19 respiratory failure. Coppo and colleagues described a prospective study in which 56 patients were recruited between March and April at San Gerado Hospital in Monza, Italy, during the COVID-19 pandemic that afflicted northern Italy. Prone positioning was feasible, and oxygenation substantially improved from supine to prone positioning; in fact PaO_2/FiO_2 (fraction of inspired oxygen) ratios increased from 180.5 ± 76.6 mm Hg in supine position to 285.5 ± 112.9 mm Hg in prone position (P <.0001). After resupination, improved oxygenation was maintained in 23 patients; however, this improvement was on average not significant compared with before prone positioning (PaO_2/FiO_2 ratio 192.9 ± 100.9 mm Hg 1 hour after resupination). Patients who maintained increased oxygenation had increased levels of inflammatory markers (C-reactive protein) and platelets within a shorter time between admission to the hospital and prone positioning. Thirteen (28%) of 46 patients were eventually intubated, 7 (30%) of 23 responders and 6 (26%) of 23 nonresponders (p = .74).[62] The same findings have been reported by other authors.[63–67]

HOW SHOULD I MANAGE A COVID-19 PATIENT WITH ARDS IN THE ICU?

Acute respiratory distress syndrome is a common finding among COVID-19 patients who require hospitalization. Earlier reports[68–71] have confirmed ARDS in up to 30% of critically ill COVID-19 patients and mortality up to 70%. To date, it is uncertain how to manage mechanically ventilated COVID-19 patients with ARDS, and a variety of recommendations are based on previous evidence from ARDS caused by different etiologies, as reported next.

Tidal Volume (Tv)

Limitation of tidal volume to 6 mL/kg of predicted body weight, and plateau pressure to a maximum of 30 cm H_2O should be recommended.[72] Although many patients seem to have high pulmonary compliance, and consequently they could be ventilated with TV of 7–8 mL/kg PWB while maintaining protective pressures, there is no scientific evidence to fully endorse such recommendation. Therefore, the panel of this chapter agree on the application of protective ventilatory strategies that may be individualized on a case-by-case approach according to the patient's pulmonary mechanics.[73]

Positive End-Expiratory Pressure (PEEP)

Positive end-expiratory pressure should be titrated according to the pulmonary mechanics of the patients. In patients with relatively normal compliance, lower PEEP (up to 8–10

cm H_2O) may be applied since higher levels may cause pulmonary overdistention and increased dead space and potentially impair right heart function.[74,75] Patients with low pulmonary compliance, present extensive areas of alveolar atelectasis and theoretically a cautious gradual increase of PEEP up to 14–15 cm H_2O may be beneficial to augment regional ventilation and prevent alveolar collapse.[76]

Prone Position

The prone position represents a rescue therapy for severe hypoxemia in ARDS.[77,78] In patients with high compliance, the prone position may increase oxygenation, facilitating redistribution of pulmonary blood flow in more aerated and ventilated areas of the lungs. In patients with low compliance, the prone position may also cause recruitment and play a crucial role in ameliorating ventilation-perfusion mismatch.[79,80] Yet, it should be considered that prone positioning should be applied in units with experience with such an intervention to avoid complications and could be unsuitable in the rapid surge of cases in understaffed units.

Nitric Oxide

In COVID-19 patients, response to iNO seems highly variable, and potential clinical markers to identify responders to this intervention are yet to be elucidated. Previous reports[81–83] from the severe acute respiratory syndrome (SARS) outbreak have shown antiviral effects of iNO, inferring additional benefits in the use of this gas during coronavirus infections. Several randomized clinical trials are investigating the use of iNO in COVID-19, and the results will shed some light to recommend or discard its use.[84–88]

Lung Monitoring

Patients with COVID-19 may benefit from continuous respiratory mechanics and lung function monitoring, such as pulmonary shunt and dead space (i.e., carbon dioxide in exhaled air/$PaCO_2$) as markers of severity. In a small monocenter study, Mauri and collaborators evaluated pulmonary mechanics through electrical impedance tomography and highlighted a large variability in lung recruitment among COVID-19 patients.[89] Finally, considering the high variability between COVID-19 patients, it is advisable to assess pulmonary mechanics and personalize ventilatory support based on specific pulmonary characteristics, rather than apply a generalized recommendation in a highly heterogeneous population. In case of consistent life-threatening levels of hypoxemia irrespective of optimized ventilatory support, additional supports should be tested prior to ECMO. Several monitoring strategies have been proposed in COVID-19 patients.[90-92]

Coagulation Monitoring

As for the general management of critically ill COVID-19 patients, prophylactic anticoagulation is advisable in the absence of absolute contraindications.[49,93] Low-molecular weight-heparins are the treatment of choice over unfractionated heparin because of better bioavailability and ease of use. However, in patients with severe renal impairment or extremely high risk of bleeding or patients on ECMO support, unfractionated heparin may be preferred. D-Dimers seem to be a valuable marker to monitor coagulopathy in COVID-19 patients. When D-dimers are already elevated at hospital admission, prophylactic anticoagulation with low-molecular-weight heparin should be given.[94] In case of a consistent increase in D-dimer levels and a patient presenting with clinical deterioration, pulmonary imaging and full anticoagulation should be considered.[95–98] In a few COVID-19 patients, systemic anticoagulation may still not be adequate, and antithrombotic interventions should also be considered.[99]

DOES V-V ECMO HAVE A ROLE IN COVID-19 RESPIRATORY FAILURE?

Even after optimization of mechanical ventilation settings, the mortality of mechanically ventilated COVID-19 patients remains high.[68–71] In patients developing severe respiratory failure refractory to standard treatment, ECMO support could be considered. ECMO allows improvement of gas exchanges and facilitates protective or ultraprotective ventilatory settings, thus reducing the risk of ventilator-induced lung injury. However, the efficacy of ECMO as rescue strategy in COVID-19 is still unclear.

There have been several viral outbreaks in recent memory, including SARS, pandemic H1N1 influenza, and the Middle East respiratory syndrome (MERS).[100–103] Unfortunately, there are only limited data on the use of ECMO in SARS and MERS. On the other hand, ECMO was widely used during the 2009 H1N1 pandemic, likely due to the characteristics of the patients at risk of becoming severely ill and technological improvements in the field during the last decades.[104,105] Shih E. and colleagues retrospectively compared the outcomes of patients with refractory ARDS from COVID-19 and Influenza placed on ECMO. The authors reported no difference in survival between the two groups, while the duration of ECMO support (14 days [IQR 9-30] vs. Influenza 10.5 [IQR 6.8-14.3] days, p=0.004) and total length of stay (37 [IQR 27-62] vs Influenza 13.5 [IQR 9.3-24] days; p=0.007) were longer in COVID-19 patients.[106]

Although ECMO may play a potential role in selected patients in the context of the current pandemic, the criteria for patient selection and timing of ECMO initiation are yet to be fully defined. Certainly, in COVID-19 patients with severe respiratory impairment and ARDS, ECMO could be a valuable option to limit ventilation-induced lung injury, specifically in patients with consistent hypoxemia, hypercapnia, and respiratory acidosis, irrespective of maximal ventilatory support.[107] During the first and second waves of pandemic, only a few single-center and retrospective analyses on ECMO support in COVID-19 were available.

Henry and Lippi reported a higher, but not significant, mortality in patients undergoing ECMO (odds ratio 2.0

[0.49–8.16]), pooling data from 17 patients enrolled into four different studies. These results are at best pooled results from case series but highlighted the need for comprehensive appraisal of ECMO in this pandemic.[108] A subsequent larger analysis has been conducted by Melhuish and colleagues on 331 ECMO cases from 10 studies and four registries. The overall pooled prevalence of mortality obtained by the random effects model was 0.46 (95% CI 0.34–0.59).[109]

On the other hand, cases with positive outcomes using ECMO have also been reported.[110–115] In a report by Zeng and collaborators from China, 11 patients on ECMO were studied, and the reported mortality was 41%.[116] In another small case series from France, in 12 COVID-19 patients on ECMO, 10 patients were successfully weaned.[117] In a subsequent published study by Mustafa and collaborators,[118] single-access, dual-stage cannula were used to provide V-V ECMO with an remarkable mortality rate of only 15%.

Schmidt and colleagues retrospectively reported a 60-day follow-up of 83 patients who underwent ECMO for severe ARDS. Thirty patients (36%) died, basically showing a survival rate similar to other studies published on ECMO for severe ARDS due to other causes.[119]

Several studies has recently reported the results of applying ECMO in patients with severe hypoxemic respiratory failure from COVID-19.[120-125] Results from this clinical trial have been pooled together in two reviews published by Ramanathan and Huang.[126,127] Huang reported: "There is evidence that ECMO may complicate the pathophysiological state in COVID-19 patients. However, many studies have shown that the appropriate application of ECMO improves the prognosis of such patients.[127] Moreover, Ramanathan included 22 observational studies with just under 2000 patients with COVID-19 reporting similar mortality in patients receiving ECMO support for COVID-19 to those with non-COVID-19-related ARDS.[126]

Nevertheless, considering the limitations of current evidence, primarily obtained by small case series and not controlled trials, it is currently challenging to provide strong recommendations on indications and management of ECMO in COVID-19 patients. Thus, readers should refer to international guidelines issued by the ELSO societies pre–COVID-19 era to efficiently commence ECMO in this population and managing the technique safely.

Several clinical trials are currently ongoing to also determine whether V-V extracorporeal CO_2 removal (VV-$ECCO_2R$) and lower tidal volume mechanical ventilation improves outcomes and is cost-effective, in comparison with standard care in patients receiving mechanical ventilation for acute hypoxemic respiratory failure. The technique of extracorporeal CO_2 removal ($ECCO_2R$) has been introduced for hypercapnic respiratory failure not requiring significant oxygen support and in the pivotal SUPERNOVA study, $ECCO_2R$ played an essential role in achieving ultraprotective ventilation.[128] $ECCO_2R$ in combination with renal replacement therapy has the potential to limit respiratory stress further by removing excess CO_2 and compensating for respiratory acidosis, thus facilitating reduction of tidal volume (<6 mL/kg) during lung-protective ventilation strategies.[129] This may be particularly appealing in patients with ARDS and concomitant acute kidney injury, where compensatory renal mechanisms are less effective in regulating acid-base homeostasis during hypercapnic acidosis.

DOES V-A ECMO HAVE A ROLE IN COVID-19 SEVERE CARDIOCIRCULATORY FAILURE?

Pulmonary failure is the hallmark of recent viral outbreaks, such as SARS, MERS, or H1N1, which were primarily respiratory illnesses. Yet, substantial cardiovascular injury has also been reported. Indeed, fulminant myocarditis was reported in H1N1 cases[130]; acute myocarditis, acute myocardial infarction, acute heart failure, pericarditis, and shock were also reported in patients with MERS.[131] In COVID-19 patients, cardiovascular complications, such as acute cardiac injury (7%–17%), shock (7%–8%), septic shock (20%), arrhythmia (16.7%), and heart failure (23%) were reported in hospitalized patients.[70,132] In addition, other complications, such as acute myocardial injury, myocarditis, arrhythmias, pericardial effusions, and venous thromboembolism, have been reported in up to 22% of the patients requiring ICU care.[25,133] Different causes of myocardial injury, such as oxygen supply/demand imbalance with or without coronary artery disease, increased right ventricular afterload associated with respiratory acidosis, hypoxemia, and positive pressure ventilation, play essential roles in the development of acute myocardial injury, and often multiple mechanisms may coexist. The extent of local tissue damage and the cytokine storm triggered by the host immune response may both contribute to the severity of the disease. An association between myocardial injury and worse outcomes have been suggested by the elevation in high-sensitivity troponin in nonsurvivors.[134] Thus, given the impact of COVID-19 on the cardiovascular system and the incidence of cardiocirculatory failure refractory to conventional medical management, V-A ECMO may be needed in selected cases to improve outcomes.[135,136]

DISCUSSION

At the end of June 2021, more than 180 million cases of COVID-19 had been reported, causing more than 3.950.000 deaths.[137] Retracing occurrence of major outbreaks worldwide,[138] the first cases were observed in China, followed by Asian countries such as Japan,[139] South Korea,[140] and Thailand.[141] At the end of February 2020, an outbreak was reported in Italy,[142] with quick diffusion across Europe in Spain, Germany, France, and the United Kingdom. The Russian Federation was also harshly shattered by the pandemic, reporting an impressive death toll.[143] In May, hundreds of thousands of cases were recorded in the American continent, making the United States of America[144] and Brazil the first two countries affected in the Western Hemisphere. Also, India reported a massive wave of contagions. In the last few months epidemic curves are affected by worldwide plan of vaccinations against COVID-19.

HOPE FOR THE BEST, PREPARE FOR THE WORST

Major COVID-19 outbreaks worldwide have shown an exponential increase in cases within a few weeks from the first patients admitted to hospitals. Given that approximately 5%–10% of hospitalized patients will require ICU care,[33,56] it is essential to promptly increase ICU surge capacity to face a rapid increase in demand of critical care services. COVID-19 patients may present extreme severity, complications, and multiorgan failure. Thus, it is mandatory to identify tertiary hospitals that could manage these patients efficiently and safely achieving best outcomes. Detailed information on how to prepare for an ICU utilization upsurge are detailed elsewhere[142] and are beyond the scope of this chapter.

HOW TO ORGANIZE AND PREPARE ECMO CENTERS FOR COVID-19

In the absence of valuable therapies for COVID-19, extracorporeal therapies are appealing options for the most complex and severe cases. Indeed, COVID-19 severely affects the cardiopulmonary system; hence, different means of extracorporeal support may be indicated in these patients.[145] At the time of writing this chapter, EuroELSO reported more than7500 COVID-19 patients supported with ECMO, with more than 90% of them supported by V-V ECMO for severe hypoxemic respiratory failure.[146] Nevertheless, the role of ECMO in the management of COVID-19 is still unclear and varies countrywide or in international registries; for instance, the COVID-19 Critical Care Consortium (https://www.covid-critical.com) has been developed to shed light on the benefits and drawbacks of ECMO in COVID-19.

It is important to emphasize that ECMO is resource intensive and expensive and requires highly skilled personnel to ensure safety. ECMO is for the most critically ill patients, and it is not a supportive therapy to be rushed to the front line when all healthcare assets are already stretched thin. Thus, in less well-resourced countries, many more lives will be saved by ensuring that oxygen and pulse oximetry are widely available. Mitigation efforts to slow the outbreak are critical so that healthcare systems are not overwhelmed and all patients receive the correct management, and ECMO only in the most severe cases.[147] Hospitals will refer early to ECMO centers in anticipation of impending clinical deterioration of COVID-19 patients. This will disproportionately affect hospitals with ECMO programs, even when ECMO is not required. In the organization of ECMO programs during major outbreaks, difficulties related to transport of COVID-19–contagious patients between facilities should also be taken into account.

Additional challenges in providing ECMO may include insufficient number of consoles or disposable equipment, suitably trained staff, or isolation rooms. Coordination centers are essential during outbreaks to standardize indications, management, data collection, and containment.[148] Monitoring of extracorporeal support capacity and making real-time updates readily available to hospitals are essential in the affected region. Total capacity depends on the number of patients that can be supported with ECMO at any given time, as well as the number of patients who can be cannulated based on available disposable supplies. In extraordinary circumstances, adult and pediatric ECMO programs may support one another through sharing of hardware, disposables, extracorporeal life support specialists, and perfusionists should referral centers become overwhelmed.

Based on these findings, the Japanese Society of Intensive Care Medicine, the Japanese Association for Acute Medicine, the Japanese Society of Respiratory Care Medicine, and the ECMO study group launched a COVID-19 ECMOnet working group in Japan. The group provided telephone consultations available 24/7 for patients with severe respiratory failure, especially those who require ECMO.[149,150] Similarly, the ECMO center in Minnesota (United States) provided detailed recommendations on how to use ECMO during a pandemic.[151] In particular, they emphasized that ECMO is a limited resource subject to saturation. Predictions about duration of support and patient outcome need to be considered to avoid late-stage saturation. Local regulatory bodies should be aware that ECMO requires a substantial investment of resources; thus, it may be necessary to limit ECMO support to patients more likely to survive. Indeed, when demand for ECMO is high and prioritization by indication is necessary, preference should be given to conditions with evidence-based superior outcomes and shorter expected duration of support. Finally, epidemics may require further prioritization or novel strategies. A process must be put in place to integrate public health and clinical expertise to address incident-specific challenges.

In conclusion, efficient preparedness for COVID-19 outbreaks requires a multidisciplinary, stakeholder-guided approach. Rational deployment of ECMO ensures that this scarce and expensive life-saving technology is available for as many patients as possible who could benefit. Detailed organization of ECMO programs for COVID-19 is fundamental to improve patient outcomes and limit healthcare costs.[152]

GUIDELINES AND EXPERTS' OPINION

At the time of writing this chapter, EuroELSO reported more than 7500 COVID-19 patients supported with ECMO since the beginning of pandemic.[146] The SARS-CoV-2 pandemic placed a significant stress on healthcare systems around the world. In this setting, providing ECMO support may be challenging in terms of both resources and ethical points of view. For this reason, EuroELSO published specific guidelines about the potential role of ECMO in cardiorespiratory support of severely ill patients.[153,154] The latest update has been available since May 2021, based on preliminary worldwide results and experience.[155] The authors recommended the use of ECMO for patients with COVID-19 and severe cardiopulmonary failure who meet traditional criteria and when

appropriate resources are available, also referring to already pre-COVID-19 existing guidelines for ECMO device and patient managements.

PRACTICAL CONSIDERATIONS

Even during the unprecedented times of a pandemic, it is advisable that ECMO be performed in dedicated centers with broad experience in the field. Consequently, centralization of ECMO cases should be attempted if possible. Considering that COVID-19 patients supported by ECMO may need a 1:1 nurse-to-patient ratio, a dedicated perfusionist, and senior ICU specialists with expertise on ECMO, monitoring of ongoing ECMO in the region is crucial. Thus, in order to provide prompt and organized assistance and minimize burden for providers, healthcare agencies should consider the creation of regional/national networks to refer potential candidates to ECMO centers, specifically in the peak period of outbreaks. Personnel managing patients on ECMO should be fully trained on the sequence for donning and doffing personal protective equipment (PPE). In addition, when ECMO cannulation is carried out remotely, prior to patient transfer to referral centers, ECMO team members should wear PPE, including emergency medical services personnel and airplane pilots, if close contact to the patient is expected (Figure 36.3). Minimizing aerosol-generating procedures during transport is vital, and the use of high-efficiency particulate air (HEPA) filters on the expiratory limbs of mechanical ventilators should be considered. There is no evidence to support the routine use of a viral filter on the exhaust line of the commonly used polymethylpentene-based ECMO membrane lungs, but further investigation in this field is required.[156] Further recommendations to prevent contamination of healthcare staff and clinical environment are reported in international guidelines.[154]

PATIENT SELECTION AND TIME OF INITIATION

Guidelines indicate that consideration for patient selection is completely different during a pandemic due to unfeasibility of providing ECMO to several patients who meet indications for ECMO at the same time and limited resources. For this reason, selection criteria must be more stringent in order to ensure extracorporeal support to those patients that could benefit most. The current recommendations are discussed next.

V-V ECMO for Respiratory Failure

- Major deviations from usual guidelines and indications have been used since more patients may require V-V ECMO support, however there is no evidence to support delaying ECMO initiation when it is indicated.
- Survival with V-V ECMO for COVID-19–related pneumonia seems to be similar to historical survival for other causes of ARDS meeting V-V ECMO criteria. This suggests that COVID-19 could be considered similarly to other causes of reversible infectious pulmonary disease.
- Attempt advanced supportive therapies (i.e., prone position or iNO) prior to ECMO support.[157]
- Cannulae: Although the majority of patients worldwide have been managed with large multistage drainage and single-stage return. In the recent report from Mustafa and collaborators,[118] an alternative approach with a single-access, dual-stage, right atrium–to–pulmonary artery cannula was used. Of note, with this approach the tip of the cannula should rest in the main pulmonary artery

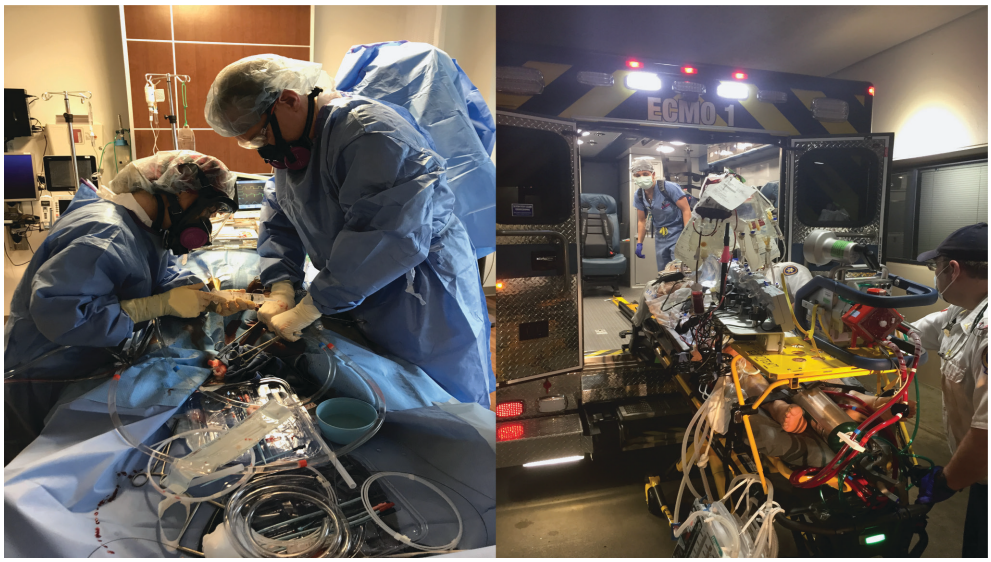


Figure 36.3 Left, Dr. Marc Maybauer and Jackie Chidester (RN, ECMO Manager) cannulating a COVID-19 ARDS patient in a remote outside hospital with full PPE. Right, Bethany White (RN, ECMO Coordinator) loading the patient into the ECMO ambulance for transport to the ECMO center.

distal to the pulmonic valve. This approach offers several advantages, such as direct pulmonary artery flow, thus improving oxygenation; early mobility; fewer cannula-associated complications, such as iliopsoas bleeding; and finally, decompression and support of the right side of the heart in case of right ventricular failure.

- Recent studies reported the potential use of V-V ECMO as supportive strategy in COVID-19 patients with severe respiratory failure instead of invasive mechanical ventilation.[158,159] Although this technique has already been described in other types of patients,[160] the role of the awake-ECMO in COVID-19 patients needs to be extensively studied.

V-A ECMO for Cardiovascular Failure

- No major deviations from usual guidelines and indications.
- Consider V-A ECMO in selected patients with severe refractory cardiogenic shock.
- Consider V-VA ECMO only in patients with ARDS plus acute stress/septic cardiomyopathy or massive pulmonary embolism with associated cardiogenic/obstructive shock failing medical therapies.
- Approach: femoro-femoral with distal limb perfusion catheter.

Specific indications, relative and absolute contraindications have been reported in international guidelines.[153] Cannulation should be provided by trained staff in isolated rooms, where possible avoiding the need to transfer the patient to a catheterization lab or operating rooms. Considering the potential risk of transmission, guidelines suggest a maximum of five team members in the room, wearing appropriate contact and airborne PPE. Cannulation should be managed through the use of plain x-ray, vascular ultrasound, transesophageal or transthoracic echocardiography, or fluoroscopy. Although some centers have experience with awake cannulation, this technique is strongly discouraged due the potential risk of emergency intubation and associated risks of personnel contamination. As with any invasive and high-risk procedure, guidelines suggest detailed preparation prior to the procedure that includes specific training of the staff, adequate checklists, and ready-to-use emergency medications.

MANAGEMENT OF ONGOING ECMO

The management of patients with ongoing ECMO should follow common existing evidence prior to the COVID-19 pandemic. In particular,

- Respiratory management: Lung-protective ventilation should be applied.[161] Percutaneous tracheostomy appears to be safe and feasible.[162,163] Prone position is feasible and preliminary reports demonstrated a potential association with outcome.[164–168]
- Anticoagulation: Use usual anticoagulation guidelines with specific and periodic monitoring and anticoagulant dose adjustment. Considering potentially hypercoagulable states in COVID-19 patients, a higher target in anticoagulation can be considered, and low-flow circuits should be avoided if possible (e.g., blood flow < 2 L/min). Bleeding remains a concern, and there are insufficient data to suggest deviation from usual anticoagulation practices. In the report from Mustafa et al.,[118] using a single-access, dual-stage, right atrium–to–pulmonary artery cannula, systemic anticoagulation with a direct thrombin inhibitor for a prothrombin time of 45–70 seconds was carried out. Finally, routine use of antifibrinolytics is not recommended.
- Blood products: There is no evidence regarding specific transfusion thresholds to be applied in COVID-19 patients. Blood products should be used judiciously, especially during major outbreaks resulting in potential shortage of blood products. The majority of patients with COVID-19 who require ECMO could be treated with lower trigger thresholds (i.e., 7 g/dL) if they are stable and not actively bleeding. Higher thresholds (e.g., 8–10 g/dL) should be applied in patients with shock or evidence of impaired oxygen delivery despite ECMO. Thus, as recommended by international guidelines, maintaining arterial oxygen saturation (SaO_2) and mixed venous oxygen saturation (S_VO_2) above 95% and 75%, respectively, in patients receiving V-A ECMO and above 80% and 70% in patients receiving V-V ECMO is a reasonable approach. As for platelet transfusions, achieving platelet counts greater than 50,000/mm^3 is a reasonable strategy also in COVID-19 patients on ECMO; however, in the case of no significant bleeding, a lower count may be tolerated considering a hypercoagulable state.
- Gastrointestinal: Early initiation of enteral nutrition according to international guidelines is recommended.
- Disease-modifying agents: Digression on the role of specific antiviral therapies against COVID-19 is beyond the scope of this chapter. Yet, it should be highlighted that pharmacokinetics and pharmacodynamics of antiviral therapies in patients on ECMO should be appraised in future investigations.
- Mobilization: Guidelines recommend application of early mobilization protocols when safe and feasible.
- Microbiological surveillance: Close microbiological surveillance can be undertaken considering the very high incidence of coinfections such as ventilator-associated pneumonias (VAP)

- Imaging: Considering patient instability and the potential risk of contamination of hospital environments, imaging techniques at the bedside should be preferred (e.g., ultrasonography, chest or abdominal radiographs, echocardiography). CT scans should be performed only if considering that obtained results may change management or outcome of the patient.
- ECMO monitoring: Guidelines recommend daily monitoring by specific trained staff.
- Procedure: COVID-19 patients on ECMO may present a higher risk of bleeding; hence, invasive procedures should be reduced to a minimum and indications carefully pondered.

WEANING FROM ECMO AND DECANNULATION

There are no specific indications about ECMO discontinuation in COVID-19 patients. General principles prior to the COVID-19 pandemic should be followed. During decannulation, the following crucial points should also be considered:

- Full PPE precautions should be observed to prevent contact with body fluids and staff contamination.
- Careful assessment of bleeding and thrombotic risks is needed. Cannulae placed by cutdown should be surgically removed at the bedside, if possible. The risks of aerosol generation during electrocautery are unclear, and optimal PPE should be used.
- Venous cannulae, placed by percutaneous access, can be removed at the bedside and bleeding controlled by topical pressure or sutures.

ICU-physician should also consider ECMO discontinuation in case of futility. Nevertheless, it is challenging to determine futility in patients receiving V-V ECMO with single-organ failure awaiting for pulmonary recovery. Lung transplant has been successfully completed in selected patients.[169]

ECMO COMPLICATIONS

The most common complications during ECMO are bleeding and thrombosis.[170] Each time an extracorporeal circuit is used to treat a patient, the patient's blood is exposed to a foreign plastic surface. Unfortunately, exposure of blood to plastic surfaces activates the coagulation cascade, leading to potentially fatal consequences in patients as a result of circuit clotting and possible systemic embolism and/or bleeding.[171–173] The only treatment for these somewhat unavoidable complications is anticoagulation.[174]

The initiation of an extracorporeal blood treatment is associated with an immediate and complex inflammatory reaction, similar to that seen in systemic inflammatory response syndrome (SIRS).[175] Unregulated activation of inflammation and coagulation can have deleterious effects, even death. Extracorporeal circulation frequently causes hemorrhage, with up to 34% of patients requiring surgery.[176] Retroperitoneal hematoma, caused by iliopsoas bleeding at the access site, has been reported in COVID-19 patients[177,178] and highlights the critical balance between thrombotic and bleeding risks in this population. These risks should be taken into account when ECMO support has been initiated in a COVID-19 severely compromised patient.[179] Several reports of extracorporeal support in COVID-19 patients describe intraparenchymal hemorrhage,[180] pulmonary embolism,[181] and lymphopenia.[182]

Understanding the crosstalk between the ECMO circuit and the patient has been a prominent research topic since the beginning of extracorporeal support. It has been proven that SARS-CoV-2 has a close relationship with angiotensin-converting enzyme 2 by a receptor-mediated endocytosis.[33] Through the renin-angiotensin system, the virus may impact the lung circulation and cause further systemic damage with a prothrombotic state. The variable involvement of the endothelium, as well as other key organs (e.g., liver), may explain the heterogeneity of the clinical picture. A complete summary of laboratory disorders in COVID-19 infection and ECMO support is presented in Table 36.1.

CONCLUSION

- COVID-19 is a viral infection caused by a novel coronavirus (SARS-CoV-2) that can result in life-threatening clinical conditions.
- COVID-19 may cause multiorgan failure; in particular, the cardiopulmonary system is mostly affected.
- COVID-19 often results in pulmonary failure characterized by severe hypoxemia and heterogeneity in pulmonary system compliance derangement and ventilation/perfusion mismatch.
- Prior to ICU admission, COVID-19 patients with respiratory failure should receive ventilatory support and potentially prone position to improve oxygenation and reduce work of breathing.
- Extracorporeal support is indicated in severely ill COVID-19 patients with hypoxemia/hypercapnia refractory to maximal rescue strategies (i.e., prone positioning).
- Veno-venous ECMO or V-A ECMO should be used following indications and international recommendations as applied in the pre–COVID-19 era.
- In case of major outbreaks, inclusive preparation and organization of healthcare systems and ECMO programs are essential to promptly increase ECMO provision. Yet, indications should be strictly pondered to provide ECMO to patients who could mostly benefit of the technique.

Table 36.1 COMPARISON OF HEMATOLOGICAL AND BIOCHEMICAL PARAMETERS IN V-V ECMO AND SARS-COV-2–INDUCED ARDS[183]

	V-V ECMO	SARS-COV-2 ARDS
Hematological Findings		
White blood cell count	Initial ↑	↑
Lymphocytes	↓	↓↓
Neutrophils	Initial ↑	↑
Neutrophil activation	Initial ↑	?
Monocytes	Initial ↑	~
$CD3^+$, $CD4^+$, $CD8^+$, T cells	↓	↓↓
Natural killer cells	↓	~ ↓
Neutrophil-to-lymphocyte ratio	↑	↑
Hemoglobin and red blood cell count	↓	~
Platelet count	↓	↓~
Inflammatory Response		
Tissue factor	↑~	?
Bradykinin	↑	?
TNF-α	↑	~↑
Interferon gamma	?	↑
IL-1-β	↑	↓↓
IL-2	?	↑
IL-2R	?	↑
IL-4	?	~
IL-6	↑	↑↑
IL-8	↑	?
IL-10	↑	↑
IgE	↓	?
IgA	?	~
IgG	?	~↑
IgM	?	~
Complement	~↑	~
	V-V ECMO	SARS-COV-2 ARDS
Coagulation and Anticoagulation		
Platelet activation	↑	?
Platelet aggregation	↓	?
Platelet activation factor	↑	?
Heparin-induced thrombocytopenia	↑	?
Von Willebrand factor	↓	?
D-Dimer	↑	↑↑

Table 36.1 CONTINUED

	V-V ECMO	SARS-COV-2 ARDS
Fibrin degradation products		↑↑
Activated partial thromboplastin time	↑	~
Prothrombin time		~
Thrombospondin	↓	?
Fibronectin	↓	?
Thrombin	↑	?
Fibrinogen	Initial ↓	↑
High-molecular-weight kininogen	↑	?
Prekallikrein	↓	?
Kallikrein	↑	?
FVIII	↓	?
FX	↑	?
FXI	↓	?
FXIa	↑	?
FXII	↓	?
FXIIa	Rapid ↑	?
FXIII	↓	?
Antithrombin	Initially ↓	↓
C-protein	↑↓	?
Activated clotting time	↑	?
R-time thromboelastography	↑	?

F, factor; Ig, immunoglobulin.

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REVIEW QUESTIONS

1. How can we classify SARS-CoV2, better known as COVID-19?

A. Parvovirus
B. Coronavirus
C. Rhinovirus
D. Adenovirus

2. Which is the pathophysiological classification of COVID-19-related acute hypoxemic respiratory failure proposed by Gattinoni and colleagues?

A. So (Soft) and St (Stiff)
B. M (V/Q Mismatch) and E (Lung Edema)
C. H (High) and L (Low)
D. P (Pulmonary) and E (Extrapulmonary)

3. Which are the criteria to define myocardial impairment related to COVID-19?

A. An elevation of highly sensitive cardiac troponin I (hs-cTnl) greater than 99th percentile
B. An increase of heart rate greater than 120 beats/min
C. A decrease of ejection fraction lower than 40%
D. Any increase of pro–B-type natriuretic peptide

4. In COVID-19 infection, inflammation and coagulation seem to have a close crosstalk. How can you define this relationship?

A. It is not relevant.
B. Inflammation and coagulation have completely autonomous pathways.
C. Not enough data are available to make a conclusion about this topic.
D. Inflammation is strictly related to coagulation.

5. How may stages of infection have been reported during COVID-19?

A. There are three: I (early infection), II (pulmonary phase), III (hyperinflammation phase).
B. There are two: I (viral phase), II (inflammatory phase).
C. COVID-19 infection seems to have a unique clinical course characterized by no differences between the various phases.
D. Not enough data are available to make a conclusion about this topic.

6. How should you manage a patient with COVID-19 infection outside the ICU?

A. Early intubation is mandatory to avoid patient self-inflicted lung injury.
B. Early extracorporeal support should be initiated in spontaneously breathing patients.
C. Helmet CPAP or mask NIPPV can be considered during the early phase of infection.
D. Experts recommend against noninvasive ventilation.

7. Which kind of rescue therapies have been proposed in severe refractory hypoxemia during COVID-19 infection?

A. Only extracorporeal membrane oxygenation is a valid support to avoid severe hypoxemia.
B. Prone position and iNO have a role in hypoxic patients. In particular, prone position has been proposed even in spontaneously breathing patients with helmet CPAP.
C. No rescue therapy is available. Severe hypoxemia is completely refractory to any support strategy. Only palliation has been proposed in severe hypoxemic patients.
D. Only patients in prone position with iNO and ECMO support had a favorable outcome.

8. According to recent ELSO guidelines, which kind of extracorporeal support has been proposed in severe hypoxemic COVID-19 respiratory failure?

A. Veno-arterial ECMO due to severe cardiovascular impairment that characterizes COVID-19 infection.
B. VV-V ECMO due to severe hypoxemia and consequent necessity to have very high blood flows.
C. Extracorporeal supports have no rule in COVID-19 infection.
D. Veno-venous ECMO is the principal kind of extracorporeal support proposed to increase oxygenation in severely impaired patients.

9. According to recent experiences all around the world, ELSO suggests using extracorporeal support:

A. In every hospital, even small ICUs without experience in managing ECMO patients
B. Only in a hospital with proven experience in ECMO support, after the creation of a specific network of information and assistance in a specific region
C. Everywhere, even on the road if necessary
D. Only in a hospital with proven experience in ECMO support, with direct contact with ECMO referral centers without coordination

10. Extracorporeal organ support has been proposed

A. Only for severe respiratory failure
B. Only for lung and cardiac severe impairments
C. Only for kidney failure
D. In case of lung, heart, kidney, and cardiovascular dysfunction with different applications, such as ECMO, continuous renal replacement therapy or plasmapheresis.

11. Anticoagulation during extracorporeal membrane oxygenation may play a crucial role in terms of efficiency, duration of treatment, and possible complications. In particular, recent ELSO guidelines suggest

A. Using usual anticoagulation protocols, with a higher target of anticoagulation related to hypercoagulable states related to COVID-19 infection.
B. Using usual anticoagulation protocols without any change in practice.
C. Avoiding anticoagulation due to the bleeding tendency of COVID-19 patients.
D. Using antifibrinolytics routinely.

12. Complications during ECMO support in COVID-19 patients:

A. Complications are less frequent because of less injured patients compared to standard ECMO-supported patients.
B. To date, there are no data available regarding complications in ECMO COVID-19–supported patients.
C. Complications are more frequent than usual, and close monitoring of ECMO is mandatory in COVID-19–supported patients.
D. Only severe bleeding has been reported in the literature.

13. Regarding ECMO initiation and cannulation, ELSO guidelines suggest

A. Using the same indications as usual for both V-V and V-A ECMO with minor precautions related to COVID-19 contagiousness and possible shortage of equipment.
B. A completely different indication with strict enrollment criteria.
C. Starting ECMO support in every patient if equipment is available in order to "buy time" against the viral infection.
D. Reducing ECMO support to strictly selected patients.

14. According to ELSO guidelines, extracorporeal cardiopulmonary resuscitation in COVID-19 patients

A. Is not recommended, independently of a center's experience.
B. Should be used in experienced centers in strictly selected patients.
C. Has technical limitations due to COVID-19 infection that limit extracorporeal cardiopulmonary resuscitation.
D. Converting from V-V to V-A ECMO in patients who suffer cardiac arrest during cannulation for V-V ECMO is highly recommended considering the high rate of survival of these patients.

ANSWERS

1. B
2. C
3. A
4. D
5. A
6. C
7. B
8. D
9. B
10. D
11. A
12. C
13. A
14. B

37.

ECMO IN PREGNANCY AND THE PERIPARTUM PATIENT

Cara Agerstrand, Antonio F. Saad, and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 33-year-old woman, gravida 2, para 1, in the 35th gestational week, presented with several days of fever, cough, and shortness of breath. She was noted to be in respiratory distress, and oxygen saturation was 85% on room air. Her chest radiograph (CXR) showed diffuse bilateral opacities suggestive of acute respiratory distress syndrome (ARDS). A respiratory viral panel was positive for influenza A (H1N1). She quickly required endotracheal intubation and advanced ventilatory settings. She received lung-protective ventilation, deep sedation, and a high level of positive end-expiratory pressure (PEEP) and was started on neuromuscular blockade. Despite these measures, an arterial blood gas (ABG) showed a pH of 7.24, a partial pressure of arterial carbon dioxide ($PaCO_2$) of 56 mm Hg and a partial pressure of arterial oxygen (PaO_2) of 70 mm Hg, with a PaO_2 to fraction of inspired oxygen (FiO_2) ratio of 70 mm Hg. Her transthoracic echocardiogram showed a left ventricular ejection fraction of 60%. She required a low-dose norepinephrine infusion at 5 μg/min to maintain a mean arterial pressure of 65 mm Hg.

Veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) was initiated using a dual-site configuration with drainage via right femoral vein and reinfusion via the right internal jugular vein. She was managed with a blood flow rate of 4 L/min and a sweep gas blood flow rate of 3 L/min. Her ventilator was reduced to lung rest settings, targeting a respiratory rate less than 10 breaths/min and an end-expiratory plateau pressure less than 24 cm H_2O, while maintaining physiologic pH and PaO_2. Shortly after cannulation, vasopressors were weaned off, and a net negative volume status was maintained with intravenous furosemide. A continuous infusion of heparin was used for anticoagulation, titrated to target an activated partial thromboplastin time of 45–50 seconds. Maternal-fetal medicine closely followed for signs of fetal distress. Betamethasone was administered to promote fetal lung development. Eight days after cannulation, her CXR and gas exchange had improved, diuresis had occurred, and she was weaned from ECMO. She delivered a healthy baby 2 weeks later.

WHERE SHOULD PREGNANT PATIENTS REQUIRING ECMO BE TREATED?

Pregnant and postpartum patients with ARDS should be referred to centers experienced in ECMO that also have the ability to care for high-risk pregnant patients and critically ill infants.[1] The specific medical unit treating the patient should have experience in ECMO as well as the underlying patient condition. For example, a pregnant patient with ARDS may be best managed in a medical intensive care unit, while a patient with a peripartum cardiomyopathy may be most appropriate for treatment in a cardiac care unit or cardiovascular intensive care unit if those units are also experienced with ECMO. Management of pregnant ECMO patients should include a multidisciplinary team of physicians, including intensivists, cardiologists, cardiothoracic surgeons, maternal-fetal medicine specialists, and neonatologists. Access to obstetric anesthesiologists experienced in high-risk deliveries and hematologists is also important. In select patients with underlying cardiac or pulmonary vascular conditions, consultation with pulmonary hypertension specialists may also be warranted.[2]

IS VAGINAL DELIVERY POSSIBLE DURING ECMO?

Vaginal delivery has been reported during ECMO; however, existing literature is limited.[3,4] Optimally, in cases of acute illness such as ARDS or status asthmaticus, a pregnant woman would be supported on ECMO and her pregnancy allowed to progress, with delivery only being considered in the setting of fetal distress or inadequate maternal oxygenation support. The means of delivery—vaginal versus cesarean—should be determined after a multidisciplinary discussion, including critical care, maternal fetal medicine, obstetric anesthesiology, and other relevant consultants.

IS CESAREAN SECTION POSSIBLE DURING ECMO SUPPORT?

Successful cesarean section has been reported during both veno-arterial and V-V ECMO for conditions such as ARDS, pulmonary hypertension, and peripartum cardiomyopathy.[2,5–7] Planning for emergent delivery should occur as soon as possible and include a multidisciplinary discussion and perioperative planning in order to optimize maternal and fetal outcomes. Surgical tools required for cesarean should be kept at the patient's bedside to allow for urgent delivery should there be signs of fetal distress. Postnatal care planning for care of both the patient and the neonate should occur prior to

delivery as well. The personnel, medications, and equipment necessary to manage a critically ill woman and critically ill neonate should be immediately available.

IS THERE A ROLE FOR ECMO IN THE MANAGEMENT OF PERIPARTUM CARDIOMYOPATHY?

Peripartum cardiomyopathy, which typically occurs during late pregnancy or postpartum, has been treated successfully with ECMO.[6,8,9] In cases of cardiac failure, veno-arterial ECMO is the preferred cannulation approach and can be used alone or in conjunction with other treatment modalities, such as inotropes, intra-aortic balloon pumps, or ventricular assist devices.[9]

WHAT IS THE ROLE OF ECMO IN PREGNANT PATIENTS WITH PULMONARY HYPERTENSION AND/OR EISENMENGER SYNDROME?

The application of ECMO in patients with pulmonary hypertension is growing.[10] In patients with pulmonary hypertension, ECMO can be used to support oxygen delivery to the developing fetus, as well as at the time of delivery. Veno-arterial ECMO is typically required in pulmonary hypertension; however, one report exists in which V-V ECMO was used to provide physiologic veno-arterial ECMO support in a patient with an uncorrected patent ductus arteriosus and Eisenmenger physiology.[11] In patients with severe pulmonary hypertension, consideration should be given to preemptive cannulation at the time of delivery or the placement of vascular access sheaths to allow for rapid ECMO cannulation should periparturition decompensation occur.[2] Use of ECMO in patients with pulmonary hypertension may substantially decrease the risks of pregnancy and childbirth in this special population.

CAN ECMO BE USEFUL IN HELLP SYNDROME?

Extracorporeal membrane oxygenation has been reported in a woman with severe preeclampsia and HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome complicated by cardiac arrest.[12] Given that thrombocytopenia and bleeding are common complications of ECMO, patients with HELLP syndrome may have an increased risk profile for ECMO.[13] That being said, patients' bleeding complications, even those with preexisting severe bleeding diatheses, have been treated successfully with ECMO.[2,14,15]

IS THE ESTABLISHED USE OF ECMO IN STATUS ASTHMATICUS TRANSFERABLE TO PREGNANCY?

Limited information exists regarding the use of ECMO for status asthmaticus during pregnancy, though it has been used successfully in pregnant women.[16–18] The effects of hypercapnic acidosis on the developing fetus are not well described, but it is reasonable to target gestational age-appropriate physiologic conditions without ECMO and to consider ECMO in the setting of refractory status asthmaticus, hemodynamic compromise or evidence of barotrauma, or signs of fetal distress.[19]

DISCUSSION

Extracorporeal membrane oxygenation has become an accepted modality to support patients with severe cardiac, pulmonary, or combined cardiopulmonary failure, supported by an increasing global experience as well as the results of several randomized controlled trials.[13,20] These trials did not include pregnant and postpartum woman, however; substantially less has been published about the use of ECMO in these populations, with existing data limited to case reports, case series, and observational studies.[2,15,21]

Modern evidence for ECMO during the peripartum period largely originates from experience obtained during the 2009 influenza A (H1N1) pandemic in patients, in which 12 peripartum patients were supported with ECMO.[15,22] Seven (58%) were pregnant, and 5 (42%) were postpartum.[15] Bleeding requiring transfusion occurred in 67% of patients. Eight patients (66%) survived to hospital discharge.[15] Importantly, there was no difference in mortality, bleeding, or infectious complications when compared to nonperipartum women of childbearing age supported with ECMO.[15] Of the total cohort, seven patients delivered vaginally, including two who required vacuum-assisted delivery. Five delivered by cesarean section, one of whom was supported with ECMO at the time. Median gestational age at birth was 31 weeks, with preterm delivery required in 25% of patients ($n = 3$) due to the severity of maternal disease. Fetal survival was 71% in patients who delivered after the initiation of ECMO, and there were no known complications by hospital discharge.[15]

In the largest single-center series study of ECMO during the peripartum period, 16 of 18 patients survived (88.9%).[2] Fetal survival was 77.8% in the entire cohort. For the three pregnant patients cannulated after fetal viability, fetal survival was 100%. The majority of patients in this series had ARDS, predominantly secondary to influenza, though indications for ECMO also included extracorporeal cardiopulmonary resuscitation ($n = 3$), pulmonary embolism ($n = 2$), amniotic fluid embolism (n = *2*), and pulmonary hypertensive crisis ($n = 1$), with some patients having more than one indication for ECMO.[2] Bleeding was the most frequently reported complication and was associated with disseminated intravascular coagulation, both of which occurred at higher rates than the center's experience with nonperipartum patients. Reassuringly, however, maternal survival was 100% in those who experienced hemorrhagic complications, including in patients placed on ECMO in the setting of massive hemorrhage or coagulopathy, suggesting ECMO may be beneficial even for high-risk patients.[2]

A systematic review and meta-analysis including a total of 78 peripartum patients from nine retrospective observational studies (including the aforementioned studies) calculated pooled maternal and fetal survival rates of 77.2% (95% CI

64.1%–88.4%) and fetal survival of 69.1% (95% CI 44.7%–89.8%), with the majority of patients being placed on ECMO for ARDS ($n = 52$), followed by cardiogenic shock ($n = 13$).[14] No statistically significant difference in survival was found for patients with pulmonary versus cardiac indications for ECMO; however, an individual patient data meta-regression showed higher survival for patients receiving V-V compared to veno-arterial ECMO, which approached statistical significance (odds ratio 3.016, 95% CI 0.901–11.144, $P = .081$). Hemorrhage was the most common complication reported, with uterine or intra-abdominal bleeding occurring most frequently, followed by cannulation site bleeding.[14]

PATIENT MANAGEMENT DURING ECMO

Management of the peripartum patient should be largely similar to that of nonperipartum patients requiring ECMO. Cannulation strategy should be determined by the patient's underlying illness, anticipated blood flow needs, clinical stability, and vessel size. For example, patients with a peripartum cardiomyopathy or pulmonary hypertension require veno-arterial ECMO support, while those with ARDS or asthma are best supported with a V-V configuration. It is important to recognize that cardiac output increases throughout pregnancy, peaking in the early third trimester, with a series of meta-analyses showing a 31% increase above nonpregnant values.[23] Thus, pregnant women will have higher blood flow requirements than nonperipartum women of similar size. Cannulation difficulties or limitations in blood flow can be managed by placing the patient in a 15° to 30° left lateral tilt position in order to reduce the compression of the inferior vena cava caused by the gravid uterus.[2,24] For ARDS patients, a strategy of ultra–lung-protective ventilation can be used in order to minimize the mechanical power exerted on the lungs.[13] Provided volume resuscitation is not needed for vasodilatory, hypovolemic, or septic shock; maintaining a net negative volume status may help reduce any pulmonary edema and optimize gas exchange. Modern literature suggests that low-dose anticoagulation is adequate in an effort to balance bleeding and thrombotic risks in ECMO-supported patients; however, oxygenator function should be monitored closely, particularly due to the thrombotic propensity of peripartum women.[2,13,25]

FETAL MONITORING AND MANAGEMENT

The preferred approach to fetal monitoring in patients supported with ECMO is not well described. Guidelines from professional societies such as the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine or the Extracorporeal Life Support Organization do not address the use of ECMO during pregnancy. Monitoring should be individualized, with specific determinations likely impacted by patient preference, gestational age, and in consultation with maternal-fetal medicine. Use of fetal heart tones, nonstress tests, and pelvic ultrasound scans has been reported in the literature.[2] Fetuses past the point of viability should receive steroids to support lung maturation in the event early premature delivery is required.

DELIVERY ON ECMO

There are several reports of delivery during ECMO, which include both vaginal delivery and cesarean section.[2,15,26] There is no consensus in the literature regarding the preferred method of delivery or the risk profile associated with each. Decisions regarding specific approach to delivery and delivery location may depend on the stability of the patient, the indication for ECMO, underlying comorbidities, and stability of the fetus. As placental oxygen delivery depends on uterine artery blood flow and oxygen content, which is 600 to 700 mL of oxygen per minute at term (approximately 10% of maternal cardiac output), the burden of the fetoplacental unit on maternal oxygen should be considered when determining the timing of delivery.[27] Regardless of ultimate approach to delivery, a delivery plan for each patient should be developed. This plan should include the approach to delivery and also anesthesia, the ECMO management plan, and contingency planning in the event of maternal or fetal decompensation. The delivery plan should include multidisciplinary input from specialists in maternal-fetal medicine, obstetric anesthesia, ECMO, cardiothoracic surgery, as well as intensivists and cardiologists. Specialized consultation with hematologists or pulmonary hypertensive specialists may be warranted in select patients. Plans for immediate postnatal care should also be developed.

Patients with underlying cardiac conditions, particularly those with cardiomyopathy or pulmonary hypertension, who are not supported with ECMO prior to delivery are at high risk for decompensation due to the fluid shifts and hemodynamic alterations that occur at the time of delivery. ECMO can be used on standby in these patients, with the cannulating ECMO team and primed ECMO circuit immediately available in the delivery room. Predelivery placement of 4F vascular access sheaths in the femoral artery and vein should be considered to facilitate rapid initiation of ECMO should clinical decompensation occur at the time of or following delivery.

CONCLUSION

The use of V-V and veno-arterial ECMO during pregnancy and the postpartum period has produced favorable maternal and fetal outcomes.[28] Similar to the application of ECMO in any population, patient selection is important, but evidence suggests that ECMO should not be withheld out of fear of adverse outcomes in the critically ill peripartum patients, even in patients with underlying comorbidities or complications. Given the complexity of caring for pregnant women, proactive, multidisciplinary planning is critical to optimize outcomes for both the patient and fetus.

- Pregnant and postpartum patients supported with ECMO have survival rates similar nonperipartum patients supported with ECMO.
- A delivery plan should be prepared for all patients supported with ECMO.

- Vaginal and cesarean approaches have been used for delivery during ECMO, with the specific strategy determined after careful consideration by a multidisciplinary clinical team.
- Patients with pulmonary hypertension or Eisenmenger syndrome may be supported with ECMO or with ECMO on standby during high-risk deliveries.
- Limited published evidence exists on the use of ECMO in pregnant patients with HELLP syndrome or status asthmaticus; however, case reports suggest favorable outcomes are possible.

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REVIEW QUESTIONS

1. What is the goal of mechanical ventilation in patients supported on V-V ECMO for severe ARDS?

   A. Minimization of ventilator-associated lung injury
   B. Reduction of mechanical power to the lung
   C. Minimization of the risk of late ARDS mortality
   D. All of the above

2. A 32-year-old woman at 36 weeks' gestation is cannulated with a V-V ECMO configuration for ARDS due to influenza A (H1N1). ECMO blood flow is 4.5 L/min, sweep gas flow is 6 L/min. Her ABG shows a pH of 7.42, $PaCO_2$ of 38 mm Hg, and PaO_2 of 80 mm Hg once she is weaned to ultralow tidal volume ventilation. Which of the following is appropriate?

   A. Establishment of a delivery plan
   B. Immediate delivery via cesarean section
   C. Induction of labor for vaginal delivery
   D. No change in approach compared to nonpregnant ARDS patients

3. A 31-year-old woman is 33 weeks' pregnant from in vitro fertilization. She presented 6 days ago with an ST elevation myocardial infarction, and during the percutaneous coronary intervention, she aspirated and required intubation. Despite successful intervention, the patient was placed on

veno-arterial ECMO due to cardiogenic shock. A pulse oximeter placed on the right hand shows a saturation of 80%; it reads 99% on the left. Preoxygenator saturation is 75%. A pulse pressure of 25 mm Hg is noted on the arterial tracing. What is the diagnosis?

A. Differential hypoxia
B. Inappropriate ventilator settings
C. Inadequate inotropic support
D. Worsening cardiac dysfunction

4. What is a major concern of the above condition?

A. Cerebral ischemia
B. Bowel ischemia
C. Lower extremity ischemia
D. Upper extremity ischemia

5. A 34-year-old woman at 34 weeks' gestation presents with status asthmaticus unresponsive to medical management. Her last ABG shows a pH of 7.07, $PaCO_2$ of 90 mm Hg, PaO_2 of 400 mm Hg, despite sedation, use of neuromuscular blocking agent, and ventilator manipulation. She is increasingly hypotensive, requiring norepinephrine at 25 μg/min. She is cannulated onto ECMO. What is the most appropriate configuration and $PaCO_2$ target 8 hours after cannulation.

A. Veno-venous ECMO, $PaCO_2$ 50 mm Hg
B. Veno-venous ECMO, $PaCO_2$ 35 mm Hg
C. Veno-arterial ECMO, $PaCO_2$ 50 mm Hg
D. Veno-arterial ECMO, $PaCO_2$ 35 mm Hg

6. A 24-year-old woman who is 29 weeks' pregnant has been receiving V-V ECMO for 4 days due to refractory hypoxemia from severe ARDS when she goes into cardiac arrest. What is the first step of management?

A. Commence chest compression (100–120/min) while displacing the uterus laterally
B. Convert to veno-arterial ECMO
C. Echocardiography
D. Set ventilator FiO_2 at 0.5

7. A 22-year-old patient with Eisenmenger syndrome from congenital heart disease becomes pregnant and progresses through her pregnancy closely followed by maternal fetal medicine. What is an appropriate management strategy as she approaches delivery?

A. Multidisciplinary discussion regarding timing of and method of delivery
B. Frequent fetal monitoring to assess for intrauterine growth retardation or signs of fetal distress
C. Placement of vascular access sheaths prior to delivery to facilitate emergent ECMO cannulation
D. All of the above

8. Peripartum patients requiring V-V or veno-arterial ECMO are at risk for which of the following?

A. Hemolysis
B. Bleeding complications
C. Disseminated intravascular coagulation
D. All of the above

9. What is the most sensitive test to confirm the suspicion of hemolysis?

A. Peripheral smear
B. Haptoglobin
C. Plasma free hemoglobin
D. Unconjugated bilirubin

10. Which of the following is an absolute contraindication to the use of ECMO during the peripartum period?

A. Prior cardiac arrest
B. Amniotic fluid embolism with severe coagulopathy
C. Massive uterine hemorrhage
D. None of the above

ANSWERS

1. D. The benefit of ECMO likely extends beyond improvement in PaO_2 and $PaCO_2$, but to the reduction of the mechanical power applied to the lung and the prevention of ventilator-associated lung injury that has been associated with late ARDS mortality.

2. A. The patient is well supported on ECMO. Provided the fetus does not show signs of distress, urgent delivery is not required. A delivery plan should be developed in case maternal or fetal decompensation occurs.

3. A. The patient has differential hypoxia, which occurs when dual circulation develops in a patient on femoral veno-arterial ECMO who has an ejecting heart and impaired pulmonary function.

4. A. The consequences of differential hypoxia may be severe, including both cardiac and cerebral ischemia, depending on the location of the mixing point in the aorta, where the patient's blood flow from native circulation meets the retrograde flow from the ECMO circuit. These complications should be considered when the innate cardiac function of a patient on femoral veno-arterial ECMO begins to recover.

5. B. Shock in the setting of status asthmaticus typically improves with correction of pH and reduction in intrathoracic pressures following ECMO cannulation and ventilator adjustments; thus, V-V ECMO is the appropriate cannulation strategy. Normal pregnancy physiology includes mild respiratory alkalosis.

6. A. For cardiac arrest in a patient on V-V ECMO, cardiac compressions must be commenced immediately. If a pregnant patient is in the third trimester, lateral tilt or lateral shift of the uterus is recommended to avoid aortocaval compression by the uterus. Since the majority of patients requiring V-V ECMO have underlying lung gas exchange deficits, oxygenation should be maximized during the cardiac arrest and conversion to veno-arterial-venous ECMO should be considered.

7. D. Patients with pulmonary hypertension are at high risk of decompensation prior to and after delivery. Advance planning and preparation are required to minimize risk.

8. D. Activation of the coagulation cascade during pregnancy places peripartum patients at risk for both bleeding and thrombosis.

9. C. Plasma free hemoglobin is the most sensitive test to confirm hemolysis.

10. D. Patients have been successfully supported on ECMO with all of those conditions. Certainly, bleeding and coagulopathy alter the risk/benefit ratio of ECMO, but ECMO should not be withheld out of concern for poor outcomes in this population.

38.

ECMO IN SICKLE CELL DISEASE AND ACUTE CHEST SYNDROME

Othman Al-Sawaf and Matthias Kochanek

STEM CASE AND KEY QUESTIONS

A 21-year-old male patient with origins from Ghana and known sickle cell disease (SCD) on hydroxyurea therapy and with severe back pain presented to his local hospital. The pain occurred suddenly and without prodromes; however, it was the third pain crisis in the same year, all of which had occurred during or after infections, particularly upper respiratory tract infections. The patient had a history of repetitive vaso-occlusive crises, salmonella sepsis with multiple organ failure, of which he had recovered without sequelae, intracranial bleedings requiring surgical intervention, and bone infarction of hips and vertebral bodies. This time, the patient reported having fever with temperature over 39°C at home as well as purulent sputum.

In his local hospital, he was treated with a standard protocol of intravenous opioids as well as fluids. While the pain initially responded to analgesic treatment, the patient rapidly developed an increasing loss of vigilance and became hypotensive as well as hypoxemic. Anti-infective treatment with piperacillin/tazobactam was initiated. The local laboratory tests showed intravascular hemolysis, thrombocytopenia, and acute renal failure. For specialized hematologic and intensive care, the patient was referred to our center. While preparing for transport, the patient's condition deteriorated further, and he was intubated due to respiratory failure. He received norepinephrine at a dose of up to 0.2 μg/kg/min.

The patient subsequently arrived at our center, and further diagnostic measures, including chest x-ray, hemoglobin electrophoresis, and bronchoalveolar lavage (BAL) were performed. The chest x-ray showed extended bilateral consolidations. Given the initial presentation with sickle cell pain crisis and dyspnea, the working diagnosis was very severe acute chest syndrome (ACS) with acute respiratory distress syndrome (ARDS). Anti-infective treatment was extended with ciprofloxacin to account for possible atypical pneumonia. Although the patient initially stabilized, he showed progressive multiorgan failure, including cardiac failure, anuric renal failure, and liver failure. Despite optimized ventilation (bilevel positive airway pressure, fraction of inspired oxygen [FiO_2] 1.0, positive end-expiratory pressure 12 cm H_2O, Pmax 29 cm H_2O, respiratory rate 20 breaths/min, I:E 1:1), the patient showed ongoing global respiratory insufficiency with a Horowitz index (PaO_2/FiO_2 ratio) of 56. After thorough discussion within the extracorporeal membrane oxygenation (ECMO) team, it was decided to establish veno-venous (V-V) ECMO. Sufficient oxygenation and decarboxylation was maintained with physiological PO_2 and PCO_2.

In the diagnostic workup, the BAL test returned positive by polymerase chain reaction for rhinovirus and *Chlamydia pneumoniae*, which was sensitive to ciprofloxacin. Hemoglobin electrophoreses showed a hemoglobin S (HbS) fraction of 96%, and a sickle cell proportion of 9‰ was observed in blood smear microscopy. Thus, red blood cell exchange was performed daily over 3 days until HbS levels reached 9%. Due to increased retention parameters and anuria, renal replacement therapy was initiated via sustained low-efficiency daily dialysis over a separate temporary dialysis catheter. Both the red blood cell exchange and dialysis worked well without interference with ECMO.

By these measures, cardiopulmonary stabilization was achieved; the patient was weaned off ECMO 7 days after cannulation and extubated after a further 7 days. The follow-up chest x-ray showed a complete resolution of pulmonary consolidations. The patient was well oriented afterward and was mobilized with the help of the physiotherapy team. Diuresis was restored, and the patient had normal urea and electrolyte values, although the creatinine remained high for several weeks onward. After transferal to our intermediate care unit and later to the hematology ward, hydroxyurea therapy was restarted. The patient was discharged in good condition 4 weeks after admission. Due to the repetitive and life-threating sickle cell crises, preparations for allogeneic stem cell transplantation were initiated.

WHAT IS SICKLE CELL CRISIS?

Sickle cell crises are usually episodes of acute pain in patients with SCD; these require quick and sufficient analgesia in order to terminate the crisis. The pathophysiology of pain in SCD patients is very complex; clinically, the pain is mainly driven by vaso-occlusions, particularly of small vessels (e.g., the fine-vessel network of vertebra or hip).[1] These vaso-occlusions occur with sickling of erythrocytes, which carry a defect hemoglobin chain.[2] Sickling can be induced or maintained by any form of stress, including infections, trauma, and also

psychological stress. The patients usually report severe, unbearable pain, particularly in the lower back and in the upper and lower extremities.[3] Pain crises are the most frequent cause for SCD patients to seek medical attention; usually, the patients have already taken nonopioid analgesics and have experienced no or insufficient symptom relief.

HOW IS SICKLE CELL CRISIS MANAGED?

The most important cornerstone in the treatment of a sickle cell crisis is pain relief. It is recommended to administer pain medication within 30 minutes of admittance and to always use opioids, preferably intravenously.[4] Nonopioid analgesics are almost never sufficient to terminate the pain episode; thus, prompt administration of morphine, hydromorphone, or fentanyl is warranted. An ongoing, sustained pain crisis leads to a vicious circle, during which the stress triggers further sickling of erythrocytes and subsequent vaso-occlusions, thereby facilitating the pain. Apart from analgesic treatment, fluid administration is necessary to ensure viscosity of blood to prevent further sickling. Oxygen therapy is not necessary when oxygen saturation and partial pressure are in normal ranges[5]; likewise, transfusions are not necessary in pain crises when patients do not show symptoms of anemia.[6]

WHAT IS ACUTE CHEST SYNDROME?

Acute chest syndrome is a life-threating condition in patients with SCD and the leading cause for mortality. It is defined by the presence of new radiodensity on a chest x-ray, together with fever (>38.5°C), thoracic pain, and/or respiratory symptoms.[7] It is often associated with a previous pain crisis that develops into an ACS. The pathophysiology behind ACS is complex and manifold; the most common triggers of ACS are pulmonary fat embolisms from the bone marrow, which occur due to vaso-occlusive crisis in the bones with subsequent infarction of fat-containing bone marrow tissue.[8] ACS is classified from mild to very severe depending on the oxygen saturation and partial pressure as well as the extent of radiographic infiltrations. Very severe ACS implicates the presence of ARDS.[9]

HOW IS ACUTE CHEST SYNDROME MANAGED?

As with vaso-occlusive pain crisis, rapid analgesic treatment is crucial to prevent further deterioration of health. Mild episodes can be managed with transfusions; however, in severe or very severe cases, exchange transfusions, as in the case outlined in this chapter, are warranted.[10] In patients with oxygen saturation below 92%, oxygen should be administered. Similar to cases of pneumonia, a chest x-ray as well as a whole blood count and preferably also hemoglobin electrophoresis should be performed. Anti-infective treatment should also cover atypical pathogens (e.g., by fluoroquinolone or macrolides).[7] Very severe cases of ACS regularly require mechanical ventilation support, in which case the established ARDS guidelines apply.

WHAT IS THE BENEFIT OF ECMO IN SICKLE CELL DISEASE?

So far, ECMO has been rarely used for management of ACS in adults. The first report[11] is from 2011 and several case reports, including from our center, have been published since then.[12–18]

As very severe ACS is associated with ARDS, the rationale for the use of ECMO is similar to ARDS: The extracorporeal life support (ECLS) is supposed to facilitate gas exchange and to reduce the intensity of mechanical ventilation in order to allow for regeneration of respiratory tissue. In ACS, lung injury is usually initially induced by pulmonary fat embolism and infection, mostly by atypical pathogens. Hence, a thorough microbiological diagnostic workup is warranted in the management of ACS.

Given the overall lack of data from clinical studies with patients with ACS, the clear benefit of ECMO as compared to conventional ventilation is not known. However, based on the published data on severe ARDS managed by ECMO, including recent metanalyses,[19,20] the use of ECMO seems to have an overall beneficial impact in patients who deteriorate despite optimized ventilation parameters.[21,22]

WHAT ARE THE CHALLENGES OF ECMO IN PATIENTS WITH SICKLE CELL DISEASE?

Patients with SCD can experience chronic organ failure, such as chronic heart failure, chronic kidney disease, and pulmonary hypertension.[1] Thus, these coexisting conditions can make management in the intensive care unit (ICU), and particularly with ECMO, challenging. Moreover, patients with ACS show enhanced sickling of erythrocytes, which causes intravascular hemolysis. ECMO frequently causes hemolysis due to the continuous extracorporeal blood flow,[23] which can induce or potentiate vaso-occlusive crisis in patients with SCD. Also, patients with SCD have hemoglobin levels below 10 g/dL, as levels above this threshold can lead to increased viscosity in vessels. Patients with higher hemoglobin levels should be treated with phlebotomy to reduce the hemoglobin and mitigate the risk of ischemic events due to increased viscosity.[24] However, in the setting of ECMO, the low hemoglobin levels can be challenging as the efficiency of ECLS highly depends on sufficient levels of oxygen carriers in the blood. Therefore, vigilant transfusion management is particularly required in SCD patients on ECMO not only to avoid hyperviscosity but also to ensure high oxygen-binding capacity.

DISCUSSION

The first report on the use of ECMO in adult patients with SCD dates to 2011, where Hoffmann et al. reported on a 28-year-old male patient who was successfully managed with V-V ECMO over 12 days and fully recovered afterward.[11] With the broader use of and availability of ECLS, several centers have reported single cases of successful use of V-V as well as veno-arterial (V-A() ECMO in patients with SCD. Recently,

the first study of ECMO in SCD patients was reported.[13] In this retrospective, multicenter study, Boissier et al. reported on the outcome of 22 patients with SCD who required ECLS between the years 2009 and 2017, with approximately half of the patients receiving V-V and the other half V-A ECMO. In contrast to the handful of available single-case reports,[11,12,15,16,18,25] which have a considerable reporting bias as mostly positive outcomes are published, the mortality in the ICU in this study was considerably high, at 73%. There was no difference in mortality between V-V ECMO and V-A ECMO; however, variables particularly associated with higher mortality were male gender and higher vasoactive inotrope score. Median time between ACS onset and ECLS was 2 days; overall, the patients in this cohort had severe comorbidities and complications, including pulmonary artery thrombosis in five patients, acute pulmonary hypertension in five patients, and three patients with delayed hemolytic transfusion reaction, which was treated with eculizumab. The majority of patients (82%) had shock at the time of ECLS, and two patients even had cardiac arrest. Despite the young age of the patients, median Simplified Acute Physiology Score (SAPS) II score was 55 at ICU admission. Thus, the overall poor outcome of patients with ACS and ECLS in this study might be attributed to the patients' severe condition at ICU referral, which is also reflected by 55% of patients receiving V-A ECMO due to left ventricular failure.

The major challenge of managing ACS with ECMO is that complications due to the disease and due to the intervention partially overlap. Patients with SCD and pain crisis and/or ACS often show ongoing hemolysis due to the high proportion of degrading sickle cells.[26] Likewise, extracorporeal blood flow, particularly when high flow rate and speed are required, can induce further hemolysis.[23] Chronic anemia in patients with SCD can reduce the oxygen saturation capacity of the blood and thereby impair the efficiency of ECMO. Patients with SCD can develop chronic cardiomyopathy due to pulmonary congestion and are per se at risk of cardiac failure or sudden cardiac death.[27] Thus, in case of very severe ACS that requires ECLS, it is important to consider the patient's cardiac history and current status in order to evaluate V-V versus V-A ECMO. Finally, the use of anticoagulants in patients on ECMO can be a challenge in SCD patients as they often have a history of strokes already at a younger age and are therefore at risk of hemorrhagic transformations.[28] In our case, the patient had experienced multiple strokes in the past; thus, careful monitoring of coagulation parameters several times daily was warranted to keep track of hemostasis while ECMO was running.

In summary, the data on the use of ECMO in adult SCD patients is quite limited, but as the majority of reports have been published in the last 2 years, this topic is of rising interest. Due to global migration, more patients with SCD are treated in specialized ECMO centers, and thereby the clinical experience in the use of ECLS in patients with hemoglobinopathies is increasing. Use of ECLS in patients with SCD and particularly with ACS is generally feasible and often the only life-saving option in the setting of severe ARDS. Due to the challenging coexisting conditions regularly found in patients with SCD, further research is warranted to elucidate the best way to manage very severe ACS with ECLS methods.

CONCLUSION

- Extracorporeal life support is feasible in patients with SCD and ACS.
- Data on the outcome of SCD managed with ECLS are sparse, with six single-case reports reporting successful management via V-V ECMO and one multicenter study reporting ICU mortality of over 70% in 22 patients managed with V-V and V-A ECMO.
- ECMO can be a life-saving procedure for patients with very severe ACS who fail conventional optimized respiratory support.

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REVIEW QUESTIONS

1. A patient with known SCD appears in the emergency room with severe, unbearable pain in the back. He had been in the emergency room several times in the past months with recurrent pain crises. What is the first thing to do?

A. Administer oxygen
B. Administer fluids
C. Order x-ray of the spine
D. Administer opioids

2. Which of the following parameters is *not* mandatory for diagnosis of ACS?

A. Infiltrations on chest x-ray
B. Fever
C. Hemoglobin less than 10 g/dL
D. Dyspnea

3. What is the most frequent trigger of ACS?

A. Infection
B. Pulmonary fat embolism
C. Infarction
D. Trauma

4. Which hemoglobin level should be aimed for in patients with SCD?

A. Less than 10 g/dL
B. Greater than 12 g/dL
C. Less than 8 g/dL
D. Less than 6 g/dL

5. Which of the following options is not suitable for controlling hemoglobin levels in patients with SCD?

A. Phlebotomy
B. Hydroxyurea
C. Transfusions
D. Cytarabine

6. Which of the following statements is correct?

A. Patients with SCD are usually of younger age and therefore have fewer complications in the ICU.
B. Patients with SCD and mild-to-severe ACS require red blood cell exchange.
C. Patients with SCD and pain crisis should always receive blood transfusions.
D. Patients with SCD and pain crisis should receive antibiotic treatment.

7. Which of the following SCD complications overlap with possible ECMO complications?

A. Cardiomyopathy
B. Hemolysis
C. Fever
D. Pain

8. A patient with SCD and ACS has been put on V-V ECMO. While the oxygenation initially shows improvement, the patient now presents progressive left ventricular failure. What should be considered?

A. Set up dialysis to reduce cardiac afterload
B. Add dopamine
C. Switch to V-A ECMO
D. Perform coronary angiography

9. Which of the following statements is incorrect?

A. ECMO is generally feasible in patients with SCD and severe ACS
B. Acute chest syndrome can present as ARDS.
C. Antibiotic treatment is mandatory for treatment of ACS.

D. Patients with SCD should always receive V-A ECMO due to frequent SCD-associated cardiomyopathy

10. Which of the following statements is correct?

A. Anticoagulants should not be used in patients with SCD.
B. Patients with SCD must receive therapeutic anticoagulation to prevent embolism and sickling.
C. Patients with SCD on ECMO should receive close coagulation monitoring.
D. Oral anticoagulants are contraindicated in patients with SCD.

ANSWERS

1. D
2. C
3. B
4. A
5. D
6. B
7. B
8. C
9. D
10. C

39.

ECMO FOR SEVERE RESPIRATORY FAILURE SECONDARY TO HIV INFECTION

Gerasimos Capatos and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 22-year-old female was brought to the intensive care unit (ICU) after presenting to the emergency department, complaining of shortness of breath, dry cough over the last few weeks and worsening over the last couple of days, and with increasing weakness. She had lost approximately 10 kg in the last 2 months. Although she was short of breath, she was able to tell that she had been unwell for the last few weeks. She has not had night sweats, but occasionally has had a fever. Except for shortness of breath, cough, and weight loss, she had no other symptoms. She had never before taken an HIV test despite the weight loss and being sexually active. She has been faithful to a partner, but he has had many different partners. She was unsure whether he has been tested. She was not on any medication at the time of presentation, including antiviral medication. She had a nonsmoking history and did not take social drugs.

On physical examination, she was in obvious respiratory distress, with nasal flaring and use of accessory muscles to breathe. Her respiratory rate was 44 breaths per minute. She was pyrexial, with a temperature of 39.5°C. Despite her weight loss, she still had a normal body mass index. Plaques suggestive of oral candidiasis were seen in her mouth. She had shotty generalized lymphadenopathy. Her cardiac examination was marked by tachycardia, but heart sounds were normal. On pulmonary auscultation, she had scattered crackles heard diffusely, especially at the bases. The rest of the examination, including neurological examination, was normal.

On arrival in the ICU, she was placed on a noninvasive positive pressure mode of ventilation, but her respiratory rate did not decrease, and since she was developing type II respiratory failure, she required endotracheal intubation and ventilatory support. Once she was intubated, tracheal lavage was sent for culture and *Pneumocystis jirovecii* polymerase chain reaction (PCR). While she was on the ventilator, there was significant ventilator-patient dyssynchrony, and as a result of this she was struggling to ventilate adequately. She required large doses of sedation to control her breathing. Her chest x-ray showed bilateral, four-quadrant veiling with a fluffy infiltrate. The Murray score was calculated to be 4. Her oxygen saturation and PaO_2 remained low with very high peak and plateau pressures despite various modes of ventilation being used. Lung compliance was extremely poor with very small tidal volumes.

An echocardiogram showed a normal left ventricle, but her right ventricle was distended, and her pulmonary pressures were high at 40 mm Hg. Her laboratory tests showed a normal hemoglobin level; white cell count was low at 3.9×10^9; and C-reactive protein was high at 200 mg/L. The D-dimer level was normal. Lactate dehydrogenase (LDH) levels were high at 1531 U/L, and (1,3)-β-D-glucan level was also raised significantly (greater than 523 pg/mL). A presumptive diagnosis of *Pneumocystis jirovecii* pneumonia (PJP) was made. HIV is endemic in the country where this patient originated. She was also sexually active. The patient had never been tested before for HIV, and neither had her partner been tested. On testing, her CD4 lymphocyte count was 8 cells/mm^3, and her viral load was greater than 500,000 copies/mL. PCR for *P. jirovecii* was positive on the tracheal aspirate. The patient was started on trimethoprim/sulfamethoxazole, which is the standard treatment of PJP. Hydrocortisone was added as well as simultaneously starting antiretroviral therapy (ART) with tenofovir, emtracitabine, and Kaletra.

The patient remained hypoxic, refractory to mechanical ventilation, with the arterial blood gas showing persistent hypoxemia (PaO_2 of 42 mm Hg) on 100% fraction of inspired oxygen (FiO_2) with positive end-expiratory pressure of 12 cm H_2O. Therefore, the decision was made to initiate veno-venous (V-V) extracorporeal membrane oxygenation (ECMO). She was on a circuit flow of 3 L/min and a sweep gas flow of 5 L/min of oxygen (FiO_2 1). During ECMO, lung-protective ventilation was continued. The patient's breathing and other parameters settled satisfactorily. Due to the severity of her illness and slow recovery, a tracheostomy was planned and inserted on day 5 of the ICU stay. The patient was weaned off sedation and began to wake and communicate with the staff. She remained dependent on both ventilation and ECMO until day 10, when it was decided she could be on minimal ventilatory support. By day 12, she was fully weaned off ventilation and was actively mobilizing. By day 14, ECMO was weaned by decreasing oxygen flow to the oxygenator, and ECMO was removed on day 15. Not long after this, the patient was transferred to the ward where she remained for a

period of recuperation that was uneventful. She was eventually sent home after 21 days in the hospital.

WHAT ARE AIDS-DEFINING ILLNESSES?

According to the Centers for Disease Control and Prevention (CDC) definition, a person has AIDS if that person is infected with HIV and presents with one of the following:

1. CD4 T-lymphocyte cell count below 200 cells/mm^3 (or a CD4 T-lymphocyte cell percentage of total lymphocytes of less than 14% (0.14).
2. Has one of the following AIDS-defining illnesses:
   - Candidiasis of bronchi, trachea, or lungs
   - Esophageal candidiasis (but not oral)
   - Cervical cancer (invasive)
     - Cervical dysplasia or carcinoma in situ are not considered AIDS-defining illnesses because these cervical lesions are common, frequently do not progress to invasive disease, and can be difficult to diagnose.
   - Coccidioidomycosis, disseminated or extrapulmonary
   - Cryptococcosis, extrapulmonary
   - Cryptosporidiosis, chronic intestinal infection for longer than 1 month
   - Cytomegalovirus disease (other than liver, spleen, or lymph nodes)
   - Encephalopathy (HIV related)
   - Herpes simplex: chronic ulcer(s) (for more than 1 month); or bronchitis, pneumonitis, or esophagitis
   - Histoplasmosis, disseminated or extrapulmonary
   - Isosporiasis, chronic intestinal (for more than 1 month)
   - Kaposi sarcoma
   - Burkitt lymphoma, immunoblastic or primary brain (but not leukemia)
   - *Mycobacterium avium* complex
   - *Mycobacterium*, other species, disseminated or extrapulmonary
   - *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia
   - Pneumonia (recurrent)
   - Progressive multifocal leukoencephalopathy
   - *Salmonella* septicemia (recurrent)
   - Toxoplasmosis of the brain
   - Tuberculosis
   - Wasting syndrome due to HIV

WHAT WAS THE MOST LIKELY DIAGNOSIS IN THIS PATIENT?

Due to the severity of the respiratory symptoms, the most likely cause was PJP. PJP is usually seen with CD4 lymphocyte counts less than 200 cells/mm^3. Patients often present with a nonproductive cough, dyspnea on exertion and fatigue, and a low-grade fever. Hypoxemia, elevated LDH, elevated (1,3)-β-D-glucan levels, and bilateral interstitial infiltrates are also typically seen.

Pneumocystis jirovecii pneumonia is most commonly seen in newly diagnosed HIV-infected patients with advanced disease. It is also seen in HIV-infected patients who are on HAART (highly active antiretroviral therapy) but not taking PJP prophylaxis. PJP typically presents when the CD4 lymphocyte count falls below 200 cells/mm^3 and is one of the commonest opportunistic infections resulting in admission to the ICU for respiratory support.[1,2–5] The risk of the first episode of infection in patients with a CD4 lymphocyte count below 200 cells/mm^3 who are not taking PJP prophylaxis or HAART is estimated to be 18% at 12 months in asymptomatic individuals, rising to 44% in those with early symptomatic disease, such as oral candidiasis.[6] PJP prophylaxis using trimethoprim has resulted in fewer episodes of PJP more recently. At CD4 lymphocyte counts of more than 200 cells/mm^3, the risk of PJP decreases substantially enough to allow for prophylaxis to be stopped.

HOW SHOULD THIS PATIENT BE VENTILATED?

The principles of protective lung ventilation should be applied. A tidal volume of less than 6 mL/kg is essential, and if the patient is not responding and remains hypoxic, it is preferable to sedate the patient and use a muscle relaxant. Should the above not succeed in oxygenating the patient sufficiently, prone positioning should be considered.

WHY WAS ECMO INITIATED ON THIS PATIENT?

Despite giving large doses of sedation and a neuromuscular blocker, there was significant patient-ventilator dyssynchrony. The patient remained hypoxic and refractory to mechanical ventilation, and arterial blood gases showed persistent hypoxemia on FiO_2 = 1.0, with positive end-expiratory pressure of 12 cm of H_2O (PaO_2/FiO_2 ratio 42 mm Hg). Her oxygen saturation measurements and arterial oxygen levels continued to deteriorate. Various modes of ventilation were attempted with no success, but all showed small tidal volumes and very high peak and plateau pressures. The decision was made to treat the patient with V-V ECMO. V-V ECMO was subsequently initiated, with a circuit flow of 3 L/min and a sweep gas of 5 L/min of oxygen (FiO_2 = 1). During ECMO, ventilatory settings were decreased to provide lung-protective ventilation, with tidal volumes well below 6 mL/kg.

HOW IS *PNEUMOCYSTIS JIROVECII* PNEUMONIA DIAGNOSED AND MANAGED?

Conventional therapeutic strategies against PJP revolve around early identification and prompt initiation of pharmacological therapy.[7] An immunofluorescence antibody stain has improved the detection rate over traditional Gomori methenamine silver or Giemsa stains.[7,8] PCR techniques are extremely useful, but these may not indicate a disease state as *P. jirovecii* colonization is increasingly found.[7–9] (1,3)-β-D-Glucan,

expressed by *Pneumocystis* in the cell wall,[10] as well as LDH levels, are raised in an acute infection.

Treatment with co-trimoxazole (trimethoprim-sulfamethoxazole) is the usual first-line therapy in treating PJP.[7,11] Second-line therapies include Clindamycin, Primaquine, atavoquone (in mild-to-moderate cases), or in severe cases of treatment-resistant PJP, intravenous pentamidine should be used.[7,11] Rescue therapy with echinocandins have also been described. In particular, caspofungin has shown activity against *Pneumocystis* in in vitro and in vivo mouse models.[12,13] Adjuvant therapy with corticosteroids has been found to contribute to significant reductions in mortality and need for mechanical ventilation.[14–20]

WHAT IS THE PATHOPHYSIOLOGY CAUSING ACUTE RESPIRATORY DISTRESS SYNDROME IN THESE PATIENTS?

As with most pathogens causing severe lung infection and acute respiratory distress syndrome (ARDS), invasion of the epithelial lining of the lung causes the severity of this illness. Once the epithelial lining has been breached, the endothelial cells are exposed, releasing pro-inflammatory cytokines, which are then able to trigger an immune response. The physiological failure seen in ARDS is a result of the infectious response either directly or passively to the subsequent damage.[21] The damage and changes in the lung may result in severe ARDS, requiring ventilation and subsequently ECMO.

WHAT OTHER FORMS OF RESPIRATORY INFECTIONS ARE COMMONLY SEEN IN HIV PATIENTS?

Community-Acquired Pneumonia

Bacterial pneumonias are seen more frequently in HIV-positive persons at all CD4 lymphocyte counts than in HIV-negative persons. There is an obvious increased risk as the CD4 lymphocyte count falls below 200 cells/mm^3 and in intravenous drug abusers.[22] The common causes of bacterial pneumonia include *Streptococcus pneumonia*, *Haemophilus influenzae*, and *Staphylococcus aureus*.[22,23] *Pseudomonas aeruginosa pneumonia* is associated with a low CD4 lymphocyte count.[23] Cryptococcal infection caused by *Cryptococcus neoformans* presents as a primary lung infection and as part of a disseminated infection presenting with anemia, meningitis, cutaneous disease, and pneumonia.[24]

Choosing the most appropriate antibiotic and the timing of the administration of the antibiotic is vital in community-acquired pneumonia as this affects outcome. If the pneumonia causes respiratory failure unresponsive to conventional ventilation, V-V ECMO can also be used in these patients. One needs to be aware of factors like increased volume of distribution when the patient is on ECMO, which may lead to suboptimal antimicrobial therapy. There is therefore a tendency to use higher doses of antimicrobial agents in critically ill patients on ECMO. This would have to be balanced with antibiotic-related toxicity.[25–27]

Tuberculosis

Individuals positive for HIV are at increased risk of infections with *Mycobacterium tuberculosis* regardless of their CD4 lymphocyte count.[28] Extrapulmonary tuberculosis tends to occur at CD4 lymphocyte counts less than 150 cells/mm^3. *Mycobacterium avium-intracellulare* and *Mycobacterium kansasii* occur late in the course of the HIV infections, when the CD4 lymphocyte counts are less than 50–100 cells/mm^3. Multidrug-resistant tuberculosis (resistant to Isoniazid and rifampicin) and extensively drug-resistant tuberculosis (resistant to first-line tuberculosis drugs) is becoming more common among HIV-positive individuals, especially in sub-Saharan Africa. Antituberculous treatment requires careful monitoring for drug interactions and toxicity, especially in the patient that is on HAART.[1]

Healthcare-Associated Infections in HIV Patients

There are few studies that have evaluated healthcare-associated infection (HAI) in the HIV population. It is suggested that HIV-positive patients have an increased risk of acquiring an HAI because they have high hospitalization rates and longer hospital stays and that they have a high risk of acquiring infections considering their immunosuppressed status.[29–31] A study conducted in Brazil evaluated the 30-day mortality caused by HAI among patients with or without HIV infections in ICU.[32] Drug abuse was more common among the HIV patients. Respiratory conditions in this study were the most common causes for ICU admissions (42.9%), and they were more frequent in the HIV-positive patients (60.0% vs. 34.6%, *P* .035). Although the commonest disease present at ICU admission among HIV-positive individuals was PJP (36.0%) and bacterial pneumonia (16.0%), there was a high 30-day mortality rate after the first HAI episode, but there were no statistical differences between the groups (HIV 52% vs. non-HIV 53.8%, *P* .812). There was no difference in the 30-day survival after HAI between HIV and non-HIV patients. The most frequent HAI in the HIV group was ventilator-associated pneumonia (VAP), despite a similar period of mechanical ventilation. There was a predominance of gram-negative organisms as causative agents of VAP in both groups (HIV 92.9% vs. non-HIV 70.0%). In HIV patients, *Acinetobacter baumanii* and *Klebsiella pneumoniae* were the commonest isolates in this study. There was an extremely high rate of carbepenamase-resistant organisms in this study. There was a predominance of gram-positive bacteria as causative agents of CA-BSI in HIV patients (60.0%). *Enterococcus faecalis* was the most frequent organism, followed by *S. aureus*. The study concluded by saying that there was no difference in 30-day mortality between HIV-infected and noninfected patients who acquired an HAI during an ICU stay. These findings are similar to other studies, including a prospective single-center study that was conducted in a high-income country. That study in particular was aimed at evaluating mortality and the risk of acquiring HAI caused by multidrug-resistant organisms. They also did not find any difference between HIV and non-HIV patients for both outcomes.[33]

These findings reinforce the evidence of high mortality associated with HAIs, which is independent of other comorbid pathologies.

Cytomegalovirus Infections

Cytomegalovirus (CMV) is frequently isolated in bronchoalveolar (BAL) washings in HIV-positive patients. Its role in causing disease is not clear. The presence of CMV in BAL is associated with a worse prognosis regarding PJP[34] The role of CMV infection during PJP is controversial and difficult to evaluate. A more recent study showed that the culture of CMV in patients receiving adjuvant corticosteroid treatment was independently associated with a 2.74 increase risk of death.[34] Based on these findings, it was proposed that the survival rates for patients with severe PJP might be improved with anti-CMV therapy. The use of corticosteroids has also been related to subsequent development of CMV retinitis and colitis in HIV-infected patients.[35]

ONCE TREATMENT FOR PJP IS INITIATED, INCLUDING HAART, WHAT CAN LEAD TO FURTHER DETERIORATION OF THE PATIENT?

Immune Reconstitution Inflammatory Syndrome

Acute respiratory failure can result from immune reconstitution inflammatory syndrome (IRIS), a paradoxical clinical worsening after the initiation of antiviral therapy in ART-naïve patients. Patients may present with various symptoms depending on the characteristics and sites of the primary opportunistic infection. Low CD4 lymphocyte counts and high HIV RNA counts are risk factors for the development of IRIS.[36] Often it is a condition diagnosed by exclusion:

1. Worsening of the primary disease
2. New bacterial infection as a complication
3. Allergic reaction to medication

An increasing CD4 lymphocyte count is a clue to establishing the diagnosis of IRIS.

How Can Ventilator Time Be Reduced and Rehabilitation of the PJP ECMO Patient Be Improved?

In recent years the timing of ECMO initiation has been readdressed, and ECMO is often started earlier in the time course of respiratory failure. Also, some centers started to use ECMO as a first-line treatment that is an alternative to invasive mechanical ventilation in awake, nonintubated, spontaneously breathing patients with respiratory failure ("awake" ECMO).[37] The rationale for this type of respiratory support is that it avoids several side effects related to sedation, intubation, and mechanical ventilation. It must be noticed that awake ECMO is not without its challenges: The complexity of the patient-ECMO interactions, the difficulties related to respiratory monitoring, and the management of an awake patient on ECMO support together may pose a major challenge for the intensive care team.

DISCUSSION

The past decade has witnessed dramatic growth in the use of ECMO to support patients with respiratory failure, especially among adults.[38–40] ECMO use in immunodeficient patients remains challenging. Among the group of immune-deficient patients, those with HIV who progressed to respiratory failure requiring mechanical ventilation have a very poor prognosis. Until recently, it was considered a contraindication to use ECMO in patients infected with HIV who were in respiratory failure. Since substantial progress has been made in the management of HIV-infected patients, those who can be supported through an episode of severe respiratory failure may expect reasonable longevity with a good quality of life. Two major developments have contributed to the contraindication of ECMO use being revised. The first was the remarkable progress made in the field of ECMO in general, with many aspects changing over the years, essentially forming the ECMO II phase. This included how patients were treated while on ECMO, as well as equipment used for ECMO. The second reason allowing for advanced therapy to be used on HIV-positive patients was the advent and use of antiretroviral treatment.

The commonest presentation to ICU of an HIV-positive patient is acute respiratory failure due to lung infection. Patients who are HIV positive in acute respiratory failure may progress quickly to ARDS. Other syndromes seen in these patients include septic shock and cardiogenic shock. These are commonly the result of infections by opportunistic organisms in these immunosuppressed patients. Attention should be given to both these opportunistic infections and to the HIV virus when treating these patients. Similar principles as for all other ARDS patients can be applied to these patients as well as specific treatment for the opportunistic infections and the HIV virus. Therefore, lung-protective ventilation, pronation, addressing driving pressures, and mechanical power during ventilation are just as relevant in these patients as in any other patients with ARDS. Since these patients have the added insult of being immune suppressed, V-V ECMO should be considered in a timely manner when they present with ARDS that is difficult to ventilate. Attempting to use ECMO in these patients as a last resort (salvage therapy) is often unsuccessful.

Several case reports and small series reports the use of ECMO in patients with HIV and respiratory failure.[40–42] The bias toward reporting successful cases is evident in the 93% survival of the 14 patients represented by the studies. In another study, Capatos and colleagues described a standardized approach within three institutions in South Africa to the management of HIV patients with severe respiratory failure.[43] The protocol included an aggressive approach, including cannulation within a relatively short period (24 hours) of initiation

of mechanical ventilation. The results were impressive, with total survival to discharge among the 22 patients of 68% in all patients and 60% in those with PJP. When combined, these studies paint a rosy picture of the use of ECMO in HIV-positive patients. However, when reviewing the Extracorporeal Life Support Organization (ELSO) Registry to describe the practice and outcomes of the use of ECMO support in a multicenter registry to determine if a broader experience has been successful, a somewhat bleaker picture emerges.[44]

Data were collected using the ELSO Registry for all patients treated with ECMO (from 1991 to 2016), where the primary or secondary diagnosis of HIV was present. Data were limited to hospitalizations that included ECMO exposure. The decision to employ ECMO was made at each center without standardized criteria. During the study, 126 patients with a diagnosis code for HIV infection received ECMO support for a total of 128 exposures (one patient received three courses of ECMO). Of the 126 patients, 45 patients (36%) survived to discharge. Recipients of renal replacement therapy, inotropic infusions, and cardiopulmonary resuscitation had significantly higher numbers in the nonsurvivors than in the survivors group.[44]

Several differences exist between this cohort[44] and the one studied by Capatos et al.[43] The first was a three-center study of patients cared for by a single ECMO team. All patients in the series presented with respiratory failure and received V-V ECMO as part of an aggressive protocol that included early screening for PJP and noninvasive positive pressure ventilation and, when that failed, initiation of ECMO within 24 hours of tracheal intubation. Significant decreases in mechanical ventilator settings were effected within 24 hours of cannulation. Endotracheal extubation was also implemented as soon as they could awaken patients. The protocol not only standardizes the approach but also may influence the attitude toward this difficult subset of patients. This group included some patients who presented with multiorgan failure. Nonsurvivors had a longer total ECMO duration (13 days nonsurvivors vs. 7 days survivors, $P = .011$). The results were promising, with an overall survival of 68% of the patients who were HIV positive who were treated with ECMO. In the cohort of patients with concomitant PJP infection, survival was 60%.

The management of HIV patients with PJP superinfection remains a formidable challenge. PJP infection often progresses rapidly in HIV-positive patients and when severe results in substantial mortality.[45] PJP infection can result in significant lung fibrosis, which contributes, at least in part, to the substantial mortality seen in patients with severe disease. A critical component of caring for these patients is early recognition, diagnosis, and initiation of treatment. A delayed diagnosis of PJP infection has been found to be independently associated with increased mortality.[46,47] The approach of the extracorporeal life support (ECLS) team in the study by Capatos et al. consisted of the following: HIV-positive patients suspected of having PJP were aggressively screened by means of a sputum sample or tracheal aspirate (if the patient was already intubated), LDH testing, and serum (1,3)-β-D-glucan test.[48,49] Once PJP was diagnosed, appropriate antimicrobial and supportive care was immediately instituted, including ART and corticosteroids. Previously, PJP patients required prolonged periods of mechanical ventilation, which increased the odds of mortality.[50] Therefore, in this study, the team adopted a strategy of early ECMO initiation in these patients.

Once ECLS was commenced, patients were transitioned immediately to an ultraprotective ventilation strategy with minimization of airway pressures and tidal volumes. Sedation was rapidly weaned to allow the patient to be awake (but restful and comfortable). ECMO sweep flow to the oxygenator was adjusted to minimize respiratory drive, and once patients were comfortable and able to maintain a normal respiratory rate, they were switched to continuous positive airway pressure ventilation, with minimal settings on the ventilator. Extubation was typically attempted soon thereafter, and once extubated, facilitated patient interaction with family and staff could take place. In addition, extubation aided in mobilization of the patient. Nutrition was instituted early, and extubated patients were supplemented with nutritional drinks. ECMO and clinical parameters were continuously assessed to determine the optimal timing for weaning from extracorporeal support. Patients were removed from the extracorporeal support as soon as they showed signs of pulmonary improvement and were deemed safe to liberate from ECLS.

The above protocol may have been the reason why the survival rate was higher than in other studies. This study had several important limitations, including that it was retrospective in nature and subject to all selection and reporting biases inherent in retrospective studies. It was also a single-team report, and center-specific practice patterns may have been present that could render the results not generalizable to the entire ECLS community. Finally, although it was the largest series to date on ECLS use in HIV-positive patients, the results must be taken in the context of the limited sample size present.

Despite these limitations, this report provides evidence that, in HIV-positive patients presenting with respiratory failure (including those with concomitant PJP infection), a strategy of early ECLS initiation and early extubation (if possible) and mobilization can lead to promising results with minimal complication rates and survival to hospital discharge exceeding 60%.

CONCLUSION

- *Pneumocystis jirovecii* pneumonia infection often progresses rapidly in HIV-positive patients and, when severe, results in substantial mortality.
- Early aggressive ART in combination with ECMO may the increase survival of patients.
- Patients may survive ART and ECMO with a reasonable quality of life.
- Early extubation and ambulation during ECMO support can lead to promising results.

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REVIEW QUESTIONS

1. Which treatment has not improved survival in patients with PJP?

A. Fluid boluses
B. Steroids
C. Trimethoprim/sulfamethoxazole
D. Initiating ART

2. What is the diagnosis of an acute chest infection presenting in acute respiratory failure commonly seen in an HIV-positive patient?

A. *Pneumocystis jirovecii* pneumonia
B. Tuberculosis
C. *Mycobacterium avium-intracellulare*
D. Aspergillosis

3. Which answer is not part of the Murray score to determine the severity of ARDS?

A. PaO_2/FiO_2 ratio
B. Lung-protective tidal volume
C. Positive end-expiratory pressure
D. Compliance of the lung

4. Awake ECMO involves

A. Keeping the nurse awake
B. Allowing the patient to be restless and therefore having to restrain the patient
C. High breath rates are acceptable
D. Early mobilization of the patient

5. What are AIDS-defining illnesses?

A. Toxoplasmosis of the brain
B. Tuberculosis
C. Wasting syndrome
D. All of the above

6. According to the CDC definition, a person has AIDS if that person is infected with HIV and presents with the following CD4 T-lymphocyte cell count:

A. CD4 T-lymphocyte cell count below 200 cells/mm^3
B. CD4 T-lymphocyte cell count of 200–300 cells/mm^3
C. CD4 T-lymphocyte cell count of more than 300 cells/mm^3
D. None of the above CD4 T-lymphocyte cell counts

7. What is not an AIDS-defining illness?

A. Pulmonary candidiasis
B. Esophageal candidiasis
C. Cervical cancer (invasive)
D. Ovarian cancer

8. What other forms of respiratory infections are commonly seen in HIV patients?

A. Community-acquired pneumonia
B. Tuberculosis
C. Cytomegalovirus infections
D. All of the above

9. Which of the following is not a common presentation of an HIV-positive patient requiring ECMO support?

A. Acute respiratory failure due to lung infection
B. Septic shock
C. Cardiogenic shock
D. Anaphylactic shock

10. Which is the most commonly used ECMO configuration in HIV/AIDS patients?

A. V-V ECMO
B. VA ECMO
C. VAV ECMO
D. VVA ECMO

11. Which of the following is a poor predictor for survival in HIV/AIDS patients on ECMO support?

A. Renal replacement therapy
B. High inotropic/vasopressor support
C. Cardiopulmonary resuscitation during ECMO run
D. All of the above

12. Which of the following ventilation modes is considered proactive ventilation management toward early extubation and ambulation?

A. Pressure control ventilation
B. Continuous positive airway pressure ventilation
C. Airway pressure release ventilation
D. Pressure-regulated volume control ventilation

ANSWERS

1 A, 2 A, 3 B, 4 D, 5 D, 6 A, 7 D, 8 D, 9 D, 10 A, 11 D, 12 B

40.

BICAVAL DUAL-LUMEN ECMO CANNULATION FOR LUNG TRANSPLANTATION

Suresh Keshavamurthy, Vanessa M. Bazan, Thomas A. Tribble, and Joseph B. Zwischenberger

STEM CASE AND KEY QUESTIONS

A 45-year-old male presented to the emergency department with worsening shortness of breath. His history was notable for a 24-year career as a firefighter with cumulative exposure to various hazardous substances and inhalation of combustion byproducts. He first noticed a cough and mild exertional dyspnea 2–3 years prior to presentation. In December 2016, he underwent bronchoscopy and transbronchial lung biopsy that were nondiagnostic, which resulted in a pneumothorax requiring chest tube placement. After recovery, he continued with mild exertional dyspnea and mild dry cough until September 2018. He then underwent surgical right lung biopsy, which was reported as showing desquamative interstitial pneumonia (DIP) with a fibrosing component. Interestingly, the biopsy caused an air leak that produced adhesions, eventually complicating lung transplant surgery. His DIP was treated with high-dose prednisone, which was slowly tapered to a low dose.

His exertional dyspnea worsened, and his prednisone dose was increased to 60 mg; mycophenolate mofetil (CellCept) and oxygen were added. Despite treatment, his dyspnea continued to worsen, and his oxygen requirement increased. After 1 month, he was barely able to do his activities of daily living, was on oxygen at 4 L/min, and was very dyspneic with any walking.

While admitted for transplant evaluation but awaiting transplant listing, the patient continued to deteriorate (Figure 40.1). He was placed on high-flow nasal cannula with a plan to initiate veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) if acute decompensation developed. Listed on day 2, on day 6 he developed worsening dyspnea, hypoxemia, and hypercapnia requiring initiation of V-V ECMO as a bridge to transplant (BTT). The patient was intubated, then stabilized to allow use of the Avalon dual-lumen cannula (DLC). He was placed in the supine position, and his neck was extended and gently turned to the left to provide access to the right neck. The groins were prepped for the option of femoral vessel access. A large drape provided access to the neck and both groins. Ultrasound imaged the right internal jugular (IJ) for puncture and insertion of a guide wire. The Seldinger technique was used to serially dilate the tract to allow insertion of a 27 French (27F) Avalon Elite™ dual-lumen (Maquet Getinge) catheter into the right IJ vein (IJV). The Avalon catheter was positioned with direct radiographic visualization using fluoroscopy at the bedside, initially passing the tip well below the diaphragm. The cannula outflow port (imaged as a defect in the wire reinforcement) was repositioned opposite the tricuspid valve. Following placement confirmation, the cannula outflow and inflow ports were connected to a Getinge Cardiohelp (HLS [heart-lung support] system set advanced 7.0) circuit, then ECMO flow was initiated.

Transesophageal echocardiography (TEE) confirmed placement and positioning by visualizing the Doppler jet across the tricuspid valve. The key to proper placement is a combination of fluoroscopy and echocardiography along with predicted blood flow relative to the cannula size, good drainage/reinfusion saturation difference, improved systemic saturation, and CO_2 removal plus clinical improvement. Three blood gases were obtained about 30 minutes after initiation of ECMO flow: from precircuit (drainage), postcircuit (reinfusion), and from the patient's arterial line (reflecting peripheral oxygenation). Figure 40.2 shows a chest x-ray of the patient after cannulation. Changes in cannula position or flow are based on the blood gas findings. For example, sweep gas flow is adjusted to remove CO_2 as determined necessary. Lung-protective ventilation is instituted as soon as dual-lumen V-V [(dl)V-V] support is confirmed. Use of either inhaled epoprostenol (iEPO) or inhaled nitric oxide (iNO) have been shown to reduce pulmonary artery pressures and decrease the risk of developing right ventricular dysfunction.[1–8]

At our institution, iEPO replaced iNO as the preferred agent since it is economical while being equally effective. A switch to iEPO eliminates the risk of methemoglobinemia, requires fewer monitoring parameters, and is cheaper and easier to administer than iNO.[7,9] Based on published cost estimates, the median cost of iEPO per patient was calculated as $363.53 ($226.00–$864.60) versus $2562.50 ($1875–$8625) for iNO ($P < .01$). The difference is approximately $118,500 in cost savings by switching to iEPO in a singular patient population over a 1-year time period.[10] Tachycardia is treated with β-blockade to decrease native cardiac output and thereby decrease shunting.

Initial pump flow was 4.0 L/min (2.0 cardiac index) with a sweep rate of 1.0 L/min. ECMO initiation restored normal arterial blood gas values within 2 hours. He was anticoagulated with 50 U/kg of unfractionated heparin (UFH) just

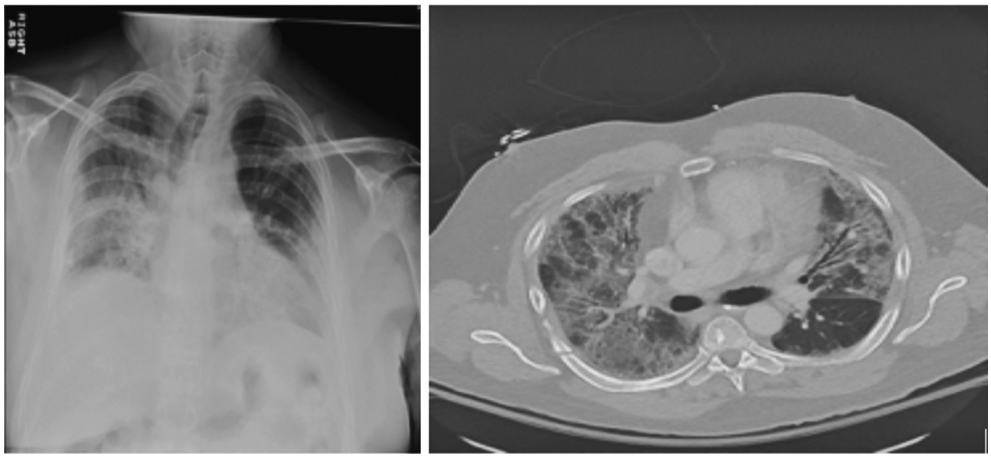


Figure 40.1 Pre-ECMO imaging. Chest x-ray (left) and computed tomography (CT) (right) show bilateral interstitial changes.

prior to cannulation, with an activated clotting time goal of more than 200 seconds. After cannulation, the patient was placed on a continuous UFH drip to maintain an anti–factor Xa level between 0.25 and 0.5 seconds with activated partial thromboplastin (aPTT) goal of 60–95 seconds. Our strategy is to extubate and maintain on high-flow nasal cannula in this subset of patients.

The patient remained stable on extracorporeal life support (ECLS) while listed with a Lung Allocation Score of 90.5. Daily physical therapy was conducted with the patient, allowing for strength and endurance exercising to maintain functional viability prior to transplant. We started with edge-of-the-bed activities, including balance, stepping, sit to stand, weight transfer, then standing activity before eventually transitioning to ambulation (Figure 40.3). On day 11 of ECLS therapy, donor lungs became available, and the patient underwent bilateral lung transplantation. The preexisting (dl)V-V ECMO was converted to a cardiopulmonary bypass (CPB) circuit for ease of the procedure during the transplant, affording excellent bicaval venous drainage. The venous limb of the CPB circuit was connected to both limbs of the (dl) V-V ECMO using a Y connector; the ascending aorta was cannulated centrally via the clamshell thoracosternotomy for the arterial inflow; the ECMO was continued postprocedure, and he was weaned off ECLS support on day 3. He had a prolonged convalescence, with need for a tracheostomy, nutrition repletion, physical therapy, temporary dialysis, and extracorporeal photopheresis for rejection. He was discharged home after months of recovery.

WHEN IS ECMO CONSIDERED?

The only effective long-term therapy in pharmacologically refractory interstitial lung disease (ILD) is lung transplantation.

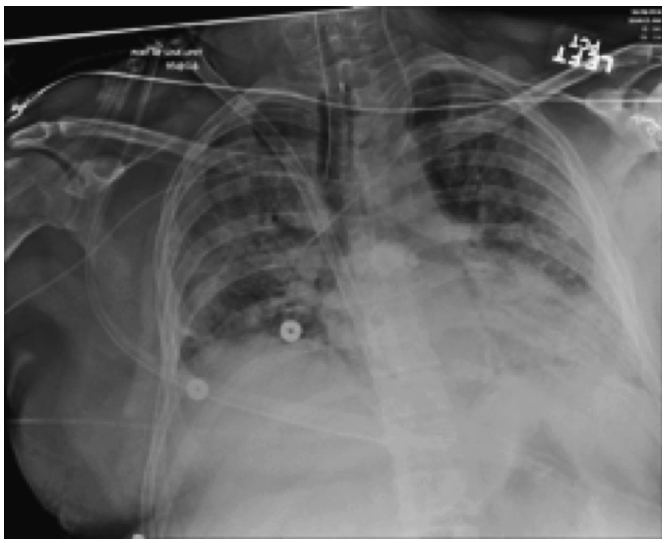


Figure 40.2 Chest x-ray demonstrating placement of the Avalon DLC in the preferred location.



Figure 40.3 Ambulatory ECMO with the Avalon DLC.

Acute respiratory failure in refractory ILD is challenging because donor lungs are prioritized to patients who are already on a transplant waiting list. In patients not yet listed, prognosis following intensive care unit (ICU) admission is usually very poor. Lung transplantation is an accepted form of treatment for patients with ILD that is progressive, refractory to other therapies, and progressing to respiratory failure. The clinical challenge lies in predicting the rate of pulmonary function deterioration or onset of acute respiratory failure. Likewise, many patients have overlapping components of lung disease, such as this patient, who had DIP with a fibrosing component. The number of lung transplants performed for patients with idiopathic pulmonary fibrosis (IPF) surpassed that for chronic obstructive pulmonary disease in 2007, when IPF became the leading indication for lung transplants performed in the United States. Lung transplantation is the only form of therapy that may improve quality of life and survival for patients with IPF, and 5-year survival following lung transplantation for IPF or other forms of pulmonary fibrosis is approximately 50%.[11–14]

The first use of ECLS as a bridge to lung transplant was reported in 1978. The patient was successfully bridged to lung transplantation but died 18 days later as a result of bronchial dehiscence.[15] Until the last 10 years, bridging with ECLS was considered a contraindication to lung transplant due to potential complications of a prolonged ECMO course, including hemolysis, bleeding complications, stroke, infection, and renal insufficiency.[16] Technical advances, management improvements, and the availability of different devices (customizable to each patient's needs) resulting in improved outcomes have resulted in a resurgence of ECLS bridging for lung transplantation. Since 2005, the use of ECMO as a BTT has increased 271%, from just 1% of all lung transplant patients in 2005 to 5% in recent years ($P < .001$).[17] This increase in use has been driven by encouraging data of ECLS application in acute respiratory distress syndrome, including publication of the CESAR (Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial, successful use in the H1N1 pandemic in 2009, and the recent EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial.[18–21] ECLS can successfully bridge acutely decompensated patients awaiting listing or listed patients awaiting donor lung availability.

WHAT ARE THE OPTIONS FOR CANNULATION IN THIS PATIENT?

Veno-venous ECMO with either two cannulae (IJ-Fem [femoral] or Fem-Fem) dual-site access or dual-lumen, single cannula (IJ), single-site access are the best options for acute respiratory failure. If no planning to initiate ECMO had been in place, emergent percutaneous cannulation at the bedside via the IJV and femoral vein or femoral-femoral veins may have been required. However, because the patient was stable enough for nonemergent cannulation, we were able to use our preferred cannulation strategy involving a single DLC via the right IJ under fluoroscopic guidance.[22] The catheter traverses the superior vena cava (SVC), right atrium (RA), and with the tip placed in the inferior vena cava (IVC). Venous drainage ports positioned in the SVC and IVC draw blood to supply the oxygenator. After gas exchange, the blood is returned to the infusion lumen of the catheter, terminating at a port directed toward the tricuspid valve, which delivers a jet of arterialized blood to the right heart.

WHAT IS THE BENEFIT OF USING A DUAL-LUMEN CANNULA IN THIS PATIENT?

The DLC achieves adequate flow for full (dl)V-V ECMO support with single-site cannulation of the IJV. Advantages of single-site cannulation include ease of participation in physical therapy, increased ambulation potential, and improved patient comfort, especially after extubation. Groin access is avoided, allowing less chance of line contamination and increased opportunity for exercise and ambulation. (dl)V-V ECMO can achieve total gas exchange both pretransplantation for native lung deterioration and posttransplant for early graft failure.[22] Early mobility reduces the length of ICU/hospital stay and improves functional outcomes at discharge.[23] Sedation cessation also encourages physical therapy, early mobilization, and rehabilitation, demonstrated to benefit ECLS patients awaiting lung transplantation.[24–26] Our institution uses an algorithm to guide patient ambulation decisions (Figure 40.4).

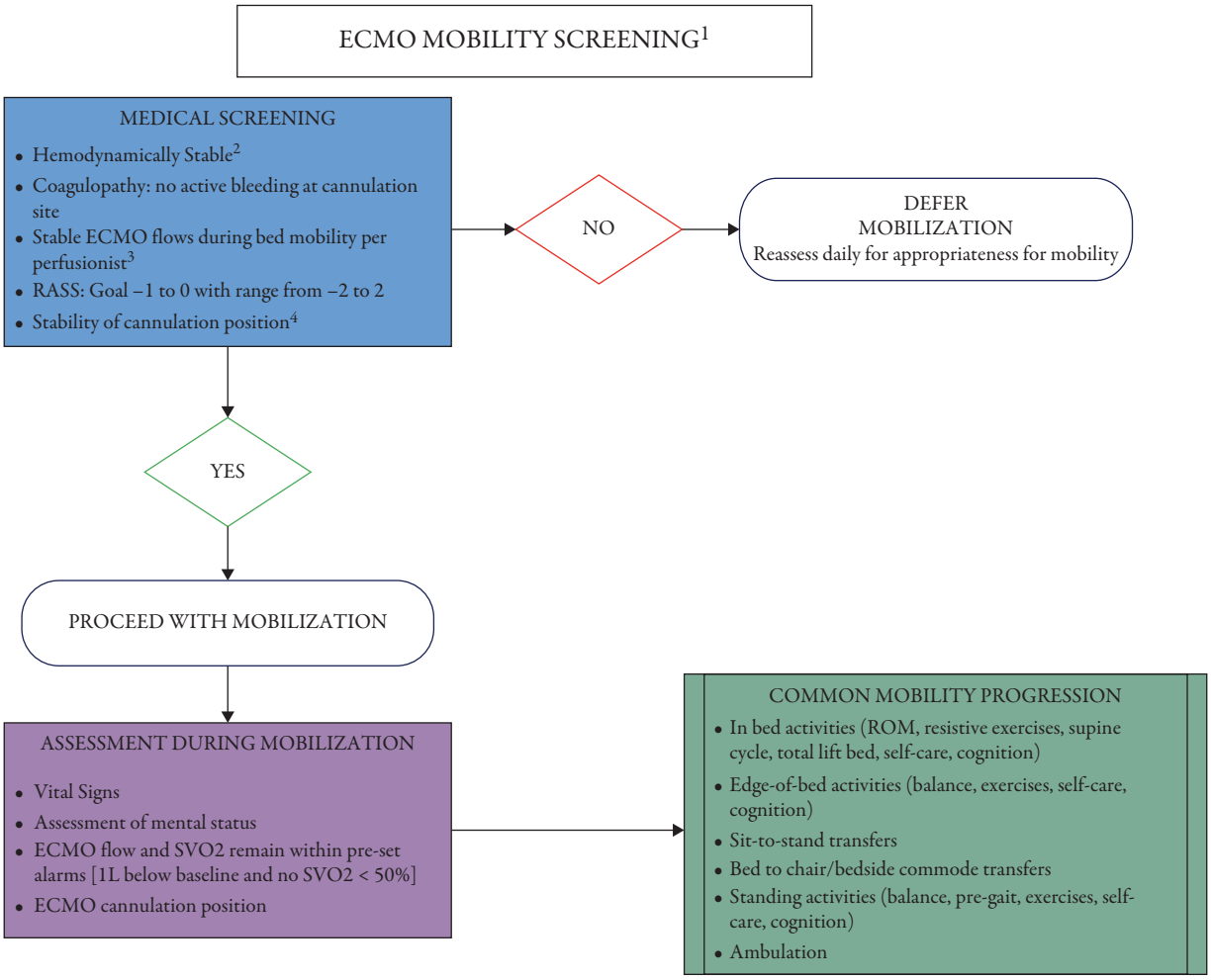
The downside of (dl)V-V is the need for image-guided insertion and the risk of displacement or perforation if improperly inserted.[27] In cases of worsening cardiac dysfunction, hemodynamic support is achieved with the addition of an infusion cannula to the subclavian artery, converting the V-V ECMO circuit to a veno-arterial-venous (V-AV) circuit.[28]

WHAT ARE THE MAIN FEATURES OF DUAL-LUMEN V-V ECMO CANNULAE?

Features of (dl)V-V ECMO cannulae include percutaneous access utilizing the IJV, a dual-lumen design with bicaval venous drainage from the SVC and IVC, and low-resistance return by the reinfusion lumen inside the drainage lumen. When appropriately positioned, the return flow directs oxygenated blood through the tricuspid valve into the pulmonary artery to avoid mixing desaturated venous return from the oxygenated reinfused blood, thereby improving systemic oxygen saturation. This design was introduced as the Avalon Elite DLC in 2009 and was quickly incorporated into the practice of adult ECMO. Competitive cannulae are now available. Table 40.1 compares the commercially available bicaval DLCs.

WHAT SIZE OF DUAL-LUMEN CANNULA DO WE CHOOSE?

Cannula size is based on patient needs determined by body habitus, cardiac index (cardiac output divided by body surface area), and required blood flow for gas exchange. DLC sizes range from 13F to 31F catheters, with the smallest 13F cannulae used in neonates larger than 2.5 kg. Adult sizes range from 20F to 31F catheters, with smaller 13F–19F cannulae sizes also available for small adults or children. The most common



1. Adapted from: Wells CL, Forrester J. Vogel J. Rector R. Tabatabai A. Herr D. Safety and feasibility of early physical therapy for patients on extracorporeal membrane oxygenator: University of Maryland Medical Center experience. *Crit Care Med.* 2018;46(1):53–59.

2. No resting HR equal to age predicted MAX HR, no third-degree heart block, no sustained VT, no A-Fib with RVR with unstable pressure, and no significant changes within past two hours, or as determined by medical team and physician order.

3. No drop in flow > 1L with flexion of hip to 90 degrees for 10 seconds.

4. Cannula sutures must be intact and line should be secured with external device (i.e., Foley strap, abdominal binder).

Figure 40.4 ECMO mobility screening algorithm. A-Fib, atrial fibrillation; HR, heart rate; MAX HR, maximum heart rate; ROM, range of motion; VT, tidal volume.

Table 40.1 **COMPARISON OF AVAILABLE BICAVAL DLCS**

CANNULA	SIZE (FRENCH)	LENGTH (CM)	CONNECTOR SIZE (INCH)	INSERTION	FEATURES
Avalon Elite (Maquet)	13–31	11 (13F) 14 (16F) 21 (19F) 31 (20F–31F)	1/4 (13F–19F) 3/8 (20F–31F)	IJV, bicaval, tip in IVC	Pediatric, adult
OriGen (OriGen)	13–32	8.3 (13F) 9.7 (16F) 13.7 (19F) 18.7 (23F) 23.1 (28F) 25.1 (32F)	1/4 (13F–19F) 3/8 (23F–32F)	IJV, tip in atrium	Neonate (13F, 16F atrial), pediatric, adult 15F polyurethane nonreinforced
Crescent (Medtronic)	24–32	30 (24F, 26F) 34 (28F, 30F, 32F)	3/8	IJV, bicaval, tip in IVC	Radiopaque markers FDA approval for V-V ECMO

bicaval DLC sizes used in adult patients are 27F–31F cannulae with larger cannulae capable of maintaining higher flow rates but associated with increased complications and bleeding at the cannulation site.[29] The Crescent 30F cannula supports up to 7 L/min of flow, and the Avalon 27F cannula supports up to 5 L/min of flow. The smaller 19F Avalon cannula supports up to 2.5 L/min of flow. The unicaval NovaPort twin DLC used for extracorporeal carbon dioxide removal is optimized for lower flows with the 22F cannula supporting up to 1.5 L/min and the 18F cannula supporting up to 1.0 L/min of flow. Lower flow rates readily accomplish CO_2 removal, but most surgeons prefer full gas exchange support when bridging patients to lung transplantation.

DO WE NEED TO INTUBATE?

Yes, there is a need to intubate. We prefer intubating the patient first to secure the airway, then cannulating for ECMO should the patient decompensate during the procedure. Second, intubation allows for a bailout strategy of using conventional Fem-IJ or Fem-Fem access should technical difficulties arise, a patient becomes profoundly hypoxic, and/or a patient develops hemodynamic compromise.

SHOULD YOU USE A FLOPPY OR STIFF WIRE DURING THE INSERTION?

Bicaval cannulation requires placement of a guide wire from the SVC across the RA and into the IVC. Perforation and tamponade occur (up to 3%–15% reported, but far less in our experience) when the guide wire is misplaced across the tricuspid valve into the right ventricle.[30,31] A floppy guide wire can loop inside the right heart chamber and cause arrhythmias or perforation secondary to cannula insertion, but a stiff guide wire can directly perforate the heart wall. To minimize risk of perforation and tamponade and ease of insertion, we start with a floppy wire and then exchange it for the stiff wire (see discussion of tricks of the trade below). User inexperience and unfamiliarity with bedside fluoroscopy and TEE have been reported as a cause of complications during DLC insertion. Fluoroscopy and transthoracic echocardiography (TTE) at bedside or TEE in the operating room should visualize the guide wire traverse the SVC, RA, and IVC and confirm placement beyond the level of the renal veins prior to cannulation.[32] Visualization of the guide wire in the SVC and IVC does not exclude looping within the RA/right ventricle.[33] A single-center chart review of 72 patients cannulated with the Avalon Elite DLC reported two cases of cardiac perforation during insertion despite use of fluoroscopic guidance.[30]

HOW IS THE CANNULA SECURED?

The distal tip of a bicaval DLC is inserted into the IVC distal to the RA and close to the hepatic vessels, with risk of injury by cannula migration.[33] We recommend the use of a purse-string suture at the insertion site with 2-0 silk. We then use number 1 ETHIBOND® to secure the DLC to the skin at multiple sites. Specifically, the suture is placed through the skin and a knot made with a couple of snug, but not tight, throws such that the skin is not cinched; this suture is then used to go around the cannula with a secure knot. Do not kink the cannula! Close to the hub there is a groove for the suture; however, we prefer to anchor at multiple places to avoid migration and dislodgement, especially for ambulation. This is repeated every 3–5 cm for both cannula limbs. To allow for patient comfort and stabilization of the ECMO lines, a 30-inch Hold-n-Place® Foley Leg Band should be placed across the patient's forehead and lines secured by the green Velcro strap.[34] Cannula migration has been reported in 6%–10% of pediatric and adult cases of (dl)V-V ECMO.[35,36] The 13F cannula (neonate) only has a distance of 2.5 cm from the IVC port to the RA infusion port and can dislodge into the right heart when the patient moves.[31] We prefer the largest cannula possible (bigger than a 13F cannula) or place the inferior tip of a 13F cannula 1 cm lower in the IVC. A single-center chart review of 25 pediatric Avalon Elite (dl)V-V ECMO patients demonstrated use of fluoroscopy during insertion decreased the need for cannula repositioning ($n = 3/14$, 21%, vs. $n = 7/11$, 64%; $P = .05$) when compared to using echocardiography alone.[37]

Transport of (dl)V-V ECMO patients between hospitals potentially adds additional risk. The largest series ($n = 170$) of patients transported on mobile ECMO (2010–2014) compared adult ECMO patients cannulated at a referral center and transported ($n = 46$) to those cannulated on site ($n = 126$). All patients were placed on V-V ECMO under fluoroscopic guidance. The authors reported no deaths on transport, no cannula misplacement, and no significant difference in complication rate (bleeding, arrhythmia, tamponade, pneumothorax), or survival (to discharge or after 6 months) compared to on-site cannulation. This high-volume center experience demonstrated the safety of transport while on DLC cannulated V-V ECMO when the mobile ECMO team is experienced with fluoroscopy at the bedside. The study further demonstrated that mobile ECMO is resource and expertise intense when utilizing a team of surgeons, intensivists, and dedicated ECMO specialists.[38]

WHAT IS THE CORRECT CANNULA POSITION ONCE SECURED?

The cannula tip at the 12th rib (T12-L1 junction) usually best aligns the flow from the return port toward the tricuspid valve. Either TTE or TEE can confirm location during or immediately after fluoroscopy guidance. We use both fluoroscopy and TEE if the insertion is done electively in the operating room. The return limb of the (dl)V-V orients anteriorly by design to direct the reinfused blood toward the tricuspid valve. Once initially correct and secured, cannula position is followed with chest x-rays and kidney, ureter, and bladder x-ray. TTE is used if the cannula position changes or is questioned.

WHAT COMPLICATIONS SHOULD I LOOK FOR DURING ECMO WITH A DLC?

Possible complications of DLC insertion include tachyarrhythmias from guide-wire migration into the right ventricle,

guide-wire coiling when using a floppy wire, and perforation while using a stiff wire. Right ventricle perforation with the guide wire and tamponade is a potentially lethal complication if undetected. After insertion, suboptimal cannula placement or inadequate fixation leads to recirculation with worsening hypoxia. Some recommend confirmation of position by x-rays on a daily basis. Others use the blood saturation difference. We assume good location if there is a wide A-V difference and adequate respiratory support.

Intracranial hemorrhage is a dreaded complication of all modalities of ECMO. Insertion of a large-bore cannula into the IJ can possibly increase cerebral venous pressure, promoting hemorrhage. A review of the Extracorporeal Life Support Organization (ELSO) Registry (2011–2016) comparing propensity-matched V-V ECMO patients cannulated with the Avalon Elite 27 F (n = 372) or 31 F (n = 372) cannula found the rate of intracranial hemorrhage was three times higher in those cannulated with the larger catheter (n = 16, 4.3%, vs. n = 6, 1.6%; P = .03). These results suggest the use of the smallest cannula able to achieve adequate ECMO flow to minimize risk of intracranial hemorrhage.[29]

HOW IS ANTICOAGULATION MANAGED?

A bolus dose of heparin is given prior to cannulation. After the first 24 hours of systemic anticoagulation, we have shifted to a protocol of using bivalirudin with the goal of maintaining a 45- to 75-second aPTT. Some centers question the need for anticoagulation with ECMO, reporting no increase in mortality, pump failure, or thrombotic complications in ECMO support without systemic anticoagulation.[39] We individualize anticoagulation based on our center's protocol, in conjunction with the ICU team and pharmacist judgment.

DOES THE USE OF DUAL-LUMEN ECMO AS A BRIDGING STRATEGY HAVE INTRAOPERATIVE IMPLICATIONS?

Dual-lumen V-V ECMO is used during lung transplantation for total gas exchange before, during, and after transplantation. If CPB or V-A ECMO is needed for additional cardiac support during the transplant, the DLC is used for venous drainage and an arterial reinfusion cannula is added.[40]

DOES THE USE OF DUAL-LUMEN ECMO AS A BRIDGING STRATEGY HAVE POSTOPERATIVE IMPLICATIONS?

Yes, the use of (dl)V-V ECMO enables early extubation and physical therapy while gradually weaning to lung dependency as lung compliance improves.

WHAT ARE THE "TRICKS OF THE TRADE" FOR CANNULATION WITH AN AVALON CANNULA?

For an Avalon cannula, "tricks of the trade" are as follows: Before insertion, prep and drape both the neck and groins. This prepares the patient for emergent femoral cannulation in case of insertion complications. Ultrasound guidance directs puncture of the right IJ and confirms needle positioning. A floppy guide wire is passed into the IVC and beyond, then using a Seldinger technique, serial dilations are performed under fluoroscopic and/or TTE insertion guidance to allow cannula insertion.

Inadequate dilation can lead to a kink in the guide wire and stall insertion or redirect the cannula. In order to decrease resistance at the skin and fascia, we sometimes use a Ciaglia Blue Rhino®-Cook Medical tracheal dilator from the percutaneous tracheostomy kit. At any point if resistance is felt, we recommend backing out the dilator and repeating the process with the smaller dilator before proceeding with larger sizes. To avoid displacement or perforation during final catheter insertion, visualize the guide wire low in the IVC beyond the renal veins or even into the iliac using image guidance. A 5F Glidecath (100 cm, Terumo Medical, Somerset, NJ) can be a useful tool to help change wires from a floppy to an Amplatzer Super Stiff guide wire (0.038 inch; 210 cm) and serial dilators (10F to 30F dilator). The introducer is removed, then serial dilation of the subcutaneous tract and IJV is performed to ensure smooth passage along the guide wire. Once the subcutaneous tissue and IJV are dilated to the appropriate caliber, the Avalon Elite cannula is introduced over the superstiff guide wire and advanced into position. Fluoroscopic navigation is still necessary as the cannula advances into position. The recognizable silhouette of a pulmonary artery catheter as it traverses the tricuspid valve may aid proper alignment of the cannula reinfusion port with the tricuspid valve. After connection with the ECMO circuit, directional inflow across the tricuspid valve may be assessed by TEE.

We recommend maintaining the hematocrit close to 30% and hemoglobin near 10 g/dL. Ideally, crossmatched blood (preferably irradiated and cytomegalovirus negative) is made available prior to ECMO initiation to anticipate compensating for hemodilution from the circuit-priming volume. Note that hemodilution is exaggerated when a tubing extension is added to the circuit to aid mobility and trips to the scanner or cath lab.

DISCUSSION

Veno-arterial ECMO first gained traction in the early 1980s as a form of temporary neonatal respiratory support. The DLC was developed as an artery-sparing alternative to V-A ECMO for newborns with respiratory distress syndrome. The underlying pathology of respiratory distress syndrome (decreased lung compliance, pulmonary edema, and atelectasis) can be resolved by supporting gas exchange with V-V ECMO. Unfortunately, in patients less than 10 kg only the IJV and carotid artery can reliably accommodate an ECMO cannula of sufficient size to accomplish enough flow for total gas exchange.[41] The neonatal DLC eliminated the need for two-site access by using one catheter with two lumens (one for drainage and the other for reinfusion), thus exploiting the large size and flow capacity of the IJV. The original design provided a 2:1 ratio between the

drainage portion cross-sectional area and the reinfusion portion to allow adequate venous drainage by gravity fluid relative to positive pressure reinfusion.[42]

In 1989, the first clinical experience with a 14F neonatal DLC was reported. Seventeen of 21 neonates with respiratory failure were successfully cannulated with a DLC placed in the RA via the IJV. One patient was immediately converted to V-A ECMO for hypotension with asystole and another was converted after 24 hours for insufficient gas exchange with maximum flow. The remaining 15 were supported with 100–150 mL/kg/min of (dl)V-V flow and successfully decannulated.[43] Initial success was amplified in a 27-center retrospective study comparing neonatal respiratory failure managed with V-A or (dl)V-V ECMO. Anderson et al. reported 87% survival for 135 V-A ECMO cases and 95% survival for 108 (dl)V-V ECMO cases, fueling expansion of (dl)V-V ECMO.[44] Widespread availability of the DLC and establishment of the ELSO database in 1989 led to larger propensity-matched studies and database reviews confirming the utility of (dl)V-V ECMO for neonatal respiratory failure.[45–48]

The initial commercial DLC (Kendall Healthcare Products Co., Mansfield, MA) was inserted through the IJV into the RA (unicaval) and included a series of drainage ports facing the SVC/RA junction opposite reinfusion ports directed distally into the RA but roughly toward the tricuspid valve. Unicaval DLCs available today include the OriGen DLC (Origen Biomedical, Austin, TX) and Novaport Twin (Xenios, Heilbronn, Germany). Several published reviews showed recirculation is flow dependent, with higher flows directly proportional to recirculation ranging from 20% to 40%.

A new generation of single-site access DLC with bicaval venous drainage from the SVC and IVC repositioned the drainage ports into the SVC and IVC, significantly reducing recirculation to as low as 2%.[49] This design was marketed as the Avalon Elite DLC in Europe in 2008 and was quickly incorporated into the practice of adult ECMO. The cannula release coincided with the H1N1 worldwide outbreak and the CESAR trial, which stimulated use of single venous bicaval access for total gas exchange in ARDS, including previously healthy young adults.[19,20] The bicaval DLC became available in the United States in 2009.[50,51] Shortly after introduction, these more efficient DLCs exploded in use, comprising 71% of all pediatric ECMO cannulae used in 2011.[52] In 2018, the Crescent bicaval DLC (MC3, Dexter, MI), named for the crescent moon–shaped division made by the reinfusion lumen inside the drainage lumen, was introduced with FDA clearance for prolonged use with V-V ECMO.

Lung transplantation is a viable treatment option for patients with end-stage lung disease. For patients who present with a rapid decline in respiratory status, they must stabilize before transplantation status can be established. These patients have a high rate of in-hospital mortality, and their candidacy for lung transplantation must be urgently assessed.[53–55] Unfortunately, donor lungs are scarce, so bridging strategies may be necessary for survival and thoughtful assessment for lung transplantation. The indication for ECMO is determined by the patient's candidacy for lung transplantation. If the patient is clearly not a candidate and has an irreversible process, then ECMO should be avoided. If the patient is already on the wait list and irreversible end-organ damage or other conditions that would preclude him or her from remaining on the list have not developed, then ECMO is certainly an option.[56] The more challenging scenarios involve those patients who are somewhere in between, such as a patient who is not yet cleared for transplantation, or if it is unclear whether a patient's critical illness is reversible. In such cases, ECMO can be used as a bridge to decision.

A report on the US trends in bridging outcomes by Hayanga and colleagues showed that in 2000–2002, the 1-year survival rate after ECMO bridging was 25%, which was increased to 74% in 2009–2011.[57] In 2012, a study by Lang and colleagues conducted in Vienna, Austria, showed a 90% success rate in bridging patients to transplant, but a 24% rate of in-hospital mortality after transplant; the median bridging time was 5.5 days (range 1–63 days). Patients who were bridged and survived the initial 3-month period after transplant had a 5-year survival rate that was equivalent to that of patients who were not bridged (63% vs. 72%, $P = .33$). This again emphasizes the importance of selecting patients who are most likely to tolerate perioperative ECMO.[58] Biscotti and colleagues reported their 9-year experience at New York-Presbyterian/Columbia University Medical Center with a 55% success rate for bridging with ECMO to transplant.[59]

Beginning in 2005, the University of Pittsburgh Medical Center began using ECMO as a BTT for patients before lung transplantation. Over a 6-year period, they used ECMO as a bridge in 31 patients, with 25 ultimately surviving to transplantation. Of the patients successfully bridged, they demonstrated a 74% 2-year survival compared with 74% for unsupported patients. The rate of primary graft dysfunction (PGD) requiring posttransplant ECMO was higher in the BTT group, but based on graft survival, they demonstrated efficacy using ECMO as a BTT.[60]

The University of Kentucky and University of California San Francisco also have used ECMO as a BTT for lung transplantation, and they had successfully bridged 31 patients as of 2013. They have achieved similar success, demonstrating 80% 3-year survival in patients bridged with ECMO, which compares favorably with a registry of similarly ill transplant patients. Of the 31 patients who they successfully bridged, 19 were ambulatory at the time of transplantation, which demonstrates one of the benefits of bridging extremely debilitated patients using ECMO.[61]

Earlier introduction of ECMO, before irreversible debilitation and persistent frailty, will likely improve the success and costs of bridging patients. Despite the challenges of ECMO BTT, this experience will likely provide the prerequisite step in the development of more long-term and durable support systems for patients requiring lung transplantation in the same way as the early left ventricular assist device experience did for bridging to heart transplantation and destination therapy. A long-term paracorporeal lung assist device and ultimately an artificial lung could potentially provide support for months to years in patients with end-stage lung disease.[62] ECMO

management strategies that are utilized for this patient group, such as elective ECMO initiation before acute deterioration requiring resuscitation, early extubation, and ambulation, can maximize pretransplant stabilization and contribute to successful BTT and recovery.

Improved outcomes have contributed to the explosion in the use of adult ECMO over the last decade. Increased knowledge and availability of ECMO have improved the likelihood of a positive outcome for refractory conditions, as in the case of end-stage ILD patients. However, careful patient selection is required in order to successfully bridge a patient to transplant and minimize the occurrence of fatal or debilitating complications.

DISCUSSION

- The use of ECMO as a bridge to lung transplantation has become evident as an effective modality for patients not responsive to conventional treatment.
- Technological advances in circuit components, improved cannulation techniques, and the development of the DLC have improved outcomes in patients needing ECMO before, during, or after lung transplantation.
- The main advantages of single-site cannulation using a bicaval DLC are decreased recirculation, decreased potential for infection, and facilitation of early patient mobilization.
- Appropriate patient selection and awareness of common complications are critical for patient success. In order to minimize risks and maximize benefits, protocols for rapid response should be established, and an interdisciplinary team should evaluate individual cases before initiating ECMO.

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REVIEW QUESTIONS

1. What is a reasonable option for patients with end-stage lung disease presenting with hypoxemic respiratory failure?

   A. Intubation
   B. 100% oxygen therapy with high flow
   C. Inhaled NO or prostaglandin I or I2
   D. ECMO
   E. All of the above

2. What is the preferred route of insertion of the double-lumen ECMO cannula?

   A. Right IJV
   B. Right subclavian

C. Left femoral
D. Left subclavian
E. Left IJV

3. Advantages of (dL)V-V ECMO include

A. Preoperative BTT
B. Intraoperative support and postoperative respiratory support
C. Ambulation
D. Participate in physiotherapy
E. All of the above

4. True or false: The (dl)V-V ECMO catheter comes in one standard size only.

5. Which answer is false regarding placement of the Avalon ECMO catheter?

A. X-ray guidance
B. Fluoroscopic guidance
C. Echocardiographic guidance
D. Easily inserted emergently without need for imaging

ANSWERS

1. E
2. A
3. E
4. False
5. D

41.

WEANING AND LIBERATION FROM V-V ECMO

Antonio Rubino, Giulia Villa, and Fabio Sangalli

STEM CASE AND KEY QUESTIONS

A 37-year-old male patient presented to our hospital with a history of a few days of upper respiratory tract symptoms. Soon after his admission to the emergency department, he was transferred to the intensive care unit (ICU). He was intubated the following day for type 2 respiratory failure and ventilated with high peak pressures.

The initial computed tomographic scan showed a dense, predominantly right-sided, pulmonary consolidation, and despite transient improvement with proning and paralysis, the patient subsequently developed a right pneumothorax, requiring surgical drainage, and a progressive worsening hypoxemia requiring increase in the fraction of inspired oxygen (FiO_2) to 1.0.

Within 3 days, he developed a worsening chest x-ray (CXR) appearance with bilateral infiltrates and inability to optimize his positive end-expiratory pressure (PEEP) due to an ongoing air leak from his chest drain and dropping tidal volumes.

Due to worsening hypoxemia and inability to optimize mechanical ventilation, the patient was brought to the operating theater, and veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) was initiated.

Prior to transfer from the ICU, the patient desaturated to 71%, requiring hand bagging. After transfer and a period of recruitment, SpO_2 (peripheral oxygen saturation) increased to the mid-80s, and hemodynamics remained stable during the procedure.

A 25 French (25F), 55-cm drainage cannula was placed in the right femoral vein using a Seldinger technique. X-ray guidance was used to confirm the position of the guidewire in the inferior vena cava.

The right internal jugular vein cannulation was performed using ultrasound guidance, and x-ray was used to confirm the position of the guidewire in the superior vena cava, where a 19F, 15-cm return cannula was placed using a Seldinger technique.

No heparin was given prior to ECMO start due to a low platelet count (40,000). One pool of platelets was transfused prior to cannulation.

Streptococcus pneumoniae was isolated from respiratory samples, and a necrotizing pneumococcal pneumonia progressively developed with multiple pneumothoraces and multiple returns to the operating theater, which led to right upper and middle lobectomy due to persistent air leak and inability to ventilate.

Due to low platelets and multiple surgical review, systemic anticoagulation was never initiated.

Resistant *Pseudomonas* was isolated in sputum, and the patient's antimicrobial treatment course was extensive, requiring combinations of multiple agents: vancomycin, meropenem, gentamicin, and ceftazidime.

While on ECMO, the patient was started on continuous renal replacement therapy, via the ECMO circuit, for fluid management and optimal fluid removal.

Three weeks after ECMO was established, after being off sweep for more than 24 hours, he was decannulated. Due to rising hypercapnia not manageable with mechanical ventilation and despite aggressive fluid removal, hypothermia, and paralysis, he was recannulated, and ECMO support was reinstituted less than 12 hours from decannulation. Fluid removal with continuous veno-venous hemofiltration was continued as his lungs appeared more congestive on CXR. Rising inflammatory markers were noted the following day, and antibiotic therapy was escalated. ECMO was continued for 6 days when a second attempt of decannulation was successfully performed.

HOW DOES MECHANICAL VENTILATION WHILE ON ECMO IMPACT WEANABILITY?

Traditionally, two different approaches are used for managing the lung while on ECMO:

- "Open lung"
- "Total lung rest"

While the objectives are similar in the two approaches and consist in limiting alveolar strain and atelectrauma and avoiding overdistension, each has advantages and limitations.

In the open lung approach, on the one hand tidal closure and reopening are limited and atelectrauma is reduced, hence the incidence of right ventricular failure is minimized. On the other hand, overdistension can still occur.

When a total lung rest approach is applied, airway pressures are dramatically reduced, so overdistension is minimized. However, this leads to more atelectrauma with the need to tolerate a higher incidence of right ventricular failure and consequently a higher need for conversion to veno-arterial support.

Due to the negligible contribution of the lung to oxygenation, moreover, patients are more dependent on the extracorporeal oxygenator, so any system malfunction can result in a severe threat to the patient's life.

No definitive evidence exists to date regarding the effect of the two different approaches on survival.

WHEN IS A PATIENT READY FOR WEANING?

Liberation from ECMO requires sufficient recovery of native lung function. According to the Extracorporeal Life Support Organization (ELSO) guidelines, at least 50%–80% of total gas exchange must be provided by the lungs in order to consider discontinuation from ECMO.

Besides this, respiratory mechanics must also be adequate for the patient to bear the entire respiratory workload without an excessive risk for ventilator-induced lung injury.

Static and dynamic respiratory system compliance/elastance, airway resistance, ventilator parameters, vital capacity, maximum inspiratory force, and respiratory rate must be evaluated and noted. Gas exchange in terms of VO_2 and VCO_2 of both the natural lung and membrane lung (ML) must be assessed.

HOW IS WEANING PERFORMED?

A weaning trial is performed before discontinuation of the extracorporeal support. At least three different techniques are used across different centers to obtain such a test.

A combination of an ECMO deoxy challenge test (EDCT) and an ECMO CO_2 challenge test (ECCT). As the terms suggest, the oxygenation function of the lung is evaluated first, followed by the decarboxylating function. This is accomplished by gradually reducing the circuit FiO_2 in the first step, followed by a reduction in the sweep gas.

A so-called physiological approach focuses mainly on the ability of the lung to control carbon dioxide. This is done by progressively reducing the sweep gas flow and adding CO_2 into the circuit to test the patient's ability to maintain normocarbia.

A "sweep off trial" simply consists in turning off the gas flow in the circuit after optimizing ventilator settings in order to evaluate oxygenation and decarboxylation functions simultaneously.

These different techniques are described in detail in the chapter.

WHAT IF WEANING FAILS?

Not all patients assisted with V-V ECMO will be weaned. In some patients, this is known from the beginning (e.g., patients who are bridged to lung transplant), and weaning attempts are generally not performed. In these patients, the strategy is often to discontinue mechanical ventilation to prevent related complications while maintaining extracorporeal support.

A number of patients who are deemed "weanable," though, do not succeed in their weaning trial. In these subjects, ECMO support should be restored to adequate values, and the reason for failure must be investigated. A new attempt can be performed once the cause of the failure has been solved.

Last, as in the case we presented, a number of patients are deemed weanable and ECMO is discontinued, but this leads to rapid worsening and the need for reinstitution of the extracorporeal support. The number of these patients should ideally be very low, and recannulation must be weighed for each single case based on several considerations, such as duration of support, likelihood of subsequent weaning success, and organ failures.

The limit to consider ECMO as futile is ill defined and represents a challenging situation. The duration of support per se is not a determinant of successful weaning, and several cases of good outcome after very long ECMO runs have been reported. When futility has been ascertained, the patient's comfort must be ensured and all supportive measures put in place according to good medical practice. ECMO consumables (circuit and oxygenator) should not be changed, and discontinuation of support must be considered.

DISCUSSION

Extracorporeal membrane oxygenation is an invasive, high-risk, and resource-intensive intervention that requires responsible handling of its indication and use. It typically acts as a bridge to either recovery or lung transplantation, and clinicians often deal with the obvious question: What is an adequate window for healing? So even more than deciding which patient is eligible for extracorporeal support, finding the optimal time for weaning patients is probably one of the greatest challenges in ECMO management.

Despite the spreading use of ECMO support triggered by the Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial[1] and the H1N1 flu pandemic, no definite criteria have been identified, and the decision is usually based on suggestions from scientific societies' guidelines[2] and local protocols.[3,4] Due to the wide range of device technology, diverse patient populations, and lack of randomized studies, a formal meta-analysis is not feasible.

IDENTIFYING A PATIENT READY FOR WEANING

Final liberation from ECMO support is based on progressive improvement in gas exchange and lung aeration on diagnostic imaging. According to ELSO guidelines,[2] discontinuation from extracorporeal support can be considered when 50%–80% of total gas exchange is provided by the native lung. A similar result was demonstrated by Mols et al. in a large cohort study on acute respiratory distress syndrome (ARDS) patients[5]: Safe weaning from ECMO was reported when the patient's own lung supplied at least 80% of total oxygen delivery.

A careful assessment of the patient's respiratory function is mandatory; multiple breathing tests are usually done prior to the discontinuation of ECMO, with respiratory mechanics

Table 41.1 PARAMETERS FOR EVALUATING A PATIENT'S LIBERATION FROM EXTRACORPOREAL SUPPORT

PARAMETERS FOR ECMO WEANING	
RESPIRATORY MECHANICS PARAMETERS	**GAS EXCHANGE VARIABLES**
• Minute ventilation • Vital capacity • Maximum inspiratory force • Respiratory rate • Static compliance and airway respiratory	Test at FiO_2 1.0 • Membrane lung: PO_2, VO_2, VCO_{2ML}, and VO_{2ML} • Natural lung: VCO_2 of the natural lung (VCO_{2NL})

parameters measured daily. Minute ventilation, vital capacity, maximum inspiratory force (also called negative inspiratory force), and respiratory rate have been used as a surrogate to determine a patient's ability to breathe on their own.

An increase in the respiratory mechanics (e.g., increase of static compliance of the respiratory system in the ARDS population and/or reduction of airway resistance in severe asthma cases).

Furthermore, most authors suggest that weaning can be considered when arterial PO_2 and PCO_2 are adequate at ventilator settings, but unfortunately no clear thresholds have been found. In the study by Grant et al.,[6] ECMO weaning was considered when the underlying pathology was resolved, patients tolerated ventilatory support settings (with FiO_2 0.5, PEEP < 10, and tidal volume 6–8 mL/kg ideal body weight to keep Ppeak [peak pressure] < 30 and Pplateau [plateau pressure] < 25 cm H_2O, maintaining SpO_2 > 90% and normocarbia).

The editorial of Vaques et al.[7] also suggested daily assessment of gas exchange variables, including the 100% test; postmembrane PO_2, VO_2, and VCO_2 of the ML (VCO_{2ML}) and VO_{2ML}; and VCO_2 of the natural lung (VCO_{2NL}) using volumetric capnometry. This allows calculating the total VCO_2 (VCO_{2tot} = VCO_{2ML} + VCO_{2NL}) and the proportion of VCO_{2tot} eliminated by the natural lung (VCO_{2NL}/VCO_{2tot}) (Table 41.1).

In the review article by Broman et al.,[8] three different weaning protocols from well-experienced ECMO centers were reviewed in order to assess adequacy and safety of V-V ECMO removal. Lee et al.[9] also proposed that high PLT counts might play a key role in successful weaning of V-V ECMO for severe acute respiratory failure.

Generally, ECMO weaning was given priority over mechanical ventilation weaning, and different strategies of mechanical ventilation can be adopted during ECMO weaning. Commonly, ECMO support facilitates the switch from controlled mechanical ventilation to an assisted spontaneous breathing mode, such as pressure support ventilation or neurally adjusted ventilatory assist.[10,11] In other words, modulating the extracorporeal assist becomes a strategy to facilitate the patient's weaning from the ventilator.

In recent years, the concept of "mechanical power"—the product of tidal volume size, plateau airway pressure, and respiratory rate—has become increasingly used. If mechanical power is "excessive," then the chemical bonds of the polymers composing the extracellular matrix could become disrupted.[12] In the future, studies of mechanical power in patients undergoing ECMO should be carried out to provide further possible indications on ECMO weaning and outcome.

Last, as reported,[13] some centers are using ECMO as a first-line treatment alternative to invasive mechanical ventilation in awake, nonintubated, spontaneously breathing patients with respiratory failure ("awake" ECMO); this type of approach avoids mechanical ventilation–associated side effects, but there are of course several challenges. In this scenario, only clinical signs and symptoms of respiratory distress, such as respiratory rate, dyspnea, rapid shallow breathing and others, can be evaluated and, if present, esophageal pressure swings can be a surrogate of variations in pleural pressure generated by the inspiratory muscles.

HOW TO ASSESS A PATIENT'S DEPENDENCE ON ECMO

Once the patient is judged as ready for weaning according to the criteria listed above, it is recommended to perform a trial of temporary discontinuation of the extracorporeal support. Before starting the trial of V-V ECMO discontinuation, controlled ventilator settings (respiratory rate, plateau pressure, FiO_2, and PEEP) should be adjusted to values that are considered acceptable off ECMO. Particular attention on adjustment of the level of inspiratory assist and a careful modulation of the level of sedation may be required in patients in assisted spontaneous ventilation.[14]

Different trials of ECMO discontinuation are reported in the literature.[2,6,7]

ECMO Deoxy Challenge Test and ECMO CO_2 Challenge Test

A widely used protocol for ECMO weaning is the one described by Vasques,[7] which is divided into two steps. The first step is the EDCT: At the very beginning, the ventilator's FiO_2 is increased to 60%. This is a preliminary phase in order to prevent frequently observed hypoxemia during ECMO weaning due to a restoration of hypoxic pulmonary vasoconstriction (HPV), suppressed by elevated SvO_2 (mixed venous oxygen saturation) during extracorporeal support.

The pulmonary vascular adaptation acts very slowly, and it can lead to a transiently worsened functional shunt (venous admixture). During the EDCT step, the physiological HPV is restored, and ventilation perfusion matching (V/Q) is optimized. If V/Q is not restored, shunt increases functional dead, and the natural pulmonary ability to eliminate CO_2 can be impaired.

After that, the FdO_2 is decreased from 100% to 60%, 30%, and 21% every 5 minutes. An SpO_2 greater than 88% and P0.1 less than 10 cm H_2O will need to be maintained throughout the test. If a patient meets the stop criteria, the test is suspended, but if EDCT is successful, FdO_2 can be kept at 21%, and the test can proceed to step 2.

The second step of the weaning trial tests the CO_2 removal ability of the natural lung and is called ECCT.

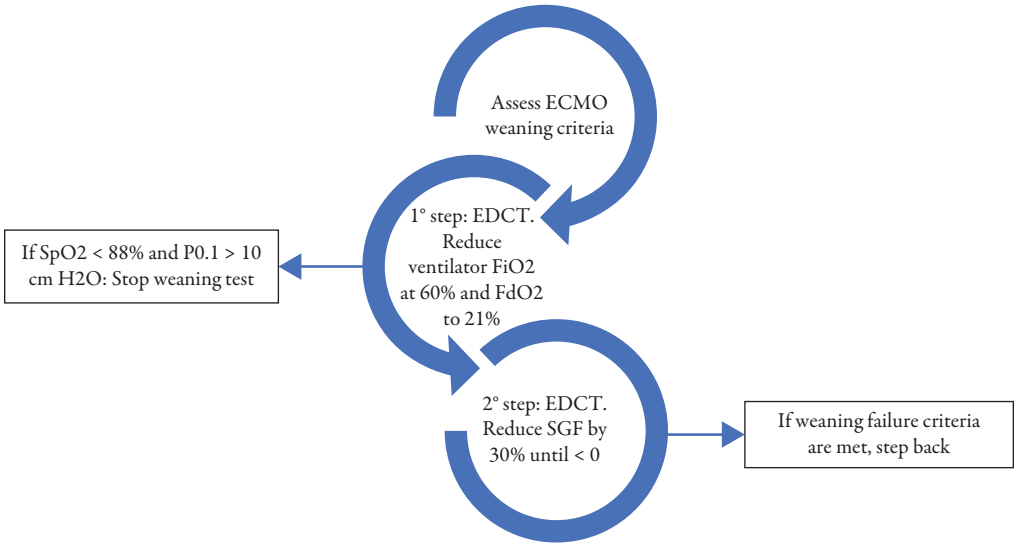


Figure 41.1 The EDCT and ECCT protocol trial.

During this phase of the weaning trial, every 10 minutes the SGF is reduced by 30%. The test is interrupted if patients meet the weaning failure criteria:

SpO_2 < 88%, respiratory rate > 35 breaths/min, and P0.1 > 10 cm H_2O

VCO_2 NL/VE fall by 20% from baseline

Negative swings of esophageal pressure < 15 cm H_2O (if present) or if any signs of distress/instability are evident

If the patient's response remains within set limits at SGF = 0 L/min, the weaning test is successful, and the clinical team will consider whether to remain off ECMO or reintroduce a variable degree of extracorporeal support pending decannulation (Figure 41.1).

A similar protocol was used by Grant,[6] but the adequate oxygenation (first step) is maintained for 24–48 hours and only after this time gas flow is reduced at 1 L/min, and serial arterial blood gases are performed to assess the patient's ability to maintain oxygenation and normocarbia.

Physiological Approach

Some centers, as at Karolinska in Sweden, used a so-called physiological approach, and the marker to progress with weaning is led by carbon dioxide clearance more than oxygenation.[8] The weaning process from V-V ECMO starts as soon as the tidal volumes start to recover. As the lung recovers and the clearance of CO_2 by the native lung increases, the ECMO specialist starts to reduce the sweep gas flow until ML size-related minimal one (adult 2 L/min; pediatric/neonatal 1 L/min). Incremental PCO_2 is than added to the sweep gas, and the efficiency of the native lung to clear CO_2 is assessed by simultaneous sampling of blood gases before and after the ML. When the PCO_2 difference (pre- and post-ML) is less than 0.2–0.4 kPa, the patient is regarded as "equilibrated." According to valid and secure SaO_2, a trial off is performed: FiO_2 is set to 35%–55%, and the sweep gas is discontinued. If no complications occur during this phase, the sweep may be turned off for hours until decannulation. Otherwise, the sweep gases are turned on again, and a new assessment will follow the next day.

Sweep Off Trial

Another weaning method is based on turning off the sweep gas to the oxygenator once the ventilator settings have been adjusted.[14]

It is important to remember that while the flow meter is turned to zero, gas tubes should be clamped since oxygen can leak around the flow meter even when it appears to be off. Oxygen will be fully consumed in around 20 minutes, and venous oxygen saturation on the extracorporeal circuit will indicate when the excess oxygen in the circuit has been used up.

The extracorporeal blood flow is continued, and no adjustment of heparin dose is required. No clear indications on the duration of the trial are defined; some centers suggest a trial off for 1–6 hours, but if needed the duration of the trial can be prolonged up to several hours. Close clinical monitoring is necessary, with particular attention to hemodynamic stability, adequate gas exchange, and respiratory mechanics.

If the ventilatory load is acceptable and the patient remains stable, the extracorporeal support can definitively be discontinued.

DECANNULATION

It is prudential to wait an interval of time between sweep off and decannulation, usually 24 hours and up to 48 hours if the patient was on ECMO for a long time.

Before starting with decannulation, the coagulation status is assessed with prothrombin time, partial thromboplastin

time, and platelet count. Ventilatory status is checked another time, and the need for the patient's sedation and comfort during the procedure should be evaluated.

Depending on the center and the cannula setup, the team involved in decannulation can involve different clinical figures (one or two operators depending on the cannula setup, ECMO specialist nurse, and perfusionist)

The cannulae can be removed whenever the patient is ready, but ideally after the heparin has been turned off for 30 to 60 minutes. Cannulae placed by direct cutdown are removed by direct cutdown. The cannulae are removed, and the vessels are simply ligated (or occasionally repaired). Venous and arterial cannulae placed by percutaneous access can be removed directly and bleeding controlled by topical pressure. When removing a venous cannula, especially jugular catheters, air can enter the venous blood through the side holes if the patient is breathing spontaneously. This is prevented by a Valsalva maneuver on the ventilator or by short-term pharmacological paralysis when removing the venous cannula.[2] Purse-string sutures with manual compression provide adequate hemostasis at the access sites. After decannulation, venous Doppler of the lower limbs and of the cannulated vessels is performed to exclude thrombotic events.

It is important to stress again the concept that ECMO liberation does not mean full recovery from mechanical ventilation. Therefore, it is extremely important to maintain the least damaging ventilation after decannulation, and close clinical evaluation is mandatory.

COMPLICATIONS POSTDECANNULATION

After weaning from ECMO, there are still many aspects to be addressed, such as the following:

- Potential for systemic inflammatory response syndrome (SIRS) postdecannulation
- Deep vein thrombosis
- Wound infection
- Renal failure requiring continuous V-V hemofiltration or short-term dialysis
- Stroke
- Gastrointestinal bleeding
- Disseminated intravascular coagulation (5%)
- Delirium
- Posttraumatic stress disorder (PTSD)

Among post-ECMO complications, SIRS is very common; it can be explained by the fact that during extracorporeal support, the patient's blood is exposed to the nonendothelialized surface of the cannula and extracorporeal circuit. This may be responsible for the widespread activation of innate immune system and subsequent development of sepsis. It remains difficult to distinguish between the post-ECMO SIRS phenomenon and a postdecannulation infection.[15] Patients with suspected SIRS should be treated similarly to patients with infection with broad-spectrum antibiotics until culture results are available, and perhaps as a preventive measure antibiotics should be considered for the first 24 hours postdecannulation.

As the application of ECMO has expanded, more patients are treated for weeks, even months; such prolonged periods invite increasing opportunity for ICU delirium and affect mortality, length of stay, cost of care, and quality of life. Conditions that are associated with ECMO contributing to delirium include drug inducement, addiction withdrawal, sepsis, electrolyte abnormalities, nutritional deficiencies, and, in general, organ failure.[16]

Current evidence from observational studies suggests that ECMO survivors have high rates of adverse mental health outcomes and cognitive impairment. Although many of the problems seen with oversedation are alleviated, PTSD has emerged.[17]

ECMO AND FUTILITY OF TREATMENT

Weaning from ECMO does not always signify patient improvement or survival and is not always life saving. If the medical team evaluates that a chance for sufficient lung recovery is impossible and no chance for lung transplantation is present, ECMO support would by definition be futile.

The extracorporeal support should be discontinued for futility if the patient's conditions evolve toward a permanent and irreversible damage of brain, lung, and/or heart function, and there is no hope of recovery or organ replacement. According to the ELSO guidelines,[2] this possibility should be explained to the family before ECMO institution, taking the patient's wishes and beliefs for shared decision-making concerning potential futility into account.

CONCLUSION

- Indications for V-V ECMO intervention have been consolidated.
- Weaning criteria still remain uncertain.
- ECMO weaning protocols should be established.
- Criteria for difficult, prolonged, and failed weaning from ECMO should be defined.
- Further investigations are necessary in order to standardize the V-V ECMO weaning process.
- The most appropriate strategy for weaning and its timing needs to be identified.

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REVIEW QUESTIONS

1. During V-V extracorporeal support, the objective of mechanical ventilation is

   A. Total lung rest
   B. Ultraprotective mechanical ventilation
   C. To limit lung strain while maintaining adequate gas exchange
   D. To extubate the patient in all cases

2. What are the main advantages of the "open lung" approach?

   A. Cyclic reopening is reduced.
   B. Atelectasis is minimized.
   C. Right ventricular function is preserved.
   D. All of the above.

3. What is one of the main limits of the total lung rest strategy?

   A. Atelectrauma is decreased.
   B. Right ventricular dysfunction is frequent.
   C. Overdistention is common.
   D. Lung recruitment is optimized.

4. What might happen to a patient treated with the total lung rest strategy in case of acute oxygenator malfunction?

   A. This represents a true emergency, and the patient's life is at risk.
   B. No significant alterations in gas exchange should occur.
   C. Oxygenation might be mildly impaired.
   D. Oxygenation might paradoxically increase.

5. Which of the following is required for weaning?

   A. A reduction in respiratory system compliance
   B. Appearance of new lung consolidations
   C. A sufficient recovery of native lung function
   D. All of the above

6. How is a weaning trial performed?

   A. With a sequential reduction in FiO_2 at the ML, followed by a decrease in the sweep gas flow (EDCT/ECCT)
   B. With a progressive reduction in sweep gas flow (physiological approach)
   C. Turning off the sweep gas flow (sweep off trial)
   D. Any of the above

7. When is an ECMO run long enough to be considered futile?

   A. One week.
   B. Two weeks.
   C. One month.
   D. A cutoff time cannot be determined.

8. How is decannulation performed?

   A. Always with surgical repair of the cannulated vessels
   B. Always percutaneously
   C. Depends on the cannulation technique (surgical vs. percutaneous)
   D. Depends on the operator's skills

9. Which are possible complications during or after weaning?

   A. Gas embolism
   B. Pulmonary thromboembolism
   C. Bleeding from the site of cannulation
   D. All of the above

10. How is ventilation managed after decannulation?

   A. No changes are made from the extracorporeal support period.

B. Mechanical ventilation is resumed with pre-ECMO parameters.
C. A lung-protective ventilation is set.
D. ECMO is removed only once the patient has been extubated.

11. What happens when severe respiratory failure occurs after decannulation?

A. ECMO is immediately resumed.
B. ECMO might be reinstituted, depending on the patient's characteristics.
C. ECMO cannot be restarted.
D. Mechanical ventilation is maximized; lung protection is not a priority in this situation.

12. What does "futility" mean in the setting of ECMO?

A. Lung function recovery is deemed impossible, and transplantation is not an option.
B. Severe irreversible neurological damage occurs.
C. Terminal heart failure without indication to long-term support ensues.
D. Any of the above.

13. What is the EDCT/ECCT?

A. It is the only possible technique for a weaning trial.
B. FiO_2 is increased, while sweep gas flow is reduced.
C. Both FiO_2 and sweep gas flow are increased.
D. FiO_2 is reduced; subsequently, sweep gas flow is reduced.

14. What is a physiological approach to weaning?

A. FiO_2 is reduced to 0.2 L while sweep gas flow is unaltered.
B. Sweep gas flow is progressively reduced and turned off.
C. No weaning attempt is performed until full radiological resolution.
D. The circuit is clamped to assess weanability.

15. What is a sweep off trial?

A. Sweep gas is turned off after ventilatory setting adjustment.
B. Sweep gas flow is kept unaltered, while ECMO blood flow is reduced.
C. Both sweep gas and blood flow are reduced.
D. Both sweep gas and blood flow are increased to test the possible improvement in gas exchange.

ANSWERS

1C. The main objective while on ECMO is to protect the lung from iatrogenic damage derived from mechanical ventilation while ensuring gas exchange. This can be obtained in various ways, from total lung rest, to ultraprotective ventilation, or to spontaneous ventilation.

2D. Keeping a certain degree of lung recruitment prevents total lung collapse and the frequently ensuing right ventricular failure. On the other hand, with this strategy overdistention can still occur.

3 B. During this approach the lung is allowed to collapse. Hence, atelectrauma is markedly increased so is the right ventricular afterload, frequently leading to right heart failure and the need to convert to veno-arterial support.

4 A. During the total lung rest approach, the lung's contribution to gas exchange is negligible, and the patient is totally dependent on the extracorporeal oxygenator. Hence, any malfunction leading to inadequate gas exchange in the extracorporeal circuit poses danger to the patient's life.

5C. A sufficient recovery in native lung function is necessary for weaning. Improvement in respiratory mechanics and gas exchange and resolution of the acute process are fundamental for successful weaning.

6D. The weaning trial can be performed in different ways depending on local protocols. The common objective is to progressively increase the breathing load before decannulation in order to ensure sufficient native lung function.

7D. The duration of support per se is not a determinant of weanability, provided the underlying pathology is compatible with recovery and organ support has been adequately maintained.

8C. Generally speaking, if a surgical cannulation technique was used, decannulation occurs with ligation or repair of the vessels, while percutaneous cannulation allows direct decannulation with pressure hemostasis.

9D. Decannulation represents a very delicate process. Air can be loaded in the venous system while removing cannulae, venous thrombi can be mobilized and cause pulmonary embolization, and life-threatening hemorrhage can develop from cannulation sites. Close attention and monitoring must be paid during and after decannulation to prevent and treat complications when they occur.

10C. Liberation from ECMO does not signify complete resolution of the respiratory failure. Hence, prevention of ventilator-induced lung injury must be ensured after decannulation.

11B. In some patients, despite positive weaning trials, acute respiratory failure occurs after decannulation. The decision whether to reinstitute the extracorporeal support is multifactorial and must be tailored to each patient.

12D. Whenever an irreversible condition leading to futility of ECMO occurs, the extracorporeal support should be withdrawn. The patient's next of kin should be made aware of this possibility right from the start and must be involved in the discussion.

13D. This is one of the possible techniques to perform a weaning trial. The oxygenating function is evaluated first, followed by the CO_2 removal function.

14B. In this approach, the decarboxylating function of the lung is mainly tested, with progressive reduction of the sweep gas flow until full suspension.

15A. After adjusting ventilation gas flow is turned off, the circuit is clamped to prevent oxygen leaks, while blood flow is maintained.

ECMO IN ADULT CARDIAC DISEASE

42.

ECMO SUPPORT FOR ADULTS WITH CONGENITAL HEART DISEASE

Akbar Vohra and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 28-year-old female patient presented with a history of severe Ebstein anomaly, atrial septal defect (ASD), and ventricular septal defect (VSD). She underwent a Da Silva–type repair of her Ebstein anomaly, followed by a bidirectional Glenn shunt and partial closure of the ASD and VSD. On admission, the patient was deeply cyanotic (oxygen saturation 70%) and erythrocytotic (hemoglobin level 26 g/dL). She presented with moderate-to-severe right ventricular (RV) dysfunction, small pulmonary arteries, a small aorta, and a small left ventricle (LV). Preoperatively, her heart disease was graded as New York Heart Association (NYHA) class IV. After two runs on cardiopulmonary bypass (CPB) for a total of 220 minutes, she was vasoplegic and could not be weaned off CPB. A stress-dose hydrocortisone (200 mg) and high doses of norepinephrine and milrinone were administered. Veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) was initiated using peripheral cannulation in order to enable chest closure without further compromising the RV.

The patient was transferred to the cardiac intensive care unit (CICU), where she remained on V-A ECMO for 5 days for cardiovascular recovery and required massive blood transfusion (12 units packed red blood cells, 4 units fresh frozen plasma [FFP], 2 units platelets, 4 units cryoprecipitates, and 400 mL 20% human albumin). After the ECMO intervention, a clot in the right atrium (RA) was diagnosed and treated with warfarin. The patient remained on prolonged mechanical ventilation because she had developed ventilator-associated pneumonia and was treated with meropenem for 12 days. After a total of 30 days in the CICU, the patient was discharged on day 35 with normal neurological function. The patient had a very favorable outcome, and she continued to improve to NYHA class I.

WHAT IS THE EPIDEMIOLOGY OF THE EBSTEIN ANOMALY?

The Ebstein anomaly was first described by Wilhelm Ebstein in 1866 in a 19-year-old patient who was a cyanotic man with dyspnea, palpitations, jugular venous distension, and cardiomegaly.[1]

It occurs in approximately 1 per 200,000 live births and accounts for less than 1% of all cases of congenital heart disease (CHD). Familial Ebstein anomaly is rare. Most cases are sporadic, but some appear to be associated with the development of the anomaly, including a family history of CHD; more common occurrence in twins; maternal exposure to benzodiazepines and lithium therapy; and rare cases of cardiac transcription factor mutations.[2–7]

WHAT IS KNOWN ABOUT THE EPIDEMIOLOGY OF CHD PATIENTS?

The incidence of CHD is 4–10 per 1000 live births. Before pediatric cardiac surgery, only 20% of patients survived to adulthood. Modern technology, facilities, monitoring, and care have led to 85% survival to adulthood, with presently more than 250,000 adults with CHD, of which a significant proportion will require surgical intervention.[8] While in 1958 the commonest cause of death in infancy was CHD, in 1986 deaths were more in adult CHD (ACHD), and this has been the case ever since.[8,9]

WHAT IS THE EXPECTED OUTCOME FOR ACHD PATIENTS REQUIRING MECHANICAL CIRCULATORY SUPPORT?

Over the last decades, diagnostic and therapeutic options for patients with CHD have significantly improved, with a significant decrease in mortality rates. Therefore, currently many patients survive into adulthood and develop the so-called ACHD or grown-up congenital heart disease. Many of these patients are not truly "repaired" but are "palliated." Long-term effects occur from residual defects and/or deterioration of prosthetic valves and surgical conduits, dysrhythmia, heart failure, clot formation, cardiogenic shock, and numerous other complications that may require mechanical circulatory support (MCS), further surgical intervention, or both.[10,11]

In a 12-year review of 2264 ACHD patients at the Mayo Clinic, 24 patients required MCS (1.1%), and of these 13 patients died, giving a 46% survival rate. There was no difference in outcome between extracorporeal membrane oxygenation (ECMO) or ECMO plus intra-aortic balloon pump (IABP).[12] The Extracorporeal Life Support Organization

(ELSO) registry has found a 40% survival rate for adults on ECMO with cardiac disease.[13] In our own institution, this high-risk group of patients in severe heart failure had a 50% survival rate.[14]

WHAT ARE THE PATHOLOGICAL CHANGES IN EBSTEIN ANOMALY?

In the normal heart, the tricuspid valve (TV) has three leaflets: anterior, posterior, and septal.[15] These are developed during normal embryogenesis by the delamination of the inner myocardial tissues to form myocardium and valve structures. This process determines the RA size, RV size, and trileaflet anatomy of the TV. In Ebstein anomaly this delamination fails to occur normally, leading to some characteristic changes.[16–21]

Apical Displacement of the Tricuspid Annulus Attachments With Deformity of Valve Leaflets

The failure of delamination leads to the tethering of the septal and posterior leaflets to the RA myocardium. Therefore, the leaflets originate from a more apical part of the RV rather than the true annulus. Hence, this functional annulus is closer to the RV apex than the true annulus (apical displacement).

Tricuspid Valve Leaflet Deformities

A varying degree of changes in the structure and attachment of the leaflets is seen in Ebstein anomaly, including TV leaflet deformities.

Anterior Leaflet Redundancy, Fenestrations, and Tethering

The anterior leaflet and its chordae tendinae will be poorly formed, and the latter are also often short. The severe deformity of the anterior leaflet may lead to displacement into the RV outflow tract (RVOT), where it may cause obstruction. It may be seen to form a large, sail-like intracavitary curtain. The anterior leaflet may become functionally redundant due to deformity, tethering or fenestration.

The septal leaflet and posterior leaflet may adhere to the myocardium leading to a range of anatomical abnormalities. The spectrum of changes may range from only minimal displacement of the septal and posterior leaflets to an imperforate membrane or muscular shelf between the inlet and trabecular zones of the RV.

Atrialization of the Right Ventricle and Change in Ventricular Cavity

The RV ends up with two different functional parts of varying size: the inlet (atrialized) portion, which is functionally integrated with the RA (atrialization). This atrialization of the RV at its inlet leaves a much smaller apical (nonatrialized) portion, which consists of the trabecular and outlet portions, which constitute the functional RV.

Two-thirds of hearts with Ebstein anomaly show dilated RVs. Dilation, which invariably involves the atrialized inlet portion of the RV, can also occur in the functional RV apex and outflow tract. In some cases, this dilation is so marked that the ventricular septum bulges leftward, compressing the LV chamber. In such cases, transesophageal echocardiography (TEE) demonstrates a circular RV and a crescentic LV (Figure 42.1).

Dilation of the True and Atrialized Right Atrium

The functional impairment of the RV and regurgitation of the TV retard forward flow of blood through the right side of the heart. In addition, during contraction of the atrium, the atrialized portion of the RV balloons out and acts as a passive reservoir, decreasing the volume of ejected blood. The overall effects on the RA are dilation and increase in size of any ASDs. Tricuspid regurgitation also increases by annular dilation.

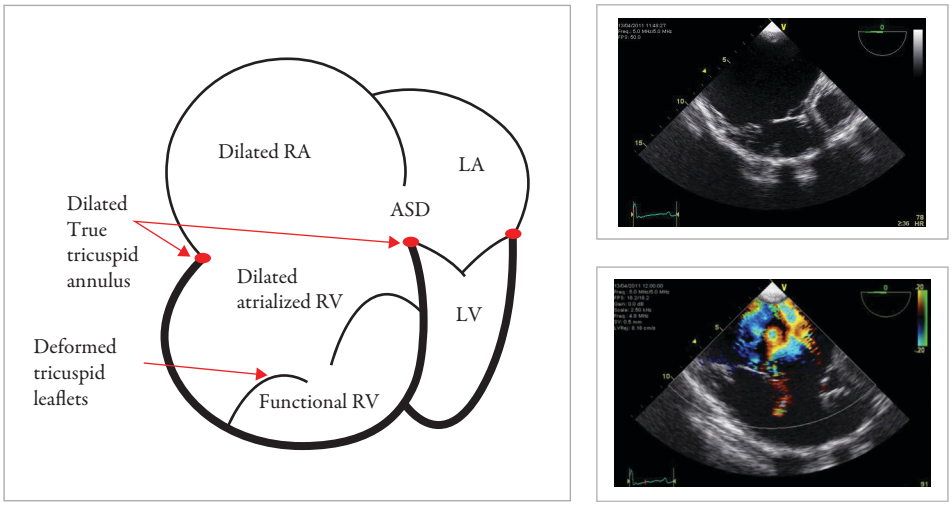


Figure 42.1

Dilation at the Site of the True Right Atrioventricular Junction

The failure of the delamination process does not affect the true TV annulus. Therefore, it remains in its normal anatomical position between the junction of the true atrium and the atrialized RV. This "true annular" area enlarges in association with the dilation of the true atrium and atrialized RV.

HOW DO WE CLASSIFY AN EBSTEIN DEFORMITY?

In 1988, Carpentier and colleagues proposed the following classification of the Ebstein anomaly[22]:

Type A: Volume of the true RV is adequate.

Type B: A large atrialized component of the RV exists, but the anterior leaflet of the TV moves freely.

Type C: The movement of the anterior leaflet of the TV is severely restricted, and it may cause significant obstruction of the RVOT.

Type D: There is almost complete atrialization of the ventricle except for a small infundibular component.

Celermajer and colleagues described an echocardiographic (ECHO) grading score for neonates, which is based on the ratio of the combined area of the RA and atrialized RV compared to that of the functional RV and left heart[23]:

Grade 1: less than 0.5

Grade 2: 0.5–0.99

Grade 3: 1.0–1.49

Grade 4: 1.5 or greater

WHAT ARE THE ASSOCIATED CARDIAC MALFORMATIONS IN AN EBSTEIN ANOMALY?

A number of congenital and acquired cardiac malformations can occur in the Ebstein anomaly[24–28]:

- Atrial septal defect (60%–90%): Patent foramen ovalis (PFO) and ostium secundum ASD.
- Pulmonary valve (30%): Including pulmonary atresia or hypoplastic pulmonary artery.
- Ventricular malformations: VSDs, tetralogy of Fallot, hypoplastic left heart.
- Aorta malformations: Transposition of great arteries (TGA; up to 50% of TGA patients have TV defects), coarctation of the aorta, patent ductus arteriosus.
- Aortic valve malformation: Bicuspid or atretic aortic valves, subaortic stenosis.
- Mitral valve: Congenital mitral stenosis and mitral valve prolapse.
- Conduction defects: Wolff-Parkinson-White syndrome.
- Atrio-ventricular discordance.
- Left ventricular outflow obstruction (LVOT): In extreme cases of RV dilation, episodic LVOT obstruction can occur.
- Right coronary flow reduction: The right coronary artery demarcates the level of the true annulus and may become kinked during plication annuloplasty procedures.

WHAT ARE THE CLINICAL FEATURES OF THE EBSTEIN ANOMALY?

All the clinical feature signs will depend on the severity of anatomical dysfunction, associated changes in hemodynamic function, and degree of right-to-left shunting. Typically, patients will have cyanosis, right heart failure, arrhythmias, and sudden death syndrome.[20,21,29]

WHAT IS THE CLINICAL COURSE OF AN EBSTEIN ANOMALY?

The Ebstein anomaly is associated with fetal cardiomegaly and hydrops. Neonatal cyanosis, cardiomegaly, and heart failure may be caused by regurgitation of the TV. Most children will progress to adolescence and adulthood but may develop progressive right-sided heart failure. The normal history with aging can include progressive cyanosis, decreasing exercise tolerance, fatigue, or right-sided heart failure. Interatrial communications increase the risk of paradoxical embolization, brain abscess, and sudden death increases. Exercise tolerance is dependent on heart size and oxygen saturation. Arrhythmias can be seen in young children (usually > 10 years) and increase with age.[19,21,30]

WHAT IS THE ROLE OF ECHOCARDIOGRAPHY IN THE EBSTEIN ANOMALY?

Echocardiography is the diagnostic investigation tool of choice for an Ebstein anomaly.

How Do We Use ECHO for Diagnosis?

Apical displacement of the septal leaflet of the TV from the insertion of the anterior leaflet of the mitral valve by more than 8 mm/m^2 body surface area is a diagnostic feature seen on ECHO.[16]

How Do We Diagnose Tethering of the Tricuspid Valve?

Finding at least three accessory attachments of the leaflet to the ventricular wall, causing restricted motion of the leaflet, defines tethering.[21]

How Do We Diagnose Marked Enlargement of the Right Atrium and Atrialized Right Ventricle?

The chamber areas are measured in the end-systolic apical four chamber.[23]

Marked dilation = RA + Atrialized RV > Functional RV + LA + LV

WHAT ELECTROCARDIOGRAPHIC CHANGES ARE THERE IN AN EBSTEIN ANOMALY?

The electrocardiogram (ECG) is abnormal in most patients with Ebstein anomaly. It may show tall and broad P waves as a result of RA enlargement.[30] Common are complete or incomplete right bundle branch block, first-degree heart block, or ECG evidence of accessory bundles.

WHAT ARE THE NATURAL HISTORY AND LONG-TERM SEQUELAE?

Celermajer and colleagues[23] reviewed 220 cases of Ebstein anomaly with 1 to 34 years of follow-up. The patients had 67% survival at 1 year and 59% survival at 10 years. Predictors of death were fetal presentation; ECHO grade of severity at presentation (increased risk ratio was 2.7 for each increased grade); and RVOT obstruction.

There were different common presentations in different age groups:

- Fetuses: Abnormal prenatal scans (86%)
- Neonates: Cyanosis (74%)
- Infants: Heart failure (43%)
- Children: Incidental murmur (63%)
- Adolescents and adults: Arrhythmia (42%)

Early presentation was frequently associated with other cardiac lesions, usually pulmonary stenosis or atresia.[31–33]

HOW ARE PATIENTS WITH EBSTEIN ANOMALY MANAGED?

All patients with Ebstein anomaly need regular specialist CHD cardiology follow-up.[8,9,23,24,34] Generally, management will require a focus on heart failure therapy, including diuretics, angiotensin-converting enzyme inhibitors and digoxin; arrhythmia treatment including medical, surgical, or catheter-based intervention; and hematological dysfunction, including clotting.

Corrective surgery should be performed if possible, including TV repair or replacement with appropriate closure of septal defects or correction of other lesions.

Celermajer and colleagues[23] found that surgery was undertaken at some stage in 86/220 (39%) patients, with an operative mortality of 5%–8%. Mortality has been found to be associated with heart failure and sudden deaths. Morbidity is mainly related to arrhythmias and cardiac failure. Celermajer and colleagues[23] found that in 155/220 survivors, 129 (83%) were in functional class I, and 104 (67%) were receiving no medical therapy. Prophylaxis for endocarditis is recommended despite its low risk in the anomaly.

IN ACHD PATIENTS, WHAT ARE COMMON CLINICAL COMPLICATIONS RESULTING IN REQUIREMENT FOR EXTRACORPOREAL LIFE SUPPORT?

Cardiac dysfunction, RA dilation, right-to-left shunting, and obstruction to the right ventricular RVOT result in a number of clinical problems.[11,12,14,24,29,30] These may lead to deterioration requiring extracorporeal life support (ECLS) intervention:

- Progressive cardiac failure
- Hypoxemia
- Arrhythmias
- Pulmonary hypertension
- Risk of endocarditis
- Polycythemia with associated risk of deep vein thrombosis
- Coagulopathy

HOW IS THE RIGHT ECLS CONFIGURATION CHOSEN?

As with all patients requiring ECMO, the first consideration will depend on whether the chest is closed or open. In addition, the underlying associated anatomical lesions, congenital or acquired such as ASDs and new connections such as Fontan circulation, will also have an influence and help one decide on central versus peripheral cannulation. In the intraoperative setting, the RV function on chest closure will influence the decision to commence ECLS.[10–14] We have used central and peripheral cannulation in our patients.[14]

WHAT ARE CLINICAL CONSIDERATIONS FOR MANAGEMENT OF ACHD PATIENTS DURING ECLS?

Daily ECHO assessment, preferably by transthoracic echocardiography in the awake and TEE in the intubated patient, is important to help assess the trend of change in ventricular function. The particular focus is on improving volume and contractility, assessment of the valve function, and improving hemodynamic function with reduction in inotropic or vasopressor support. Improvement in metabolic function with markers such as acid-base balance, lactate, base deficit, and venous saturations is a cornerstone in the management of these patients. In addition, the renal and hepatic function must be monitored for early detection of complications, such as hepatic congestion resulting from poor RV function.[10–14]

HOW ARE ACHD PATIENTS ANTICOAGULATED DURING ECLS?

The primary goal for anticoagulation of ACHD patients is to avoid clotting in the ECMO circuit without excessive bleeding. This is affected by ECMO flow rates: The higher the flow, the less anticoagulation is needed and vice versa. The activated clotting time (ACT) and coagulation factors need regular monitoring. In our clinical practice, intraoperatively ACT is used with a range of more than 500 seconds for CPB and 160–200 seconds for ECMO management. Postoperatively in the CICU, depending on bypass time and derangement of coagulation or even coagulopathy, increasing the activated partial thromboplastin time (aPTT) ranges (30–39, 40–49, and 50–59) are used and adapted to the amount of postoperative bleeding, while anticoagulation remains fully stopped during phases of coagulopathy with significant bleeding. However, this type of management always depends on local protocols and the experience of the staff involved. ECHO control of right heart blood flow and potential occurrence of spontaneous contrast ("smoke") will help to prevent clot formation.[10–14]

HOW ARE ACHD PATIENTS VENTILATED DURING ECLS?

Normal lung-protective ventilation principles apply. In addition, the reduction in pulmonary ventilation when on full ECMO support is acceptable. Hypercapnia can be managed by adjustments of sweep flow. In patients with Fontan circulation, reduction in pulmonary pressures and early spontaneous respiration need to be considered since blood flow in Fontan circulation is passive and not supported by RV contraction and is therefore also preload dependent.

WHAT IS THE FUTURE FOR ECLS IN ACHD?

Improvements in equipment technology with better pumps, oxygenators, and tubing is likely to make ECLS more routine. The increased number of ACHD patients surviving and having operations is likely to lead to more patients requiring ECLS in the perioperative period.[33]

DISCUSSION

Veno-arterial (V-A) ECMO is a frequently used bridge to recovery in patients with cardiogenic shock. For patients who do not recover, it serves as bridge to a ventricular assist device or cardiac transplantation. In patients with ACHD, it may serve as a bridge to surgery and provide respiratory and/or circulatory support for postcardiotomy complications. V-A ECMO can be particularly useful in ACHD patients who present with diminished RV function, or even Fontan or Glenn circulation, given that the RV is fully bypassed in these patients.[35] The experience and literature for this patients population, however, is extremely limited and reduced to case reports or case series. Our group has used ECMO in three ACHD patients with failure to separate from CPB post–cardiac surgery and in one patient requiring circulatory support prior to surgery.[14] The first patient presented with an untreated severe Ebstein anomaly with secundum ASD and severe cyanosis (oxygen saturation 74%). He underwent a Da Silva–type repair with bidirectional Glenn shunt and partial ASD closure. Unfortunately, he failed two attempts at separation from CPB. Therefore, percutaneous peripheral V-A ECMO was commenced and maintained for 6 days. He required the massive blood transfusion protocol during ECMO and, conversely, developed a RA thrombus when he was off ECMO. However, he survived all complications and was discharged home after 37 days.

A second patient, with a background history of complex double-outlet RV and palliative surgery (lateral tunnel fenestrated Fontan, tricuspid valve (TV) repair and pacemaker, underwent a redo TV replacement and insertion of biventricular epicardial pacing leads. He failed two attempts to separate from CPB, and central V-A ECMO was initiated using the cannulae that had been used for CPB. His sternum was left open with only the skin closed. V-A ECMO was maintained for 6 days. During this period, he developed a coagulopathy and also required massive transfusion; he further developed acute kidney injury and was started on renal replacement therapy. He developed leg ischemia and progressed very poorly, so the family decided to withdraw care.

A third patient who presented with Ebstein anomaly and ASD underwent TV repair, ASD closure, RA reduction, insertion of a bidirectional Glenn shunt, and placement of epicardial pacing leads. She failed weaning off CPB and was commenced on central V-A ECMO. Her chest was also left open when she was admitted to the intensive care unit. She was maintained on ECMO for 13 days. An attempt to convert to an RV assist device failed. She had problems with flow through the atrial cannula, requiring repositioning. She developed multiorgan failure and died on postoperative day 13.

A fourth patient who presented with Duane syndrome, Ebstein anomaly, ASD, and VSD had previously undergone pulmonary artery surgery, septal defect closure, and mechanical TV replacement. He developed severe low-output cardiac failure and multiorgan dysfunction due to TV obstruction from acute-on-chronic thrombosis. After initial treatment with inotropes and vasopressors, V-A ECMO was initiated using percutaneous peripheral cannulation. After 3 days of V-A ECMO, he underwent TV replacement. He made an excellent recovery and was discharged to the ward after 5 days.

This case series represents a high-risk group of patients for which a 50% survival rate could be achieved instead of certain death after repeated failure to separate from CPB. The results are in line with those of Luo et al., who also presented two cases with Ebstein anomaly and a 50% survival rate.[36] Even though V-A ECMO is the dominantly used configuration, veno-venous (V-V) ECMO may be used for the occasional patient with isolated respiratory failure. Chimot et al. reported about a 52-year-old man with Ebstein anomaly who was admitted with severe hypoxemia, pleural and pericardial effusions, moderate RV dilation, good LV function, and a PFO.[37]

After a pericardiocentesis for cardiac tamponade and worsening hypoxemia, the patient required tracheal intubation and mechanical ventilation. The progressing severe hypoxemia necessitated the use of V-V ECMO. In addition, the patient developed hepatic and renal failure. The TEE revealed severe RV dilation associated with a large PFO resulting in intracardiac shunt. The authors had a very sophisticated response to this challenging situation; they discontinued mechanical ventilation, limited ECMO to minimal blood flow, and added inhaled nitric oxide, resulting in decreased flow across the PFO and an improvement in respiratory, circulatory, hepatic, and renal function. The patient was weaned from V-V ECMO and discharged from the hospital 28 days after the surgery. At 6 months, the patient was healthy and had resumed his normal activities.

In patients with Ebstein anomaly, ECMO can provide respiratory support but is mainly useful to buy time for RV recovery and postoperative volume adjustment. The survival rate in the ELSO Registry for adults with cardiac disease averages 40%. While ECMO intervention in ACHD patients is uncommon, the outcomes are comparable despite the complexity of these patients. The slow adaptation of RA and RV volumes enabled by ECMO may be a significant factor in these patients' recovery.

Uilkema and Otterspoor[35] described their experience of a patient with acute right-sided heart failure due to severe outflow tract stenosis on a background of treated tetralogy of Fallot. This patient had ECMO as a bridge to surgery with peripheral cannulation. She developed bleeding complications and multiorgan failure during this initial period. She came off ECMO 6 days after surgery. However, she died from catastrophic arterial bleeding from an old femoral cannulation site. In contrast, Bautista-Hernandez and colleagues have described successful use of ECMO as a bridge to surgery in pediatric patients.[38]

There were similarities relating to bleeding complications, high transfusion requirements, and excessive clotting in all the different publications.[14,35,38] Bleeding is, in part, secondary to coagulopathy or anticoagulation. Transfusion requirements have been reported to average 45 units of packed red blood cells transfused per adult ECMO patient, and hypertension increases the daily FFP requirements. Recent antiplatelet agents, bleeding, and longer ECMO duration also increase platelet requirements. Patients with sepsis or receiving ECMO for medical reasons have longer ECMO durations, which is associated with increased total transfusion requirements. Some of these factors may be identified early to optimize blood product support.[39]

A large series of ACHD patients was recently presented by Paden and colleagues from the Mayo Clinic[13] who reported that, out of 2264 operations of ACHD patients over 12 years, 24 patients (1.1%) required MCS with either ECMO or a combination of ECMO and IABP. Thirteen patients (54%) died and 11 (46%) survived without any difference in outcome between the ECMO and ECMO/IABP groups. Their overall outcome compared to our institution is similar.

Adult CHD patients who undergo cardiac surgery are at risk for poor outcomes, including the necessity for ECMO and death. Dolgner and colleagues have examined risk factors for ECMO or death without ECMO (DWE) in adults (≥18 years) undergoing congenital heart surgery in the Pediatric Health Information System database between 2003 and 2014. The patients were classified into three groups: ECMO-free survival, requiring ECMO, and DWE. Out of 4665 ACHD patients, 51 (1.1%) patients required ECMO and 64 (1.4%) patients experienced DWE. Of the 51 ECMO patients, 34 (67%) died. Increasing patient age, surgical complexity, diagnosis of single-ventricle heart disease, preoperative hospitalization, and the presence of noncardiac complex chronic conditions were identified as risk factors. Additionally, low and medium hospital ACHD surgical volume was associated with an increased risk of DWE in comparison with ECMO.

Burstein et al.[40] reported that acute heart failure in children and young adults with CHD is increasing and is associated with significant morbidity, mortality, and resource utilization. Many risk factors for mortality may not be modifiable for this complex population, with the highest risk reported for patients with a single ventricle.

Esteve-Ruiz and colleagues[41] performed a retrospective analysis of patients older than 14 years of age with CHD and heart transplantation (HT) in 10 patients (age 25 ± 7 years old, 60% male), which represented 2.2% of the entire series of HT; 9 of the 10 patients were electively transplanted, and 1 was under support with ECMO. Patients with CHD had a lower median age and more previous cardiac surgeries prior to HT. Primary graft failure was more common in patients with CHD. Therefore, survival at 1-month follow-up was lower than for the rest of the series but equalized after 1 year of follow-up. This long-term survival reaffirms the possibility of HT in adult patients with CHD despite the fact that its postoperative period is more difficult.

In a study by Aiello and colleagues, data from the Nationwide Inpatient Sample was used, for which 186,829 admissions with ACHD over 18 years of age with documented cardiac surgery were included. Of these, 446 (0.2%) required ECMO. Those with acute kidney injury, double-outlet RV, or total anomalous pulmonary venous connection were more likely to require ECMO. ECMO was also significantly more utilized in patients undergoing septal defect repair, complete repair of tetralogy of Fallot, atrial switch, and HT. ECMO may significantly increase the length of stay and costs for a healthcare system.

CONCLUSION

- The ACHD population is increasing.
- More patients will present for cardiac and noncardiac surgery as well as critical care for severe illness due to medical problems.
- Extracorporeal life support may be offered more routinely for these patients.

- Special complications, anatomy of CHD, and palliative or corrective surgery will pose additional problems for the anesthesiologist and critical care provider.
- Patient's with Ebstein anomaly seem to have better outcomes than those with other types of CHD.

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REVIEW QUESTIONS

Indicate true (T) or false (F) for each option for each question.

1. During development the Ebstein anomaly is associated with

   A. Failure of delamination, leading to an annulus that is higher than normal.
   B. Environmental factors are not important in developing this condition.
   C. Familial associations have been reported.
   D. The true annulus position is unchanged.
   E. Environmental factors have been implicated in its development.

2. Characteristics for diagnosis of Ebstein anomaly include

   A. The functional tricuspid annulus is displaced 5 mm below the level of the mitral annulus.
   B. The true tricuspid annulus is displaced more than 8 mm below the level of the mitral annulus.
   C. The functional tricuspid annulus is more than 8 mm below the true annulus.
   D. The RA is dilated.
   E. The apical segment of the RV is atrialized.

3. The following conditions may be seen in patients with Ebstein anomaly:

   A. Atrial septal defects
   B. RVOT obstruction
   C. Atrioventricular conduction abnormalities
   D. Hypoxemia
   E. Pulmonary stenosis or atresia

4. Valvular anomalies of the TV include

   A. Redundancy, tethering, and fenestration of the septal leaflet is often seen.
   B. Tethering of the anterior and septal leaflets is found.
   C. Tethering of the posterior and septal leaflets occurs.
   D. Atresia of the three leaflets is possible.
   E. Tethering of the anterior leaflet is found more commonly.

5. Atrialization of the RV involves

   A. Apical displacement of the functional tricuspid annulus occurs.
   B. The true annulus demarcates the junction of the true RA and the atrialized part of the RV.
   C. The RA and the atrialized RV will dilate.
   D. The functional RV will be reduced in size.
   E. The functional RV will be trabeculated.

6. In the classification of Ebstein anomaly

   A. Carpentier classification has four types (A–D).
   B. Carpentier classification involves analysis of the tricuspid leaflet and the volume of the functional RV.
   C. Celermajer classification is based on the volume ratio of the functional RA compared to that of the functional RV and left heart.
   D. Celermajer classification is used in neonates and has three grades.
   E. A more than 8-mm displacement of the functional annulus below the true annulus is diagnostic of Ebstein anomaly.

7. In terms of presentation and progress of Ebstein anomaly,

   A. Fetal hydrops and cardiomegaly may occur.
   B. Neonatal cyanosis occurs.
   C. Arrythmias are seen in childhood.
   D. Right heart failure may be seen in adulthood.
   E. Paradoxical embolization is not a feature of Ebstein anomaly.

8. On ECHO,

   A. Measurement of chamber size helps with classification.
   B. Tethering is associated with at least three accessory attachments of the leaflet to the RV wall.
   C. The true annulus does not need to be identified.
   D. Flow through septal defects is irrelevant.
   E. RVOT obstruction may be identified.

9. Common problems leading to need for ECLS include

   A. Hypoxia from right-to-left shunting
   B. RVOT obstruction
   C. Primary infection requiring ECLS
   D. Progressive cardiac failure
   E. Renal failure

10. When using ECLS in these patients,

    A. Central cannulation cannot be used.
    B. Peripheral cannulation cannot be used.
    C. Anatomy and previous or current surgery may affect the decision on cannulation site.
    D. Central cannulation is always better.
    E. These patients have very poor outcomes when ECLS is used.

11. Monitoring during ECLS in these patients should include

    A. Daily ECHO assessment is needed.
    B. Infection markers will be unreliable during ECMO.
    C. Markers of metabolic function such as lactate and venous saturations are unhelpful.
    D. Hepatic dysfunction from congestion may occur.
    E. Renal failure is rare.

12. In the management of coagulation,

    A. Blood transfusion is rarely necessary.
    B. An ACT of 160–200 is satisfactory for patients on ECLS.
    C. Activated partial thromboplastin time values do not need to be monitored.
    D. Platelet count should be maintained.
    E. Patients may need to be managed without anticoagulation.

13. In terms of general intensive care principles,

A. High tidal volumes are indicated to avoid atelectasis.
B. Spontaneous breathing should be avoided.
C. Increased tidal volumes during ECLS will help reduce hypercapnia.
D. Increased sweep speed during ECMO will help to reduce hypercapnia.
E. High preload may be necessary in patients with a Fontan circulation.

14. In ACHD patients,

A. ECMO can be used as a bridge to recovery.
B. ECMO can be used as a bridge to surgery.
C. ECMO can be used for postsurgical support for failure to wean from bypass.
D. Survival rates of 40%–50% have been seen in ACHD patients having ECLS support.
E. Bleeding is a common complication.

15. Coagulation problems in patients on ECMO include that

A. Patients can average more than 45 units of packed cell transfusion.
B. Bleeding is always due to primary coagulopathy.
C. Bleeding is always due to anticoagulation.
D. Recent antiplatelet therapy is associated with increased bleeding.
E. Nonsurgical reasons for commencing ECMO in ACHD patients are associated with increased transfusion requirement.

16. Presenting signs in Ebstein anomaly include

A. Almost 90% of fetuses will have abnormal prenatal scans.
B. Pulmonary stenosis or atresia commonly lead to an earlier presentation.
C. Incidental murmurs are uncommon in children presenting for the first time.
D. New arrhythmias are a common presentation in adults.
E. Heart failure is rarely seen in infants.

17. In ACHD patients on ECMO,

A. The chest should be left open to allow assessment of the heart.
B. Inotropes and vasopressor must not be avoided.
C. Protamine should be avoided in the post–bypass period.
D. Prophylactic antibiotics may be indicated.
E. Patients should be kept heavily sedated until they are off ECMO.

18. During ECMO,

A. Higher flow rates on ECLS will require an increase in anticoagulation to reduce hemolysis.
B. Flow rates through the cardiac chambers need to be maintained in order to reduce thrombogenesis.
C. Multiorgan failure is not always prevented by ECLS.
D. Septal defects are a contraindication to ECLS.
E. Therapy should aim to achieve high blood pressure during ECLS.

19. In patients with TVA malformation,

A. Aortic valve malformations are uncommon.
B. Patent ductus arteriosus may occur.
C. Half of patients with TGA have malformation of the TV.
D. LVOT obstruction can be caused by RV dilation.
E. Atrioventricular conduction defects may occur.

20. In the classification of Ebstein anomaly,

A. Adequate functional RV volume is Carpentier type A.
B. Carpentier type C is associated severe restriction of the anterior leaflet.
C. Carpentier type D is associated with almost complete nonatrialization of the RV.
D. Celermajer grade 4 equals a 1.5 or greater ratio of the RA compared to the RV and LV.
E. Carpentier type C may be associated with RVOT obstruction.

ANSWERS

1. a F; a F; c T; d T; e T. Failure of delamination does not affect the true annulus, which remains in its normal position. However, the functional annulus will arise at a lower level than the true annulus. Most cases are sporadic but a family history of CHD; maternal exposure to benzodiazepines and lithium therapy; and rare cases of cardiac transcription factor mutations have been reported.[2–7]

2. a F; a F; c T; d T; e F. The true annulus remains unchanged and the basal, not apical, segment of the RV becomes atrialized. The false annulus has to be greater than 8 mm below the true annular line.

3. a T; a T; c T; d T; e T. All of these conditions may be seen in patients with Ebstein anomaly.

4. a F; a F; c T; d T; e F. Anterior leaflet redundancy, tethering, and fenestration are seen. The septal and posterior leaflets tend to adhere to the myocardium. The leaflet may become completely atretic.

5. a T; a T; c T; d T; e T. The lack of lamination leads to apical displacement of the functional annulus. The true annulus remains unchanged. The true and atrialized RA and the true annulus will become dilated in these patients. The size of the functional RV will reduce depending on the degree of delamination. The apical part of the RV will remain trabeculated.

6. a T; a T; c T; d F; e T. A greater than 8 mm displacement of the functional annulus below the true annulus is diagnostic. The Carpentier classification has four types (A–D) depending on the RV volume and tricuspid leaflet anatomy. Celermajer classification is based on the volume ratio of the functional RA compared to that of the functional RV and left heart and is also graded into four types (1–4).

7. a T; a T; c T; d T; e F. Paradoxical embolus can occur in patients who have septal defects. The time of presentation

will depend on the severity of the lesion. Arrythmias and heart failure occur with age in most, if not all, ACHD patients. This is in part due to the abnormality in development and in part a consequence of previous surgical intervention.

8. a T; a T; c F; d F; e T. ECHO is an important tool for diagnosis, classification, and monitoring in these patients. The true annulus has to be identified in order to assess the displacement of the functional annulus. Associated defects need assessment in their own right.

9. a T; a T; c F; d T; e F. Potentially, there are numerous reasons for the use of ECLS. Infection or renal failure leading to cardiac failure may require support. However, they are not primary reasons for commencing ECLS.

10. a F; a F; c T; d F; e F. Cannulation for ECLS will depend on timing (e.g., peri-operative) and anatomy of the patient. In our limited experience and personal view, we feel that peripheral cannulation may be associated with less morbidity than open central cannulation. A success rate of approximately 50% makes it a viable option. Greater experience may enable improvements in this treatment option.

11. a T; a F; c F; d T; e F. Monitoring of all markers of perfusion and assessment of the cardiac function are almost mandatory. Improvements in cardiac function will enable decision-making. Infection and multiorgan failure will always be a risk in this patient population.

12. a F; a T; c F; d T; e T. The primary goal is to avoid clotting in the ECMO circuit without excessive bleeding. This is affected by ECMO flow rates; the higher the flow, the less anticoagulation is needed and vice versa. The ACT and coagulation factors need regular monitoring. We aim for 160–200 seconds for ECMO management. The aPTT ranges (30–39, 40–49, and 50–59) are used and adapted to the amount of bleeding. Anticoagulation may have to be stopped during phases of coagulopathy with significant bleeding.

13. a F; a F; c F; d T; e T. Lung protection principles remain important during ECLS. V-A ECMO will provide oxygenation and CO_2 control. Hence, the lungs may not be required to function at normal physiological levels. Depending on anatomy, flow through the pulmonary circulation and to the systemic circulation is important to reduce risk of thrombosis. Hence, ventilation will need to be maintained to reduce shunting. This becomes particularly important in patients with Fontan circulation.

14. a T; a T; c T; d T; e T. All these are important indications. More indications may develop as techniques improve.

15. a T; a F; c F; d T; e T. Transfusion averages of 45 units is common. All the different factors that lead to bleeding in any other clinical setting need monitoring and treating. Surgical/cannulation site problems, treatment with heparin, primary clotting factor, and platelet deficiency will need to be addressed to reduce bleeding. Patients treated with antiplatelet medication, ECMO for nonsurgical reasons, and hypertension during ECMO are also associated with increased bleeding.

16. a T; a T; c F; d T; e F. A number of congenital and acquired malformations can occur.[24–28] Abnormal prenatal scans and heart failure will be seen in many fetuses, and heart failure is associated with more severe abnormality. Patients with mild deformity may present late with incidental murmurs or arrhythmias.

17. a F; a F; c F; d T; e F. Normal surgical and critical care processes should be applied in these patients. Leaving a chest open can only be because of surgical necessity. The unclosed sternum will risk bleeding and infection. Closure of the chest has to happen before a patient is awakened. Anticoagulation is much lower for ECLS compared to full bypass for surgery.

18. a F; a T; c T; d F; e F. It is important to maintain flow through all chambers in order to reduce the risk of thrombogenesis. A balance between anticoagulation and flow enables optimization. Higher flow rates may enable a lower anticoagulation level. It is important to maintain end-organ perfusion. However, high blood pressures are associated with increased risk of bleeding.

19. a F; a T; c T; d T; e T. Left-sided lesions and conduction defects are found in such patients.

20. a T; a T; c F; d T; e T.

Carpentier type D is associated with almost-complete atrialization of the RV.

43.

ECMO FOR MYOCARDIAL INFARCTION WITH CARDIOGENIC SHOCK

Daniel Rob and Jan Bělohlávek

STEM CASE AND KEY QUESTIONS

A 69-year-old female with a medical history of arterial hypertension, dyslipidemia, and systemic scleroderma called the emergency medical service (EMS) for progressive dyspnea in the last 7 days. She was brought by EMS to the emergency department of a regional hospital. On admission she had the following: blood pressure 103/67 mm Hg, tachycardia 123 beats per minute (beats/min), and low peripheral O_2 saturation of 81%. An electrocardiogram (ECG) showed a Q wave anterior ST elevation myocardial infarction (MI). X-ray of the chest revealed lung edema and bilateral fluidothorax, and transthoracic echocardiography (TTE) revealed left ventricular (LV) systolic dysfunction with ejection fraction of 29% and ventricular septal rupture (VSR) (Figure 43.1). The tertiary cardiovascular center is asked to admit this patient.

HOW WOULD YOU RESPOND?

A. "Wait, send us your ECG and echocardiographic (ECHO) findings, and the heart team will discuss this case."

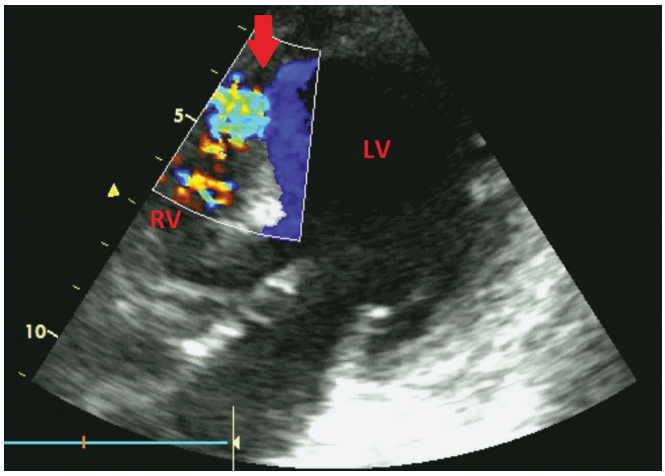


Figure 43.1 Bedside transthoracic echocardiography, atypical apical view with color flow Doppler showing ventricular septal rupture (red arrow), left ventricle (LV), right ventricle (RV).

B. "Transport the patient to the catheterization laboratory (cath lab); she needs immediate percutaneous coronary intervention (PCI)."

C. "Yes, send the patient to our cardiac intensive care unit (ICU)."

D. "Transport this patient immediately to our operating room; emergent surgery is needed."

Delaying transport of this patient by heart team discussion is not a good approach as this patient needs the care provided by the tertiary cardiac center because hemodynamic deterioration as well as cardiac arrest (CA) may occur at any time. Straightforward admission to the cath lab is possible; however, this MI is obviously subacute (7 days of lasting symptoms with Q waves on ECG and mechanical complication). Furthermore, in patients with lung edema and respiratory insufficiency, horizontal position in the cath lab frequently worsens respiratory insufficiency and may require orotracheal intubation to perform coronary angiography. Current American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) ST-segment elevation myocardial infarction (STEMI) guidelines recommend urgent/emergent surgical repair in patients with VSR, but revision of clinical findings, preparing the patient for a procedure, and heart team evaluation should be done. Therefore, we decided to admit this patient to our cardiac ICU. She was brought by EMS helicopter, and on admission her blood pressure was 89/45 mm Hg, she had persistent tachycardia at 129 beats/min, with oxygen saturation 86% on 8 L oxygen via mask, and arterial lactate level 3.1 mmol/L. Repeated TTE confirmed VSR and severe LV dysfunction (ejection fraction 26%) together with right ventricular (RV) dysfunction (tricuspid annular plane excursion 11 mm) and increased pulmonary pressure (tricuspid gradient of 60 mm Hg).

WHAT WOULD YOU DO NEXT?

A. Call the surgeon and convince the surgeon that emergent surgery is the best option.

B. Try to stabilize the patient with diuretics and inotropes and call the surgeon to discuss the timing of surgery.

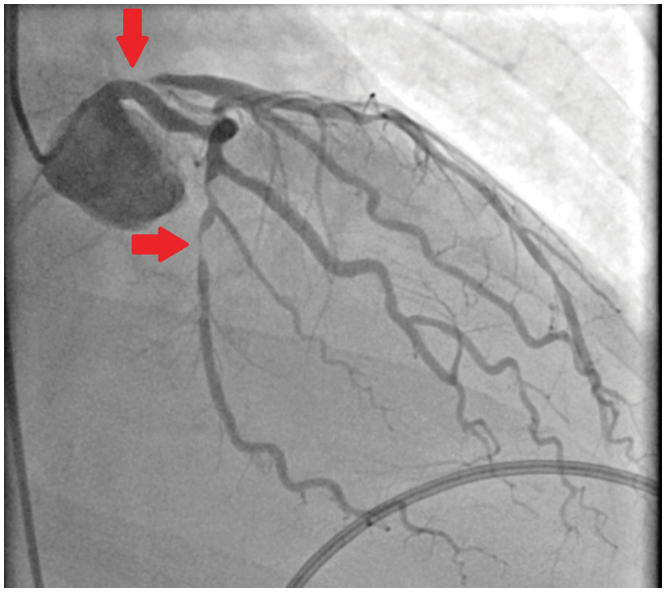


Figure 43.2 Coronary angiography of the left coronary artery revealing tight stenosis of the left anterior descending artery and the left marginal branch (red arrows).

C. You start veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) cannulation and call the surgeon to discuss the timing of surgery.

All responses are viable options. We initially treated the patient with intravenous furosemide, levosimendan, noninvasive ventilation, and left-sided fluidothorax puncture (1200 mL of transudate) to provide relief from dyspnea. Her blood pressure was 103/56 mm Hg on 0.23 μg/kg/min noradrenalin and 0.2 μg/kg/min levosimendan. Her blood lactate level was 2.9 mmol/L. We transported the patient to the cath lab. Cardiac surgeons were called to the cath lab to discuss further treatment options. Coronary angiography revealed two-vessel disease, critical proximal LAD (left anterior descending coronary artery) stenosis and tight stenosis of the left marginal branch (Figure 43.2). Surgeons deemed this patient unsuitable for urgent surgery as she was in persistent cardiogenic shock (CS) with severe LV dysfunction, RV dysfunction, and advanced systemic scleroderma.

HOW WOULD YOU PROCEED NEXT?

A. Transfer the patient back to the ICU and continue with conservative CS management.

B. Immediate PCI of the proximal LAD stenosis and then conservative CS management.

C. Immediate PCI of the LAD stenosis and percutaneous closure of the VSR.

D. First ECMO implantation, PCI, and percutaneous closure of the VSR after stabilization.

Conservative management of the VSR carries a grave prognosis. Percutaneous closure of the VSR is a technically challenging procedure that needs to be prepared as detailed assessment of VSR position and size has to be known for correct occluder placement. Persistent signs of CS (tachycardia, elevated blood lactate levels, and increasing doses of noradrenaline to sustain blood pressure) led us to a decision for ECMO implantation. Two ProGlide™ sutures were installed in the left femoral artery before ECMO arterial cannula insertion. V-A ECMO cannulation was done with ultrasound and x-ray guidance with a 17 French (17F) left femoral arterial cannula and a 21F left femoral venous cannula. After ECMO initiation, we recognized almost immediate loss of LV pulsatility, which is a common problem in patients with severe LV dysfunction. Loss of LV pulsatility threatens the patient by worsening of pulmonary edema, LV blood stasis, and thrombosis. Therefore, an Impella CP was inserted in the LV through the right femoral artery. The combined support with V-A ECMO and Impella led to rapid hemodynamic and respiratory improvement. The patient was transferred back to the ICU and was not intubated.

The next day the patient underwent a computed tomographic (CT) scan to assess the technical feasibility of ventricular septal defect percutaneous closure. CT revealed an 11 × 14 mm VSR in the apical part of the septum (Figure 43.3). On the third day of hospitalization, our interventional cardiologists performed percutaneous closure of the VSR with a Figulla Flex occluder together with PCI of the proximal LAD and left marginal branch stenosis (Figure 43.4). This procedure was done with local anesthesia of the groins only using 20 mL of 1% trimecaine. During occluder placement, the patient suffered repeated sustained ventricular tachycardia, which was well tolerated on ECMO and Impella support. ECMO together with Impella were quickly weaned and extracted a few hours after the procedure with perclose a ProGlide technique. The further course of hospitalization was complicated 3 days later by an arrhythmic storm, which was treated successfully by intravenous metoprolol and amiodarone. A transvenous cardioverter-defibrillator was implanted before

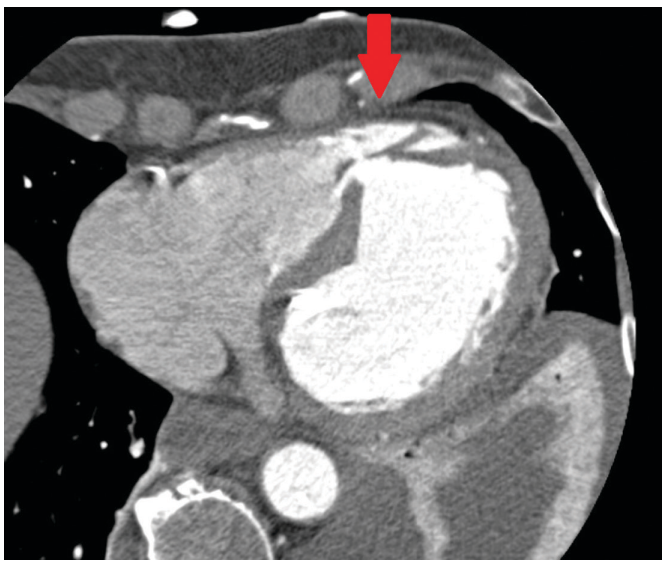


Figure 43.3 Cardiac CT scan confirmed 11 × 14 mm ventricular septal rupture (red arrow).

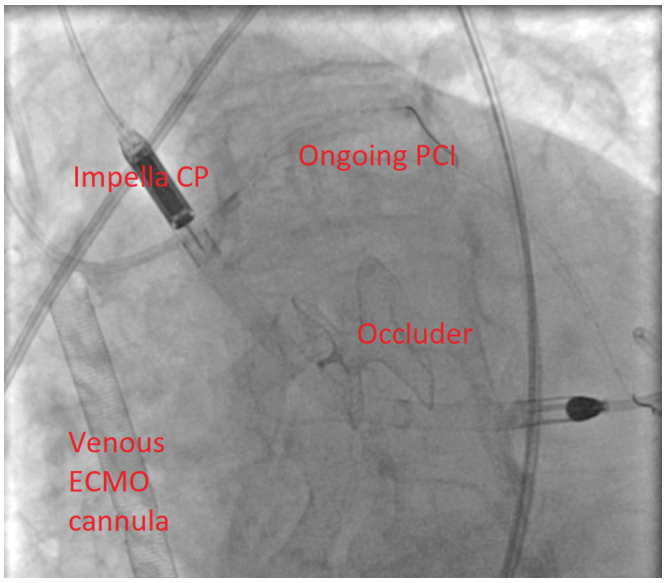


Figure 43.4 Angiogram from the complex procedure showing ECMO venous cannula, Impella CP in the LV, implanted occluder in the VSR, and ongoing PCI.

discharge. Repeated TTE revealed significant improvement of the LV function (ejection fraction increased from 26% to 44%). During the whole course of hospitalization, the patient was not intubated or sedated; lung edema was managed by diuretics, noninvasive ventilation, and Impella CP. If possible, we strongly prefer spontaneously breathing patients ("awake" ECMO) as the benefits of this approach far outweigh the risks. The patient was discharged home after 3 weeks of hospitalization in good condition, walking independently.

HOW IS CS AND REFRACTORY CS DEFINED?

Cardiogenic shock is a state of reduced cardiac output with critical end-organ hypoperfusion. Hemodynamic criteria are persistent systolic blood pressure less than 90 mm Hg and a cardiac index of 2.2 L/min/m^2 or less with evidence of end-organ hypoperfusion (oliguria, cool extremities, altered mental status, serum lactate > 2.0 mmol/L) despite adequate intravascular volume.[1]

A universal and generally accepted definition of refractory CS (RCS) has not been established. Persistent hypotension and/or low cardiac index, high lactate, and/or low central venous O_2 (SvO_2) levels despite aggressive pharmacological treatment (norepinephrine and dobutamine) is closest to a real-life clinical scenario.[2]

In our institution, the diagnosis of CS and RCS is based on easily accessible clinical criteria (clinical signs of hypoperfusion, invasive blood pressure, serum lactate and SvO_2 levels, initial response to therapy, ECHO) without advanced hemodynamic monitoring as it saves time and avoids complications associated with pulmonary catheter insertion.[3,4] Moreover, any catheter manipulation in the RV or LV in the settings of MI and VSR is risky as it may trigger arrhythmias or cause LV perforation and cardiac tamponade.

WHAT ARE THE MAIN CAUSES FOR CARDIOGENIC SHOCK?

Most patients with CS (70%) present with MI; of them, approximately 10% have a mechanical complication (acute mitral regurgitation, VSR, or rupture of the free wall).[5] CS occurs in between 3% and 10% of all MI patients.[5] Other CS causes consist mainly of worsening of chronic heart failure, cardiomyopathies, valvular disease, stress-induced cardiomyopathy, myocarditis, pulmonary embolism, and postcardiotomy CS.[5] Fast evaluation of medical history, ECG and bedside ECHO usually reveals the CS etiology in a few minutes. V-A ECMO has been used successfully in all above-mentioned conditions. Expected survival to discharge in patients with CS treated by V-A ECMO is around 40%.[6] The highest survival rate (65%) has been reported for patients with myocarditis.[6]

WHAT ARE THE MOST COMMON CARDIOGENIC SHOCK SCENARIOS WHERE ECMO IS CONSIDERED?

Clinical presentation and symptoms onset of CS may significantly differ even in the most common STEMI and CS scenario. Patients may be in profound CS at admission; some patients can develop or worsen CS during PCI; quite frequently, CS may develop during the ICU stay, usually within the first 24 hours after admission. When CS develops in a previously stable patient after successful PCI, in-stent thrombosis or mechanical complication should be immediately considered and excluded. ECHO is the technique of choice to rule out mechanical complications.[1] Hemorrhage or sepsis may also contribute to hemodynamic deterioration and should be ruled out promptly.

Cooperation of an intensivist and an interventional cardiologist in CS settings is of paramount importance. Patients with MI and left main disease, proximal LAD occlusion, and/or severe LV dysfunction are always at high risk for CS development. The experienced interventional cardiologist and intensivist should expect this worst-case scenario. Decision including assessment of inclusion, exclusion criteria, the most suitable type of mechanical circulatory support (MCS), strategy (implantation before PCI or standby approach), and implantation technique should be made within minutes to avoid the risk of profound CS development and/or CA.

The preferred vessel access is femoral percutaneous implantation of ECMO. Percutaneous ECMO cannulation can be done at the ICU with ultrasound guidance; however, if possible, we prefer ECMO implantation in the cath lab. Its x-ray guidance, equipment, and sterile conditions make it the perfect place for implantation and solution of possible difficulties (e.g., tortuous iliac and femoral arteries, stenoses).

A less common scenario is when the patient is not capable of transport from a regional hospital due to severe hemodynamic instability. In such cases, the mobile ECMO team can get quickly to the regional hospital by ambulance or helicopter to retrieve a patient. Transport from remote hospitals with V-A ECMO is safe and effective in most CS patients, and the survival rates are comparable to in-hospital patients.[7]

The retrieval team consists usually of the cannulating physician (being it interventionalist or intensivist) and perfusionist and occasionally also the nurse or ECMO coordinator. The remote cannulation scenario may often be a challenging experience and requires advanced experience of the team. Mainly, the cardiac intensive care experience, vascular ultrasound, and ECHO knowledge are prerequisites, together with advanced ECMO cannulation history. Frequently, cannulations are being performed under desperate hemodynamic conditions or even imminent CA. Distal perfusion cannula insertion is usually also necessary. Once the patient is stabilized, the patient can be safely loaded to the ambulance and transported for further evaluation and treatment in the tertiary center. Many possible complications may occur during the retrieval, mainly cannulation complications like bleeding, inadvertent vessel puncture, impossible distal perfusion cannula placement, nonpulsatile flow development, and more, and the retrieval team has to be capable of its initial management.

HOW ARE PATIENTS WITH CARDIOGENIC SHOCK MANAGED BEFORE ECMO IS CONSIDERED?

Standard therapy of CS consists of catecholamines, inotropes, fluids, and oxygen therapy, together with primary PCI in the acute MI setting.[8,9]

Despite the routine use of catecholamines and inotropes, there is only limited evidence from randomized trials comparing catecholamines and inotropes in CS.[10] The first-line vasopressor agent for CS is norepinephrine as it has been associated with a better outcome compared to dopamine and epinephrine.[11] The most used inotropic agent for CS is dobutamine, whereas levosimendan can be used as a second-line agent or preferentially in patients previously treated with β-blockers.[12] All vasopressors increase myocardial oxygen consumption and the risk of arrhythmias and may impair microcirculation and increase afterload, while inotropes mostly decrease afterload. Therefore, any vasopressors should be administered at the lowest possible dose and for the shortest possible duration.[8,9]

Fluid therapy in CS should be individualized as there is a lack of evidence-based approach. Fluid challenge in hypotensive patients is recommended,[10] but special consideration must be given to the risk of fluid overload and worsening lung edema.

Early restoration of coronary blood flow is a major predictor of survival in CS,[13] and during the acute shock phase, culprit vessel only PCI is associated with better results compared to multivessel PCI.[9] Therefore, immediate PCI should never be delayed or postponed due to other therapeutic procedures (e.g., intubation or central venous cannulation). Close "shock" team cooperation, mainly between interventional cardiologists and cardiac intensivists, is of paramount importance.

Cardiogenic shock is frequently complicated by multiorgan failure; among the most common are respiratory and renal failure. In case of acute cardiogenic pulmonary edema, noninvasive ventilation may rapidly improve the respiratory distress and reduce the need for intubation.[14] Intubation of patient in CS is always risky and may lead to profound hypotension and peri-intubation CA. If mechanical ventilation is necessary, a lung-protective ventilation regimen (below 6 mL/kg predicted body weight tidal volume) should be respected to prevent pulmonary injury.[10] Acute renal failure is common among CS patients and is associated with significant increase in mortality; renal replacement therapy (RRT) is frequently required. Earlier initiation of RRT had no effect on outcome.[9]

WHEN IS THE RIGHT TIME TO THINK ABOUT ECMO IN CARDIOGENIC SHOCK?

Timing of ECMO in CS is of great importance. Similarly, the time to ECMO implementation in extracorporeal cardiopulmonary resuscitation (ECPR) is a major factor in obtaining a good outcome, and this also applies to CS, except that the time window for ECMO initiation in CS is usually longer. Contrary to this view, ECMO in CS is usually perceived as salvage therapy, and many patients receive ECMO in a situation of RCS with already developed multiorgan failure with consequently worse outcomes.[10,15] Moreover, current ESC and AHA/ACC guidelines may support this view as these guidelines state that MCS may be considered as a rescue therapy in RCS.[16,17]

According to our experience, this approach has a low success rate. If the patient is not improving on standard therapy, it is always time to think about MCS because the frequently used approach of escalation of vasopressors to high doses is rarely successful. The critical question whether the patient is a suitable candidate for ECMO should be responded in all patients at risk of CS or right after CS diagnosis. If the patient is a suitable candidate, the ECMO team should be alerted and prepared for implantation as rapid deterioration in CS is common. This may prevent CA and in-hospital ECPR scenarios. In conclusion, for the best results, ECMO must be used early to preserve organ perfusion, prevent multisystem organ dysfunction, and decrease the need for invasive mechanical ventilation, sedation, and RRT.

WHO IS THE RIGHT CANDIDATE FOR ECMO IN CARDIOGENIC SHOCK?

Appropriate patient selection remains an unresolved issue.[10,15] As shown in large prospective trials, approximately 50% of CS patients survive without any device.[9] Inserting a device in patients who will respond to standard therapy may lead to device-related complications and possibly result in worse outcomes.[10] Among the 50% not surviving, there are futile situations where even the best available device and ICU care will not be able to change the clinical outcome.[10] However, our experience suggests that in most cases, it is hard or almost impossible to predict the patient outcome before ECMO treatment. Outliers who survive despite a bad starting position occur. On the other hand, adequate evaluation and avoidance of futile care is of major importance. Scoring algorithms could support the decision to initiate ECMO (e.g., http://www.save-score.com).[18] Age, CS etiology, LV function, and renal failure are good predictors of survival.[18,19] Despite these predictors, the ECMO team's clinical judgment remains the cornerstone of

a decision as no scoring systems can substitute for the complexity of clinical decisions in such a situation. In our case, the ECMO team were discussing the 69-year-old female with systemic scleroderma and subacute MI complicated by VSR and biventricular dysfunction. High age, systemic scleroderma, severity of biventricular cardiac dysfunction, and VSR were predicting very poor outcome. However, we were convinced that PCI together with a successful occluder implantation might lead to a reasonable cardiac recovery, and that ECMO was the only way to stabilize the patient and perform the procedure.

WHICH DEVICE SHOULD BE CHOSEN FOR A PATIENT WITH CARDIOGENIC SHOCK?

There are no evidence-based recommendations for short-term MCS device selection in CS.[10,15] Device selection should first and foremost consider the type and severity of cardiac failure (left, right, or biventricular).[10,15] In addition, operator and medical staff experience, device availability, costs, and patient characteristics are all important cofactors.[15]

In the presented case, we decided to use V-A ECMO. Our decision was led by signs of RCS due to biventricular failure with VSR and associated respiratory insufficiency. V-A ECMO can provide high flow of 5 L/min or more and biventricular and oxygenation support, in contrast to an intra-aortic balloon pump (IABP) and Impella CP. After V-A ECMO initiation, we had to face the anticipated ECMO-related complication with the loss of LV pulsatility. The Impella CP represents an effective way for LV unloading. Our institutional approach to V-A ECMO use in CS is summarized in Figure 43.5.

WHAT ARE THE MAJOR COMPLICATIONS RELATED TO ECMO IN CARDIOGENIC SHOCK?

The most important complication related to outcome is bleeding.[15] Most patients with CS and MI are treated with PCI. Stent implantation requires dual antiplatelet therapy, and ECMO needs effective anticoagulation. This "triple" therapy together with numbers of invasive procedures and alterations in the coagulation pathway due to ECMO and CS create a high-risk bleeding situation. This risk can be mitigated by

1. ECMO cannulation under ultrasound and x-ray guidance by an experienced operator
2. Strict coagulation control (target activated coagulation time is 180–220 seconds, activated partial thromboplastin time of 1.5–2.5 times normal)
3. Platelet level control and its substitution when appropriate
4. Minimizing blood loss in case of bleeding (discontinuation of heparin, plasma and coagulation factor infusions, surgery)
5. Early ECMO weaning

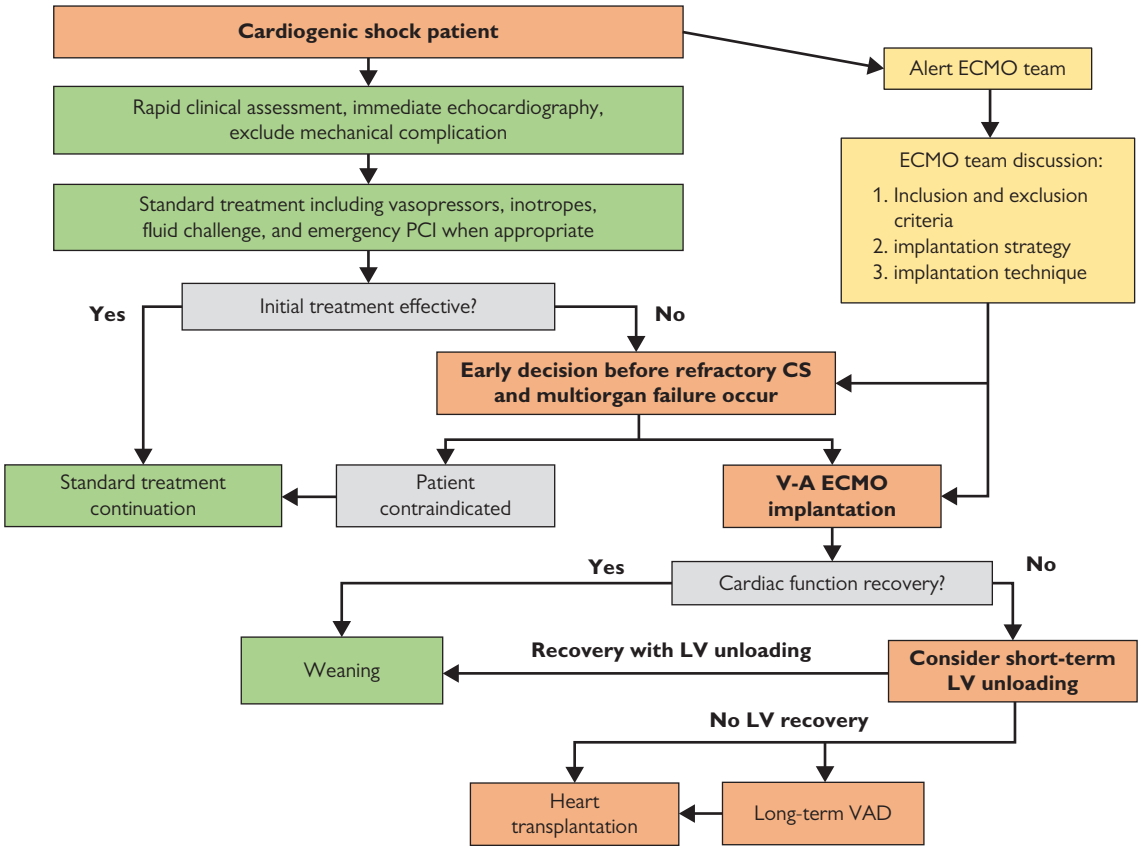


Figure 43.5 Treatment algorithm: the use of V-A ECMO in cardiogenic shock. VAD, ventricular assist device.

The second major complication likely to occur in patients with severe LV dysfunction on V-A ECMO is the worsening or even loss of LV contractility.[20] ECMO retrograde blood flow increases the LV afterload and LV end-diastolic pressure, which may cause pulmonary edema and even LV blood stasis with thrombosis.[15,20] There are several strategies to lower this risk, and the presence of LV pulsatility must be monitored by arterial waveform and ECHO. The first strategy should be to keep ECMO flow as low as necessary for sufficient organ perfusion. Inotropes may sometimes help to sustain LV contractility and aortic valve opening. However, LV unloading is sometimes inevitable and has been associated with decreased mortality in adult patients with CS treated with V-A ECMO.[20] An expensive but effective approach for LV unloading used in our institution is percutaneous Impella CP.[21,22] Direct surgical decompression "venting" of the LV is invasive and associated with bleeding risk and wound complications. Some centers are using an IABP or percutaneous balloon atrial septostomy to open a left-to-right atrial shunt.[15,23] Larger clinical studies evaluating and comparing the most effective method for LV decompression are missing.

Table 43.1 summarizes complications associated with V-A ECMO use in CS. Daily monitoring is required to provide early detection and treatment of these complications. Prespecified institutional protocols should include careful monitoring of device components, hemodynamics, anticoagulation, blood gas analysis, and the brain and cannulated limb tissue perfusion.[15]

HOW IS WEANING FROM ECMO ACCOMPLISHED?

Weaning from ECMO and its tempo are dependent on the CS cause reversibility (e.g., success of PCI) and the resulting LV function recovery. Extracorporeal blood flow is being gradually decreased, and heart function is closely monitored by the arterial pressure waveform, heart rate, catecholamine dosages, central venous oxygen saturation ($ScvO_2$), and lactate levels together with repeated ECHO assessment. A Doppler ECHO aortic velocity time integral (VTI) of 10 cm or greater and left ventricle ejection fraction (LVEF) greater than 25% at minimal ECMO flow support to less than 1.5 L/min together with stable blood pressure and lactate levels are reliable predictors of successful weaning.[24] Hemodynamic deterioration may sometimes occur several hours after ECMO extraction despite fulfilling all the weaning criteria. This complication is usually triggered by supraventricular and/or ventricular arrhythmias, which should be recognized and treated immediately, or sepsis, where rapid intravenous antibiotic treatment usually stabilizes the situation.

WHAT IS THE EXPECTED OUTCOME FOR CARDIOGENIC SHOCK PATIENTS?

Despite all the current therapies, short-term survival (to hospital discharge and/or 30 days) in CS remains around 50%.[9]

Table 43.1. **THE COMMONEST COMPLICATIONS ASSOCIATED WITH V-A ECMO USE IN CARDIOGENIC SHOCK**

COMPLICATION	DESCRIPTION
Major bleeding	Reported among 40% of patients. Most frequently occur in invasive procedural sites and gastrointestinal and retroperitoneal space but may arise anywhere. Heparin and antiplatelet therapy discontinuation, source control, and plasma and coagulation factor substitution are the mainstays of treatment.
Increased LV afterload	Common complication, especially in patients with preexisting LV dysfunction. Pulse pressure and ECHO monitoring are required. If loss of LV pulsatility occurs, decrease ECMO flow if possible; use inotropes. LV venting by Impella, IABP, atrial septostomy, or surgical vent is frequently required.
Acute kidney injury and kidney failure	Occur in 50% of ECMO patients and are associated with significant increase in mortality. Exclude hemolysis, avoid nephrotoxic medication, optimize fluid management, ensure mean arterial pressure control at 70–75 mm Hg, give diuretics, and if inevitable use RRT.
Infections	Sepsis occurs in almost 1/3 of ECMO patients. Identification of source and pathogen together with early proper antibiotic treatment ares important.
Acute limb ischemia	Occurs in 10%–15% of peripheral V-A ECMO patients. Distal perfusion catheter and NIRS monitoring of limb tissue perfusion are necessary to avoid fasciotomy or even amputation. Percutaneous angioplasty and/or surgical embolectomy is usually an effective treatment.
Hematological disturbances	Frequent but differ in severity. Causes include hemolysis (accelerated in combination with Impella), acquired von Willebrand disease, thrombocytopenia (routine monitoring of platelet count is necessary), heparin-induced thrombocytopenia, venous thromboembolism. High level of suspicion, routine coagulation monitoring, and appropriate treatment are key.
Stroke	Intracranial bleeding as well as ischemic stroke may rarely occur but are devastating complications. If recognized early, ischemic stroke can be treated by mechanical thrombectomy.
Differential oxygenation	Also called Harlequin syndrome; occurs when poorly oxygenated blood from the LV supplies the ascending aorta. NIRS monitoring of the right hemisphere is helpful. Treatment consists of increased oxygenation support on ventilator, increased ECMO blood flow. In rare situation, veno-arterial-venous ECMO configuration is needed.

NIRS, near-infrared spectroscopy.

MCS devices are used in patients with profound and RCS where the prognosis is expected to be significantly worse. In the adult population of the ELSO Registry, 42% of patients with CS supported by V-A ECMO survived to hospital discharge.[6] Adults with congenital heart disease had the lowest survival (37%), and those with myocarditis had the best survival (65%) in this population.[6]

In patients surviving the acute phase of CS due to MI, there is still an increased risk of death after the acute event, with annualized death rates of 8% to 10% up to 6 years of follow-up.[25] Long-term data for patients after successful ECMO therapy are scarce, but these patients often struggle with persistent physical and social problems.[26] A dedicated outpatient clinic within a tertiary cardiac center with trained medical staff who can provide tailored medical and psychosocial interventions for these patients is of great advantage. Moreover, the feedback from long-term follow-up visits (to see the quality of life and personal patient perspectives) gives ECMO team members an invaluable experience.

WHAT ARE THE ETHICAL ISSUES IN CARDIOGENIC SHOCK AND ECMO?

Inevitably, the use of ECMO in CS is associated with several ethical questions. The decision whether to implant ECMO is usually done under time pressure and a short supply of information, and reliably predicting outcomes in a real-time complex clinical situation is difficult and sometimes even impossible.[15] Contraindication of the patient to receive ECMO or other MCS therapy is another dilemma and should always be based on objective criteria and ECMO team discussion. Furthermore, when ECMO is no longer meeting its intended goals, a discussion of limiting treatment to either no escalation of life support or withdrawal of life support should be considered as ECMO should not be used simply to prolong the dying process.[10,15]

In our case, we decided to use MCS in a 69-year-old lady who was deemed too risky for an early VSR surgery. If the PCI and VSR closure did not lead to expected LV recovery, we might have ended in the "bridge-to-nowhere" scenario as the patient was not a candidate for transplantation or a destination therapy. Despite all the possible risks associated with our decision, we were convinced that MCS was the only way to stabilize and effectively treat this patient. Our decision was also influenced by a good quality of life before the MI event in this patient.

DISCUSSION

Since the landmark SHOCK study more than 20 years ago,[13] short-term mortality of CS in MI remains around 50% despite current therapies.[9] If standard therapy of CS is ineffective, MCS usually represents the last treatment modality to reverse hemodynamic deterioration with multiorgan failure. The use of MCS (especially V-A ECMO) in CS therefore has been increasing in the last two decades despite limited high-quality evidence from prospective studies.[6,15] According to current ESC and AHA/ACC STEMI guidelines, the use of short-term MCS in CS may be considered as a rescue therapy on an individual basis (class II, level of evidence C—expert consensus).[16,17]

The IABP is one of the oldest MCS devices, introduced in the early 1960s.[10] Despite its persistent use in many cardiac centers, IABP did not improve outcomes in patients with STEMI and CS without mechanical complications in a large prospective trial.[27] This passive device should not be routinely used in this indication anymore according to ESC guidelines (class III, level of evidence B).[16] In our cardiac center, we have abandoned the use of IABP even in mechanical complications as IABP provides only small, temporal, and short-lasting support insufficient for patients with profound and RCS.[28,29]

A tandem heart can reverse hemodynamic and metabolic parameters in CS more effectively than standard treatment with IABP.[30] However, more complications were seen in the tandem heart patients compared to those who received IABP, with no difference in mortality.[30]

The Impella CP has been increasingly used in the last decade but failed to prove effective in several retrospective as well as small prospective CS trials[31] questioning the effect of Impella CP as well as unrealistic and underpowered trial design.[10,15] Impella CP can generate intermediate (2–4 L/min) blood flows, which may not be sufficient for patients in RCS. A larger prospective trial with Impella CP in CS is ongoing.[32]

The use of V-A ECMO in CS has several advantages compared to other MCS. It provides high-flow support (≥5 L/min) sufficient even in CA and biventricular and full oxygenation support, in contrast to IABP and Impella CP. Therefore, in CS patients with concomitant respiratory failure, RV failure, or CA, V-A ECMO represents the MCS of first choice.[15] Developments with miniaturized systems and percutaneous cannula insertion have led to wider adoption of V-A ECMO by interventional cardiologists for the treatment of CS.[10] Several retrospective studies showing improved outcomes with V-A ECMO compared to standard therapy in CS are available; however, ongoing prospective randomized trials focusing on the use of ECMO in patients with CS will determine its clinical use in the near future.[2,15] Of note, a meta-analysis revealed a significant 33% higher 30-day survival in patients with CS treated by V-A ECMO compared to IABP ($p = 0.0008$; NNT 3).[33]

Concomitant implantation of Impella in addition to V-A ECMO (sometimes called ECPELLA) successfully unloads the LV and eliminates the major disadvantage of ECMO.[21,22] However, this approach should also be studied in rigorous prospective trials as the rates of complications with combined MCS are high, and the reported rate of hemolysis[22] that may trigger endothelial dysfunction, inflammation, and renal impairment is of particular interest.

Despite ongoing prospective randomized trials, there are many barriers to proving survival benefit in CS trials. High baseline mortality despite current therapies; different severity of shock; study population heterogeneity (age, comorbidities); delivering MCS too late to affect outcomes; study protocol deviations; and crossover rates (usually done in the best intention of investigators to rescue the patients' life) make even prospective randomized data difficult to evaluate and interpret and mortality benefit hard to prove.

CONCLUSION

- ECMO therapy in RCS may offer a chance for survival in patients who would otherwise die.
- Early ECMO initiation before multiorgan failure development, careful patient selection, and comprehensive intensive care by an experienced team are key to a successful outcome in patients with CS.
- ECMO-associated bleeding risk and increased LV afterload represent the biggest obstacles to better results. Strict coagulation control and venting of the LV to prevent these complications are often necessary.

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REVIEW QUESTIONS

1. The use of ECMO in CS is

   A. Experimental therapy used only in human clinical trials.
   B. A broadly used therapeutic approach with a high level of recommendation in guidelines.
   C. The last instance and rescue therapy used only in developed multiorgan failure.
   D. An established treatment method for patients with failed standard therapy of CS.

2. The most common cause of CS where ECMO is used is

   A. Myocarditis
   B. Ventricular septal rupture
   C. Myocardial infarction
   D. Postcardiotomy CS

3. What is the most frequent complication related to ECMO outcome in CS?

   A. Acute limb ischemia of the cannulated limb
   B. Infections
   C. Bleeding
   D. Acute stroke

4. A 49-year-old woman was admitted for STEMI; PCI of the LAD did not lead to reperfusion. The LVEF was 21%, and blood pressure was 88/44 mm Hg on dobutamine and noradrenaline treatment; she has overt signs of lung edema. How would you proceed?

   A. Call the ECMO team and prepare for MCS implantation.
   B. Give a fluid challenge and increase the dobutamine and noradrenaline dosages.
   C. Call the interventional cardiologist to repeat the coronary angiography and PCI.
   D. Wait for the clinical improvement that should occur.

5. With loss of LV pulsatility on ECMO therapy, LV unloading can be achieved with

   A. Impella device.
   B. Intra-aortic balloon pump.
   C. Surgical venting.
   D. All answers are correct.

6. You have a night shift in the ICU of a regional hospital. A 66-year-old man was admitted in the afternoon from a tertiary cardiac center after successful PCI of the LAD. At admission, he was stable; now he suddenly develops hypotension and sinus tachycardia. What would you do?

   A. Call the cath lab and request repeated coronary angiography.
   B. Check ECG, hemoglobin, lactate levels; do rapid bedside TTE; try fluid bolus; and call the cardiologist in the tertiary cardiac center to discuss this case.
   C. Give a fluid challenge; start noradrenaline; correct hypotension; and wait until morning.

7. What is the most common ECMO setting in CS?

   A. Percutaneous veno-venous ECMO
   B. Surgically implanted veno-arterial ECMO with IABP
   C. Percutaneous femoral V-A ECMO.

8. What is the expected 30-day survival for CS patients treated by ECMO?

   A. 93%
   B. 68%
   C. 24%
   D. 42%

9. What is the reliable predictor of ECMO weaning?

   A. Doppler ECHO aortic VTI 10 cm or greater and LVEF greater than 25% at minimal ECMO flow support to less than 1.5 L/min
   B. Blood lactate levels 3.5 mmol/L or greater at minimal ECMO flow support to less than 1.5 L/min
   C. Heart rate 110/min or less
   D. Pulse pressure 15 mm Hg or more

10. An IABP in the settings of MI and CS

    A. is the MCS of first choice.
    B. should not be used in this indication anymore.
    C. is used in patients with unsuccessful PCI only.
    D. is effective and should be used in mechanical complications.

ANSWERS

1. D
2. C
3. C
4. A
5. D
6. B
7. C
8. D
9. A
10. B

44.

ECMO SUPPORT FOR PATIENTS WITH MYOCARDITIS

Jan Kunstyr, Michal Lips, and Petr Kuchynka

STEM CASE AND KEY QUESTIONS

A 32-year-old gentleman sought medical advice after a few days of weakness, headache, and finally nausea with vomiting and shivering. He was a healthy and sporty male who underwent tonsillectomy a few years ago and had a normal electrocardiogram (ECG) registered prior to the surgical procedure (Figure 44.1). During his first physician contact at the emergency room of a municipal hospital, there were no signs of a serious condition. The patient was afebrile, slightly hypotensive; his ECG was not recorded, and no blood samples were taken. He was given nonopioid pain killers and discharged from the hospital. At bedtime, he went to sleep.

At 12:40 AM, a dispatcher of the Emergency Medical Service received an urgent call from the patient's apartment. His spouse realized he had been unconscious and gasping. The service operator, together with guiding a "telephone-assisted cardiopulmonary resuscitation," sent a medical rescue team on site. After 10 minutes of a lay resuscitation, the professionals took over, and their life-saving effort continued for another 15 minutes. The first recorded rhythm was ventricular fibrillation (VF). Immediate defibrillation resumed sinus rhythm. The patient was intubated; a peripheral vein access was secured, and he was transported to the intensive care unit (ICU) of the university hospital.

On admission to the ICU, VF occurred again. He was defibrillated, but during the next 30 minutes this life-threatening arrhythmia repeated 31 times! This malignant "arrhythmogenic storm" was both pharmacologically treated and continuously defibrillated. His lactate level did not rise above 2.5 mmol/L, and his arterial blood gases showed only minor acidosis. His pupils were narrow with a short photoreaction. Empirical antibiotic treatment with ciprofloxacin was started. All standard samples were sent to the biochemistry, toxicology, microbiology, and hematology laboratories, recorded no significant findings.

In between shocks, a narrow ORS complex sinus rhythm with normal conducting times and normal QT interval always resumed. The first 12-lead ECG showed sinus tachycardia 100/min with right bundle branch block (Figure 44.2). Bedside transthoracic echocardiography (TTE) showed severe left ventricular (LV) systolic dysfunction with ejection fraction (EF) 20% due to diffuse hypokinesis, no signs of right ventricular dysfunction or dilation, and no pericardial

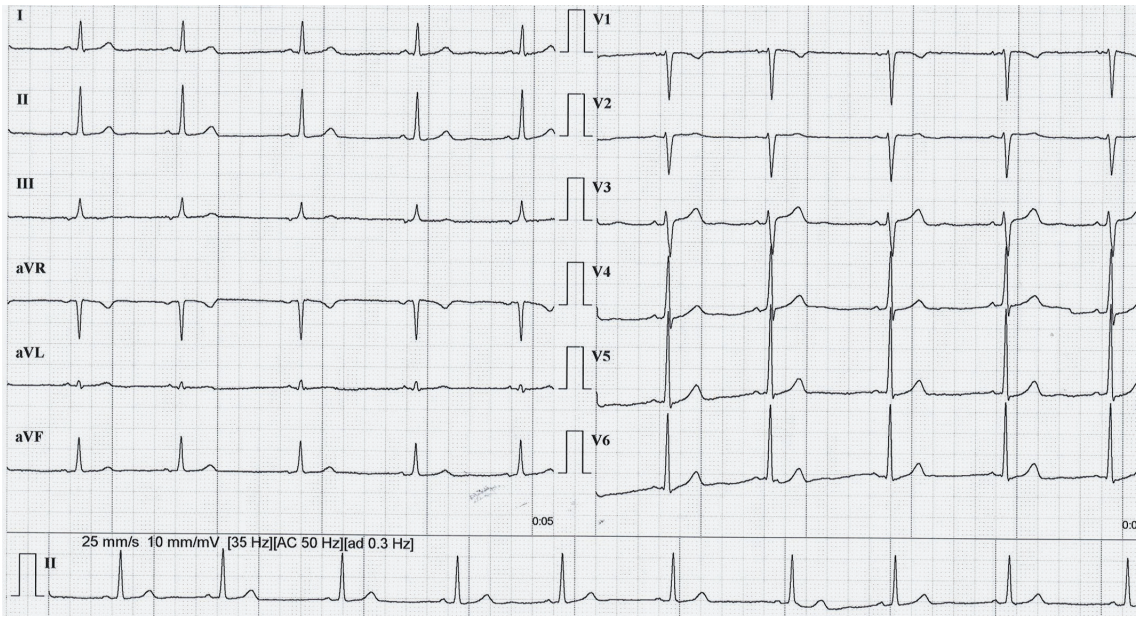


Figure 44.1 Electrocardiography registered 2 years before the onset of fulminant myocarditis was without significant abnormality.

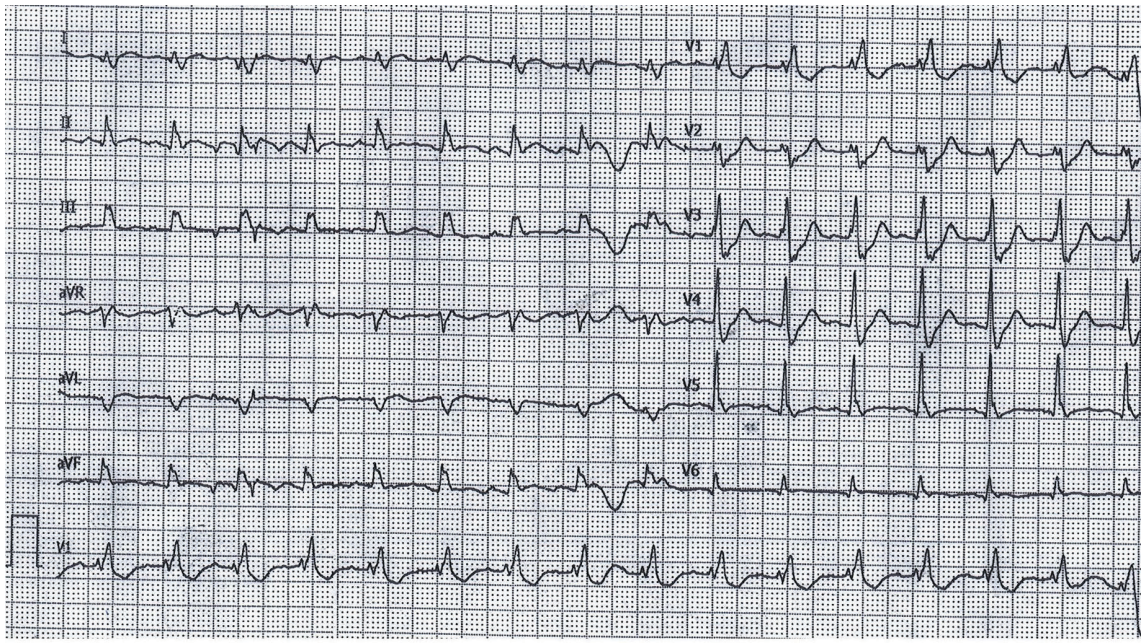


Figure 44.2 Twelve-lead ECG, registered on admission of the patient to the hospital, shown in between defibrillations for ventricular fibrillation. Mild sinus tachycardia with wide ORS complex and right bundle branch block with vertical axis and borderline first-degree atrioventricular block is depicted.

effusion. Cardiac output (CO) was estimated at around 3 L/min. Invasive monitoring of blood pressure and central venous pressure was started.

The catheterization laboratory was contacted; while waiting for the catheterization team, sheaths were inserted into the groin vessels to be prepared for both coronary intervention and extracorporeal membrane oxygenation (ECMO) introduction. The investigation in the catheterization laboratory was negative. In addition, brain computed tomography (CT) scan was taken on the way back to the ICU; it was also without any pathology. However, during the transport and imaging itself, VF reoccurred 11 times.

On return to the ICU, the patient was in severe cardiogenic shock with LVEF 10%–15%, with an TTE measured stroke volume of 20 mL. The required noradrenalin dose was 0.2 μg/kg/min. Immediately, peripheral veno-arterial (V-A) ECMO was started via previously inserted sheaths in the left groin vessels without any complication using 23 French (23F) venous and 19F arterial cannulae. Heparin was given to reach an activated partial thromboplastin time of 60–65 seconds, and a 7F cannula for antegrade/distal perfusion of the left leg was inserted. Approximately 3 hours after admission to the department, full V-A ECMO flow of 4 L/min was established.

After mechanical circulatory support (MCS) commencement, a TTE showed massive spontaneous echocontrast in the severely hypokinetic, dilated, almost nonejecting LV. Therefore, a small dose of intravenous dobutamin was given, which caused fast disappearance of the LV "smoke" and occurrence of at least some ejections of the LV together with its significant unloading.

Endomyocardial biopsy (EMB) was indicated due to suspicion of myocarditis and performed the next day. Three myocardial samples obtained from the interventricular septum were evaluated by histopathology and immunohistochemistry, four specimens by polymerase chain reaction (PCR), and one by electron microscopy. The finding of acute myocarditis was confirmed not only by immunohistochemical analysis but also based on histopathological Dallas criteria. Lymphocytic myocarditis was present; granulomas or giant cells were absent. PCR and electron microscopy were weakly positive only for parvovirus B19. Therefore, no specific treatment was indicated.

His course on ECMO was uneventful, with fast improvement of cardiac function. Within 4 days, slow weaning of the ECMO support was started and eventually was surgically explanted on the 7th day. Weaning of artificial ventilation was prolonged due to an unstable chest with several rib fractures. However, after 17 days on ventilator support, he was successfully extubated. Three days later, he was moved to a rehab center with the final diagnosis of fulminant myocarditis and complete LV systolic function recovery (Figure 44.3). Subsequently performed genetic analysis was negative for pathogenic mutations linked with cardiomyopathies, including laminopathies. Two years after the episode of myocarditis the patient remained asymptomatic and had normal LVEF.

HOW IS MYOCARDITIS DEFINED?

Myocarditis is defined as heart muscle inflammation, which should be confirmed using established histological, immunological, and immunohistochemical criteria.[1,2] Causes of myocarditis can be both infectious (bacterial, viral, protozoal, parasitic, and fungal) and noninfectious (immune mediated or toxic).[3]

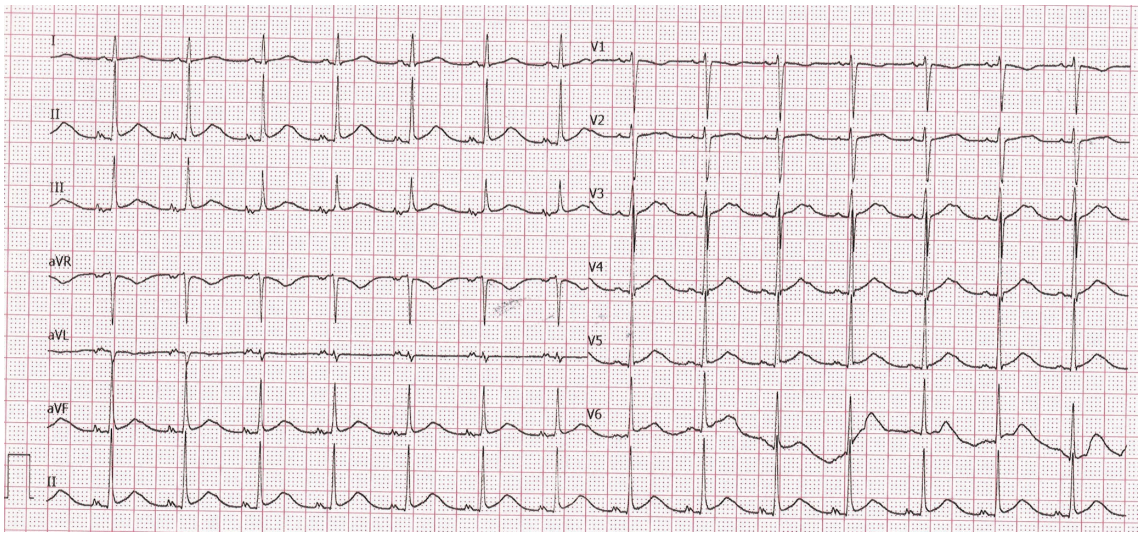


Figure 44.3 Twelve-lead ECG recorded 1 week after the admission of the patient for fulminant myocarditis. The ECG shows sinus rhythm with a normal PR interval, normal QRS width, mild repolarization changes with U waves, and an early repolarization pattern in the inferolateral leads.

WHAT IS THE INCIDENCE OF MYOCARDITIS?

The exact incidence of the myocarditis is not well known. EMB, representing the gold standard for establishing the diagnosis of myocarditis, is performed relatively unfrequently. Moreover, mild forms of myocarditis may be unreported by the patients or unrecognized by physicians due to vague symptoms and signs.[4] An incidence of 22 out of 100,000 patients is estimated based on the *International Classification of Diseases* hospital discharge.[4] Biopsy-proven myocarditis is reported in 9%–16% of adults and approximately 50% of children with unexplained dilated cardiomyopathy (DCM).[1]

WHAT IS THE ETIOLOGY OF MYOCARDITIS?

The etiology of myocarditis is of either infectious or noninfectious origin. Infectious myocarditis in general dominates and is caused by a wide range of viral, bacterial, protozoal, parasitic, or fungal agents. In industrialized countries, these pathogens are primarily viruses, and the most often reported viral agents causing myocarditis are parvovirus B19, herpetic viruses, influenza viruses, enteroviruses, and adenoviruses. Noninfectious causes are immune mediated (allergens, alloantigens, and autoantigens) or toxic (drugs, heavy metals, hormones, physical agents, or miscellaneous).[1] Among the noninfective causes, it is important to mention mainly connective tissue diseases, inflammatory bowel diseases, vasculitis, and drug hypersensitivity reactions.

WHAT IS THE PATHOGENESIS AND PATHOPHYSIOLOGY OF MYOCARDITIS?

Pathogenesis of the myocarditis is dependent on the cause of the disease and is influenced by the immune system of the affected individual and at least in some cases also by genetic factors. In a murine model of viral myocarditis, three phases can be distinguished.[5] The first phase, known as initial myocardial injury, is initiated by virus internalization. At this stage, direct destruction of cardiomyocytes occurs by virus-mediated lysis. In the second phase after viral invasion, the myocardium is infiltrated by natural killers. Their activation plays a key role in the inhibition of further viral invasion and replication. Production of various cytokines, including interleukin 1, tumor necrosis factor αalpha, or interferon γ, is increased. These cytokines potentiate activity of inducible nitric oxide synthase, which has a positive role in anti-infective defense mechanisms. On the other hand, these cytokines may worsen the clinical course of myocarditis due to their negative inotropic effect. In this subacute phase, cellular immunity (lymphocytes and myocytes, respectively, granulocytes) is involved, and antibodies (neutralizing) are also produced. The third phase, present in only approximately 30% of subjects with myocarditis, is characterized by cardiac remodeling and development of the DCM phenotype. At this stage, ongoing myocardial involvement is caused by microbial (typically viral) persistence or autoimmune inflammation.

HOW DOES MYOCARDITIS PRESENT?

Clinically, it can occur in a wide spectrum of presentations, which varies from subclinical asymptomatic courses to life-threatening situations, including refractory cardiogenic shock.[6] In case of fulminant myocarditis, patients usually have a short history of an acute flu-like manifestation with fever, weakness, fatigue, and joint and muscular pain, and after several days they present with nonspecific symptoms, including cough, dyspnea, chest pain, or palpitations. If the situation progresses into severe heart failure with circulatory collapse, MCS is the mainstay of therapy when full medical treatment fails to improve the patient's status.

HOW IS THE CLINICAL PRESENTATION CLASSIFIED?

Four different types of manifestation are usually described: acute coronary syndrome-like; acute heart failure; chronic heart failure (duration > 3 months); life- threatening condition (cardiogenic shock, malignant arrhythmia, aborted sudden cardiac death). Fulminant myocarditis is a subtype of acute myocarditis characterized by (a) acute illness (often flu-like symptoms) with a short history of symptoms (<4 weeks, frequently < 1–2 weeks); (b) hemodynamic instability with low CO due to cardiogenic shock or arrhythmias; and (c) need for hemodynamic support (inotropes, MCS).[7]

WHAT ARE TYPICAL ECG FINDINGS?

Electrocardiography is abnormal in the majority of patients suffering from myocarditis, and often diffuse ST-T changes of nonischemic type are present. However, there are no pathognomonic changes for myocarditis on ECG. On the other hand, the presence of atrioventricular block (mainly of second or third degree) should always raise suspicion of cardiac sarcoidosis, giant cell myocarditis, or Lyme disease in the differential diagnosis. Moreover, a prolonged QRS complex is a well-known negative prognostic factor for patients suffering from myocarditis.

WHAT IS THE ROLE OF ECHOCARDIOGRAPHY?

Echocardiography represents the first-line imaging modality in patients with suspicion of myocarditis. However, there are no specific echocardiographic features for myocarditis, and this imaging method is primarily useful to rule out non-inflammatory diseases and to monitor changes in cardiac chamber size, ventricular function, and pericardial effusions. Echocardiography is also useful to exclude intraventricular thrombi prior to EMB. In fulminant myocarditis, the LV usually shows significantly reduced systolic function, but the cavity is often of normal size, and LV wall thickness might be increased. To the contrary, in chronic myocarditis associated with development of inflammatory cardiomyopathy, the LV is dilated, and the walls are typically of normal thickness.

WHAT IS THE ROLE OF CARDIAC MAGNETIC RESONANCE FOR NONINVASIVE INVESTIGATIONS?

Cardiac magnetic resonance (CMR) represents the gold standard in noninvasive tissue characterization and is thus also a key noninvasive diagnostic tool for assessment of myocardial inflammation. In patients with myocarditis, CMR has the ability to visualize edema using T2-weighted imaging (Figure 44.4) or T2 mapping, myocardial hyperemia respectively capillary leakage (by early gadolinium enhancement [EGE]) and late gadolinium enhancement (LGE) with nonischemic distribution (Figure 44.5). The previously used Lake Louise criteria were consistent with myocarditis if two of three (edema in T2-weighted images, EGE or LGE) were

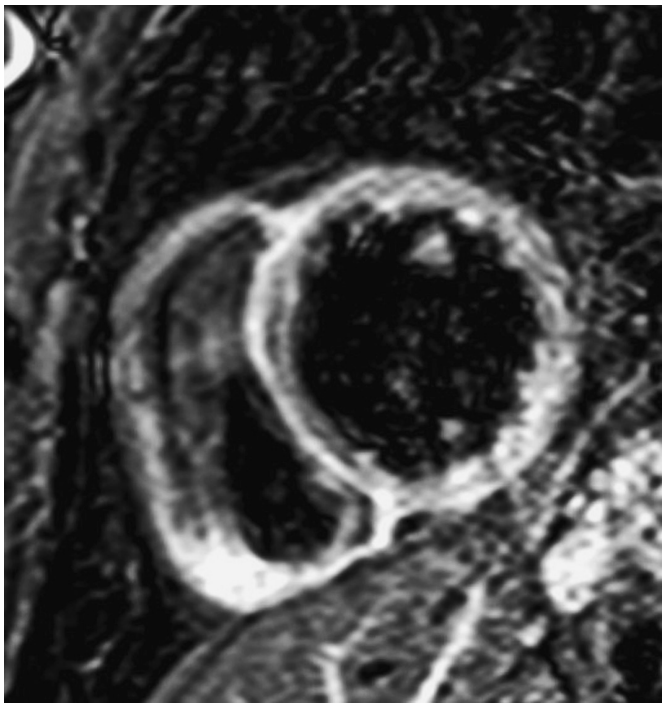


Figure 44.4 Cardiac magnetic resonance (short-axis view), T2-weighted image demonstrating diffuse myocardial edema involving the left and right ventricles in a patient with fulminant myocarditis.
Published with courtesy of Martin Masek, MD, PhD, Department of Radiology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic.

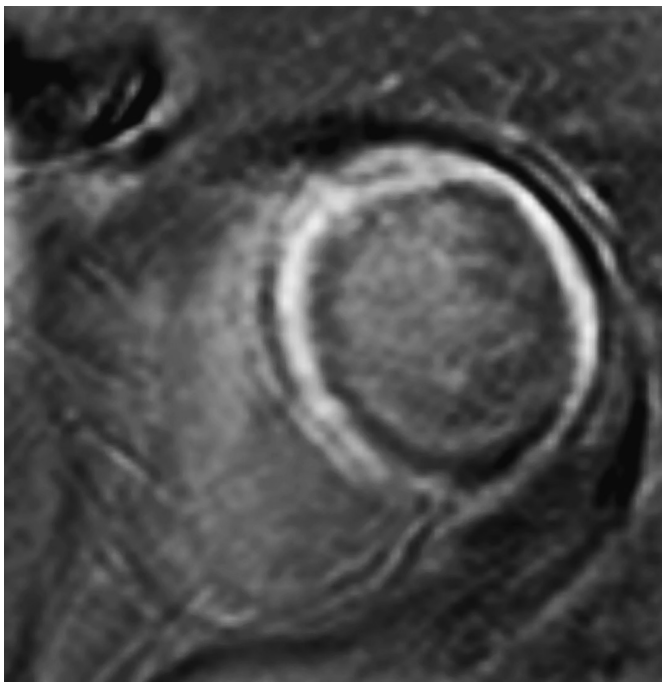


Figure 44.5 Cardiac magnetic resonance (short-axis view) image showing late gadolinium enhancement involving entire left ventricle in midmyocardial and subepicardial layers in a patient with fulminant myocarditis.
Published with courtesy of Martin Masek, MD, PhD, Department of Radiology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic.

detected. Moreover, the presence of LV systolic dysfunction or pericardial effusion provides additional, supportive evidence for myocardial inflammation.

Recently, updated Lake Louise Criteria were published,[8] and currently CMR criteria for myocarditis are fulfilled when at least one of T1-based imaging criteria (regional or global increase of native myocardial T1 relaxation time or extracellular volume using T1 mapping or presence of nonischemic LGE) and at least one of T2-based imaging criteria (regional or global increase of myocardial T2 relaxation time using T2 mapping or regional/global high T2 signal intensity in T2 weighted images) are present. Performing CMR is usually limited in the critically ill; thus, only a minority of subjects suffering from fulminant myocarditis undergoes this examination in the acute phase of the disease. In patients with fulminant myocarditis, a diffuse pattern of LGE dominates and is present in approximately 80%, which is significantly higher than in the subjects with nonfulminant acute myocarditis.[4]

IS THERE A ROLE FOR ENDOMYOCARDIAL BIOPSY?

Endomyocardial biopsy (EMB) is considered the gold standard for diagnosis of myocarditis. Moreover, this invasive method is essential for definitively confirming myocardial inflammation and has the ability to reveal underlying etiology. Because this invasive procedure carries the risk of serious complications, it is indicated only in more severe forms of myocarditis or in a suspicion of a specific form of myocarditis requiring specific treatment. Apart from a nonnegligible complication rate, other facts that limit the use of EMB are sampling time, sampling error, and pathological interpretation. Additionally, it should be noted that viral myocarditis is usually characterized by a focal infiltration, predominantly in the lateral free wall of the LV; therefore, there may be false-negative results when right ventricle biopsies are analyzed.[9]

Fulminant myocarditis represents a clear indication for EMB. Myocardial samples are analyzed for the presence of inflammation histologically (based on Dallas criteria) and immunohistochemically (≥14 leukocytes/mm^2, including up to 4 monocytes/mm^2 with the presence of CD3$^+$ T lymphocytes 7 cells/mm^2 or more, is needed for diagnosis of myocarditis) and for the presence of microbial agents by PCR or electron microscopy. The myocardial infiltrate is subsequently specified, and the myocarditis is labeled as lymphocytic (most prevalent type in both fulminant and nonfulminant myocarditis), eosinophilic (Figure 44.6), granulomatous, or giant cell. Based on the recently published data from an international registry comprising 220 subjects with histologically proven acute myocarditis, lymphocytic myocarditis was present 73% of fulminant myocarditis and 71% of nonfulminant myocarditis; eosinophilic in 12% and 18%, respectively; giant cell in 15% and 4%, respectively; and granulomatous in cardiac sarcoidosis in 1% and 7%, respectively.[10] The lowest prevalence of granulomatous myocarditis might be influenced by the known fact that for this type of patchy myocardial inflammation, the EMB has the lowest sensitivity, reaching approximately only 25%. As mentioned, indication for EMB is always a matter of decision between risk and benefit.

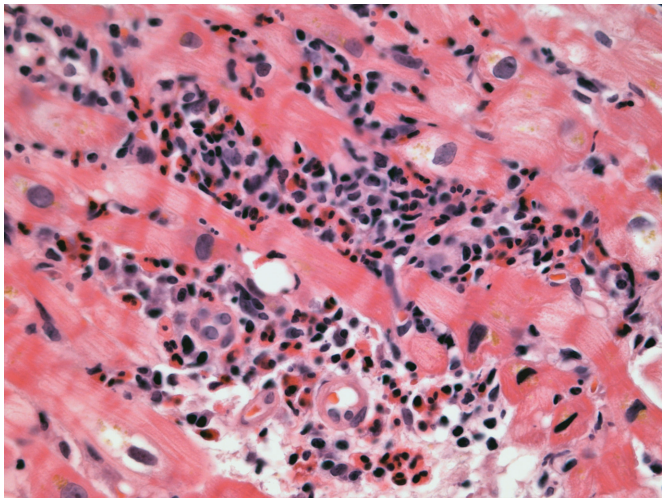


Figure 44.6 Endomyocardial biopsy demonstrating positive histopathology (Dallas criteria) for eosinophilic myocarditis in a patient with fulminant myocarditis (hematoxylin-eosin staining, magnification ×400). Published with courtesy of Ivana Vitkova, MD, PhD, Institute of Pathology, First Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic.

WHAT IS THE CONVENTIONAL MEDICAL TREATMENT OF MYOCARDITIS?

There are no specific recommendations for treatment of heart failure or arrhythmias in patients with myocarditis, so management should be in line with current European Society of Cardiology and American Heart Association/American College of Cardiology guidelines.[1,11] Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen) recommended in the treatment of pericarditis are generally not indicated in myocarditis. Hemodynamically unstable patients such as patients with suspicion of fulminant myocarditis should be sent to ICUs in specialized centers with respiratory and mechanical cardiopulmonary support facilities. Cardiac transplantation should be deferred in the acute phase because recovery may occur. On the other hand, heart transplantation can be considered in hemodynamically unstable patients if optimal pharmacological and nonpharmacological treatment, including MCS, is unable to stabilize the patient.

WHAT ARE SPECIFIC TREATMENTS?

The specific treatment should be optimally based on the finding in the EMB. Infectious myocarditis is treated with antimicrobial therapy, including antibiotics in patients with bacterial myocarditis or antivirals in subjects with viral infection. A high dose of intravenous immunoglobulin may be used in myocarditis refractory to conventional heart failure therapy, for both viral- and autoimmune-mediated forms. In giant cell myocarditis, cardiac sarcoidosis, and eosinophilic myocarditis of noninfectious origin, immunosuppressive treatment represents

the mainstay of the pharmacological treatment. In cases of cardiac sarcoidosis or eosinophilic myocarditis, monotherapy with corticosteroids may be enough. In subjects with giant cell myocarditis, combined immunosuppression is started as soon as possible. In this type of myocarditis, corticosteroids are usually combined with antimetabolites like azathioprine or mycophenolate and with calcineurin inhibitors such as cyclosporine or tacrolimus.

WHAT TYPE OF SHORT-TERM MECHANICAL CIRCULATORY SUPPORT IS PRESENTLY AVAILABLE?

In clinical practice, support usually involves either V-A ECMO or a ventricular assist device (VAD).[12,13] According to our experience, ECMO represents an effective MCS modality to support profound cardiac dysfunction in acute myocarditis. Outcomes can be improved by early institution prior to cardiac arrest or period of prolonged tissue hypoperfusion. ECMO permits a period of hemodynamic stabilization, time for myocardial recovery, and additional time for comprehensive risk stratification and evaluation for contraindications to transition to a more durable device with subsequent bridge to long-term recovery or transplant.

DISCUSSION

V-A ECMO OR VAD

Acute fulminant myocarditis (AFM) with rapidly evolving cardiogenic shock can lead to the patient's death unless MCS is immediately instituted. In 2001, Acker[14] in his review compared different modes of MCS in treatment of adult fulminant myocarditis. The highest survival rate was reported with the biventricular VAD (BiVAD), resulting in recovery or transplant in 70% of patients. In 2005, Chen and colleagues[15] published their own data about 15 patients, with a survival rate of 73% and mean time spent on ECMO of 5.7 days. This is probably the first study that suggested, that V-A ECMO should be the first option to mechanically support the patient with AFM and serious hemodynamic alteration. In 2009, Pages[16] compared a group of 10 patients with AFM. An overall survival rate of 70% did not differ between ECMO and VAD, but patients on ECMO had significantly lower need for transfusions, fewer infections, and better hepatic and renal functions and spent less time on a mechanical device than BiVAD patients.

According to the Extracorporeal Life Support Organization (ELSO) Registry, from 1995 to 2011, there were 147 patients reported with a diagnosis of acute myocarditis. Of them, 69% had been successfully decannulated, with an overall survival rate of 61%. Survival rates from published single-center trials ranged from 66% to 100%.[15–21] Previously published multicenter studies reported survival rates of 58%–70%.[14,22] The largest data relating to 255 pediatric patients from the ELSO Registry were published by Rajagopal[23] in 2010; there was a survival to discharge of 61%. Different types of MCS have been used to support patients with AFM (intra-aortic balloon pump, ECMO, VADs).

ADVANTAGES OF V-A ECMO

Veno-arterial ECMO in patients with AFM has been proven as the first-line MCS based on relatively easy and fast implantation, providing biventricular as well as respiratory assistance, and with limited resource consumption compared to other mechanical assist devices.[14–16,19,21,22,24,25] V-A ECMO is easy to set up and quickly insert into the patient, even at bedside in emergent settings. ECMO is less invasive than a VAD, which requires a surgical operation. A patient can be cannulated in the ICU without the need to transfer to the operating room. Percutaneous ECMO cannulation can be performed not only by surgeons, but also by cardiologists or intensivists. ECMO flow may be up to 6 L/min. The presence of the oxygenator is very useful in cases of cardiogenic shock with pulmonary congestion leading to lower oxygen content.

An important advantage of V-A ECMO in urgent situations is the fact that V-A ECMO supports both left and right ventricles. In cases of myocarditis, the function of both ventricles is usually impaired, and it could be challenging to distinguish the degree of the right ventricular dysfunction in the acute setting. The extent of right ventricular impairment may not be appreciated until after the LV assist device implantation, with risk of another operation for conversion to biventricular support.[24] In some patients, ECMO can be set up under local anesthesia, and orotracheal intubation can be avoided. In his study, Pages[16] referred to better pulmonary outcome with no pneumonia observed in patients on ECMO devices implanted under local anesthesia versus 100% incidence of pneumonia in patients who underwent implantation of a mechanical support device under orotracheal intubation (BiVAD or ECMO). ECMO is cost-effective in an emergent situation when there is not enough time to gather all relevant data to assess the prognosis of the patient.

DRAWBACKS OF V-A ECMO

The main drawback of peripheral V-A ECMO is that it does not unload the LV. Additionally, it has insufficient power for circulatory support compared to VADs, potentially resulting in end-organ damage and poor outcomes, especially in a patient with multiple organ failure, who requires higher flow than usual to reverse the deteriorating end-organ function. In case of an emergent cannulation under cardiopulmonary resuscitation, when smaller diameter cannulae are chosen for safety reasons, inadequate support flow can lead to more tissue hypoxia due to low oxygen delivery. Frequent echocardiographic control of the performance of the LV is important for early detection of the above-mentioned complications. If any of these drawbacks of percutaneous ECMO appears, urgent intervention is needed. Peripherally inserted V-A ECMO limits patient mobility and rehabilitation; a VAD or other modes of MCS are more suitable for long-term support. The high rate of complications associated with ECMO is usually related to the long course of ECMO, which is relatively rare in patients

with a diagnosis of acute myocarditis, who usually spend 7–10 days on ECMO.[12–14,17,19,20,22,23] Patients who cannot be weaned off ECMO after a week of support should be considered for transition to an alternative MCS system.

LEFT VENTRICULAR UNLOADING METHODS

Quite frequently, the LV overloading and distension together with decrease of the aortic valve opening occur as a "surrogate" hemodynamic effect of peripheral V-A ECMO. It is caused by high retrograde flow in the aorta and may be a major limitation to myocardial recovery. Additionally, it increases the risk of pulmonary edema and intraventricular thrombosis.[26,27] Therefore, depending on the severity of the problem and skills of the team, several, more or less invasive, techniques are recommended to achieve LV unloading.[28] They are used in 15%–30% of patients with peripheral V-A ECMO support for cardiogenic shock due to fulminant myocarditis.[15,25,29]

If there is high support dependency of the patient due to severe LV failure, then intravenous inotropes are the first possible therapeutic options. Both dobutamine, like in our case, or epinephrine can increase inotropy and improve ejection of the LV detected as lower or higher "peaks" on the previously recorded flat line of the arterial tracing. However, sinus tachycardia and supraventricular or ventricular arrhythmias caused by catecholamines can increase oxygen consumption of an already severely failed heart. Another option is using a several-hour infusion of a single dose of the calcium sensitizer levosimendan, which is reported to have fewer side effects.

INTRA-AORTIC BALLOON COUNTERPULSATION

Active deflation of a counterpulsation balloon during systole creates the brief vacuum causing LV afterload reduction. Although intra-aortic balloon counterpulsation (IABC) can increase the CO by no more than approximately 0.5 L/min and it does not improve the survival rate in patients with cardiogenic shock complicating acute myocardial infarction,[30] in patients on peripheral V-A ECMO its major effect is afterload decrease, allowing the LV to unload. It can increase pulse pressure and reduce both pulmonary artery and pulmonary artery occlusion pressures, thus showing effective LV unloading and decreasing the risk of hydrostatic pulmonary edema development.[31–33]

PERCUTANEOUS ATRIAL SEPTOSTOMY

Iatrogenic creation of an artificial atrial septal defect allows left heart decompression through a left-to-right shunt. The efficacy of this technique depends mainly on the technical skills of the interventional cardiologists, who can use either balloon or blade.[34,35] If necessary, the defect may be closed by an Amplatzer occluder later. The literature also reported several other percutaneous LV unloading techniques, consisting of placement of a draining cannula in the left heart or pulmonary artery using transseptal, transaortic, or retrograde arterial routes.[36–39]

IMPELLA PUMP

The Impella is a microaxial, catheter-based, short-to-midterm LVAD. It works on the principle of an ancient Archimedes' screw, allowing continuous pumping of blood from the ventricle into the aorta. Usually, it is inserted through a peripheral artery into the LV across the aortic valve. There are several types of Impella (2.5, CP, and 5.0) available on the market able to effectively unload the LV. However, only the Impella 5.0, which necessitates surgical placement, usually using a vascular prosthesis sutured at the right subclavian artery, can gradually replace the full ECMO flow whenever oxygenation function of the lungs improves, but the LV still needs some support. Additionally, there are studies reporting successful ambulating of patients switched from V-A ECMO to the Impella.[40]

PERIPHERAL-TO-CENTRAL V-A ECMO CONVERSION

The surgical technique for peripheral-to-central V-A ECMO conversion is invasive, but it is the most effective way to unload the LV. An outflow cannula returning the blood from V-A ECMO is inserted in the ascending aorta to provide a "physiologic" flow, thus reducing the afterload, and a cannula in the right upper pulmonary vein or LV apex is used to decompress the chamber. However, possible bleeding, tamponade, infection, or other complications related to an inevitably repeated sternotomy increase the risk of this approach. A little bit less invasive technique is cannulation of the LV either via an anterolateral minithoracotomy at the fourth-fifth intercostal space or through the subxiphoid way by which the apex is exposed. A low-caliber cannula is inserted and is then connected to the venous draining cannula of the peripheral V-A ECMO. Hemothorax is a major risk of this minimally surgical approach.

PREDICTORS OF RECOVERY

Several biomarkers were studied to identify possible predictors of myocardial recovery during V-A ECMO. The most frequently studied markers were troponins. Of the troponins, a high level of troponin T before MCS commencement with its rapid decline after several days was identified as a probably useful tool to estimate successful weaning of V-A ECMO. According to some authors, the trend of the troponin decline provides a more specific guide to evaluate myocardial recovery and to estimate the timing of weaning of the V-A ECMO rather than the absolute peak. In addition, the same authors discovered there was a statistically significant increase in mortality when the troponin T level did not decrease within 72 hours after V-A ECMO implantation.[28]

Other authors showed that patients who died on V-A ECMO exhibited a higher peak of creatine kinase myocardial band level than those who were weaned from V-A ECMO.[2] These findings indicate that the extent of myocardial dysfunction and necrosis caused by inflammatory responses may determine the acute outcome in myocarditis patients, although also high troponin I levels were associated with unsuccessful

weaning and ICU mortality. Recent single-center data showed that cardiac biomarkers were not useful for identifying those patients who would recover from refractory cardiogenic shock requiring V-A ECMO support.[41] Besides selective cardiac enzymes, other indicators, especially those pointing at hypoperfusion of visceral organs, may have some prognostic value. The most sensitive are aspartate aminotransferase[42] and bilirubin. The fast lactate normalization after ECMO commencement indicates less profound organ hypoperfusion and is a strong determinant of cardiac recovery, successful weaning from ECMO, or hospital discharge.[25]

Apart from biochemical markers, some echocardiographic parameters were also studied in relation to predicting recovery and successful weaning of MCS. Of the markers, the most frequently used are LVEF, fractional shortening of the LV, and LV posterior wall thickness.[2,19] Additionally, cardiac rhythm disturbances that continue several days after commencement of MCS were considered an unfavorable sign, predicting failed recovery.[2] Use of a combination of biomarkers, echo findings, and electrocardiographic evaluation could facilitate appropriate decision-making regarding ECMO weaning versus transition from ECMO to a long-term MCS.

ECMO FOR CHILDREN WITH ACUTE MYOCARDITIS

Similar to adults, myocarditis is a potentially life-threatening disorder that can present in the most severe cases as cardiogenic shock in children. Children less than 1 year of age often present with poor appetite, fever, cyanosis, or diaphoresis. Older children more commonly present with abdominal pain, diarrhea, and lethargy. Pediatric myocarditis is often difficult to diagnose when both respiratory and gastrointestinal symptoms have been reported as common symptoms. But patients may also show some central nervous system manifestations, like irritability, seizures, or syncopes. Having in mind the quite high incidence of febrile seizures, especially in small infants and toddlers, myocarditis should be considered a differential diagnosis when examining patients experiencing seizures. The diagnosis of myocarditis in children is a challenging problem, and many patients are diagnosed during the second or subsequent visits to their doctors.

When considering a type of MCS, one must have in mind that ECMO remains the most common circulatory assist system with both high survival and discharge rates in use for children. In addition, myocarditis is one of the most common etiologies (4.5%) of cardiac failure in neonates and children reported to the ELSO Registry, and up to 50% of pediatric patients who present with AFM necessitate MCS.[43] For neonatal and pediatric cardiac failure, survival to separation from ECMO reaches more than two-thirds of patients and survival to discharge occurs for almost half of them[44]; some authors refer to a survival to discharge of nearly 75% for ECMO patients with fulminant myocarditis.[15,19] The advantages of ECMO in children include its relatively "easy" way to introduce, mostly without major surgery; its universal availability across different weight categories; combined cardiac and respiratory support; and low cost compared to other systems. Like in adults, ECMO may be used as a bridge to recovery, transplantation, or VAD implantation. Recovery from myocarditis occurs within weeks, with mortality in children suffering from this diagnosis and supported with ECMO increasing by 15% for each additional week of support. Survival of support lasting more than 4 weeks is almost not observed.[23]

The elective introduction of ECMO before the completion of end-organ dysfunction has a positive effect on outcomes in pediatric myocarditis cases; therefore, transfer to a specialized institution that can provide pediatric ECMO support should be promptly considered when managing such patients. ECMO has been reported to be an effective rescue strategy for patients with pediatric myocarditis when maximal medical management is insufficient.[45] Neck cannulation is preferred for small children and femoral cannulation for older ones. Central cannulation through a median sternotomy is carried out if there is difficulty with the peripheral approach or left-sided decompression is required. Ventriculostomy for MCS implantation or venting in children should be even more carefully considered than in adults due to a higher risk of development of arrhythmias or ventricular dysfunction in the future.[23] Also like in adults, rhythm disturbances were identified as predictors of unfavorable outcome. Other risk factors for in-hospital mortality are renal failure requiring replacement therapy, poor LVEF, high liver enzymes, high lactate levels, and not surprisingly cardiopulmonary resuscitation preceding the MCS.

Weaning off ECMO should only start when obvious signs of myocardial recovery and resolution of complications, such as systemic inflammation, pulmonary dysfunction, sepsis, or infection, occur. Apart from hemodynamic parameters, including elevation of both systolic and pulse pressures and rising end-tidal CO_2, the major guide should be regular echocardiographic monitoring repeated on a daily basis and performed under gradually decreasing ECMO flow conditions with potential left atrial vent clamped or removed.

LONG-TERM CONSEQUENCES

The outcome of patients with myocarditis depends on etiology (the worst prognosis is associated with giant cell myocarditis), clinical presentation, and stage of the disease. Acute myocarditis resolves in 1 moth in approximately 50% of the affected subjects, but 12%–25% may acutely deteriorate and either die or progress to end-stage DCM requiring heart transplantation.[1] Approximately 20%–30% will develop DCM. For many years, fulminant myocarditis was considered to have an unfavorable short-term outcome (unless early and appropriate support, including MCS, was administered), but the long-term prognosis of patients surviving the acute episode seemed to be very good and much better in comparison with nonfulminant forms of myocarditis. This idea was mainly supported by the study of McCarthy et al.[46] that included 132 patients with nonfulminant myocarditis and 12 subjects with fulminant myocarditis. In this study, 93% of patients with fulminant myocarditis and only 45% of subjects with nonfulminant myocarditis survived 11 years without the need for heart transplantation. These paradoxical results were challenged by

a very recently published study comprising 55 patients with acute nonfulminant myocarditis and 165 patients with fulminant myocarditis from a multicenter international registry. Based on the data the from international registry of acute myocarditis, the 60-day mortality or heart transplantation occurred in 1.8% of subjects with nonfulminant myocarditis and in 28% of patients with fulminant myocarditis; the rate of mortality/heart transplantation was observed as 10.4% and 47.7%, respectively, in 7 years of follow-up.[10]

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REVIEW QUESTIONS

1. What is the estimated survival rate for patients with a diagnosis of AFM requiring any form of mechanical support system (V-A ECMO or VAD)?

A. 30%–50%
B. 40%–60%
C. 60%–70%
D. 70%–90%

2. After how many days can you expect myocardial recovery to take in patients with acute myocarditis?

A. 3–6 days
B. 6–10 days
C. 10–21 days
D. More than 30 days

3. What is the main disadvantage of peripheral V-A ECMO as MCS in patients with myocarditis and serious LV systolic dysfunction?

A. Support only of LV
B. Need for surgical approach for arterial cannulation
C. Higher afterload for LV
D. Brain hypoperfusion due to Harlequin syndrome

4. Which of the following statements is false for V-A ECMO?

A. A long course of V-A ECMO is associated with a high incidence of complications.
B. Veno-arterial ECMO provides biventricular and respiratory support.
C. Veno-arterial ECMO can be instituted by surgeons, cardiologist, or intensivists.
D. Veno-arterial ECMO without an oxygenator can work as biventricular support with no serious drawbacks.

5. Left ventricular overloading and distension together with a decrease of the aortic valve opening frequently occurs after peripheral V-A ECMO commencement. What is the best way to unload the LV?

A. Intra-aortic balloon counterpulsation
B. Atrial septostomy
C. Switch to central V-A ECMO
D. Impella

6. Fulminant myocarditis is defined by

A. Specific immunohistochemical pattern in the EMB
B. Clinical course of myocarditis
C. Pathognomonic changes on ECG
D. Normal systolic function on echocardiography

7. What is the typical echocardiographic finding for fulminant myocarditis?

A. Significant decrease of LVEF usually with nondilated LV cavity.
B. Restrictive LV filling and preserved systolic function
C. Severe concentric LV hypertrophy
D. Large pericardial effusion with a high risk of cardiac tamponade

8. Which type of myocarditis should be treated with immunosuppressive therapy?

A. Myocarditis associated with bacterial infection
B. Nonfulminant acute viral myocarditis
C. Giant cell myocarditis
D. Any type of myocarditis

9. What is the gold standard for diagnosis of myocarditis?

A. Positron emission tomography–computed tomography
B. Echocardiography
C. Cardiac magnetic resonance
D. Endomyocardial biopsy

10. What is the commonest histological type of myocarditis?

A. Lymphocytic myocarditis
B. Giant cell myocarditis
C. Granulomatous myocarditis
D. Eosinophilic myocarditis

11. Which of the following statements concerning pediatric myocarditis is false?

A. It is one of the commonest etiology of cardiac failure in neonates and children.
B. Clinical diagnosis is a challenging problem, and many patients are diagnosed during the second or subsequent visit to the doctors.
C. ECMO remains the commonest MCS in use for children.
D. Groin cannulation is preferred for small children and neonates.

ANSWERS

1. C: According to data from the ELSO Register and results of previously published studies, reported survival of AFM with need for MCS is estimated between 60% and 70%.

2. B: In case of acute myocarditis, we can usually expect myocardial recovery in 1 week. Patients with this diagnosis in most cases spent 6–10 days on ECMO—.

3. C: Due to retrograde flow in the aorta, one of the main drawbacks of peripheral V-A ECMO is higher afterload for the LV, with a lower chance of recovery.

4. D: V-A ECMO without an oxygenator would act as a right-to-left shunt, resulting in serious hypoxemia.

5. D: Currently, Impella insertion using either catheterization or combined catheterization and a surgical technique became a very popular and effective way to unload the LV. Its limitation is high cost.

6. B. Fulminant myocarditis is characterized by a short duration of symptoms and hemodynamic instability with low CO and the need for hemodynamic support.

7. A. A majority of the patients with fulminant myocarditis have moderate or severe systolic dysfunction, a normal size LV, and in the acute phase also quite often a mild increase in wall thickness.

8. C. Giant cell myocarditis indicates the initiation of combined immunosuppressive therapy as soon as possible in order to prevent an unfavorable outcome for the patient.

9. D. Myocardial biopsy evaluation represents the method of choice for confirming myocarditis.

10. A. Lymphocytic myocarditis is the most prevalent type of fulminant, acute nonfulminant, and chronic type of myocarditis.

11. D. Surgical neck cannulation is preferred for small children and femoral cannulation for older ones. Central cannulation through a median sternotomy is carried out if there is difficulty with the peripheral approach or left-sided decompression is required.

45.

LEFT VENTRICULAR VENTING STRATEGIES DURING ECMO

Mario Gramegna, Giulia Nardi, and Federico Pappalardo

STEM CASE AND KEY QUESTIONS

A 44-year-old man without past cardiological history except for smoking suffered an out-of-hospital cardiac arrest, witnessed by his wife. A dispatcher-assisted bystander initiated cardiopulmonary resuscitation immediately. At emergency medical service arrival, an electrocardiogram (ECG) showed ventricular fibrillation, and the paramedics delivered five direct current (DC) shocks without success. The patient was intubated on site and then transferred to the nearest extracorporeal cardiopulmonary resuscitation (ECPR) center under mechanical chest compression with the LUCAS 2 device. On hospital arrival, the patient was in asystole: Due to his young age and witnessed arrest, the decision was made to initiate extracorporeal membrane oxygenation (ECMO) for resuscitation. Peripheral veno-arterial (V-A) ECMO access was obtained using a 17 French (17F) arterial cannula and 29F venous cannula. An intra-aortic balloon pump (IABP) was implanted, and inotropes were administered. The total time was about 2 minutes of no flow and 90 minutes of low flow. Echocardiography revealed severe left ventricular (LV) systolic dysfunction with left ventricular ejection fraction (LVEF) at 15% without significant valvular disease or mechanical complication.

The patient was put on V-A ECMO support for urgent cardiac catheterization, which showed total occlusion of the proximal right coronary artery (RCA), total occlusion of the left anterior descending coronary artery (LAD), the diagonal branch, and the circumflex coronary artery (CX) with multiple critical stenoses. Left ventriculography confirmed the echo findings: large dyskinesia of the LV apex and akinesia of the anterior wall with severely impaired LV systolic function, with the LVEF less than 20% with high end-diastolic pressure (40 mm Hg). Therefore, the IABP was upgraded to femoral Impella CP to maximize LV unloading.

Two drug-eluting stents were placed in the RCA and two in the proximal and mid-LAD with bifurcation stenting of a large first diagonal branch. An additional stent was placed in the CX to obtain complete revascularization with good angiographic result (Thrombolysis in Myocardial Infarction [TIMI] 3 flow) on all vessels. His initial laboratory investigations demonstrated severe acidosis, with a pH of 6.9, lactate of 10 mmol/L, and elevated liver enzymes. Pulmonary artery catheterization revealed elevated pulmonary venous pressure and wedge pressure (Central venous pressure [CVP] 16 mm Hg, wedge pressure 35 mm Hg). On day 1, sedation was witheld, and the patient was woken up with an unremarkable neurological examination result. On day 3, the chest x-ray was clear without signs of congestion. The patient was extubated and remained on V-A ECMO and femoral Impella CP support until day 7, when V-A ECMO was discontinued following clinical, echocardiographic, and hemodynamic improvement. However, after 2 days the patient suffered from complete atrio-ventricular block and developed acute pulmonary edema while he was supported by Impella CP only, requiring intubation and reimplantation of V-A ECMO.

Due to this clinical picture with extreme difficulty/implausibility of achieving sufficient recovery of the native heart, it was decided to upgrade the LV support by implanting an Impella 5.0 via axillary surgical access as a bridge to LV assist device (LVAD) or heart transplantation. On the following day, with Impella providing 4.8 L/min flow, it was possible to remove V-A ECMO. The patient was extubated and free from inotropes. Over the following days, he underwent progressive mobilization and oral feeding with full restoration of his functional status. He was also screened for heart transplant and was listed with emergent priority. Twenty days later, heart transplant allocation failed; therefore, a HeartMate III LVAD was implanted without any complication. The postoperative course was free of complications, and the patient was discharged home. At 6-month follow-up, he had no native heart recovery and was still waiting for a donor heart.

WHY IS IT CRUCIAL TO INTRODUCE THE CONCEPT OF UNLOADING WITH V-A ECMO?

Veno-arterial ECMO guarantees end-organ perfusion and reduces CVP; however, this technology is characterized by an increase in LV afterload secondary to retrograde flow delivered from the arterial cannula, which may ultimately further impair or delay cardiac contractility recovery[1] and also negatively impact prognosis.[2]

This is explained by the fact that the extracorporeal oxygenated blood flow pumped into the arterial circulation and the increased aortic pressure guaranteed by the extracorporeal life support (ECLS) system are opposed to the ejection of the native, failing heart.[2] Therefore, ECMO has indeed a very

limited effect on reducing LV end-diastolic pressure (LVEDP) and pulmonary pressures; these phenomena can cause ventricular distension with secondary myocardial ischemia, pulmonary edema, and, finally, LV and pulmonary artery thrombosis due to flow stasis. These complications definitely increase mortality. As a matter of fact, despite increasing use, clinical outcomes associated with V-A ECMO for cardiogenic shock (CS) remain poor.[3]

By relying on the purpose to overcome the limitations of retrograde femoral flow that lead to an increased afterload to the LV, it is appropriate to introduce the concept of LV unloading during V-A ECMO support. This would target primarily not only the LV, but also the respiratory system as it would protect also from injurious mechanical ventilation and the inherent risk of cranial district malperfusion.

In a recent meta-analysis conducted by Al-Fares et al. published in *Circulation*,[4] the authors revealed that the in-hospital mortality rate was around 60% among 7995 patients implanted with either central or peripheral V-A ECMO. Interestingly, the authors reported that weaning off V-A ECMO and 30-day survival were higher among patients who received concomitant LV venting, and that initiation of LV venting within 12 hours of V-A ECMO implantation was associated with better outcomes.

Another recent meta-analysis by Russo et al. showed that LV unloading was associated with decreased mortality in adult patients with CS treated with V-A ECMO. The meta-analysis included 3997 patients, with 1696 (42%) receiving a concomitant LV unloading strategy while on V-A ECMO (IABP in 91.7%). Mortality was lower in patients with (54%) versus without (65%) LV unloading while on V-A ECMO.[5]

WHAT IS THE ROLE OF UNLOADING IN PATIENTS WITH V-A ECMO SUPPORT?

The reduction in afterload leads to several advantageous consequences:

- First, the reduction in LV afterload by reducing filling pressures results in a less dilated and overdistended LV. This prevents pulmonary edema and its associated complications, such as pneumonia, acute lung injury, and Harlequin syndrome, all contributing to increased mortality.[6]
- Second, a dilated and overdistended LV with an increased end-diastolic pressure and wall tension determines an increase of myocardial oxygen demand. This turns into subendocardial ischemia, followed by cardiomyocyte necrosis, which is further magnified by the systemic inflammatory response syndrome triggered by ECMO support.[7]
- Third, unloading also has positive effects on myocardial injury since it has been shown that LV unloading before percutaneous coronary intervention (PCI) in ST-segment elevation myocardial infarction (STEMI) reduces infarct size.[8]
- The risk of cardiac thrombus formation due to blood stasis and permanent aortic valve closure is reduced.
- Furthermore, the impact of any blood volume in the LV cavity is dependent on the primary pathology and, subsequently, the function of the mitral valve: In acute myocardial infarction (AMI) and myocarditis, the mitral valve is usually competent, and blood in the LV mirrors a significant increase in left ventricular end-diastolic pressure (LVEDP) but not much pulmonary edema; on the contrary, in patients with dilated cardiomyopathy with functional mitral regurgitation, this would turn into more pulmonary edema with lower LVEDP. Therefore, regarding the primary pathology, the therapeutic effects of direct unloading would be more evident on a chronically dysfunctional LV as compared to fulminant diseases.
- Last, lowering afterload is one of the main targets of any successful heart failure medical or device therapy.

HOW CAN WE UNLOAD THE LV DURING ECLS SUPPORT?

Multiple tools, either percutaneous or surgical, have been adopted in order to directly or indirectly unload the LV as bridge to recovery, transplant, or LVAD or other destination therapies, and they all have a different mechanism of action.

Russo et al.[5] demonstrated that the LV unloading strategy was associated with decreased mortality in V-A ECMO patients. Most patients in this metanalysis were treated with an IABP, which acts only indirectly on the LV.

In recent years, the Impella device has gained momentum in unloading the LV, and this has been consistently reported by multiple groups. Moreover, the growing evidence for Impella support in high-risk STEMI and CS is structuring a patient population that, in the need for V-A ECMO, is already supported by an LV pump.

The surgical approach has many options for placing a drainage cannula: LV apex, left atrium (LA), right superior pulmonary vein, or pulmonary artery with different size cannulae. Surgical venting of the LV apex via minimally invasive procedures (left anterior minitoracotomy incision at fourth intercostal space) has also been described to show an improvement in outcome.[9]

These procedures are not technically simple and expose the patient to a number of potential complications besides those inherent in cardiac surgery, including laceration of the myocardial wall or damage to the epicardial coronary arteries.

As a general rule, any surgical vent is connected to the venous side of the ECMO; therefore, some physiological background has to be acknowledged. First, any centrifugal pump exerts a negative pressure at the cannula's tip, which is dependent on lengths and diameters of each inflow tubing. Second, competition of flow at a Y connector might produce stagnation in the branch, with lower flow and suction in the higher flow. This phenomenon might drive generation of air emboli. Third, if the heart ejects any left-sided vent will decrease its efficacy. Last, the flow through the vent has to be monitored with a dedicated transonic probe and cannot be manipulated by the clinician (except via reduction of overall ECMO flow or with adjustable screws that trigger hemolysis).

In the light of these considerations, it is mandatory to have strict surveillance of the circuit by a dedicated perfusionist as flow changes may occur abruptly and drive major adverse events. That turns into increased resources required to run mechanical circulatory support (MCS). The same considerations apply if a pulmonary artery vent is inserted via a single-stage venous cannula through the right internal jugular vein floated as a Swan-Ganz catheter or a transseptal cannula is placed in the LA. The surgical approach, moreover, has the major limitation of "violating the chest"; this results in not only an increased risk of bleeding and infection, but also a hostile surgical field for any future procedure (LVAD implantation, heart transplantation). As far as the LV apex, this is very important because that tissue should accommodate with an optimal position the LVAD inflow cannula.

Among the percutaneous unloading options, pulmonary artery drainage, LA venting, transaortic catheter venting, atrial septostomy, IABP, and the Impella 2.5 and CP have been described.

Pulmonary drainage consists of the percutaneous placement of a venous cannula (10F–15F cannulae) into the main pulmonary artery trunk, through the inferior vena cava with a femoral approach or the superior vena cava with a jugular approach.

Transaortic catheter venting is an alternative percutaneous venting method in which the venting cannula (5F–7F cannulae) can be inserted through an arterial access and is usually connected to the ECMO venous line.

Atrial communication can be produced using percutaneous techniques by performing a transseptal puncture and placing an (8F–15F) LA drain cannula as described by Aiyagari et al. or via blade or balloon septostomy.[10] Atrial communication patency can eventually be maintained by means of atrial stenting. The major advantages of this procedure are the possibility to define the size of the atrial shunt and, obviously, the preservation of flow over time. In case of LVAD implantation, the atrial defect should be repaired.[11]

Another minimally invasive technology is represented by the TandemHeart (Cardiac Assist, Inc., Pittsburgh, PA), which could be an optional technology to decompress the LV. This device consists of two cannulae: The inflow cannula drains blood from the LA and is usually transseptally placed into the LA via the femoral vein. The other pumps blood into the aorta via a femoral access point.[1] Li et al. previously reported a case series of five patients treated with TandemHeart and V-A ECMO; however, only two survived to the time of discharge.[12]

Conversely, the Impella device and the IABP can be inserted percutaneously and can provide hemodynamic support independently from the V-A ECMO circuit.

HOW CAN IABP SUPPORT THE LV IN V-A ECMO?

Recent studies are still conflicting and do not unequivocally support the routine combination of V-A ECMO and IABP as a clinical standard strategy.[13–15]

The IABP device is commonly inserted through a percutaneous access, most frequently in the femoral artery. The inflation in diastole and the active deflation in systole of the balloon placed in the descending thoracic aorta induces higher diastolic perfusion pressures in the open coronary arteries and unloads the diseased heart by reducing LV afterload during systole. Volume shifting by the balloon of 30–40 mL per beat depending on the balloon size increases LV stroke volume and cardiac output (by up to 1 L/min or about 15%–30%, with the best effects seen at very low cardiac output).[16]

From a mechanical point of view, indeed, it has been demonstrated that the combined use of ECMO and IABP can improve coronary and bypass graft perfusion and lower LV filling pressure by lowering pulmonary artery pressure (PAP), CVP, and pulmonary capillary wedge pressure (PCWP); and reduce myocardial O_2 consumption and the risk of intracardiac thrombosis by improving cardiac output. On the other hand, IABP may have a negative impact on the spinal cord and cerebral blood flow, especially when the native cardiac function is severely impaired and a beneficial impact on the microcirculation seems to be lacking.[2] For this reason, its use remains controversial. However, the IABP has been the most employed device for LV venting in the last two decades.

Donker et al. reviewed percutaneous and surgical unloading interventions,[2] concluding that the indication for using IABP is still unclear. The use of concomitant IABP has been considered to be an independent predictor of improved survival and facilitates weaning from V-A ECMO by creating a pulsatile flow and reducing LV afterload.[17] The IABP could play a fundamental role in combination with V-A ECMO, especially in case of a persistently nonejecting LV, where the risk of LV thrombosis is high and systolic afterload reduction may allow aortic valve opening.

These data collected by the authors[2] suggest that this combination not only may have a beneficial effect on pulmonary edema,[18] which is thought to complicate at least 30% of V-A ECMO treatments, but also may improve prognosis, even after successful bridge-to-bridge long-term LVAD strategies.

Demodion et al.[19] reported an incidence of 31.6% of pulmonary edema in patients supported with ECMO for acute myocardial infarction cardiogenic shock [AMICS], regardless of the use of IABP; moreover, 51.3% of the population developed pneumonia. Brechot et al.[18] showed that the use of IABP was associated with lower pulmonary edema as assessed with the Weinberg score and with longer times on ECMO free from mechanical ventilation. Patients with IABP also received lower positive end-expiratory pressure (PEEP), less need for conversion to central cannulation (switching for pulmonary edema in a propensity-matched population 19% vs. 9%) and had a higher probability of being successfully bridged to a durable LVAD.

Moreover, the inflation of the IABP during ECMO was not associated with increased neurological, gastrointestinal, and limb-related complications. Also, IABP possibly plays an important role in providing a pulsatile flow for patients having ECMO, which could improve the microcirculation of patients with severe CS.[20] Indeed, pulsatile perfusion during cardiopulmonary bypass may improve the microcirculation, maintain capillary patency and decrease the systemic inflammatory mediators throughout the early postoperative period.[21]

WHY WAS IABP IMPLANTED TO SUPPORT ECMO IN THIS CASE?

Current data also do not inform regarding the optimal timing of unloading. The timing of unloading the LV may be taken into consideration at different times, either at the beginning of MCS concomitant to ECMO implantation or at a later time in case of impaired LV recovery and worsening of hemodynamic conditions, when the signs of LV overloading are impending. In the first case, it represents a preemptive and prophylactic strategy to avoid LV dilation and before the onset of the so-called hemometabolic shock.[22]

Although the timing to start unloading is crucial, currently there are no clear indications on when to proceed. Some centers adopted a standardized protocol on concomitant early implantation of IABP and ECMO in patients presenting with advanced heart failure, revealing a reduction in mortality in patients supported by these two MCS systems. Conversely, other groups experimented with the concomitant implantation of Impella and ECMO[23] for all consecutive patients presenting at their institution, making this therapy the standard of care for patients presenting with severe CS and impaired LV function, demonstrating a clear benefit of this approach.[24]

Vallabhajosyula et al.[25] showed that the early and high cardiac output support with two MCS devices likely results in less multiorgan dysfunction. In this review, in patients with AMI, concomitant use of IABP and V-A ECMO was associated with 18.5% lower mortality in comparison to patients on V-A ECMO alone. Crucially, the timing of IABP and V-A ECMO is important because earlier unloading of the LV before development of vasoplegia and multiorgan failure has important prognostic implications.[26]

Similarly, Aso et al.[27] concluded via the national Japanese inpatient database that IABP combined with V-A ECMO was associated with reduced mortality and successful weaning from V-A ECMO. Li and Yan[21] reported that the cumulative in-hospital mortality rate for patients on ECMO alone was higher than for patients treated with adjunctive IABP, and the concomitant use of the two MCSs is fundamental to neutralize the increase in afterload that leads to significant LV distension, which occurs in 10%–60% of patients on ECMO.

Concurrent initiation of IABP with ECMO provides better short-term survival for postcardiotomy cardiac shock [PCS], with reduced peripheral perfusion complications.[28]

Al-Fares et al.[4] reported that weaning off V-A ECMO and 30-day mortality were lower among patients who received concomitant LV venting, and further reported that initiation of LV venting within 12 hours of V-A ECMO initiation was associated with better outcomes.

WHY WAS IT DECIDED TO UPGRADE IABP SUPPORT WITH IMPELLA CP?

In our clinical case, in the catheterization laboratory the IABP was substituted with a percutaneous femoral Impella CP, thus taking advantage of the dual rationale to the use of Impella device: circulatory support and LV unloading. The escalation of the MCS to Impella CP is guided by the necessity to maximize the LV unloading in a severely dysfunctional heart, as shown by significantly increased LVEDP (31 mm Hg).

WHAT ARE THE COMMONEST SIGNS OF LV LOADING?

We have clinical, echocardiographic, radiological, and hemodynamic parameters that may guide in the identification of LV overloading.

At echocardiographic evaluation, an overloaded LV is identified by an augmented indexed end-diastolic diameter and volume (left ventricular end-diastolic diameter [LVEDD], left ventricular end-diastolic volume [LVEDV]), a high relationship between E/e′ waves (E/e′ > 15). Another elegant parameter that can estimate LV overloading is the ratio of pressure change in the ventricular cavity during the isovolemic contraction period (dP/dT) in case of mitral regurgitation since it is an index of myocardial function and tends to increase with LV overloading. The hemodynamic parameters are those derived from pulmonary artery catheter measurements as PAP (normal systolic pressure range 15–30 m mHg, diastolic range 4–12 mm Hg); wedge pressure (normal range 2–15 mm Hg); CVP (normal range 3–8 mm Hg); and those calculated by left ventriculography as LVEDP (normal range 5–12 mm Hg).

Chest x-ray is a very potent marker of LV overload as pulmonary edema is hydrostatically driven by the increased LV pressures; however, we should strongly work to avoid such late identification of LV overload. Similarly, intracardiac preclotting status/thrombosis is a late sign.

On clinical grounds, a nonejecting LV without any pulse pressure on the arterial tracing should be aggressively investigated and treated.

WHAT ARE THE ADVANTAGES OF THE IMPELLA SUPPORT IN V-A ECMO?

Impella is a percutaneous (2.5 and CP) or surgical (5.0) transaortic LVAD composed of a microaxial impeller pump that provides continuous blood flow from the LV into the ascending aorta, thus reducing LV afterload and consecutively decreasing LV end-diastolic and pulmonary venous pressure and providing an increase in the net forward flow.

The 2.5 and CP devices are implanted via a percutaneous approach, and they are usually employed as a short-term mechanical support during high-risk PCI or CS. Since they provide up to 2.5–3.5 L/min blood flow, respectively, they may not be able to guarantee an adequate support in case of severe LV dysfunction and multiorgan failure.[29,30]

Described for the first time in 2013 by Pappalardo on top of peripheral V-A ECMO in a patient with severe CS and impaired LV function,[23] the combination of ECMO plus Impella has led to the development of a new therapeutic strategy, termed ECPELLA or ECMELLA in order to achieve LV unloading during V-A ECMO and avoid the complication related to LV overload.

The multiple advantages of the combination of the two devices are the following: All available Impella devices for LV support (i.e., 2.5, CP, and the surgical 5.0 device) have been combined with V-A ECMO to reveal a clear reduction of right atrial pressure, PCWP, LV volumes, and pulmonary edema in adults and, also, increasing pulmonary blood flow and right ventricular performance.[30–32] Moreover, the ECPELLA avoids LV-related blood stasis and dilation and the related risk of ventricular thrombosis, confirming that the concomitant use of the two systems might be more advantageous in terms of patient outcome.[33]

Last, MCS with Impella can improve distal coronary pressure and coronary perfusion pressures in the presence of critical coronary stenosis by increasing mean and diastolic blood pressure with a concomitant reduction in LVEDP. Prior studies have demonstrated that IABP improves coronary hemodynamics only in nonstenotic coronary arteries.[34,35]

By a propensity score analysis, the authors showed that the association of such assist devices was beneficial in terms of better hospital survival and with a higher rate of patients who ultimately achieved cardiac recovery or were successfully bridged to further therapy, as compared with those supported with ECMO alone. However, the authors reported a high incidence of hemolysis and need for continuous veno-venous hemofiltration in the ECPELLA group.[33]

Besides its impact on survival and complication rate, LV distension might play a role in myocardial recovery. Pappalardo et al.[23] showed that patients supported with the ECPELLA strategy had not only improved outcomes but also a trend toward higher LVEF after weaning. This was further corroborated by the work of Truby et al.,[36] which showed that myocardial recovery was higher in patients without LV distension, prompting the need for LV venting. They also identified ECPR as the clinical scenario with higher need for decompression. Interestingly, these figures were independent from the site of arterial cannulation (femoral, central, or axillary) and were reported in a group of patients receiving an average ECMO flow of 3.6 L/min.

In addition to a reduction in pulmonary venous pressure, cardiac unloading with an axial flow catheter can have therapeutic effects by reducing myocardial oxygen demand and potentially reducing myocardial infarct size. It has been demonstrated, indeed, that primary LV unloading in STEMI with Impella in a population of dogs and then delaying reperfusion for 1 hour reduces myocardial infarct size compared with traditional reperfusion strategies. This surprising result might be consistent with the activation of a myocardial protection program that upregulates stromal cell derived factor (SDF)-1a/chemokine receptor 4 (CXCR4) expression, increases cardioprotective signaling, reduces apoptosis, and hence limits myocardial damage in AMI.[8,37,38] Relying on this purpose, the "Door to Unloading" (DTU) ongoing trail (NCT03947619) aims to evaluate whether using the Impella CP system temporary circulatory assist device for 30 minutes prior to a catheterization procedure has the potential to reduce the damage to the heart caused by a heart attack compared to the current standard of care.

WHAT COULD BE DISADVANTAGES OF THE ECPELLA STRATEGY?

Some limitations of the ECPELLA approach should be acknowledged: first, the higher rate of hemolysis (reported between 30% and 100%), though this did not translate into a higher incidence of bleeding[39]; second, the high incidence of veno-venous hemofiltration[33]; and third, the current contraindications for Impella (mechanical aortic valve, LV thrombus), which still drive the application of different venting strategies. Last, the Impella console has been designed for LV support, and its alarms and function monitoring tools might be misleading in the ECPELLA setting, especially with a nonejecting heart.

Moreover, patients supported with peripheral V-A ECMO can develop the Harlequin syndrome, defined as the perfusion of coronary and cerebral districts with deoxygenated blood; this results from ejection, either from the native heart or from an Impella, of the blood coming from the LV. This issue, which is predominantly encountered in so-called cardiopulmonary failure (mostly in myocarditis with also lung involvement or in patients with pulmonary edema on top of poor respiratory function), should not be overlooked. However, strict monitoring is mandatory, and there is no guarantee for avoidance; therefore, prevention is key for success. Evaluation of parameters of mechanical ventilation (fraction of inspired oxygen [FiO_2], PEEP, plateau pressure) can provide a rough idea of the amount of lung involvement and therefore dictate the need for LV venting. This would focus not only the LV in terms of unloading, but also the respiratory system as it would unload also for injurious mechanical ventilation and risk of cranial district malperfusion by ECMO. V-VA ECMO is suggested as an alternative in this setting; however, management complexity is far higher; indeed, this strategy is not supported by strong evidence. On top of that, it does not overcome the limitations of retrograde femoral flow and increased afterload to the LV.

WHEN IS SUPPORT WITH IMPELLA IN V-A ECMO ESCALATED?

The ECPELLA approach is also attractive if we assume that treatment of CS should be effective within a short time frame after initiation of MCS: Significant reduction of lactates and of the inotropic score should take place within 24 hours maximum. So, the upgrade with Impella should be achieved in the first 48 hours from ECMO implantation to benefit from the adjunctive flow and to lower the toxic effect of catecholamines.

The ECPELLA approach guarantees the chance for shorter duration of ECMO support, which is associated with more side effects, but a longer duration of the total time the patient is on a pump. If we assume that medical treatment is the target for the management of heart failure after the acute crash, the LV pump might avoid the use of inotropes during weaning and might facilitate the titration of angiotensin-converting enzyme inhibitors and β-blockers under progressive lower levels of Impella support.

WHERE AND HOW SHOULD PATIENTS BE CANNULATED?

As compared to surgical vents, the use of Impella should also be viewed positively from a logistics point of view. The system can be easily implanted at bedside in the intensive care unit in an ECMO patient with the aid of transesophageal echocardiography, which avoids transfer to the catheterization laboratory or to a surgical theater, with reduction of a patient's risk due to mobilization and of hospital costs in terms of resources.

Management of the vascular access is a key factor for this approach; indeed, ECPELLA requires two arterial accesses. In order to proceed, it is imperative to

- Exchange the Impella with the IABP (if present) with an over-the-wire technique in order not to lose the vascular access;
- To expand the skills for axillary cannulation; and
- To consider transcaval Impella implant if no peripheral access is available.

The ECPELLA strategy also provides a solution to the potential side effects of the Impella: Limb ischemia can be eventually managed by reperfusion of the leg via a sheath implanted homolateral to the pump and perfused by a port from the arterial ECMO cannula.

HOW CAN IMPELLA FACILITATE WEANING FROM V-A ECMO?

It is obvious that before starting proper weaning, the patient should be hemodynamically stable. Pappalardo et al.[23] also demonstrated that the ECPELLA approach may increase the possibilities and speed of a successful weaning from V-A ECMO by guaranteeing the necessary flow to the systemic circulation while V-A ECMO flow is withdrawn. As previously affirmed, the presence of the Impella allows shortening the total duration of V-A ECMO and prevents an increase in afterload on the LV derived from reduced ECMO support. This is the reason why weaning is started by first removing the ECMO and not the unloading device in order to avoid LV overloading and the related consequences as pulmonary edema. Finally, the patient remains with only the unloading system until the Impella is removed if a complete LV recovery is obtained or until heart replacement therapies are available (heart transplant-LVAD-total artificial heart).

Therefore, the Impella proved to be a powerful LV decompression system and a useful tool that allows a separate, asynchronous weaning by MCS by a stepwise deescalation strategy.

WHAT WAS THE REASON FOR THE FAILURE OF THE FIRST ATTEMPT TO UNLOAD?

The failure of the first attempt demonstrates that these percutaneous LVADs may not provide adequate blood flow to patients in profound LV failure. In this situation of complicating CS, it is appropriate to maximize hemodynamic support with the Impella 5.0.

WHY WAS IT DECIDED TO UPGRADE THE HEMODYNAMIC SUPPORT BY IMPLANTING AN IMPELLA 5.0?

Since the first attempt to wean from V-A ECMO failed because of the persistent severe LV dysfunction and the lack of myocardial recovery, a decision was made to upgrade the support with a surgical axillary Impella 5.0. By providing greater flow, the Impella 5.0 allows safe and early weaning from V-A ECMO. Significant advantages of this approach include the potential for early extubation, ambulation, and physiotherapy and the possibility to share clinical decisions with the patient.[40]

Previous reports have shown that early mobilization with the device in place have led to successful weaning strategies or bridging to durable LVAD and may be associated with improved survival.[4]

Furthermore, Impella 5.0 support allows evaluation of right ventricular function and pulmonary vascular resistance in a bridge-to-decision strategy (LVAD or heart transplantation).

The Impella 5.0 is also a feasible bridge-to-decision option following ECLS implantation and allows further evaluations of a patient's neurological state since a durable LVAD implantation is contraindicated in patients with an unclear neurological status, especially after resuscitation.[41]

DISCUSSION

Clinical management of V-A ECMO patients requires a proper balance between the circulatory need and the cardiac condition of each patient since one of the dark sides of ECMO support is represented by the increase in LV afterload due to the retrograde flow from the arterial cannula in the descending aorta.[2] This also results in an increase of the filling pressure and in a higher risk of development of pulmonary edema together with the respiratory complications associated, thus raising the mortality rate. The consequences of LV pressure overload may account for LV dilation, with augmented risk of clot formation due to blood stasis.[1] Furthermore, LV overload increases wall stress and myocardial oxygen consumption, thus hampering cardiac recovery.

However, besides increasing LV afterload, ECMO has detrimental effects: bleeding, limb ischemia, thrombosis of cannulae, and Harlequin syndrome (partial hypoxia of the head and upper extremities). Moreover, it induces a systemic inflammatory reaction and needs anticoagulation to avoid massive thrombosis in the circuit.[33]

Most V-A ECMO patients receive pharmacological agents as standard of care, as inotropes and vasopressor drugs, but these strategies tend to increase myocardial workload, heart rate, and oxygen consumption and thus should be used with caution since their ongoing use is associated with excess mortality.[24]

The introduction of unloading strategies turns out to be the key element in the management of patients in CS in combination with the short-term mechanical support by V-A ECMO.[1] Left-sided unloading during ECMO support is also crucial to improve myocardial recovery.[33]

Through the years, several unloading strategies have been developed, either percutaneous or surgical, that provide LV venting by operating in different ways. In recent years, the use of temporary assist devices has increased as a means of stabilizing patients before long-term assist device implantation or cardiac transplantation.

The IABP remains the device most widely used over the years in combination with ECMO support since it indirectly assists the LV by reducing the afterload, and it is the easiest, fastest MCS, but its use is still under discussion.[14]

The concomitant use of an Impella on top of V-A ECMO represents the second largest therapeutic option following the IABP in order to provide unloading of the LV[24] with the additional hemodynamic effect of increasing the net forward flow.[23]

Indeed, Impella support appears to provide the greatest and most direct means of LV decompression.[24] This is the new combination strategy that is gaining momentum currently.

A combined CS treatment with an Impella and V-A ECMO has been proven to be safe and feasible.[23] One of the main limitations of the Impella is represented by hemolysis.[42] This was confirmed by Pappalardo et al.,[23] showing increased hemolysis in the V-A ECMO and Impella group (76% vs. 33%, $P = .004$). However, no differences were found in the rates of major bleeding.

The Impella device should, therefore, be considered as a powerful LV unloading device during V-A ECMO, which is also supported by simulation experiments, indicating a maximum reduction of PCWP of 10 mm Hg and LV volume of 20% as a function of Impella flow.[43]

Other studies also demonstrated that this device reduces infarct size and facilitates cardiac recovery.[8]

Last, the Impella 5.0 allows safe and early weaning from V-A ECMO. Significant advantages of this approach include the potential for early extubation, ambulation, and physiotherapy.[40]

CONCLUSIONS

- ECMO is an effective MCS as long as you avoid the following:
  - Left ventricular distension
  - Lack of aortic valve opening
  - Left ventricular clots
  - Lung congestion and pulmonary edema
- Left ventricular unloading is one of the cornerstones in the management of patients in CS in combination with the short-term mechanical support by V-A ECMO.
- The ECPELLA strategy appears to provide the greatest and most direct means of LV decompression, at the expense of a higher rate of hemolysis.
- Impella 5.0 support allows evaluation of right ventricular function and pulmonary vascular resistance in a bridge-to-decision strategy (LVAD or heart transplantation) and allows early patient extubation and ambulation.

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REVIEW QUESTIONS

1. What are the commonest dark sides of ECMO support?

   A. Left ventricular distension and clot formation
   B. Increased pulmonary pressures and pulmonary edema
   C. Secondary myocardial ischemia
   D. All of the above

2. Which of the following statements is incorrect?

   A. Left ventricular unloading prevents pulmonary edema.
   B. Left ventricular unloading before PCI might reduce infarct size in STEMI.
   C. Left ventricular unloading decreases myocardial oxygen demand.
   D. Left ventricular unloading increases the risk of thrombosis.

3. Which of the following statements is incorrect?

A. Left ventricular unloading strategy is associated with decreased mortality in V-A ECMO patients.
B. The IABP acts only indirectly on the LV.
C. The surgical approach is preferred to the percutaneous strategy.
D. The ECPELLA strategy could represent a valid technology to unload LV concomitant to ECMO support.

4. What kind of mechanical support should be used in a patient with CS secondary to a STEMI to directly unload LV and improve myocardial recovery?

A. Intra-aortic balloon counterpulsation
B. Impella
C. TandemHeart
D. None of the above

5. Which of the following statements regarding LV support with Impella is incorrect?

A. Impella support should be always combined with inotropes.
B. Impella support reduces wedge pressure.
C. Impella can reduce infarct size in patient with AMI.
D. Impella directly unloads the LV.

6. What should be the proper timing most of time to escalate support with Impella in V-A ECMO?

A. In the first 72 hours
B. In the first 48 hours
C. On day 7 from V-A ECMO implantation
D. Immediately after removing V-A ECMO support

7. Which of these situations does not represent a dark side of the ECPELLA strategy?

A. Higher rate of hemolysis
B. Higher incidence of hemofiltration
C. Increased rate of bleeding
D. The presence of LV thrombosis

8. What should be the proper strategy in the management of CS resuscitated with ECMO or ECPELLA achieving hemodynamic improvement but NO myocardial recovery with preserved right ventricular function?

A. To continue with ECMO or ECPELLA support
B. To implant an Impella 5.0 via axillary artery
C. To increase inotropic support
D. To implant TandemHeart

9. What are the PROS of the escalation strategy with Impella 5.0?

A. Powerful LV unloading and increased chances for recovery of the native heart
B. Early extubation, ambulation, physiotherapy, and shared decision with the patient
C. Evaluation of LVAD or heart transplant
D. All the above

10. In which of these situations would venting be appropriate?

A. LVEDV 91 mL/m^2, CVP 18 mm Hg, wedge pressure 25 mm Hg
B. LVEDP 12 mm Hg, CVP 7 mm Hg, wedge pressure 12 mm Hg
C. LVEDV 60 mL/m^2, CVP 8 mm Hg, wedge pressure 12 mm Hg
D. LVEDV 55 mL/m^2, E/e′ 5, PAP 25/12 mm Hg

ANSWERS

1. D. This is explained by the fact that the extracorporeal oxygenated blood flow pumped into the arterial circulation and the increased aortic pressure guaranteed by the ECLS system are opposed to the ejection of the native heart. Therefore, these phenomena can cause ventricular distension with secondary myocardial ischemia, pulmonary edema, and, finally, LV and pulmonary artery thrombosis due to flow stasis.[2]

2. D. The reduction in LV afterload by reducing filling pressures results in a less dilated and overdistended LV. This prevents pulmonary edema. Furthermore, LV unloading determines a decrease of myocardial oxygen demand by reducing the end-diastolic pressure and wall tension. LV unloading also has positive effects on myocardial injury since it has been shown that LV unloading before PCI in STEMI reduces infarct size.[8] The risk of cardiac thrombus formation due to blood stasis and permanent aortic valve closure is reduced by LV unloading.

3. C. Surgical venting procedures are not technically simple and expose the patient to a number of potential complications besides those inherent to cardiac surgery, including laceration of the myocardial wall or damage to the epicardial coronary arteries. The surgical approach, moreover, has the major limitation of "violating the chest"; this turns into not only an increased risk of bleeding and infection, but also a hostile surgical field for any future procedure (LVAD implantation, heart transplantation).

4. B. It has been demonstrated, indeed, that primary LV unloading in STEMI with Impella in a population of dogs and then delaying reperfusion for 1 hour reduces myocardial infarct size compared with traditional reperfusion strategies. This surprising result might be consistent with the activation of a myocardial protection program that upregulates SDF-1a/CXCR4 expression, increases cardioprotective signaling, reduces apoptosis, and hence limits myocardial damage in AMI.[8,37,38] Relying on this purpose, the DTU ongoing trial (NCT03947619) aims to evaluate whether using the Impella CP System temporary circulatory assist device for 30 minutes prior to a catheterization procedure has the potential to reduce the damage to the heart caused by a heart attack, compared to the current standard of care. Remember that IABP acts only indirectly on the LV, and its use in patients with CS in V-A ECMO support remains controversial nowadays.

5. A. Impella is a percutaneous (2.5 and CP) or surgical (5.0) transaortic LVAD composed of a microaxial impeller pump that provides continuous blood flow from the LV into the ascending aorta, thus directly reducing LV afterload

and consecutively decreasing LV end-diastolic and pulmonary venous pressure and also providing an increase in the net forward flow. Also, LV unloading with Impella has positive effects on myocardial injury since it has been shown that LV unloading before PCI in STEMI reduces infarct size.[8]

6. B. The upgrade with Impella should be achieved in the first 48 hours from ECMO implantation to benefit from the adjunctive flow and to lower the toxic effect of catecholamines since significant reduction of lactates and of the inotropic score should take place within 24 hours maximum.

7. C. Some limitations of the ECPELLA approach should be acknowledged: first, the higher rate of hemolysis (reported between 30% and 100%), though this did not translate into a higher incidence of bleeding[39]; second, the high incidence of veno-venous hemofiltration[33]; and third, the current contraindications for Impella (mechanical aortic valve, LV thrombus), which still drive the application of different venting strategies.

8. B. In case of failure of weaning from V-A ECMO due to the persistent severe LV dysfunction and the lack of myocardial recovery, an appropriate decision should be to upgrade the support with a surgical axillary Impella 5.0 after right ventricular function assessment. By providing greater flow, the Impella 5.0 allows safe and early weaning from V-A ECMO. Other advantages are early extubation, ambulation, and physiotherapy and to sharing the clinical decision with the patient.

9. D. By providing greater flow, the Impella 5.0 allows powerfull LV unloading and safe and early weaning from V-A ECMO. Significant advantages of this approach include the potential for early extubation, ambulation, and physiotherapy and sharing the clinical decision with the patient.[40] Furthermore, Impella 5.0 support allows evaluation of right ventricular function and pulmonary vascular resistance in a bridge-to-decision strategy (LVAD or heart transplantation). The Impella 5.0 is also a feasible bridge-to-decision option following ECLS implantation and allows further evaluations of a patient's neurological state.

10. A. At echocardiographic evaluation, an overloaded LV is identified by an augmented indexed LVEDD, LVEDV, a high relationship between E/e′ waves (E/e′ > 15). The hemodynamic parameters are those derived from pulmonary artery catheter measurements as PAP (normal systolic pressure range 15–30 mm Hg, diastolic range 4–12 mm Hg), wedge pressure (normal range 2–15 mm Hg), CVP (normal range 3–8 mm Hg), and those calculated by left ventriculography as LVEDP (normal range 5–12 mm Hg).

46.

ECMO SUPPORT FOR PATIENTS WITH MAJOR AORTIC SURGERY OR DISSECTION

Massimo Capoccia and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 49-year-old man was admitted to the Accident & Emergency Department of a University Hospital with sudden onset of central chest pain radiating to his back. A gated computed tomographic (CT) scan showed the presence of acute type A aortic dissection with an entry tear in the distal ascending aorta extending just above the origin of the right coronary artery and involving the origin of the epiaortic vessels. The presence of a diastolic murmur on clinical examination was suggestive of aortic regurgitation, which was quantified as significant on echocardiographic assessment in the context of biventricular systolic dysfunction. A cardiac surgical opinion was sought and immediate surgical intervention considered. The patient was consented and transferred to the operating theatre.

Invasive arterial and venous monitoring was obtained through the left and right radial artery, left femoral artery, and right internal jugular vein. The patient was prepped in the supine position. Cardiopulmonary bypass (CPB) was established through the right femoral artery and right atrial cannulation. Antegrade and retrograde cold blood cardioplegia was delivered for myocardial protection. Body temperature was lowered and maintained at 18°C. Antegrade cerebral perfusion was achieved with cannulation of each epiaortic vessel following longitudinal incision of the ascending aorta and arch. Continuous, noninvasive monitoring of cerebral oxygen saturation was maintained with near-infrared spectroscopy (NIRS) using an INVOS™ 5100C Cerebral/Somatic Oximeter monitoring system.

A modified Bentall procedure with a 23-mm St. Jude composite mechanical conduit was performed followed by a frozen elephant trunk with a 26/28/150-mm Thoraflex™ Hybrid Plexus 4 device (Vascutek, TERUMO Aortic, Inchinnan, UK). The distal anastomosis within zone 2 (just above the origin of the left subclavian artery) was achieved under circulatory arrest. Then, distal reperfusion was commenced through the side arm of the Thoraflex. The true lumen placement of the stent of the Thoraflex was guaranteed by the presence of a stiff wire previously inserted through the left femoral artery under image intensifier. Then, the proximal anastomosis was completed maintaining further myocardial protection. Finally, the innominate and left common carotid arteries were debranched and anastomosed to the Thoraflex device. The procedure had been technically challenging in view of the poor quality of tissues and the extent of the dissection.

The patient was finally rewarmed, but weaning off CPB proved difficult in view of his preoperative biventricular systolic dysfunction. An additional resting period was considered, but further weaning off CPB failed. After 16 hours of theatre time and 10 hours on CPB, extracorporeal membrane oxygenation (ECMO) support was considered as an attempt at myocardial recovery. Central cannulation through the side branch of the aortic graft and the right atrium was considered to achieve chest closure. A Levitronix Centrimag (Thoratec) device was inserted, and the patient was transferred to the intensive care unit.

The postoperative course was complicated by prolonged mechanical ventilation leading to tracheostomy, inotropic support, and renal impairment requiring continuous veno-venous hemofiltration (CVVHF). After 6 weeks of ECMO support, the device was successfully weaned and removed. Subsequent recovery was uneventful, requiring monitoring of his renal function. A CT aortic angiogram was completely satisfactory with appropriate placement and sealing of the stent component of the Thoraflex device. Finally, the patient was discharged home 8 weeks postoperatively with a follow-up appointment.

WHAT ARE THE INDICATIONS FOR ECMO SUPPORT?

Extracorporeal membrane oxygenation has become increasingly available for the treatment of a diverse population of critically ill patients, and recent reviews have highlighted its indications and the evidence basis to justify its use.[1,2] Veno-arterial (V-A) ECMO is a suitable approach in the context of cardiac failure.[3] Veno-venous (V-V) ECMO is appropriate in the context of acute respiratory disease syndrome.[4] More recently, ECMO has been considered in the setting of extracorporeal cardiopulmonary resuscitation. Despite increased application of the technique, overall survival rates have remained unchanged with a 50%–70% range for respiratory support and 40%–60% range for cardiac support.[5]

WHAT IS THE CURRENT APPROACH FOR TYPE A AORTIC DISSECTION?

Traditionally, early surgical repair has been the treatment of choice for acute type A aortic dissection, with variable outcome and controversy about timing and patient selection,[6,7] although over the years the attitude has shifted toward a more delayed and planned repair.[8,9] Nevertheless, preoperative malperfusion syndrome rather than timing[10] remains a critical issue which affects outcome according to the type and the number of organs involved,[11] with particular reference to mesenteric malperfusion and coma, where percutaneous intervention and delayed surgical treatment are more appropriate in view of the adverse prognosis following an immediate surgical approach.[12,13] The use of β-blockers remains beneficial both preoperatively and postoperatively[14] despite enthusiasm about the potential more effective action of angiotensin II type 1 receptor antagonists such as losartan, which has not been confirmed by several large randomized trials.[15] Controversy remains about the surgical strategy between ascending aorta with hemiarch replacement and total arch with frozen elephant trunk.[16–18]

WHAT ABOUT TYPE B AORTIC DISSECTION?

Aggressive medical treatment remains the preferred choice for uncomplicated type B dissection. Endovascular intervention is considered for type B dissection complicated by aortic rupture, end-organ ischemia, persistent pain, and hypertension despite full medical treatment, early false lumen expansion, and large single entry.[19,20] Endovascular intervention for uncomplicated type B dissection seems an attractive option in view of the suboptimal long-term outcome of medical treatment alone, with up to 50% mortality at 5 years and up to 50% delayed expansion of the false lumen at 4 years.[21] Although two randomized trials (ADSORB and INSTEAD) have shown a higher rate of favorable aortic remodeling compared to medical treatment alone, it remains unclear whether these findings may lead to reduced long-term mortality sufficient to balance the early perioperative hazards of endovascular intervention.[22]

WHAT ARE THE DIFFERENT CANNULATION APPROACHES?

Traditional configurations for ECMO support include the V-V through the right internal jugular vein (Avalon cannula) and the V-A either through the ascending aorta and the right atrium (central cannulation) or the femoral vessels (peripheral cannulation).[23,24] Hybrid ECMO configurations have been increasingly considered recently as an attempt to improve outcome. Triple-cannulation configurations may help with concomitant cardiac and respiratory failure. Veno-veno-arterial ECMO consists of double-venous cannulation through the right internal jugular vein and a femoral vein for drainage with femoral artery cannulation for perfusion. Veno-arterial-venous ECMO consists of single-venous drainage through a femoral vein with arterial and venous perfusion cannulae. The V-Pa configuration through the insertion of a long venous cannula in the pulmonary artery, usually via the right internal jugular vein, may be a suitable option for patients with right heart failure.[23]

WHAT IS THE APPROPRIATE RANGE OF PRESSURE AND FLOW DURING ECMO SUPPORT?

The blood assist index (BAI) may be used to evaluate the level of ECMO support.[25]

The BAI is defined as the ratio of ECMO energy to total energy as follows:

$$BAI = \frac{1}{T}\int_0^{(T_C)} \left(\frac{F_E(t)}{F_E(t)+F_C(t)}\right)dt$$

where $F_E(t)$ is the waveform of the blood flow through the outlet ECMO cannula, $F_C(t)$ is the waveform of the native cardiac output and T_C is the cardiac cycle. When BAI = 1, full ECMO support is observed, and the native cardiac output is zero. When BAI < 1, partial ECMO support is observed. When BAI = 0, no ECMO support is observed.

Partial ECMO support with mean pressure around 80–85 mm Hg seems a better option compared to full ECMO support with a mean pressure around 70–75 mm Hg, as shown by computational fluid dynamics simulations.[26] Central ECMO support may be the preferred choice.[25,27]

An increased left ventricular (LV) afterload leading to left ventricular distension may affect the intended beneficial effects of V-A ECMO support.[28,29] Experimental evidence confirms the clinical findings and highlights the presence of reduced LV ejection fraction and stroke work as markers of LV dysfunction during V-A ECMO support.[30] The impact of V-A ECMO on LV function can be explained in terms of pressure-volume loops and Starling curves[31] following a simulation approach based on a previously developed model.[32,33] V-A ECMO does not affect LV function directly. When LV afterload is maintained constant at a specific systemic pressure, the Starling curve generated before V-A ECMO support predicts the filling pressure related to any target stroke volume at that systemic pressure. The mechanism by which that specific pressure is achieved does not change the relationship between filling pressure and native LV stroke volume. A maintained Starling relationship during V-A ECMO support may help predict ventricular distension and optimise the balance between LV unloading and systemic perfusion.[31] The optimal balance between LV unloading and systemic perfusion remains critical. The degree of LV unloading during V-A ECMO support significantly depends on the absolute flow and the recruitable contractile reserve of the left ventricle. Maintaining a certain degree of LV ejection in the absence of pulmonary edema is highly desirable clinically and as per simulation studies.[34]

CAN ECMO CANNULATION CAUSE AORTIC DISSECTION OR MIMIC IT?

Imaging evaluation from a contrast-enhanced CT scan in patients on V-A ECMO can be challenging due to pump-related hemodynamic alterations and contrast enhancement patterns. Clearly delineated contrast-blood layering

starting from the aortic valve through the ascending aorta into the right carotid artery suggestive for aortic dissection has been reported.[35] Further evaluation of the venous phase of the CT-scan images showed no filling defects or dissection membrane, and postmortem examination confirmed the absence of aortic dissection. Unequal distribution of venous contrast in the aortic arch has also been reported following V-A ECMO insertion through femoral cannulation,[36] raising initial suspicion for aortic dissection. Further review confirmed the presence of normal ECMO flow with mixing in the aortic arch due to competitive flow between the native circulation and the retrograde perfusion through the cannula in the femoral artery.

Partial enhancement of the ascending aorta with sagittal and coronal views showing an adjacent intimal flap suggestive for aortic dissection following initial CT scan using cardiac-triggering acquisition and administration of contrast material through a jugular venous catheter has been reported in a patient on peripheral V-A ECMO.[37] Again, further image evaluation supplemented with transesophageal echocardiography and further CT scan ruled out the presence of aortic dissection, confirming the flow-mixing pattern between the enhanced ECMO blood flow with the unenhanced blood from the left ventricle in the initial portion of the ascending aorta causing turbulence with apparent features of aortic dissection.

Finally, findings may be related to blood stagnation but can be so misleading to require supplementation of direct vision with trans-esophageal echocardiography.[38]

IS THERE ANY ADVANTAGE FOR THE CONCOMITANT USE OF ECMO AND AN INTRA-AORTIC BALLOON PUMP (IABP) OR IMPELLA?

Simulations of combined V-A ECMO and intra-aortic balloon pump (IABP) support show an increase in pulsatility and LV stroke volume between 5% and 10% due to afterload reduction although pulmonary capillary wedge pressure (PCWP) and LV end-diastolic volume (EDV) are only marginally affected. Significant LV unloading is achieved during combined V-A ECMO and Impella support, although aortic valve opening and improved diastolic coronary perfusion pressure are not observed in comparison with IABP.[34] Nevertheless, the pulse contour is higher and more similar to the physiological pattern during partial ECMO support, where some degree of LV ejection is allowed.[26]

The concomitant use of IABP and V-A ECMO shows reduced in-hospital mortality in patients with cardiogenic shock secondary to postcardiotomy failure, ischemic heart disease, and myocarditis,[39,40] which is in contrast with the outcome of the SHOCK II trial.[41–43] The study was designed as a multicentre, randomised, open-label trial. Between 2009 and 2012, 600 patients with cardiogenic shock following acute myocardial infarction and requiring early revascularisation were randomised to IABP versus control. Long-term follow-up (6.2 years) showed no difference in mortality, recurrent myocardial infarction, stroke, repeat revascularisation, or hospital readmission for cardiac reasons between the two groups. Nevertheless, the use of IABP in cardiogenic shock remains the subject of significant debate and controversy. Beneficial findings have been reported for the combined use of Impella and V-A ECMO on LV unloading and survival.[44,45] Impella 2.5 has been used for additional LV unloading in patients on peripheral V-A ECMO as a bridge to long-term LV assist device (LVAD) insertion with HeartMate II.[44] A large retrospective study of the use of Impella 2.5, Impella CP, or Impella 5 with V-A ECMO in patients with refractory cardiogenic shock showed lower all-cause 30-day mortality, lower requirement for inotropic support, and comparable safety profiles in relation to V-A ECMO alone.[45]

Finally, rotational speed modulation in synchrony with the cardiac cycle enables an increase in coronary artery blood flow with a decrease in LV workload and afterload during V-A ECMO in an experimental setting, with the potential to offer the effects of IABP and V-A ECMO combined in a single device.[46]

WHAT IS THE CURRENT AVAILABLE EVIDENCE FOR ECMO IN AORTIC SURGERY/DISSECTION?

A recent systematic literature review[47] has retrieved 29 publications relevant to this controversial matter of the use of ECMO in aortic surgery/dissection. The key findings are listed in Tables 46.1 and 46.2.

DISCUSSION

ECMO support following major aortic surgery has not been usually recommended because of its potential to further exacerbate lesions of the aortic wall and increased bleeding with delayed thrombosis of the false lumen due to the use of anticoagulation.[16,48,49] Nevertheless, 3 retrospective studies[50–52] and 1 observational study[53] have shown the feasibility of ECMO support in patients undergoing major aortic surgery for aneurysmal disease and dissection in contrast to current scepticism.[54] In many countries, the argument is to make for a balance between the costs involved in running ECMO support and selecting those patients who would benefit the most from a period of circulatory support following repair for acute aortic dissection. Monitoring the outcome of those patients who required ECMO support postoperatively and developing a specific database may be the way forward to shed further light on the role of ECMO support in patients undergoing major aortic surgery.

Although 1 retrospective study[52] reported 88% mortality rate in 35 patients who underwent ECMO support following surgical treatment for type A aortic dissection, there is no mention about indications for ECMO support; a profile and comorbidities of these patients; cannulation site (peripheral or central); or cause of death. Twenty seven patients received ECMO support on the day of surgery, and 8 patients required ECMO support on postoperative day 1 or later. Most unusual, 4 additional patients with type A aortic dissection underwent

Table 46.1 GRADING OF MANUSCRIPTS WITH KEY INFORMATION AND OUTCOME

FIRST AUTHOR, YEAR	STUDY DESIGN/ LEVEL OF EVIDENCE	ECMO PATIENTS	OUTCOME
Abouliatim, 2012[60]	Brief communication Level 3	AAA repair on ECMO support in 2 patients after failed EVAR	Both patients were discharged 12 days postoperatively.
Lorusso, 2019[61]	Surgical technique Level 3	2 patients requiring elective aortic arch replacement and treated with minimally invasive central ECMO, which avoids resternotomy and maintains antegrade blood flow	Successful outcome for both patients. The technique is suitable only in those patients where a side-armed prosthetic graft had been used.
Lazar, 2017[54]	Invited commentary Level 3	Comment to Sultan, 2017, with further considerations about ECMO in aortic dissection	
Guenther, 2014[62]	Retrospective case review Level 3	6 patients with acute TAAD involving the coronary arteries treated with ECMO support	Mortality 67% (4 patients)
Lin, 2018[53]	Observational study Level 2-	510 patients with TAAD between 2007 and 2018 17 required ECMO postoperatively	Comparison between low LVEF and preserved LVEF
Lin, 2017[50]	Retrospective study Level 2	162 patients underwent TAAD repair between 2008 and 2015 20 patients required ECMO support postoperatively	Mortality: ECMO group 65%; non-ECMO group 8.5% Factors predicting postop ECMO: hemodynamic instability; aortic cross-clamp time; postop peak CK-MB Younger age for ECMO survivors
Zhong, 2017[51]	Retrospective study Level 2-	5637 patients underwent major aortic surgery between 2009 and 2016 36 patients required ECMO support: 20 with TAAD; 3 type B; 12 with thoracic aortic aneurysm; 1 with aortic coarctation	Mortality 50% Three main factors for in-hospital mortality: retrograde flow cannulation; preop CK-MB level 100 IU/L; peak lactate level 20 mmol/L
Sultan, 2017[52]	Retrospective study Level 2-	Database review between 2004 and 2014 35 patients with TAAD underwent ECMO support	Overall mortality 88% No mention about indications for ECMO support; profile and comorbidities of these patients; cannulation site (peripheral or central); cause of death
Guihaire, 2017[63]	Retrospective study Level 2-	92 patients required ECMO support following valve surgery (66%), acute aortic dissection (10%), and CABG (9%)	Survival for patients with aortic dissection was not specified
Gennari, 2019[64]	Case report Level 3	1 patient with iatrogenic TAAD requiring ECMO support	Successful weaning off ECMO after 4 days
Chatterjee, 2018[65]	Case report Level 3	3 patients requiring ECMO support after thoracoabdominal aneurysm repair	1 patient discharged after 128 days but died 2 months later 1 patient discharged after 35 days and alive at 3-year follow-up 1 patient discharged after 19 days and alive at 6-month follow-up
El Beyrouti, 2018[66]	Case report Level 3	1patient with aortic dissection involving the left mainstem requiring ECLS and subsequently LVAD	Discharged after 27 days
Yukawa, 2018[67]	Case report Level 3	Acute aortic dissection with out-of-hospital cardiac arrest requiring ECMO support	Discharged after 49 days
Stroehle, 2017[68]	Case report Level 3	Traumatic aortic dissection treated with TEVAR on ECMO support	Discharged after 42 days to neurorehabilitation

Table 46.1 CONTINUED

FIRST AUTHOR, YEAR	STUDY DESIGN/ LEVEL OF EVIDENCE	ECMO PATIENTS	OUTCOME
Szczechowicz, 2016[69]	Case report Level 3	2 patients with acute TAAD complicated by right ventricular failure requiring ECMO support	First patient discharged after 27 days; second patient discharged to the ward after 8 days in ITU but no mention about how many days before discharge
Ishida, 2015[70]	Case report Level 3	Two-stage procedure on ECMO support in 1 patient who sustained acute TAAD in a background of chronic thromboembolic pulmonary hypertension	Prolonged hospital stay; no mention how many days before discharge
Yavuz, 2015[71]	Case report Level 3	ECMO following TEVAR in 1 patient	No mention about outcome
Amako, 2013[72]	Case report Level 3	1 patient with TAAD treated with ECMO support	ECMO weaned off after 65 hours uneventfully
Doguet, 2010[73]	Case report Level 3	1 patient with acute TAAD involving the coronary arteries treated with ECMO support	Discharged after 29 days postoperatively
Koster, 2007[74]	Case report Level 3	1 patient with acute TAAD requiring ECMO support who developed treated successfully with bivalirudin	LV recovery during VA-ECMO support but RVAD required; successful ECMO weaning; RVAD removed after 6 weeks
Fabricius, 2001[75]	Case report Level 3	2 patients who sustained acute TAAD during pregnancy treated with ECMO support	Successful ECMO weaning
Yamashita, 1994[76]	Case report Level 3	1 patient with acute aortic dissection treated with ECMO support	Successful ECMO weaning
Jorgensen, 2019[77]	Conference abstract Level 3	Elective femoro-femoral VA-ECMO support for thoracoabdominal aortic aneurysm repair in a 82-year-old patient	Discharged 11 days postoperatively
Heuts, 2017[78]	Conference abstract Level 3	Surgical technique for ECMO insertion (the Maastricht approach)	See Lorusso, 2019. in this table
Yang, 2017[79]	Conference abstract Level 3	Retrospective analysis of 1695 patients who underwent surgery for aortic dissection between 2008 and 2015; 42 patients required VA-ECMO support	30 patients successfully weaned off VA-ECMO and 19 patients discharged Higher lactate levels, pre-ECMO cardiac arrest, major hemorrhage, and renal replacement therapy were related to in-hospital mortality.
Goldberg, 2017 [80]	Conference abstract Level 3	185 patients requiring repair of acute TAAD between 2005 and 2016 4 patients required VA-ECMO support	All 4 patients survived to hospital discharge.
Schmidt, 2016[81]	Conference abstract Level 3	Acute TAAD presenting as acute coronary syndrome requiring ECMO support in the catheterization lab as a bridge to surgical intervention	Fatal outcome
Nierscher, 2012[82]	Conference abstract Level 3	Observational study of patients undergoing cardiac surgery in 2008; 35 patients required ECMO support; only 1 patient with aortic dissection was reported	Survival not specified for the patient with aortic dissection
Shinar, 2011[83]	Conference abstract Level 3	Observational study over a 14-month period of ECMO support initiated by accident and emergency physicians; the procedure attempted in 19 patients	Four patients discharged without neurological injury: 2 patients after MI, 1 after aortic dissection with cardiac tamponade, and 1 after profound hypothermia

CABG, coronary artery bypass graft; ECLS, extracorporeal life support; LVEF, left ventricular ejection fraction; RVAD, right ventricle assist device; TAAD, type A aortic dissection.

Table 46.2 ETIOLOGY, TYPE OF PROCEDURE, AND TYPE OF CANNULATION

FIRST AUTHOR, YEAR	STUDY DESIGN/LEVEL OF EVIDENCE	ECMO PATIENTS
Lin, 2018[53]	Observational study Level 2-	510 patients with ATAAD between 2007 and 2018 Entry tear exclusion 73.1% Aortic root replacement 11.4% Ascending aorta replacement 65.9% Aortic arch replacement 25.3% Hemiarch 13.3% Total arch 12.0% Frozen elephant trunk 8.2% Combined CABG 3.7% 17 required ECMO support but no procedure breakdown available
Lin, 2017[50]	Retrospective study Level 2-	162 patients underwent TAAD repair between 2008 and 2015 20 patients required ECMO support as follows: Ascending aorta interposition graft 6 Aortic root/valve procedure 9 Aortic arch procedure 10 Combined CABG 5 Combined mitral replacement/repair 1 Combined femoro-femoral crossover 1
Zhong, 2017[51]	Retrospective study Level 2-	5637 patients underwent major aortic surgery between 2009 and 2016 36 patients required ECMO support as follows: Type A aortic dissection 20 Type B aortic dissection 3 Thoracic aortic aneurysm 12 Aortic coarctation 1 Emergency surgery 9 Second operation 7 Ascending aorta replacement 34 Arch replacement 21 Descending aorta stenting 17 Thoracoabdominal aorta replacement 2 Combined valve replacement 21 Combined CABG 16 Central ECMO cannulation 7 Peripheral ECMO cannulation 29 Femoro-femoral 20 Femoral vein to right axillary artery 7 Femoro-femoral + right axillary artery 2 IABP 9
Sultan, 2017[52]	Retrospective study Level 2-	Database review between 2004 and 2014 35 patients with TAAD underwent ECMO support No procedure and cannulation breakdown available
Guihaire, 2017[63]	Retrospective study Level 2-	92 patients underwent ECMO support between January 2005 and December 2014 for postcardiotomy cardiogenic shock as follows: Valve surgery 66% Acute aortic dissection 10% CABG 9% Breakdown of procedures and cannulation not available
Nierscher, 2012[82]	Conference abstract Level 3	35 patients underwent ECMO support in 2008 following CABG (7), valve procedure (8), heart transplant (8), LVAD insertion (1), combined procedure (10), aortic dissection (1) Cannulation was peripheral (23), central (7), subclavian artery (5)
Gennari, 2019[64]	Case report Level 3	1 patient with iatrogenic TAAD requiring ECMO support through peripheral cannulation; ascending aorta replacement including right coronary sinus with interposition graft and single-vessel coronary artery bypass grafting
Jorgensen, 2019[77]	Conference abstract Level 3	1 patient with thoracoabdominal aortic aneurysm requiring ECMO support through peripheral cannulation; multibranched Gelweave Dacron graft was used

Table 46.2 CONTINUED

FIRST AUTHOR, YEAR	STUDY DESIGN/LEVEL OF EVIDENCE	ECMO PATIENTS
Chatterjee, 2018[65]	Case report Level 3	3 patients requiring ECMO support after thoracoabdominal aneurysm repair 2 patients had previous TAAD repair; 1 patient had ascending aorta and hemiarch replacement for TAAD and subsequent TEVAR procedure. ECMO cannulation between left axillary artery and femoral vein (1 patient), femoro-femoral (2 patients).
El Beyrouti, 2018[66]	Case report Level 3	1 patient with aortic dissection involving the left main stem treated with ascending aorta interposition graft and CABG requiring ECLS through central cannulation and subsequently LVAD
Yukawa, 2018[67]	Case report Level 3	Acute aortic dissection with out-of-hospital cardiac arrest requiring ECMO support through peripheral percutaneous femoral cannulation and treated with ascending aorta replacement using an interposition graft
Yang, 2017[79]	Conference abstract Level 3	1695 patients underwent repair for aortic dissection between 2008 and 2015. 42 patients required ECMO support. Procedure and cannulation break down is not available
Goldberg, 2017[80]	Conference abstract Level 3	185 patients underwent surgical intervention for acute TAAD between January 2005 and May 2016. 4 patients required VA-ECMO support. Break down of procedures, concomitant procedures and type of cannulation are not available
Stroehle, 2017[68]	Case report Level 3	Traumatic aortic dissection treated with TEVAR on ECMO support
Schmidt, 2016[81]	Conference abstract Level 3	Emergency ECMO insertion in the catheterization lab with findings of acute TAAD resulting in fatal outcome
Szczechowicz, 2016[69]	Case report Level 3	2 patients with acute TAAD complicated by right ventricular failure requiring ECMO support
Ishida, 2015[70]	Case report Level 3	Two-stage procedure on ECMO support in 1 patient who sustained acute TAAD in a background of chronic thromboembolic pulmonary hypertension
Yavuz, 2015[71]	Case report Level 3	ECMO following TEVAR in 1 patient
Guenther, 2014[62]	Retrospective case review Level 3	6 patients with acute TAAD involving the coronary arteries treated with ECMO support
Amako, 2013[72]	Case report Level 3	1 patient with acute TAAD treated with ECMO support
Abouliatim, 2012[60]	Brief communication Level 3	AAA repair on ECMO support in 2 patients after failed EVAR
Shinar, 2011[83]	Conference abstract Level 3	19 cases of ECMO insertion in accident and emergency department through percutaneous cannulation of the femoral vessels
Doguet, 2010[73]	Case report Level 3	1 patient with acute TAAD involving the coronary arteries treated with peripheral ECMO support through femoro-femoral cannulation; CABG as concomitant procedure
Koster, 2007[74]	Case report Level 3	1 patient with acute TAAD requiring ECMO support using bivalirudin
Fabricius, 2001[75]	Case report Level 3	2 patients who sustained acute TAAD during pregnancy treated with ECMO support
Yamashita, 1994[76]	Case report Level 3	1 patient with acute aortic dissection treated with ECMO support

AAA, abdominal aortic aneurysm); ATAAD, acute type A aortic dissection; EVAR, endovascular aortic repair; TEVAR, thoracic endovascular aortic repair; ITU, intensive therapy unit.

ECMO support without surgical intervention, but none of them survived.

The other two retrospective studies[50,51] are more detailed, with more favorable outcome in line with the Extracorporeal Life Support Organization registry.[5,55] One study[51] included 36 patients who required V-A ECMO for postcardiotomy failure following major aortic surgery. In-hospital mortality was 50%, with multiorgan failure the main cause of death. Preoperative levels of CK-MB (creatine kinase MB) greater than 100 IU/L and peak lactate levels greater than 20 mmol/L were considered relevant factors for in-hospital mortality. Retrograde flow cannulation was identified as another key factor for reduced survival compared to antegrade cannulation, although the risk for early mortality was related to the preoperative clinical and hemodynamic status rather than the cannulation technique.[49]

The other study[50] compared short- and long-term outcomes between patients who required ECMO support and those who did not. In-hospital mortality was higher in the ECMO group (65%) compared to the non-ECMO group (8.5%). Preoperative hemodynamic instability, aortic cross-clamp time and postoperative peak CK-MB were identified as predicting factors for postoperative ECMO support. ECMO survivors had younger age and less postoperative blood transfusion. Interestingly, those patients who survived after ECMO support following repair for acute type A aortic dissection showed a long-term survival rate comparable to patients who did not require ECMO support postoperatively.

These findings were confirmed by a very detailed observational study[53] comparing patients with and without LV systolic dysfunction who underwent surgical intervention for acute type A aortic dissection. A total of 510 patients were considered: 86 with LV systolic dysfunction (group I) and 424 patients with preserved LV systolic function (group II). ECMO support was required in 7 patients from group I and in 10 patients from group II. The overall mortality was 79 patients out of 510: 20 from group I and 59 from group II. Multivariate analysis confirmed that a preoperative serum creatinine greater than 1.5 mg/dL and the requirement for ECMO support intraoperatively were significant independent predictors of in-hospital mortality, but survival following ECMO support was not specified. Although patients with preoperative LV systolic dysfunction showed higher surgical risk for in-hospital mortality, their 3-year cumulative survival rate (77.8%) was comparable with those with preserved LV systolic function (82.1%). Serial echocardiographic assessment did not show further deterioration of LV systolic function during the 3-year follow-up.

CONCLUSION

- There is no compelling evidence in favor or against the use of ECMO support following major aortic surgery for aneurysmal disease or acute aortic dissection.
- There is enough evidence to justify the use of ECMO in those patients who develop hemodynamic instability refractory to inotropic support.
- Despite the limitations of ECMO support, there is potential for the technique to become a more routine approach in patients undergoing major aortic surgery.

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REVIEW QUESTIONS

1. What are the indications for V-A ECMO support?

   A. Postcardiotomy failure
   B. Early graft failure following heart transplant
   C. Temporary support as a bridge to long-term LVAD
   D. All of the above

2. What is the difference between type A and type B aortic dissection?

   A. Type A involves the whole of the aorta.
   B. Type B starts just below the origin of the left subclavian artery.
   C. Type B is usually treated conservatively.
   D. All of the above.

3. How can we classify aortic aneurysms?

   A. True and false
   B. Saccular or fusiform
   C. Atherosclerotic, dissecting, or mycotic
   D. All of the above

4. Which of the following answers is wrong?

   A. V-A ECMO + IABP is beneficial in patients with cardiogenic shock.
   B. Central V-A ECMO + IABP is an appropriate configuration.
   C. A combination of peripheral V-A ECMO + IABP is detrimental.
   D. V-A ECMO + IABP reduces LV afterload.

5. A 40-year-old gentleman presents with central chest pain radiating to the back. After symptoms control, clinical examination reveals a diastolic murmur in the absence of ischemic changes on the electrocardiogram (ECG). A CT aortic

angiogram shows a type A dissecting aortic aneurysm. What is the most appropriate option for this patient?

A. Interposition graft to ascending aorta and aortic valve cusps resuspension
B. Aortic valve–sparing root replacement (David's procedure)
C. Aortic valve–sparing root replacement (Yacoub's technique)
D. Aortic root replacement with a composite mechanical graft (modified Bentall procedure)

6. A 90-year-old lady with a background of coronary artery disease and chronic obstructive pulmonary disease (COPD) presents to an accident and emergency department with chest and abdominal pain. A CT aortic angiogram confirms an intramural hematoma with a penetrating aortic ulcer in the descending thoracic aorta. What would you do?

A. No intervention is indicated in this patient.
B. Medical management and repeat CT-scan at 3-month interval.
C. Endovascular stenting may be appropriate.
D. None of the above.

7. What are the factors likely to predict the need for postoperative ECMO support following major aortic surgery?

A. Biventricular systolic dysfunction
B. Propagation of the dissection into the coronary arteries
C. Aortic cross-clamp time
D. All of the above

8. What are the factors related to survival after V-A ECMO support following major aortic surgery?

A. Younger age
B. Higher rate of antegrade cannulation
C. Lower lactate levels at 12 hours
D. All of the above

9. What are the factors related with adverse outcome after V-A ECMO support following major aortic surgery?

A. Limb ischemia
B. Prolonged inotropic support
C. Visceral ischemia
D. All of the above

10. What is the most widely used investigation for the diagnosis of acute type A aortic dissection?

A. Contrast-enhanced CT scan
B. Transesophageal echocardiography
C. Magnetic resonance imaging
D. Aortic angiogram

11. How would you monitor a patient undergoing surgery for type A aortic dissection?

A. Arterial lines: right radial artery, left radial artery, and left femoral artery
B. Central venous access, nasopharyngeal temperature, and urinary catheter
C. Cerebral oximetry with near infrared spectroscopy (NIRS)
D. All of the above

12. What are the indications for intervention in the presence of an acute type B aortic dissection?

A. Rupture or impending rupture of the descending thoracic aorta
B. Extension of the dissection with difficult pain control
C. Evidence of malperfusion syndrome (limb, visceral, or spinal cord)
D. All of the above

ANSWERS

1. D is the correct answer. All of them are recognized indications for V-A ECMO support.

2. D is the correct answer. The Stanford classification is now widely used.

3. D is the correct answer. The key difference is that a true aneurysm is caused by extrusion of all three layers of the vessel wall; a false aneurysm or pseudoaneurysm consists of clots contained by the adventitia and the surrounding tissues. Shape and etiology are quite often used for additional information.

4. C is the correct answer. Recent reviews[39,40] supported the combined use of IABP and ECMO despite the controversial outcome of the SHOCK II Trial. IABP does improve myocardial oxygen supply/demand balance when combined with both peripheral and central V-A ECMO.[56–58] Nevertheless, IABP + peripheral V-A ECMO would not be appropriate in the context of low peripheral flow because of reduced upper body perfusion pressure. In contrast, IABP + central V-A ECMO preserves mean aortic pressure and maintains diastolic augmentation even in a low-pressure environment.[59]

5. B is the correct answer. Option A is a "convenient" operation and more appropriate in an older patient. Options B and D are more appropriate in this patient with a preference for David's procedure if feasible. Option C leaves residual diseased tissue in the aortic root.

6. B is the correct answer. Given the background and age, conservative management with a follow up CT scan would be the most appropriate course of action. Endovascular stenting may have a role to play on this particular occasion.

7. D is the correct answer.[50,52,53]

8. D is the correct answer.[50,51]

9. D is the correct answer.[51,53]

10. A is the correct answer. Contrast-enhanced CT scan imaging is highly sensitive (95%) and widely available with immediate result. Transesophageal echocardiography (TOE) is also highly sensitive (98%), with clear images and the ability to quantify the degree of aortic regurgitation, although it is operator dependent, requires sedation, and has a blind spot in the distal ascending aorta and proximal aortic arch. Magnetic resonance imaging (MRI) is again highly sensitive (99%) but not widely available. An aortic angiogram is reasonably sensitive (80%) but now is rarely used and potentially iatrogenic.

11. D is the correct answer.

12. D is the correct answer.

47.

MECHANICAL SUPPORT FOR POSTCARDIOTOMY RIGHT VENTRICULAR FAILURE

Valeria Lo Coco, Maria E. De Piero, Mariusz Kowalewski,

Giuseppe M. Raffa, and Roberto Lorusso

STEM CASE AND KEY QUESTIONS

A 55-year-old woman was hospitalized to undergo elective surgery for mitral valve insufficiency due to acute endocarditis (*Streptococcus mitis*) with a big vegetation (maximum 2.3 cm) on the posterior mitral leaflet. At preoperative echocardiogram, the tricuspid valve had normal function without any sign of endocarditis, and normal contractility of both ventricles was also observed. Her cardiovascular risk factors were moderate obesity, hypertension, hypercholesterolemia, and type 2 diabetes mellitus.

The primary surgical plan consisted of mitral valve repair through a minithoracotomy approach. After an attempt at a quadrangular resection with anuloplasty, the mitral valve was still incompetent.

Therefore, the decision was to proceed with a median sternotomy to facilitate the mitral valve replacement (mechanical prosthesis, size 25 mm, Medtronic) and to avoid further prolonged cardiopulmonary bypass (CPB) time. After a few hours in the intensive care unit (ICU), she developed cardiogenic shock. Transesophageal echocardiography (TEE) showed a severely dysfunctional right ventricle (RV) and a hypertrophic left ventricle (LV) with preserved systolic function. High dosages of inotropes to support the RV cardiac function were instituted. Due to the persistent hemodynamic instability despite inotropic support and progression of hepatic and renal failure, it was necessary to commence renal replacement therapy with continuous veno-venous hemofiltration. The decision to mechanically support the RV was made, and the patient was transferred to the hybrid operating room. The chosen strategy was to implant an RV assist device (RVAD) in the form of a double-lumen cannula into the pulmonary artery (PA) through the right internal jugular vein by means of a percutaneous approach (ProtekDuo 29 French [29F] cannula) in order to obtain dedicated and isolated RV support. The flow of the extracorporeal life support was maintained at around 2.5 L/min. After the start of the RV support, the hemodynamics improved progressively with a reduction of lactate, the dosage of inotropes, and an improvement of renal function until a complete recovery. The patient was weaned from the RV support cannula after 8 days, with an improvement in RV function as shown in an echocardiogram and complete normalization of hemodynamics as well as liver and renal functions.

During the ICU stay, the patient developed ventilator-associated pneumonia for which specific antibiotic therapy was commenced. Due to respiratory insufficiency, a tracheostomy was performed to facilitate respiratory weaning. After 40 days of hospitalization, the patient was transferred to a rehabilitation hospital in good condition.

WHAT IS THE DEFINITION OF RIGHT VENTRICULAR FAILURE?

Right ventricular failure (RVF) is a complex condition characterized by inability of the RV to provide adequate blood flow through the pulmonary circulation at normal central venous pressure (CVP).[1,2] The genesis may be multifactorial, and it is usually associated with various causes and different pathways (Table 47.1).

Table 47.1 CAUSE OF RIGHT VENTRICULAR FAILURE POSTCARDIOTOMY

Long CPB time
Myocardial stunning for inadequate intraoperative myocardial protection (insufficient amount of cardioplegia, calcified coronary ostia, etc.)
Coronary embolism (air, clots, atherosclerotic calcified fragment) or problems with graft (occlusion) causing RV ischemia
Donor heart ischemia and pulmonary vascular dysfunction in heart transplant
Ventilation-induced lung injury and acute respiratory distress syndrome due to invasive mechanical ventilation
Shift of the IVS into the LV and volume overloading of the right heart after LVAD placement

WHAT IS THE INCIDENCE AND PROGNOSIS OF RIGHT VENTRICULAR FAILURE AFTER CARDIAC SURGERY?

Right ventricular failure is associated with high mortality, as high as 75% after routine cardiac surgery and up to 40% in patients with an LV assist device (LVAD).[3,4] The prevalence varies from 0.1% after common cardiac surgery to 20% after LVAD implantation. RV dysfunction is also the major cause of graft rejection in case of heart transplantation (HTx) (rate of 2%–3%).[5,6]

WHAT ARE THE RISK FACTORS AND PROGNOSTIC SCORES OF RIGHT VENTRICULAR FAILURE AFTER CARDIAC SURGERY?

In the last decade, growing interest was observed in identifying risk factors for RVF after cardiac surgery. Predictors were then divided into three principal settings for postcardiotomy (Figure 47.1).

WHAT ARE THE RISK FACTORS AND PROGNOSTIC SCORES OF RIGHT VENTRICULAR FAILURE AFTER ROUTINE CARDIAC SURGERY (VALVE, AORTA, AND CORONARY SURGERY)?

The preoperative evaluation of the RV is fundamental in cardiac surgery, particularly in the case of mitral and tricuspid repair and replacement.

A RV fractional area change less than 35% is a strong prognosticator for 3-year mortality.[7] A tricuspid annular plane systolic excursion (TAPSE) less than 17 mm is also associated with an increased 5- and 8-year mortality compared to patients with higher TAPSE values (39% vs. 17% and 52% vs. 23%, respectively).[8]

Other echocardiographic parameters that may be considered predictors of RVF after cardiac surgery are

- Pulsed Doppler systolic myocardial velocity less than 9.5 cm/s
- Right ventricular ejection fraction (RVEF) less than 45%
- Pulsed Doppler RV index of myocardial performance greater than 0.43
- Ratio of peak velocity flow in early (E wave) to late (A wave) diastole (E/A) less than 0.8 or greater than 2[9–11]

Hemodynamic variables that may be indicative of RVF after cardiac surgery are

- CVP greater than 20 mm Hg
- Low pulmonary capillary wedge pressure (PCWP)
- Cardiac index (CI) less than 2.1 L/min/m^2 despite adequate filling[12]

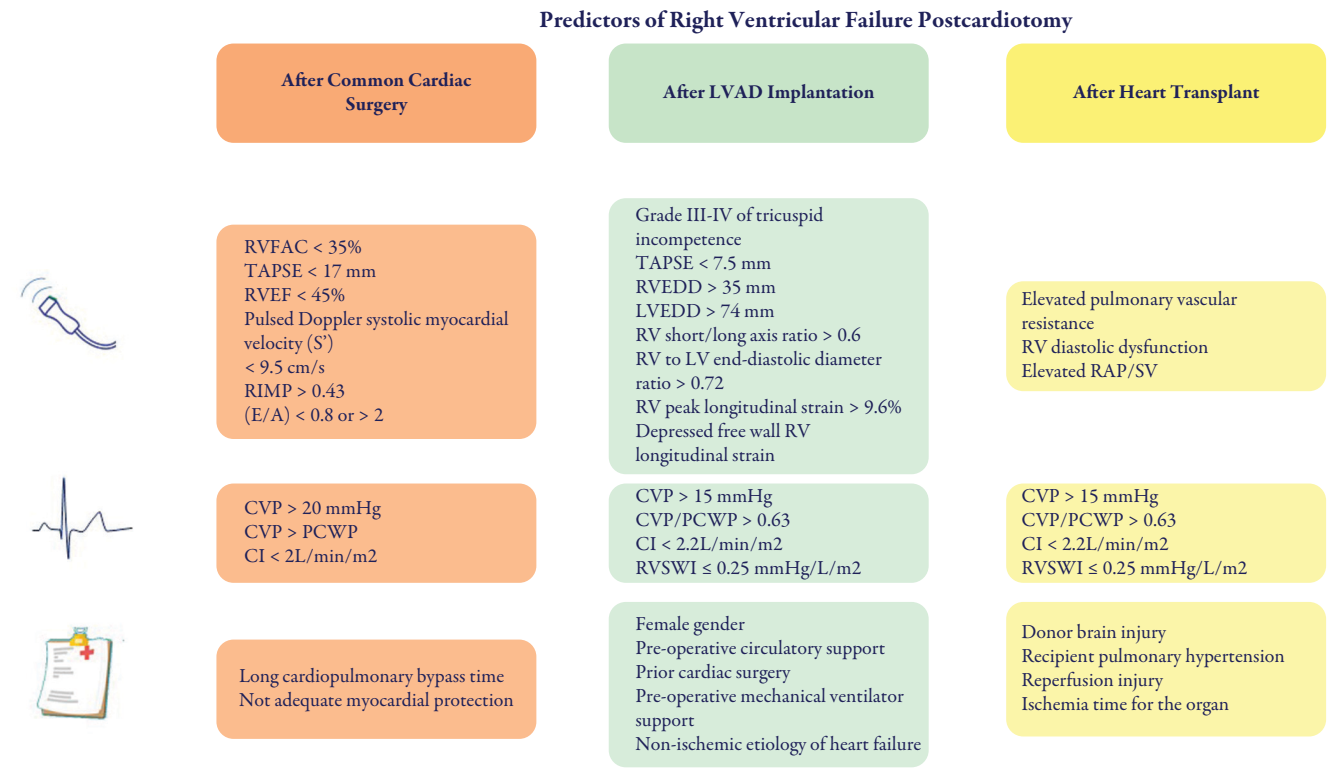


Figure 47.1 Predictors of right ventricular failure in postcardiotomy patients.
CI, cardiac index; CVP, central venous pressure; E/A, peak velocity flow in early (E wave) to late (A wave) diastole; LVEDD, left ventricle end-diastolic diameter; PCWP, pulmonary capillary wedge pressure; RAP, right atrium pressure; RIMP, right ventricular index of myocardial performance; RV, right ventricle; RVEDD, right ventricle end-diastolic diameter; RVEF, right ventricle ejection fraction; RVFAC, right ventricle fractional area change; RVSWI, right ventricle stroke work index; SV, stroke volume; TAPSE, tricuspid annular plane systolic excursion.

Post-LVAD

The principal risk factors in the post-LVAD scenario are

- Female gender
- Preoperative circulatory support
- Prior cardiac surgery
- Nonischemic etiology of heart failure[13,14]
- CVP/PCWP greater than 0.63
- Preoperative mechanical ventilator support
- Blood urea nitrogen greater than 39 mg/dL[15]
- Grade of tricuspid incompetence (III–IV)
- Geometry of the RV (RV end-diastolic diameter greater than 35 mm, RVEF greater than 30%, and right atrial [RA] dimension greater than 50 mm) in relation to high pulmonary vascular resistance (PVR)
- Elevated CVP
- Evidence of liver and renal impairment[16,17]
- CVP greater than 15[18]
- Low RV stroke work index (RVSWI)
- Low PA pressure[19]
- CI less than 2.2 L/min/m^2
- Diastolic pulmonary gradient and elevated PVR[20,21]
- RVSWI 0.25 mm Hg/L/m^2[,22] or less
- TAPSE less than 7.5 mm[23]
- RV short-/long-axis ratio greater than 0.6[16]
- RV-to-LV end-diastolic diameter ratio greater than 0.72[24]
- RV peak longitudinal strain greater than 9.6%[25]
- LV end-diastolic diameter greater than 74 mm[26]
- Depressed free wall RV longitudinal strain[27]
- Moderate-to-severe mitral regurgitation[28]

Scores such as Michigan,[29] central venous pressure >15 mmHg ("C"), severe RV dysfunction ("R"), preoperative intubation ("I"), severe tricuspid regurgitation ("T"), heart rate >100 (Tachycardia - "T"),[18] ALMA: 1 or 0 point is allotted for each of the following five variables in the institutionally defined "ALMA" score: DT (destination therapy) intention, PAPi (pulmonary artery pulsatily index) <2, RVSWi (right ventricular stroke work index) <300 mm Hg/ml/m^2, RV/LV ratio (right to left ventricular end-diastolic diameter ratio >0.75, and MELD-XI (model for end stage liver disease excluding international normalized ratio) score >17. The predicted rate of RVF was significantly (p for linear trend <0.001) increased from 9% for a score of less than 2, to 57.1% for a score of 2–3, and to 100% for a score of 4–5,[30] and Pennsylvania[22] may be calculated preoperatively to identify high-risk patients. Unfortunately, the preoperative risk assessment cannot account for intraoperative events, such as suboptimal myocardial protection, air embolism, blood transfusion, and others, which may influence the hemodynamic status and, consequently, the ultimate RV function.

Post–Heart Transplant

In the post–HTx scenario, PVR represents the major determinant for the outcome, and it was shown to have a linear impact on mortality.[31] Other insults seem to have a role in the genesis of RVF after heart transplant, including

- Donor brain injury
- Recipient pulmonary hypertension (PH)
- Reperfusion injury and
- Ischemia time for the organ[32,33]

Right ventricular diastolic dysfunction as well as elevated RA pressure/stroke volume ratio are strong predictors of 1-year mortality.[34]

WHAT IS THE PATHOPHYSIOLOGY OF RIGHT VENTRICULAR FAILURE AFTER CARDIAC SURGERY?

The normal RV function is driven and largely dependent on preload (systemic venous return), afterload (pulmonary arterial resistance), pericardial compliance, and native contractility of the RV free wall and interventricular septum (IVS). Pathological events can increase RV afterload, decrease RV preload, or impair the contractility, resulting in RV dysfunction[35] (Figure 47.2).

After Routine Cardiac Surgery

Postcardiotomy RVF represents a great challenge due to the severity of this condition, the paucity of treatment modalities, and the high mortality rate (Table 47.2). It is more likely associated with cardiovascular and pulmonary complications related to CPB.

Myocardial stunning may develop during cardiac surgery due to suboptimal protection and/or ischemia-reperfusion effects. These are potentially reversible injuries, resulting in temporarily reduced contractility and low cardiac output, requiring pharmacological support with inotropes.[36] The stunning of the myocardium can be limited to the RV exclusively, with preserved LV function; it can develop subsequently after stunning of the LV with concomitant backward failure and reduced RV function[37] or be associated with biventricular injury.

In particular, ischemia, PH primarily associated with CPB, preexisting PH, and ventricular interdependency are the most relevant mechanisms.[38]

During cardiac surgery, a known complication is the occurrence of air emboli into the right coronary artery causing acute

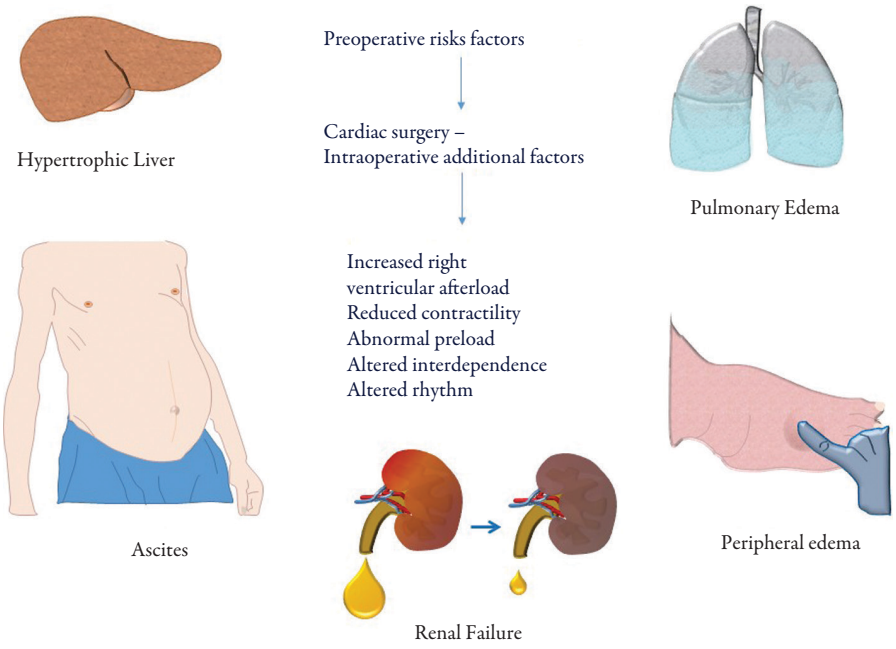


Figure 47.2 Pathogenesis of right ventricular failure.

ischemia. The right coronary artery has a higher risk of air emboli due to its anatomic location, with the right coronary ostium arising from the anterior part of the aortic root, leading to air entrapment in this area.[39] The risk of this complication is particularly present in procedures where the LV is filled with air, such as surgery of the mitral valve, aortic valve, or ascending aorta. An additional mechanism, which may occur during cardiac surgery, is the disruption in the native RV contractile pattern due to the opening of the pericardium. Failed tricuspid or pulmonary valve repairs leading to moderate-severe regurgitation may result in excessive preload and subsequent RVF.[40]

The RV is very sensitive to increases in afterload, which is poorly handled by the thin-walled RV. An increase in afterload results in distension of the ventricle with an accompanying increase in oxygen consumption. This will result in a rightward shift on the Frank-Starling curve that, if uncompensated, will lead to reduced contractility of the RV and decreased cardiac output.

In particular, the increased afterload may be caused by pulmonary vasoconstriction and mechanical obstruction. Pulmonary vasoconstriction is induced by hypoxia, hypercarbia, metabolic acidosis, protamine-based reaction, and cytokine release, often associated with large transfusions and prolonged CPB. Afterload may also be increased if the pulmonary vascular bed is compressed or reduced by mechanical ventilation/positive end-expiratory pressure (PEEP), acute respiratory distress syndrome, pulmonary embolism, and pneumothorax.[41]

Other factors not directly related to the surgery may occur, such as PEEP, which was described to decrease preload by increasing intrathoracic pressure and increasing afterload by changing transpulmonary distending pressure.[42]

Right ventricular failure is frequently seen within 5 days after cardiac surgery and may persist despite improvements in LV function.[43]

Table 47.2 MECHANISMS OF RIGHT VENTRICULAR FAILURE

MECHANISMS	CAUSES
Increased afterload	**LV backward failure** **Pulmonary embolism, chronic thromboembolic PH** **Pulmonary artery hypertension, chronic pulmonary disease** **Acute lung injury/ARDS** **Sleep-related breathing disorders, obesity-hypoventilation syndrome** **Mechanical ventilation** **RV outflow obstruction**
Reduced contractility	**RV ischemia/infarction** **RV injury, systemic inflammatory response** **Myocarditis** **Cardiomyopathies** **Arrhythmogenic RV cardiomyopathy**
Abnormal preload	**Hypo-hypervolemia** **LV forward failure** **Pericardial tamponade** **Mechanical ventilation** **Chronic left-to-right shunt**
Altered interdependence	**Pericardial tamponade** **Pericardial disease** **Septal shift**
Altered rhythm	**Brady/tachyarrhythmia**

ARDS, acute respiratory distress syndrome; LV, left ventricle; RV, right ventricle.

Post-LVAD

The genesis of RVF is multifactorial: Preoperative existing RV dysfunction is aggravated from physiologic changes

after LVAD implant, which lead to pathophysiologic events beginning in the early postoperative period or even intraoperatively.[44,45]

Early studies suggested that increasing LV output could precipitate RVF through two mechanisms: volume overloading of the right heart owing to an increased flow in the systemic circulation or a decrease in RV pump function caused by a septal shift into the LV due to an exaggerated drainage.[2,46] The two ventricles have a mechanical interdependence owing to their anatomical position; in particular, the thin-walled RV is dependent on the function of the IVS for the maintenance of an adequate pump output.[2,46] Thus, emptying the LV by exaggerated LVAD pump flow could interfere with RV function by compromising the contribution of the IVS to RV contraction. On the other hand, the reduction in LV congestion obtained by appropriate draining may relieve the RV by reducing RV afterload; increasing the aortic, and thus coronary, blood flow; and reversing a septal shift into the RV from a distended LV.[47] The acute unloading of the LV, the increase of right-sided preload, and the cardiac output lead to a septal shift, thereby altering RV shape and size with modifications in RV contractility. In addition, in the setting of an incompetent tricuspid valve, the increased RV volume and the leftward shift of the septum may cause tethering of valve leaflets, intensifying tricuspid regurgitation.[48] Among other reasons, an increased RV afterload due to pulmonary vasoconstriction and tachyarrhythmia, which can double the risk of RVF, have been also proposed.[49–51]

While those are the most common explanations, the full physiological picture of LVAD-related RVF remains not well elucidated. These considerations have major implications for pre- and postoperative management, including pump settings and volume control, also relative to other factors such as preexisting but unrecognized right myocardial dysfunction.

Post–Heart Transplantation

In patients undergoing cardiac transplant, the dysfunction of the RV is considered a very common condition and represents one of the causes of acute and severe dysfunction of the graft with clinically discouraging outcomes.[52,53]

Indeed, it seems to be associated with the exposure of the donor heart, which is not adapted to high PVR, to an increased afterload in the recipient. Indeed, in patients with chronic heart failure, varying degrees of PH are commonly present owing to the increase of backpressure onto the pulmonary circulation. This is further complicated by reactive pulmonary vascular vasoconstriction with increased PVR, which, in the long term, may become irreversible.[54]

Recipients with fixed irreversible PH have a higher incidence of RVF and worse outcome.[55–57]

Perioperative and intraoperative factors can aggravate the PVR as well; particularly prolonged CPB, blood transfusions, and vasoactive drugs as well as prolonged ischemic time, poor myocardial preservation, warm ischemia during surgery, and reperfusion injury are all associated with poor outcome. Therefore, the management of RVF after HTx is intended to

- Preserve coronary perfusion through maintenance of systemic blood pressure
- Optimize RV preload
- Reduce RV afterload by decreasing PVR
- Limit pulmonary vasoconstriction through a protective ventilation with high inspired oxygen concentrations (FiO_2 1.0), increased tidal volume, and optimal PEEP ventilation

Since the outcome depends on the patient selection, it is very important to carefully evaluate the following parameters before the transplantation: PVR, PVR index, peak systolic PA pressure, and transpulmonary gradient.[58]

HOW IS THE DIAGNOSIS OF RIGHT VENTRICULAR FAILURE AFTER CARDIAC SURGERY MADE?

The RV assessment after cardiac surgery may represent a challenge due to the loss of longitudinal contraction and a concomitant gain of transverse contraction as well as the poor quality of the transthoracic echocardiography (TTE) image. Several diagnostic methods have been used to determine RVF in postcardiotomy patients, but there is no consensus about the most appropriate and reliable approach.

Echocardiography is frequently used to assess cardiac function in the perioperative setting. It is a fast, simple, and easily available method, but after cardiac surgery air in the thoracic cavity can cause artifacts and limit acoustic windows on the TTE. TEE provides better acoustic windows postoperatively, but many echocardiographic modalities are angle dependent, and correct alignment can be very challenging with TEE.[59,60]

Another method to evaluate RVF is the magnetic resonance imaging (MRI), which represents the gold standard for functional measurements, such as the RVEF and the stroke volume. Additionally, it gives precise assessment of the RV in terms of end-diastolic and end-systolic volumes. Despite these advantages, it has some limitations compared to echocardiography: less availability, higher costs, but foremost, logistical problems for performing several evaluations in patients in the ICU who are in cardiogenic shock.[61]

Other more invasive techniques are as follows:

- Thermodilution techniques for measuring the cardiac output and pressure through a PA catheter[62]; and
- Conductance catheter technique through the injection of a bolus of hypertonic saline in order to have an immediate rise in conductance, making it possible to deduct intraventricular volumes.[63]

Of course, all of these diagnostic strategies are not used anymore due to the availability of less invasive methods, such as MRI and most of all echocardiography with three-dimensional capabilities, which may be useful in long-term RV assessment.

WHAT IS THE MEDICAL MANAGEMENT FOR POSTCARDIOTOMY RIGHT VENTRICULAR FAILURE?

The medical management for postcardiotomy RVF often represents the first line of treatment and aims to lower CVP (diuresis and/or ultrafiltration), optimize RV preload (diuretics and volume expanders), decrease the systolic PA pressure (inhaled nitric oxide and phosphodiesterase-5 inhibitors), and promote pulmonary vasodilation, at the same time decreasing the RV afterload (milrinone).[64,65] In case of persistent hemodynamic instability, inotropic agents (β_1-adrenergic receptor agonists) may be necessary and useful.[35] Although there is no consensus, in case of tricuspid valve anomalies (annulus > 40 mm, moderate or severe regurgitation), a tricuspid valve repair concomitant with the cardiac surgery may be performed.[17,66] Other intra- and perioperative requirements aim to avoid excessive transfusions, which can lead to pulmonary edema and transfusion-related lung injury, as well as minimize CPB adverse effects and maintain good gas exchange.[67]

WHAT IS MECHANICAL CIRCULATORY SUPPORT?

Mechanical circulatory support is a device that provides hemodynamic support in patients with acute or chronic heart decompensation when the conventional approaches fail.

WHAT ARE THE MECHANICAL CIRCULATORY SUPPORTS FOR RIGHT VENTRICULAR FAILURE?

Perioperative RVF is a serious complication with high morbidity and mortality rates following cardiac surgery.[38] Temporary mechanical circulatory support is needed in case of RVF refractory to the conventional medical treatment.[68,69]

Several devices can be used in postcardiotomy RVF, including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), or insertion of an RVAD.

Intra-aortic Balloon Pump

Among the available mechanical circulatory support for perioperative RVF, the IABP improves coronary blood flow in the setting of RVF after acute myocardial infarction but is not designed for direct RV support.[70] Early attempts at dedicated RV support devices include PA balloon counterpulsation, which required surgical implantation and had limited clinical application.[71,72] It has been shown, however, that the positive actions of IABP on the LV may translate also into indirect beneficial effects on the RV function (reduced LV end-diastolic pressure with reduced PCWP, enhanced RV-related coronary blood flow, and others).

Extracorporeal Membrane Oxygenation

Undoubtedly, centrally instituted veno-arterial (V-A) ECMO (with cannulae already in place) and a delayed sternal closure represent valuable options to support the failing RV in the operating theater; however, postoperative bleeding and infection are the main drawbacks of these strategies.[73,74] Alternative cannulation options may allow sternal closure and, in some instances, the retrieval of the cannulae without resternotomy.[75]. In contrast, a possibly less invasive strategy may be peripheral V-A ECMO, which provides both cardiac and pulmonary support with simple implantation, no resternotomy, and less expensive cost. However, after LVAD implantation, it reduces the preload, and by delivering retrograde blood flow, it increases LVAD afterload with the risk of low blood flow through the LVAD.[76,77]

Venopulmonary ECMO represents an alternative cannulation strategy. It was instituted with the MAQUET Rotaflow centrifugal pump (Rastatt, Germany) using femoral venous cannulation withdrawing blood to the pump. Outflow from the MAQUET Rotaflow was then attached to an 8-mm Dacron graft tunneled through the precordium and sutured end to side to the proximal PA trunk, enabling separation from extracorporeal support to be conducted in the ICU without returning to the operating room.[78]

Right Ventricular Assist Device

According to the central strategy, the RVAD is implanted with a cannulation of the RA and the PA to assist the RV. The surgical approach may be performed through a direct PA cannulation or via a prosthetic graft anastomosed to the main PA ("chimney technique"). The prosthetic graft is tunneled at the skin level, at either the abdominal or subxyphoid area. Those techniques may be considered intraoperatively with open-chest implant.[72,79,80] These strategies allow adequate RV unloading and provide adequate pulmonary flow. However, retrieval of the device requires reopening of the sternum, with the risk of bleeding or device infection.[72,79,80] The circuit may also be enriched by the addition of an oxygenator, in the OxyRVAD (Figure 47.3) mode, which may be useful in case of gas exchange impairment.[81]

WHAT ARE THE STRATEGIES FOR FULL PERCUTANEOUS SUPPORT OF THE RIGHT VENTRICLE?

Pulmonary Artery Cannulation

The cannulation of the PA is a well-known strategy for indirect unloading of the LV; it may also serve as a perfusion cannula during RVF.[35,77]

Recently, new tools have been created for a dedicated RV support through an entirely percutaneous procedure. In particular, there are two options for the minimally invasive approach to the PA; both use the internal jugular vein as the access site.

The first one is represented by a single-lumen cannula, which can be used as a perfusion port, together with a cannula in the femoral vein as drainage, in case of right heart failure.

The second one, instead, is a double-lumen cannula composed of one lumen working as inflow in the RA and a second

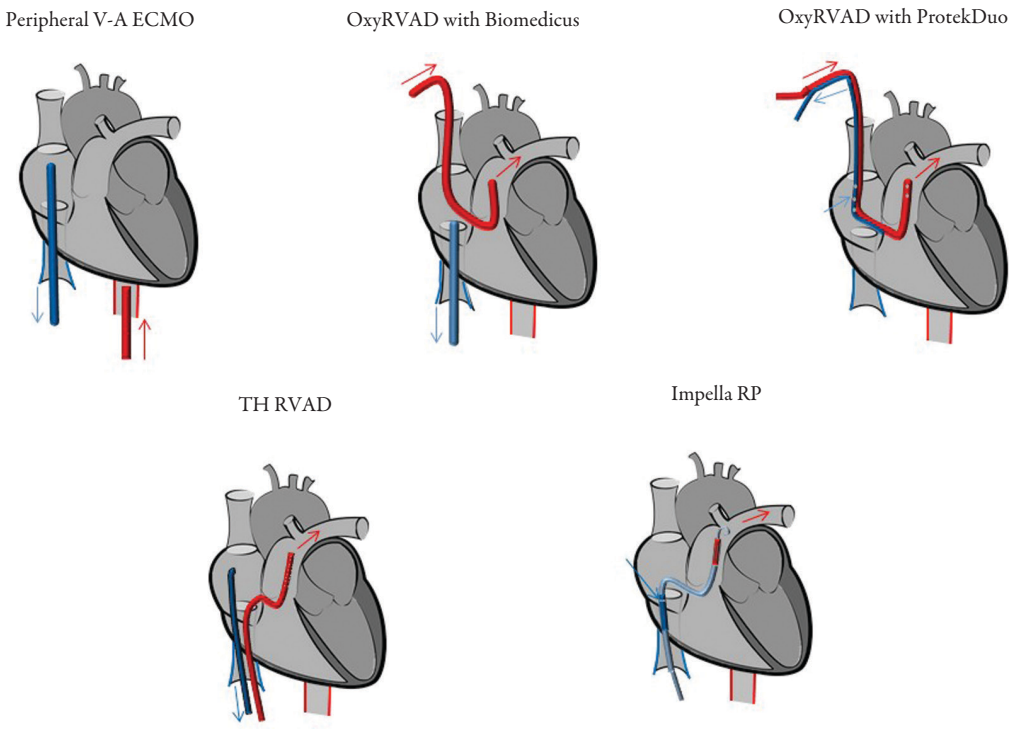


Figure 47.3 Mechanical devices for right ventricular support.
RVAD, right ventricular assist device; V-A ECMO, veno-arterial extracorporeal membrane oxygenation.
Modified by Lo Coco V, De Piero ME, Massimi G, Chiarini G, Raffa GM, Kowalewski M, Maessen J, Lorusso R. Right ventricular failure after left ventricular assist device implantation: a review of the literature. J Thorac Dis 2021;13(2):1256-1269. doi: 10.21037/jtd-20-2228.

lumen delivering blood in the PA thanks to a multifenestrated tip. Such an attractive procedure allows achieving RV support through a single access site without cannulae in the groin, facilitating early mobilization of the patient. Both percutaneous cannulae also find perfect use in the case of hybrid and/or dynamic extracorporeal life support.[82,83] In fact, in case of complications or hemodynamic changes, they can be used as a third cannula to achieve extra drainage (i.e., LV distension) or upper body perfusion (i.e., Harlequin syndrome). In addition, they allow more flexible management through a change of the flow direction without changing cannula position according to the patient's status.[83,84]

A minimally invasive strategy to approach the PA improves patients' rehabilitation, minimizes blood loss and risk of infection, while shortening procedure time and improving clinical outcomes in RVF.[85–88]

Impella RP

The Impella RP is a partially implantable microaxial blood pump with an outer diameter of 11.5–12.3 mm designed for temporary RV support. The recommended maximum use is 10 days. The pump is located within the RA inflow cannula, connected to the outflow cannula by a ring-reinforced polytetrafluoroethylene flexible vascular prosthesis. It is connected by a drive line to the mobile console, which also monitors all the device parameters. A flow rate of 5 L/min can be achieved at a maximal speed of 32,000 revolutions per minute. The pump is also connected to the Impella purge by the same drive line.[89,90]

TandemHeart RVAD

The TandemHeart percutaneous device includes a drainage cannula placed in the RA via the left femoral vein and a perfusion cannula in the PA through the right femoral vein. Another vascular access is achieved by the right internal jugular vein for the outflow. This is a feasible strategy whenever it is not possible to cannulate the femoral vein directly, such as thrombosis, infection, or inferior cava filters or in the case of tall patients (distance from the femoral vein to the fifth intercostal space exceeds 58 cm).[35,91,92]

DISCUSSION

Right ventricular failure in the postcardiotomy setting is a complex syndrome that includes many causes, pathways, and pathological events. It impacts prognosis negatively since it prolongs the ICU and hospital stay and significantly increases mortality.[35,93]

Medical treatment leads to improvement of cardiac contractility, optimizes preload, and reduces pulmonary resistance. However, when medical therapy is not sufficient, the use of mechanical cardiocirculatory support is warranted. The perfect timing of implantation as well the optimal mechanical device is controversial, making the management of RVF challenging. Postoperative RVF may occur in different clinical scenarios (after routine heart operations, following LVAD implantation, and after HTx) with various patient profiles and prognoses.

The commonest approach to the failing RV is represented by V-A ECMO support. In the study by Riebandt and associates,[77] temporary ECMO support was applied for perioperative RVF in 32 consecutive patients. ECMO cannulation was preferentially performed via the subclavian artery and femoral vein or percutaneous cannulation of the femoral artery and vein. Three (9.4%) patients expired during ECMO support. ECMO support improved RV function and hemodynamic parameters. Thirty-day and in-hospital mortality were 18.8% and 25%, respectively. Causes of death during ECMO support were ischemic stroke, sepsis, and multiorgan dysfunction syndrome. Shehab and collaborators[78] reported concerning 75 patients with the isolated HeartWare LVAD, 23 with a concomitant LVAD and venopulmonary arterial extracorporeal life support, and 14 with durable biventricular assist device support. One-year survival was 84% for those with an isolated LVAD compared with 62% for those with venopulmonary arterial extracorporeal life support and 64.3% for those with the biventricular assist device. In an article by Noly and colleagues,[94] 10 patients were treated for RVF after LVAD implantation using femoro-femoral V-A ECMO and were compared with 8 patients who underwent RVAD implantation. Better outcome and fewer thromboembolic events were observed when RVAD was implanted using a femoral vein and PA cannulation.

Another support for the RV is represented by the RVAD, which finds application in the three different postcardiotomy scenarios. In particular, Chen and collaborators[95] assessed 11 patients with RVF following orthotopic HTx (n = 9) or LVAD insertion (n = 2) who were implanted with an RVAD (6 patients with Biomedicus and 5 with Abiomed 5000 BVS device). Four patients required renal support following RVAD implantation. Six patients were weaned and discharged, and 5 patients died on support. In these patients, a decrease in CVP (P < .01) and a decrease in PA diastolic pressure were observed, and an increase in cardiac output was found. A study by Moazami and colleagues[6] addressed RVF following coronary artery bypass graft with or without valve (n = 12), valvular surgery (n = 5), ascending aortic dissection repair (n = 6), HTx (n = 3), and pulmonary thromboendarterectomy (n = 4). Centrifugal pumps were used most commonly, with 21 patients having open-chest cannulation of the RA for venous return and of the PA for arterial outflow. In 8 patients, ECMO was used with arterial outflow cannulation to the aorta. One patient underwent placement of an RVAD pump. Thirteen of the 30 patients were weaned from the RVAD, with 10 surviving to discharge. The cause of death was RVF in 40%.

In the study of Morgan and associates,[96] 17 patients required an Abiomed RVAD (Abiomed, Danvers, MA) in addition to an LVAD as a bridge to transplantation. Ten patients underwent early (<24 hours) while 7 had delayed (>24 hours) RVAD insertion. Eleven patients were successfully transplanted, 9 of whom were weaned preoperatively. The 10-year survival rate was 71.4% in those bridged to transplant. Pretransplant RVAD support was not a risk factor for posttransplant mortality (P = .864).

Haneya et al.[79] reviewed eight patients with acute RVF following LVAD placement requiring an RVAD. Six patients were successfully weaned, and five patients survived to hospital discharge. Significant increases in cardiac output and RVEF were observed, and a decrease in PA pressure, CVP, and right heart dimensions followed use of the RVAD.

Lang and collaborators[97] showed that RVADs have been successfully used to bridge patients to recovery after cardiac surgery. In this elegant review, they reported a significant reduction in CVP and mean PA pressure during and after RVAD support. Additionally, they described an increase in RV cardiac output and stroke work and an increase in PA oxygenation saturations. Furthermore, following RVAD explantation on postoperative day 7, they demonstrated an increase in RVEF up to 40% and also a significant reduction in right heart chamber dimensions.

In a study by Saeed and associates,[98] 21 patients were supported with RVAD. Seventeen patients (81%) had RVF after LVAD implantation, and 4 patients developed postcardiotomy RVF. The median duration of RVAD support was 9 days (range 2–88 days). Eleven patients (52%) were successfully weaned from the RVAD. Two patients were bridged to transplantation. Eight patients died on LVAD and/or RVAD support. The survival rates to discharge or HTx and to 1 year were 62% and 52%, respectively.

Fischer et al.[69] reviewed their series of 44 LVAD patients, 22 of whom required an Oxy-RVAD. Despite the severity of preimplant conditions in the Oxy-RVAD group, clinical outcomes did not differ in both groups, with similar survival rate at 6 months (60.4% ± 12% vs. 71.4% ± 9.9%; P = .585).

In the series of 27 patients with RVAD after LVAD discussed by Leidenfrost and colleagues,[99] 12 received an Oxy-RVAD. Support was weaned in 66% (10 of 15) of patients with RVAD alone versus 83% (10 of 12) of those with RVAD with membrane oxygenation (P = .42). Patients with RVAD with membrane oxygenation had a 30-day mortality rate of 8% versus 47% for those with RVAD alone (P = .04). The survival rate after discharge was 86%, 63%, and 54% at 3, 6, and 12 months, respectively, for both groups combined.

Instead, Coromilas et al.[92] compared 19 patients who received percutaneous RVADs and 21 patients who received surgical RVADs for RVF after LVAD implantation. An Impella RP (n = 4) or Protek Duo (n = 15) with either TandemHeart (Tandemlife, Pittsburgh, PA) or Centrimag (Thoratec, Pleasanton, CA) were used in the percutaneous group. Hemodynamic parameters improved immediately with the use of a percutaneous RVAD; CVP decreased (P < .001), and the CI increased (P< .001). Among survivors, ICU and hospital days were fewer with the use of percutaneous RVAD. There was no significant difference in 30-day mortality with the use of percutaneous RVAD compared with surgical RVAD (P = .14), but there was a trend toward a higher rate of discharge free from hemodialysis (P = .09).

Bhama et al.[100] reviewed the use of a CentriMag RVAD (St .Jude Medical, St. Paul, MN, formerly Thoratec Corp.) in postcardiotomy cardiogenic shock in 13 patients (16%), HTx in 25 patients (31%), and LVAD in 42 patients (53%). The device was successfully weaned in 6 postcardiotomy cardiogenic shock cases (46%), 21 HTx cases (84%), and 35 LVAD cases (83%). Survival was worse for patients with postcardiotomy

cardiogenic shock compared with patients with an LVAD. Survival up to 3 months was better for patients who received immediate ($n = 43$) versus delayed ($n = 37$) support (79% vs, 46%; $P = .003$).

Loforte and associates[101] supported 6 patients with RVAD, alongside LVAD support, following failure to wean from CPB ($n = 2$), or on an elective basis because of poor preoperative RV function ($n = 4$). All the patients survived to discharge with no complications. Seven days after removal of the RVAD, RVEF was between 38% and 40%, and CVP was 10–15 mm Hg.

Currently, the interest in percutaneous devices is growing; their main objective is to reduce surgical complications and mobilize patients sooner. Reiss and colleagues[102] reviewed 9 patients implanted with a Biomedicus centrifugal pump RVAD following RVF postcardiac transplantation. Two patients were retransplanted for persistent RVF and subsequently died. Six patients were successfully weaned. Bleeding and multiorgan failure complicated recovery in these patients.

In contrast, Cheung and associates[103] published their experience with the Impella right direct and right peripheral temporary ventricular assist devices (Abiomed). The etiology of RVF necessitating RVAD implantation was acute myocardial infarction in 7 patients (39%), postcardiotomy in 4 (22%), posttransplant in 3 (17%), post-LVAD in 2 (11%), and myocarditis in 2 (11%). A total of 18 patients were supported for up to 19 days, with a 1-year survival rate of 50%.

In another small multicenter clinical trial,[104] the Impella showed immediate hemodynamic improvements. Although the study showed favorable outcomes, the lack of a control group prevented drawing definitive conclusions with respect to survival. Instead, Kapur and collaborators[72] reported their experience with the percutaneous TandemHeart RVAD. They studied nine patients supported for medically refractory RVF due to acute inferior wall myocardial infarction ($n = 6$), postcardiotomy syndrome ($n = 2$), severe sepsis ($n = 1$), and five supported with an isolated surgically implanted RVAD (all postcardiotomy). The percutaneous RVAD produced a significant increase in mean arterial pressure, CI, PA oxygen saturation, and RV stroke work index, as well as a significant decrease in RA pressure ($P < .05$). Mortality was 44% in the percutaneous RVAD patients compared with 80% in the surgical RVAD group. Bleeding complicated four of the nine percutaneous RVAD and all the surgical RVAD recoveries.

The new generation of cannulae covers the double-lumen cannula ProtekDuo for PA cannulation, which is a full percutaneous device specific for right heart support. Unfortunately, only a few experiences have been reported in the literature, mostly constituting small studies and case reports. One of these was reported by the group of Ravichandran[87]; they supported 17 patients with RVF postcardiotomy with the ProtekDuo, 12 of whom were post-LVAD implantation. The weaning from the device was around 23%, and mortality was 40% due to late treatment.

Kazui and collaborators[86] described the use of the dual-lumen cannula in a patient with RVF post-LVAD. After right heart support placement, cardiac output and hemodynamics improved exponentially, reducing the need for pharmacological support. After 11 days, the RV was recovered, and the patient was weaned from the device. In this study, attention was drawn to the minimal blood loss as well as the risk of infection due to the shortening of the procedure's duration.

CONCLUSION

- Postcardiotomy RVF of various causes, pathways, and pathological processes still represents a challenge.
- Despite risk models and scores, prediction of RVF occurrence is difficult and unreliable.
- Several mechanical strategies have been described for right heart support in case of RVF unresponsive to medical therapy. Though those devices are valuable tools, bleeding, infections, and other complications must be considered.
- Improvements in technology and the recent interest in cannula design and implant approach have been achieved and successfully applied.
- New devices dedicated to right heart support through an entirely minimally invasive approach have been introduced, enhancing the management of this complex population and leading to a better outcome with reduced ICU and in-hospital stays in all of the scenarios of postcardiotomy RVF, theoretically applicable also in additional fields other than the perioperative setting.

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REVIEW QUESTIONS

1. The major factor impacting the patient's physiologic and hemodynamic status following cardiac surgery is related to

A. Completeness of repair of the cardiac defect.
B. The intraoperative course as determined by the duration of aortic cross-clamp, duration of CPB, and any unexpected findings during the course of procedure.
C. The degree of preexisting dysfunction.
D. The urgency of the procedure.
E. All the previous definitions.

2. Which of the following statements is incorrect?

A. Vasoplegia is defined by a low mean arterial pressure, a normal or elevated CI, and a low systemic vascular resistance.
B. The pathophysiology and etiology of vasoplegia may occur intraoperatively during CPB, after weaning from CBP, or postoperatively.
C. Patients who develop hypotension during CPB are at increased risk of worse cardiac or neurologic outcome compared with patients who develop vasoplegia after CPB.
D. Right ventricular failure after cardiac surgery could represent a consequence of vasoplegic shock.
E. Mechanical cardiocirculatory device in a postcardiotomy setting could precipitate in a vasoplegic condition.

3. The insertion of RV support into the PA through a percutaneous approach could lead to (Which statement is incorrect?)

A. Cardiac arrhythmias.
B. Mechanical damage of intracardiac structures.
C. Thrombosis.
D. Information about the right and the left sides of the circulation.

4. Which is the incidence of RVF after cardiac surgery?

A. 40% in patients with LVAD
B. 70% in patients after HTx
C. 0.1% after common cardiac surgery

5. Which conditions induce RVF related to an increase in afterload? (Which statement is incorrect?)

A. Increased oxygen consumption
B. Pulmonary vasodilation
C. Cytokine release with large transfusion and CBP
D. Mechanical ventilation and PEEP

6. Could LVAD pump flow interfere with RV function? (Which statement is incorrect?)

A. If there is preexisting RV dysfunction
B. If there is LV exaggerated drainage
C. In case of an incompetent tricuspid valve
D. After a long implant time

7. The RV could be fully supported by percutaneous techniques such as (Which statement is incorrect?)

A. Pulmonary artery cannulation
B. Veno-arterial ECMO
C. Intra-aortic balloon pump
D. Impella RP

8. The gold standard for the diagnosis of RVF after cardiac surgery is represented by

A. Transthoracic echocardiography.
B. Cardiac magnetic resonance.
C. Transesophageal echocardiography.
D. Pulmonary artery catheter.
E. All of the above.

9. Which of the mechanical cardiocirculatory support options for RVF represents the transvalvular suction device?

A. TandemHeart
B. Impella RP
C. Biomedicus cannula
D. ProtekDuo cannula
E. All of the above

10. Which mechanical device for right heart support causes indirect unloading of the RV?

A. Impella RP
B. TandemHeart
C. Veno-arterial ECMO
D. ProtekDuo
E. All of the above

11. Impella RP and TandemHeart can indirectly cause pulmonary edema in case of

A. Biventricular failure in patients with absent preserved LV function and without an additional LV support device.
B. Biventricular failure in patients with preserved LV function and without an additional LV support device.
C. Biventricular failure in patients with absent preserved LV function and with an additional LV support device.
D. Isolated RVF in patients with preserved LV function and with an RV support device.
E. None of the above.

12. Which is the commonest cause of RVF after Htx?

A. Elevated PVR
B. Tricuspid regurgitation
C. Coronary artery disease
D. Body mass index greater than 20
E. All of the above

13. The IABP in post-operative RVF

A. Provides full hemodynamic and respiratory support.
B. Is fast and easy to insert and can be used to stabilize patients.
C. Needs the sternum opened.
D. Can be inserted through the femoral vein.
E. None of the above.

ANSWERS

1.E To effectively manage the course of the postoperative cardiac surgical patient's recovery and to achieve the best possible outcome, knowledge of the presence, severity, and effects of preexisting disease; understanding of physiologic abnormalities inherent to CPB; consideration of intraoperative time and course; and knowledge of appropriate supportive and corrective therapies are essential.

2.E Temporary mechanical circulatory support is needed in case of RVF refractory to conventional medical treatment to restore adequate perfusion and a reduction in oxygen consumption, all conditions that maintain a vasoplegic status.

3.D Pulmonary artery cannulation is a strategy for indirect unloading of the LV and represents the major form of RV support, not a PA catheter for assessing volume status, diagnosing of PH.

4.B The incidence of RVF in case of HTx is 2%–3% and is the major cause of graft rejection.

5.B Pulmonary vasoconstriction induced by internal factors such as hypoxia, hypercarbia, or metabolic acidosis or related to external factors such as pneumothorax, PEEP, or pulmonary embolism are the major mechanisms that induce increased afterload.

6.D Left ventricular assist device implant leads to RV dysfunction in the early postoperative period or even intraoperatively.

7.C An IABP improves coronary blood flow in RVF after acute myocardial infarction but is not designed for direct RV support.

8.E Extensive monitoring is required for patients who develop RVF after cardiac surgery because of severe and often unstable hemodynamics, coexisting multisystemic disease, and abnormal physiologic conditions associated with CPB must be detected.

9.B The Impella RP is a microaxial flow catheter designed to drain blood from the inferior vena cava into the PA.

10.C Veno-arterial ECMO displaces and oxygenates blood from the RA to the femoral artery, thereby indirectly bypassing the RV. Instead, the Impella RP, TandemHeart, and the ProtekDuo cannula directly bypass the RV, moving blood from the RA to the PA.

11.A For patients with biventricular failure, the Impella RP or a TH-RVAD directly reduce the pressure of the RA, increase mean PA pressure, and increase LV preload. In the absence of preserved LV function and without an additional LV support device, native cardiac output remains unchanged or increases slowly. However, cardiac filling pressures could increase significantly, leading to pulmonary edema.

12.A Misdiagnosed elevated PVR in HTx candidates is a frequent cause of postoperative RVF.

13.B An IABP can improve coronary perfusion and the hemodynamic status of patients, although the support on the failing RV is markedly less than on the LV.

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ECMO FOR THE COMPLICATED POSTCARDIOTOMY CARDIAC ARREST

Espeed Khoshbin and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A fifty-five-year-old policeman presented with unstable angina. A computed tomographic coronary angiogram diagnosed three-vessel coronary artery disease. His coronary anatomy revealed a dominant right coronary artery with an anomalous origin from the left coronary sinus. This vessel was subtotally occluded with a long segment of soft plaque. The patient was loaded with dual antiplatelet medication, and a coronary angiogram was carried out. This confirmed severe three-vessel coronary artery disease. The interventional cardiologist was unable to engage the anomalous right coronary, but flow was detected in that vessel on the root injection. During the course of a difficult coronary angiogram, the patient developed significant bradycardia and hypotension, leading to ST-segment elevation in the inferior territory. Subsequently, an intra-aortic balloon pump (IABP) was inserted for hemodynamic support, and he was urgently referred for inpatient coronary surgery. In the first 24 hours, the patient remained hypotensive, but the ST segments settled. The patient was known to have sickle cell trait. His hemoglobin levels were normal prior to the angiogram, but had begun to drop due to excessive bleeding from the site of insertion of the IABP. In view of that, the IABP had to be removed; a multidisciplinary decision was made to operate without a delay.

The patient was transferred to the operating theater, anesthetized, and prepared for surgery. In view of his sickle cell trait status, he was kept well hydrated, oxygenated, and warm throughout the procedure. The operation was performed using cardiopulmonary bypass (CPB), and a top up blood transfusion was given. The operation was performed without active systemic cooling, but cold blood antigrade cardioplegia (St. Thomas solution) was used to stop the heart and protect his myocardium during the period of aortic cross-clamp.

Coronary artery bypass grafts CABG x 5 were performed using leg veins to the following targets: posterior descending artery (PDA), first and second obtuse marginal branches of the circumflex arteries, and first diagonal branch and the left anterior descending coronary artery (LAD). The internal thoracic artery was of very small caliber and unsuitable for use. The cross-clamp time was 64 minutes, and bypass time was 156 minutes. Intracoronary shunts were used for all grafts, and all grafts were anastomosed directly to the ascending aorta. The patient was successfully weaned off the CPB, and the transesophageal echocardiogram (TEE) showed good function in both right and left ventricles with no regional wall motion abnormalities (RWMAs).

A considerable amount of time had to be spent resolving significant bleeding diathesis and making sure the operation sites were dry; however, platelet transfusion was indicated according to the findings of the thromboelastogram. Coinciding with transfusion of the second pool of platelets, the patient developed sudden severe hypotension. He did not respond to intravenous boluses of vasoconstrictors. The platelet infusion was immediately discontinued, but the patient suffered a cardiac arrest. Epinephrine and steroids were administered. A short period of internal cardiac massage was followed by full heparinization and reinstitution of the second CPB. The TEE showed a stunned heart with global severe reduction in function.

At this point, the coronary grafts were reexamined as a potential cause of his sudden demise. The grafts to the LAD and PDA were detached and reanastomosed. The grafts appeared patent; however, there was absence of flow through the native right coronary artery. An additional bypass graft was performed to the distal right coronary artery (sixth graft) on bypass with the heart beating. This was to improve right ventricular perfusion. An IABP was redeployed in the left femoral artery after an unsuccessful attempt on the right side (site of previous IABP). Unable to wean off CPB, the bypass circuit was converted to central veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO). The patient's chest was tightly packed with swabs to stop any bleeding points but allowing the ECMO cannulae to exit the top of the sternotomy wound closed only by the skin and covered by an antibiotic impregnated dressing.

The patient appeared stable on ECMO and IABP, but prior to leaving the operating room for the intensive care unit he was noted to have a distended and tense abdomen. It was also noted that there was little urine output, indicative of abdominal compartment syndrome with poor visceral organ perfusion. An on-table abdominal ultrasound could not exclude an intra-abdominal catastrophe, which was suspected at this point. An immediate exploratory laparotomy was performed

on ECMO; however, it revealed no intra-abdominal bleeding or gut ischemia. However, there was severe edema of the abdominal viscera. The abdominal cavity was left open and the protruding bowel covered with an antibiotic-impregnated dressing to prevent contamination. Additional antimicrobial prophylaxis was administered. Throughout this period, the patient remained stable with adequate urine output, indicative of adequate organ perfusion.

The patient was transferred to the cardiac intensive care unit on V-A ECMO and IABP support. Opinions were obtained regarding diagnostic imaging of the native coronary arteries; however, the collective decision was that this could do more harm as any intervention likely would now be even more difficult than the preoperative attempt and could jeopardize his stability and renal function.

In the next few days, while the heart was rested to improve its metabolic state, the abdomen was closed, the chest was reexplored for bleeding twice, and the packs were changed. There were some encouraging signs of visible improvement in cardiac function, with the ECMO flows weaned to as low as 2 L/min and IABP reduced to 1:3 augmentations. At this point, 4 days postsurgery, an infusion of Levosimendan was commenced, followed by a near-successful attempt at weaning off ECMO. The patient tolerated weaning the circulatory support, however failed to sustain ventilator parameters that would allow weaning pulmonary support as the lungs' compliance and gaseous exchange were poor due to pulmonary edema. In order to facilitate negative fluid balance, continuous veno-venous hemofiltration (CVVH) was instituted. The patient was visibly dried out.

Another attempt at weaning off ECMO was sustained within 2 days. The left ventricle had sufficiently recovered; however, there were concerns regarding the function of the right ventricle to provide adequate preload for the left as the inferior wall remained significantly hypokinetic. A temporary right ventricular assist device (RVAD) allowed weaning from ECMO, decannulation, and chest closure while allowing time for the right ventricle to make further recovery. On ECMO, an 8-mm reinforced silver-impregnated polytetrafluoroethylene (PTFE) graft was sewn to the pulmonary artery and tunneled through the chest wall on the left side of the hemisternum at the level of the second intercostals space, then tunneled down under the skin to the level of the fourth space and connected to a 21 French (21F) return cannula. A 19F, multihole, venous drainage cannula was also introduced into the femoral vein through the saphenous vein, with its tip manually positioned at the level of the right atrium.

The ECMO was then gradually weaned off, and patient was decannulated while the RVAD was switched on. At this point, the chest was closed in the standard fashion with stainless steel wires. The patient returned to the intensive care unit. He was extubated while supported with RVAD. He made sufficient progress in terms of right ventricular recovery with the help of intravenous diuretics and angiotensin converting enzyme inhibitors (ACEIs) to be weaned off the RVAD and was decannulated under local anesthetic. He made remarkable recovery and was discharged home after a period of rehabilitation on heart failure medication.

WHAT ARE THE COMMONEST CAUSES OF REFRACTORY CARDIOGENIC SHOCK AFTER ADULT CARDIAC SURGERY?

Postcardiotomy shock is most commonly associated with either poor myocardial preservation or failure of adequate revascularization during surgery. The outcome is affected by the preoperative functional state of the ventricles and exacerbated by the complexity of the surgery, which may result in prolonged bypass time.

HOW LIKELY IS THAT THE ABOVE COULD EXPLAIN THIS SUDDEN DETERIORATION?

Poor myocardial preservation is unlikely to be a cause of the sudden deterioration as the patient had come off CPB without difficulty. Failure of adequate revascularization was also unlikely as the patient underwent five grafts, all tested and demonstrated adequate flow, and the immediate postrevascularization echocardiogram did not demonstrate any RWMAs shortly after bypass.

WHAT COULD BE THE LINK BETWEEN PLATELET TRANSFUSION AND CARDIOGENIC SHOCK IN THIS CASE?

One hypothesis for the link between platelet transfusion and cardiogenic shock in this case would suggest a sudden period of hypotension caused by transfusion-related histamine release. The sudden period of hypotension may have triggered thrombosis and graft failure. A sudden thrombosis of one or more grafts may have triggered a chain reaction, leading to extensive myocardial infarction. However, during the second period of CPB, the grafts were reexplored and proved to be patent.

WHAT OTHER PHENOMENON COULD EXPLAIN THIS PATHOPHYSIOLOGY?

When checking the grafts for patency with the heart beating but supported by CPB, there was good flow through the grafts. There was however absence of blood flow in the native right coronary artery. The transfusion of platelets may have triggered occlusion of the native diseased coronary arteries. The tight anomalous right coronary with a long segment of soft plaque is a possible culprit. Another hypothesis is that a sudden variation in blood pressure led to soft plaque rupture in the anomalous native vessel, with distal embolic myocardial infarction.

WHAT OTHER PATIENT FACTORS MAY HAVE LED TO NATIVE VESSEL OCCLUSION?

The patient was confirmed to have sickle cell trait. Severe narrowing in the native anomalous right coronary as well as the left system with long segments of soft plaques is a potential site for red blood cell clumping or sickling. At that stage in the operation after successfully separating from CPB, sickling may have been precipitated by the platelet transfusion or inadvertent dehydration during long period of hemostasis.

THE TEE SHOWED GLOBAL BIVENTRICULAR DYSFUNCTION. WHAT ARE THE DIFFERENT MODES OF MECHANICAL CIRCULATORY SUPPORT AVAILABLE TO COMBAT CARDIOGENIC SHOCK IN THIS SCENARIO?

An IABP is often a temporary fix by supporting the stunned left ventricle, giving hemodynamic stability and improving coronary flow in diastole. In the presence of right ventricular dysfunction, however, IABP has limited potency. V-A ECMO is the mechanical support of choice in this scenario, where both ventricles are significantly affected. However, V-A ECMO may exacerbate left ventricular dysfunction in a failing heart as it increases systemic afterload. This in turn would cause loss of ejection, ventricular distension, and pulmonary congestion.

WHAT COULD BE THE ROLE OF IABP IN THE PRESENCE OF V-A ECMO IN THIS CASE?

Veno-arterial ECMO bypasses the pulmonary circulation and hence off loads and rests the right ventricle. However, it increases the systemic afterload and may increase the work of the stunned but ejecting left ventricle by forcing liters of blood back into the aorta. The IABP would reduce the afterload in systole by deflating and increasing the mean pressure and coronary flow in diastole by inflating. It reduces the work of the left ventricle, allowing it to eject, and prevents left ventricular distension. In the above case, the IABP was initially reinserted as a primary solution; however, the patient failed to be weaned off CPB. Using the same bypass cannulae, the CPB was converted to central V-A ECMO. The IABP was left in place as an adjunct to reduce the afterload to the left ventricle.

IS THERE ANY OTHER WAY TO ENSURE THAT THE LEFT VENTRICLE IS OFFLOADED?

There is another way to ensure that the left ventricle is offloaded. This is accomplished by reducing the preload to the left ventricle by adequate venous drainage and additional venting of the left ventricle.

WHAT ARE THE DIFFERENT METHODS OF VENTING THE LEFT VENTRICLE?

Additional methods to prevent ventricular distension and venting the left ventricle include the following:

- Surgical: Through a pulmonary artery vent or direct left ventricular venting through the left superior pulmonary vein or the cardiac apex.
- Percutaneous: Through a transvenous transatrial septostomy or transseptal placement of a left ventricular vent. Placement of an Impella through the aortic valve is another option. This option would have the advantage of allowing extended left ventricular support after the right ventricle has recovered and ECMO weaned. The residual left ventricular dysfunction may be supported as a bridge to decision on implanting a durable mechanical support device or listing for a heart transplant.

HOW DO YOU ASCERTAIN THAT THE HEART IS RESTED ON V-A ECMO?

During CPB, the surgeon can readily evaluate the exposed heart; however, during V-A ECMO with the chest closed, this may be assessed by examining the arterial wave form on the monitor. However, the most reliable method of ascertaining a nondistended rested heart is through echocardiography.

WHAT COULD BE THE MOST LIKELY CULPRIT FOR ABDOMINAL DISTENSION IN THIS CASE?

It is unlikely that central V-A ECMO in this case would give rise to hemorrhagic or embolic intra-abdominal catastrophe. This could potentially be a phenomenon associated with peripheral V-A ECMO, when an intra-/retroperitoneal bleeding is caused by surgical cannulation or embolism is caused by retrograde blood flow in the descending aorta. Also, insertion of an IABP could be the culprit in a fully heparinized patient and may lead to catastrophic intra-/retroperitoneal bleeding during insertion or cause embolism or obstructive visceral ischemia as it is advanced into position or when it inflates in an atheromatous descending aorta. However, most likely in this case, a transfusion reaction led to systemic inflammatory response syndrome, which was followed by a transient episode of hypotension, prolonged CPB time, and attempts to separate from CPB, necessitating the use of high-dose vasoconstricting agents. This resulted in shunting blood away from the splanchnic area toward areas of higher priority, for example, the brain. These factors promote that the hepatic artery, portal vein, and gut mucosal microcirculatory flow is reduced. CPB also activates inflammatory cells and the release of cytokines, which promote systemic fluid sequestration, splanchnic edema formation, and swelling.

APART FROM EXCLUSION OF AN INTRA-ABDOMINAL CATASTROPHE, WHAT WAS THE BENEFIT OF THE EXPLORATORY LAPAROTOMY IN THIS CASE?

The increased intra-abdominal pressure led to abdominal compartment syndrome, followed by oliguria. This, if untreated, would have led to acute renal failure and increased mortality risk. Release of intra-abdominal pressure breaks this vicious cycle. However, a laparotomy after prolonged CPB time and on V-A ECMO bears the risk of significant bleeding complications. The risk and benefit of a laparotomy in a potentially coagulopathic patient need to be weighed and discussed within the team.

WHY WAS IT IMPORTANT TO PERFORM AN ON-TABLE LAPAROTOMY ON ECMO?

Timing of interventions is key to a successful outcome in a complicated scenario such as this. A high index of suspicion and prompt action (e.g., performing an on-table laparotomy) is needed to change the course of this condition.

WHY WAS THE STERNUM LEFT OPEN IN THIS SITUATION?

The sternum was left open in order to facilitate exit of the cannulae from the chest; reduce compression on the heart, especially by large ECMO cannulae; and to provide quick access to them in an emergency.

WHAT ARE THE POTENTIAL COMPLICATIONS ASSOCIATED WITH PACKING THE CHEST AND LEAVING THE STERNUM OPEN? WHAT COULD BE DONE TO MINIMIZE THEM?

There are major disadvantages to leaving the sternum open. The open sternum is a major point for excessive bleeding. In the first 24 hours postcardiotomy, the coagulation abnormalities are corrected, and heparinization is generally avoided. Multiple organisms, including fungal infections, are commonly associated with central ECMO cannulation in this way. It is recommended that if central ECMO is prolonged beyond 5 days, then the cannulae should be tunneled to facilitate sternal closure and minimize the risk of infection.

WHAT IS THE MECHANISM OF ACTION AND THE EVIDENCE FOR LEVOSIMENDAN?

Levosimendan is a potent inodilator. It increases cardiac contractility by calcium sensitization of troponin C and also causes vasodilation. There is trial evidence that indicates hemodynamic improvement with levosimendan following cardiac surgery. It is generally given as an infusion that lasts 24 hours prior to ECMO weaning. The effects last for over 72 hours.

WHY WAS IT IMPORTANT TO WEAN FROM ECMO TO RVAD?

Instituting the RVAD as described by using a reinforced silver-impregnated PTFE graft would allow permanent closure of the chest, hence reducing the risk of infection, bleeding, and the need for further blood transfusion. The described method facilitates weaning and decannulation from RVAD to the point of making it feasible under regional anesthesia.

COULD THIS PATIENT HAVE BENEFITED FROM AN IMPELLA INSTEAD OF AN RVAD?

The Impella technology has opened the way to minimal invasive right heart temporary mechanical support. It uses the femoral route with its inlet positioned in the inferior vena cava as it crosses the tricuspid and pulmonary valves and its outlet positioned in the main pulmonary artery.

DISCUSSION

Postcardiotomy refractory cardiogenic shock after cardiac arrest is often fatal.[1] The use of V-A ECMO in this condition is most commonly associated with CABG or a combination of that and valve surgery and is strongly indicated.[2] Its prevalence in adults after heart surgery has been reported as high as 3.6%.[3] Following transplantation, its incidence ranges between 10% and 15% for primary graft dysfunction in heart transplantation or pulmonary hypertension–related right ventricular failure after lung transplantation. Relative contraindications, such as acute aortic dissection, have also been considered.[4,5]

Central V-A ECMO is a convenient mode of ECMO in post–cardiac surgery cardiogenic shock. The open chest provides ease of access to the heart and the great vessels. The right atrial and aortic cannulae used for CPB are often utilized and connected to a preprimed ECMO circuit. It is of utmost importance that the cannula is securely fastened to the heart and the patient to prevent catastrophic dislocation during handling of the patient. Ideally, the cannulae should be tunneled out of the chest via the neck, right chest, or the subxiphoid region to facilitate closure of the sternum within the first few days of ECMO. This would minimize the risk of infection, reduce the bleeding, and facilitate patient turning and mobilization. However, more often it is necessary to leave the chest open for the first 24–48 hours to release pericardial pressure caused by perioperative tissue edema.

Peripheral femoral V-A ECMO, on the other hand, has the advantage that the chest may be closed immediately after surgery. This will considerably reduce the risk of sepsis and bleeding on ECMO. Femoral cannulation may be performed percutaneously (Seldinger technique) in an emergency or through a cutdown (semi-Seldinger technique).[6] When direct cannulation is performed, care should be taken to choose an appropriate size cannula that does not obstruct distal arterial flow (15F–19F cannulae).

Distal limb perfusion is the Achilles heel of peripheral V-A ECMO.[7] A small peripheral (5F–7F) cannula may be inserted in the femoral artery (antegrade) for distal perfusion of the limb.[8] The side arm of the arterial cannula is commonly used to directly feed this cannula. Using the femoral vein from the opposite side for venous drainage would also prevent overcrowding of the groin and improve venous drainage of the lower limb. This potentially reduces venous congestion of the lower limbs and prevents compartment syndrome.

When time allows, an 8-mm graft may be sewn directly on to the femoral artery end to side at a 45° angle. This graft could then be tunneled, connected, and secured to a standard 21F or 24F arterial cannula for arterial return. A bidirectional flow of blood into the femoral artery supplying both the body and the limb would be a clearer advantage of this technique. However, a high flow rate of blood through the graft necessitates meticulous sewing technique and the use of topical hemostats to prevent bleeding at the site of arterial anastomosis. A reinforced tube graft is desired as it withstands pressure when tunneled away from the groin. The venous drainage should be adequate for the size of the patient. Suboptimal right-sided decompression has a negative impact on the outcome of V-A ECMO.[9] A 19F to 23F, multihole, venous cannula is commonly used in a standard 75-kg adult. This may be inserted into the femoral vein either directly or through the saphenous vein at the sapheno-femoral junction and secured with a purse string. The

tip of the drainage cannula should be at the level of the right atrium. The position of the cannula may be assessed by direct palpation of its tip by the surgeon or using TEE.

Despite adequate drainage of the right atrium, the left ventricle receives blood from the pulmonary and bronchial circulation. In absence of left ventricular ejection, this would lead to ventricular distention, end-diastolic wall stress, reduced coronary flow, pulmonary edema, and subsequently hypoxemia. Absence of aortic valve opening also would lead to thrombus formation in the left ventricle. It is essential to monitor arterial trace for pulsatility to confirm ejection of blood by the left ventricle during V-A ECMO. The use of inotropes or inodilators in the first instance may help forward ejection; however, in the presence of impaired ventricular function, this may cause increased work of the heart and further myocardial depression.

An IABP is a good adjunct that would reduce systolic afterload and improve diastolic coronary blood flow, which helps the injured myocardium. This in turn may also allow a reduction in ECMO flow and left ventricular afterload. Other adjuncts would reduce the preload by ensuring adequate offloading of the left ventricle, such as surgical or percutaneous left ventricular vents, atrial septostomy, or the use of an Impella. Manipulation of the filling state through use of diuretics or more commonly in intensive care CVVH could also be helpful. The use of adjuncts in this setting is associated with significantly improved survival (53% vs. 65%).[10]

Peripheral (femoral) ECMO has the disadvantage of retrograde arterial flow and reduced venous return. Reinjection of oxygenated blood counter-current into the descending aorta is associated with shearing forces, especially at the bifurcation of the femoral artery, which may induce vascular complications, lower the oscillatory shear index of the aortic arch and femoral artery, which predisposes to development of vascular complications, increased left ventricular afterload, and severe hydrostatic pulmonary edema. This is further aggravated by mitral regurgitation induced by left ventricular dilation.

Cannulation of the axillary artery is an alternative halfway technique that may be used in combination with jugular or femoral venous cannulation. This provides antegrade flow similar to central ECMO. The advantages of this mode of cannulation are first to prevent a phenomenon commonly associated with peripheral femoral V-A ECMO called the Harlequin syndrome; the second advantage is that the patient may sit up and even awakened to aid with physiotherapy.

In Harlequin syndrome, the upper and the lower halves of the body are supplied by different sources–the lower half by V-A ECMO and the top half by blood that passes through the heart and lungs. It is therefore essential to ventilate the lungs with a minimum FiO_2 (fraction of inspired oxygen) of 0.5 at rest setting in order to oxygenate the blood that supplies the heart and the upper extremities. Arterial blood sampling from the right radial line confirms oxygenation of the head and neck and the coronary arteries during peripheral femoral V-A ECMO.

Complications of femoral V-A ECMO include limb ischemia, which may lead to amputation, stroke, and neurologic dysfunction, compared to acute kidney injury requiring renal replacement therapy and major bleeding, which are more common in central ECMO. Bleeding after cardiac surgery is associated with mortality and morbidity. Post-ECMO bleeding is challenging and one of the major limiting factors in successful outcome of postcardiotomy cardiogenic shock.[11] It is of utmost importance that meticulous hemostasis is achieved to prevent cannula site/surgical site bleeding. The heparin should be fully reversed at the end of surgery, and there is no need for active heparinization in the first 2 days post–cardiac surgery on ECMO. Heparin can be withheld for even longer periods in patients with continued postoperative bleeding by maintaining high ECMO flows.[12] Heparinization is recommended in the absence of bleeding to prevent clot formation in the circuit. Central nervous system complications occur in approximately 15% of the adult patients supported with V-A ECMO. Although postcardiotomy V-A ECMO can improve survival of patients with acute refractory pump failure, the above associated morbidities should be incorporated in the risk-benefit analysis when initiating ECMO.[13] Overall, there has been no difference in survival between peripheral and central V-A ECMO for postcardiotomy cardiogenic shock.[14]

The experience gained from the use of V-A ECMO following primary graft dysfunction posttransplant suggests recovery in roughly 5 days or more in cases of refractory pulmonary hypertension.[15] However, in cases of postcardiotomy cardiogenic shock if recovery occurs, it is usually observed early. It has been shown that pretreatment with levosimendan (Symdax, Abbot), a calcium sensitizer (inodilator), 24 hours prior to ECMO weaning facilitate weaning, improving the rate of successful wean from 27% to 83%. This would also reduce the need for high-dose inotropes.[16] Survival to hospital discharge, however, is far less, ranging from 16% to 52%.[2] Although there has been a huge increase in the use of ECMO in adults in general,[17] based on the most recent reports from the Extracorporeal Life Support Organization Registry, survival of postcardiotomy refractory cardiogenic shock has not improved in the last 20 years.

CONCLUSION

- Veno-arterial ECMO represents potentially life-saving mechanical circulatory support in complicated postcardiotomy cardiac arrest.
- Its outcome is improved when used in conjunction with an adjunct that reduces the left ventricular afterload or promotes left ventricular unloading.
- Central V-A ECMO has its advantages; however, the commonest associated complications are bleeding and renal impairment.
- Despite technologic advances, the overall outcomes of complicated postcardiotomy cardiac arrest disappointingly have been unchanged over the last two decades.
- Death is commonly caused by complications that lead to multiorgan dysfunction.
- A high index of suspicion is imperative for the early diagnosis and treatment of associated complications.

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REVIEW QUESTIONS

1. What is the commonest underlying pathology responsible for postcardiotomy cardiac arrest?

   A. Perioperative myocardial infarct
   B. Anaphylactic reaction
   C. Protamine reaction
   D. Paravalvular leak
   E. Other

2. What are the clinical manifestations of postcardiotomy cardiogenic shock?

   A. Low systolic pressure
   B. Pulmonary blood pressure greater than 25 mm Hg
   C. Central venous pressure greater than 15 mm Hg
   D. Cardiac index less than 2.0
   E. All of the above

3. What is/are the most likely causes of perioperative infarction?

   A. Poor myocardial preservation
   B. Poor coronary revascularisation
   C. Embolic phenomenon
   D. A and B
   E. A, B, and C

4. What is/are the possible contributing factor(s) for the development of the infarct in the above case?

   A. Hematological disease
   B. Native coronary artery disease
   C. Technical error in myocardial preservation
   D. Congenital anomalous coronary artery
   E. All of the above

5. What was the most likely trigger for postcardiotomy cardiac arrest here?

   A. Sickling
   B. Blocked grafts
   C. Poor myocardial preservation
   D. Thrombus from a ruptured plaque
   E. Transfusion reaction

6. What is the best cannulation approach for postcardiotomy V-A ECMO?

   A. Central with the chest open
   B. Central tunneled with the chest closed
   C. Peripheral cannulation with the chest closed
   D. Peripheral cannulation with the chest open
   E. All are the same

7. What is the advantage of peripheral versus central V-A ECMO?

   A. Reduced shearing stress on the aorta
   B. Reduced bleeding
   C. Increased risk of limb ischemia
   D. Reduced Harlequin syndrome
   E. All of the above

8. What is the benefit of the IABP in postcardiotomy V-A ECMO?

   A. Reduced left ventricular afterload
   B. Improve end-diastolic coronary flow
   C. Reduce pulmonary edema

D. Reduce likelihood of left ventricular thrombus formation
E. All of the above

9. Which of the following would act as an adjunct to V-A ECMO by reducing the left ventricular afterload?

A. Impella
B. Intra-aortic balloon pump
C. Atrial septostomy
D. Left ventricular vent
E. Continuous veno-venous hemofiltration

10. During femoral V-A ECMO, peripheral arterial sampling

A. Should be done from the left radial arterial line to ensure coronary oxygenation.
B. Is from the femoral line in the opposite groin to the ECMO cannulation.
C. Should be done from the right radial arterial line to detect Harlequin syndrome.
D. Reflects mixed venous saturation.
E. Is a waste of time.

11. Abdominal distension on V-A ECMO may be related to

A. Peripheral cannulation
B. Insertion of IABP
C. Visceral organ edema
D. Embolic phenomenon
E. All of the above

12. Temporary right ventricular support may be provided by all except for

A. Impella
B. Veno-arterial ECMO
C. Surgical RVAD
D. Intra-aortic balloon pump
E. A durable mechanical support device

13. What percentage of patients treated with postcardiotomy ECMO typically survive?

A. 75%
B. 90%
C. 10%
D. 50%
E. 2%

ANSWERS

1A The commonest underlying pathology responsible for postcardiotomy cardiac arrest is perioperative myocardial infarction.

2E All of low systolic pressure, high PA pressure, and CVP and low CI are clinical manifestations of postcardiotomy cardiogenic shock.

3D The most likely causes of perioperative infarction are poor myocardial preservation and poor coronary revascularization.

4E All of hematological disease, native coronary artery disease, technical error in myocardial preservation, and the presence of congenital anomalous coronary artery may be contributory.

5E The most likely trigger for postcardiotomy cardiac arrest here is transfusion reaction; this was confirmed by mast cell tryptase blood test.

6E There is no correct answer as there is no proof for either central or peripheral being superior.

7B The advantage of peripheral versus central V-A ECMO is reduced bleeding from the sternum and the cannulation sites.

8E The benefits of the IABP in postcardiotomy V-A ECMO are is reduction of the left ventricular afterload, improvement of the end-diastolic coronary blood flow in diastole, reduced pulmonary edema, and reduced likelihood of left ventricular thrombus formation.

9B The IABP is the only one that reduces the left ventricular afterload.

10C If the arterial blood gases from the right arm in particular are low, it may indicate Harlequin syndrome.

11E Abdominal distension on V-A ECMO may be related to peripheral cannulation insertion of IABP, visceral organ edema, or embolic phenomenon.

12E A durable mechanical support device provides long-term ventricular support. Right-sided durable devices are rarely used.

13D Despite technologic advances, the overall outcomes of complicated postcardiotomy cardiac arrest are disappointingly poor at about 50%, unchanged over the last two decades.

49.

ECMO FOR ACCIDENTAL HYPOTHERMIA AND CARDIORESPIRATORY ARREST

Jean Bonnemain, Marco Rusca, and Lucas Liaudet

STEM CASES AND KEY QUESTIONS

CASE 1

A 64-year-old man known for schizophrenia runs away from a psychiatric hospital at 2 AM. He is found at 6:30 AM by walkers, partially immersed in water, with his head out. The rescue team arrived 20 minutes later. The patient was unresponsive, not shivering, with a weak, very slow pulse and hypoventilation. His body temperature was 19.9°C with no indication of the method used to measure it. On that day, water temperature was 7°C. During mobilization on the stretcher, he presented with cardiac arrest (CA) with ventricular fibrillation (VF) at 7:05 AM. Cardiopulmonary resuscitation (CPR) was immediately initiated with manual chest compression and thereafter with mechanical chest compression. Endotracheal intubation was also carried out without complication.

The patient was transported to the hospital's emergency department under CPR. In the context of a persistent CA despite high-quality resuscitation, a core temperature of 21°C, potassium 4.2 mmol/L, and persisting VF, the decision is made to proceed to extracorporeal life support (ECLS). Veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) was inserted peripherally through femoral access in order to support systemic perfusion and rewarm the patient. At the same time, a reperfusion cannula was inserted into the ipsilateral femoral artery. ECMO was running at 9:02 AM, after a total of 117 minutes of CPR. The patient was then transferred to the intensive care unit (ICU).

When core body temperature reaches 28°C, a unique electrical shock is given, allowing restoration of sinus rhythm and return of spontaneous circulation (ROSC). Due to severe hemodynamic instability, treatment with high doses of norepinephrine is mandatory. Transesophageal echocardiography (TEE) showed moderate left ventricular dysfunction and severe right ventricular failure. The patient's temperature was progressively increased to reach 36°C over 10 hours, and hemodynamic status gradually improved. Vasopressors were progressively weaned. The next day, ECMO was removed after a successful weaning test, and echocardiography showed a good biventricular function. He was extubated on day 4. He was discharged from the ICU to the intermediate care unit on day 9 with complete neurological recovery.

CASE 2

A 55-year-old backcountry skier was found unconscious early in the morning, with several other people in the same condition, by mountain rescuers on a glacier at high altitude (3000 m). The team of mountaineers got lost the previous day and therefore had to improvise a bivouac on the glacier. On site, the patient was in CA with asystole as the initial rhythm. The patient's pupils were mydriatic, with no light reflex. The time of CA could not be determined, but the chest was compressible, and there were no signs of trauma. Core body temperature was 17°C. CPR was immediately started, and the patient was transferred to our hospital under mechanical chest compression. Epinephrine was not administered.

On admission, the patient still presented with asystole, and a blood gas analysis displayed severe metabolic lactic acidosis. Potassium was not measurable, even after three successive attempts. The decision was made to perform ECLS with implantation of peripheral V-A ECMO under continuous CPR. Insertion in the right groin of the venous cannula was performed without complication, but dilation of the arterial side led to local dissection, and there was no blood in the cannula when aspirating. The second attempt on the left femoral artery was made without complication. ECMO was finally running 180 minutes after the initiation of CPR.

The patient was admitted to the operating room to explore the right femoral artery, and a short femoro-femoral bypass needed to be performed. He was then transferred to the ICU. One hour after ICU admission, his serum potassium could finally be obtained, yielding a value of 18.8 mmol/L. Owing to this extreme value, not compatible with any chance of survival, the decision was made to withdraw therapies 4 hours after ECMO initiation.

WHAT IS THE DEFINITION OF ACCIDENTAL HYPOTHERMIA?

Accidental hypothermia (AH) is defined by a drop in core body temperature below 35°C related to an unexpected and uncontrolled cause and thus should be clearly distinguished

from hypothermia induced for medical purposes, including therapeutic hypothermia after CA or induced hypothermia during anesthesia for cardiovascular procedures.[1]

Accidental hypothermia refers to primary hypothermia, which develops on exposure to a cold environmental temperature when physiological mechanisms of heat production (shivering, active movement) and reduced heat loss (peripheral vasoconstriction) can no longer counteract the cooling effects of an environmental excessively cold temperature.[2] Primary AH is aggravated in the presence of factors impairing thermoregulation, primarily alcohol and drug ingestion, extremes of age, and comorbidities.[1] AH should be distinguished from secondary hypothermia, which can occur even in the absence of a cold environment in persons suffering from a number of medical conditions impairing thermoregulation. These include disorders of the central nervous system (e.g., brain trauma, stroke); endocrine pathologies (adrenal insufficiency, hypothyroidism); exposure to toxics and drugs (opioids, alcohol, sedatives); metabolic failure (exhaustion, malnutrition, anorexia nervosa); impaired shivering (neonate and advanced age, neuromuscular disorders); or conditions associated with increased heat losses, such as burns, multiple trauma, sepsis, and circulatory shock.[1–3]

HOW SHOULD TEMPERATURE BE MEASURED IN ACCIDENTAL HYPOTHERMIA?

The use of adequately calibrated, low-reading thermometers is essential for an accurate measurement of core temperature in the setting of AH.[1] Skin, oral, and infrared thermometers are inaccurate for this purpose and should not be used. Rectal and bladder thermometers can be used in mild-to-moderate hypothermia but should be avoided in severe hypothermia, especially during rewarming as they may not adequately reflect core temperature and may be influenced by peritoneal lavage with warm solutes. An esophageal probe inserted in the lower third of the esophagus, which can be placed following intubation, is the preferred and most accurate method. Epitympanic thermometers can be used, provided there is adequate circulation and the ear canal is not obstructed and is insulated from the environment.[1,2,4]

HOW IS ACCIDENTAL HYPOTHERMIA CLASSIFIED?

Accidental hypothermia is classified according to core temperature as cold stress, mild, moderate, and severe (or profound) hypothermia (Table 49.1).[5] In the prehospital setting, where accurate core temperature may be difficult to obtain, a clinical staging system taking into account the level of consciousness, vital signs, and the presence or absence of shivering is used to assess the severity of AH. This system, referred to as the Swiss system (Table 49.2), grades hypothermia in four clinical stages, with putative correlations with core temperature.[1] Characterizing the different stages of AH is essential in the clinical decision-making process regarding which therapy should be implemented, as detailed further in this chapter.

Table 49.1 CLASSIFICATION OF HYPOTHERMIA ACCORDING TO CORE TEMPERATURE

STAGE	CORE TEMPERATURE (°C)
Cold stress	35–37
Mild hypothermia	32–35
Moderate hypothermia	28–32
Severe hypothermia	<28

WHAT IS THE INCIDENCE OF ACCIDENTAL HYPOTHERMIA?

It is difficult to determine the exact incidence of AH due to insufficient documentation, frequent lack of temperature measurements, and because only hospitalized cases of hypothermia are generally reported, thereby reflecting solely the proportion of the most severe forms of AH. Furthermore, there is a frequent lack of specific imputation of hypothermia diagnosis to either primary or secondary causes (notably related to trauma-associated hypothermia).[5] Therefore, current estimates of AH incidence are likely to be largely underestimated.[6]

Estimation of the annual incidence of AH in the general population ranges from 1–5/100,000 inhabitants in Europe to 5.6 per million in the United States, with mortality rates ranging from 0.2 to 1.8/100000.[5] More specifically, in a study on the epidemiology of hypothermia and other cold-related morbidity requiring visits to US emergency departments, Baumgartner et al.[7] reported about 15,574 cases in the period 1995–2004,and about 1500 hypothermia-related annual deaths occurred in the US between 1999 and 2011 according to the Centers for Disease Control and Prevention.[6] In Europe, a recent large epidemiological study by Kosinski et al. reported an annual incidence of AH of 5.05 cases per 100,000 residents, with 75.5% diagnosed as mild, 16.5% as moderate, and 8% as severe hypothermia.[8]

WHAT ARE THE CLINICAL FEATURES OF ACCIDENTAL HYPOTHERMIA?

The clinical manifestations of AH are related to the progressive loss of adaptive measures to combat cold and the deterioration

Table 49.2 CLINICAL CLASSIFICATION OF HYPOTHERMIA (THE SWISS SYSTEM)

STAGE	CLINICAL SIGNS	PUTATIVE TEMPERATURE (°C)
Stage I	Conscious, shivering	35–32
Stage II	Impaired consciousness, shivering or not shivering	28–32
Stage III	Unconscious, not shivering, vital signs present	<28
Stage IV	No vital signs (hypothermic cardiac arrest)	Variable

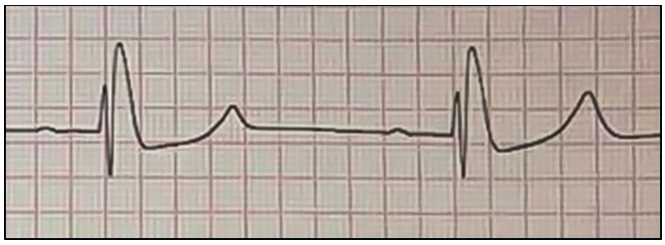


Figure 49.1 The Osborn wave. Osborn wave or *J* wave is a positive deflection at the *J* point of the ECG, which can be seen in hypothermic patients at a core temperature less than 32°C. It is not specific for hypothermia.

of cardiorespiratory and neurological functions.[4] In mild hypothermia (32°C–35°C), symptoms and signs reflect the activation of defense mechanisms to maintain the core temperature, including shivering, peripheral vasoconstriction, tachycardia, hypertension, and hyperventilation. With the onset of exhaustion, neurological signs progressively develop, including dysarthria and impaired judgment.[3] Polyuria may be present due to "cold diuresis" elicited by relative central hypervolemia and reduced antidiuretic hormone action.[2] In moderate hypothermia (28°C–32°C), shivering ceases, hypoventilation and progressive bradycardia develop,[3] as well as atrial dysrhythmias, PR and QT prolongation, and appearance of a positive deflection at the J point of the electrocardiogram termed the *Osborne wave* (Figure 49.1).[9] Progressive decreased level of consciousness and general hyporeflexia develop. Below 30°C, the pupils are dilated, and the light reflex disappears at about 28°C.[1] Severe hypothermia (<28°C) is characterized by coma, apnea, oliguria, and CA due to VF or asystole.[3]

WHAT ARE THE BASIC PRINCIPLES OF MANAGEMENT OF ACCIDENTAL HYPOTHERMIA?

Several general rules are important to remember before dealing with specific therapies. First, due to the marked reduction of brain metabolism in hypothermic conditions (for each 1°C decrease of core temperature, oxygen consumption is reduced by ~ 6%), the brain may be protected from significant hypoxic injury even after prolonged periods of circulatory arrest,[10] implying that resuscitation efforts should always be maintained until the patient has been rewarmed. Second, except for an awake and alert patient with stage I AH, no active movements should be allowed due to the risk of further drop of core temperature by heat redistribution, a condition termed *temperature afterdrop*.[11] Third, external rewarming should be applied to the torso, back, and neck, but not to the extremities, to avoid peripheral vasodilation, hypotension, and recirculation of cold blood from the periphery, precipitating afterdrop.[1,4] Fourth, the hypothermic patient should be kept in the supine position, as mobilization may increase the risk of VF.[1]

Specific therapies for AH comprise both passive and active rewarming techniques. Passive rewarming includes insulation from the cold environment, the covering of the patient with blankets or aluminum foils to prevent further heat loss and to promote intrinsic heat production, as well as the provision of a vapor barrier such as a plastic outer layer or a bubble wrap.[4,10,12] Active rewarming is mandatory for patients in stages II–IV AH or patients in stage I unable to rewarm with passive techniques. Active external rewarming techniques include the application of fluid-heated pads (Arctic Sun® device), chemical or electrical blankets, and forced warmed-air devices, which increase core temperature at a rate of 0.5°C–4°C/h.[1,2,10,13] In the out-of-hospital setting, only passive and some forms of active external rewarming can be used. More details on the prehospital management of hypothermic patients can be found in several extensive reviews[1,4] and published guidelines.[11,14]

Active internal rewarming applies to the in-hospital management of AH. As a rule, patients with CA (AH stage IV) or patients in AH stage III with severe circulatory instability should undergo internal rewarming using ECLS (see information that follows). The other techniques can only be applied in patients with adequate circulation. Minimally invasive techniques should be used as a first line, including infusion (through a peripheral or femoral intravenous line, an intraosseous catheter, and insulated tubing) of warm solutions (glucose and saline solutions heated at 40°C–42°C) and airway rewarming with heated humidified oxygen.[1,2,4,10] Techniques of invasive internal rewarming include intravascular heating catheters (core T° [temperature degree] increase up to 2.5°C/h),[15] bladder, peritoneal and pleural lavage with heated (40°C) saline (T° increase of 0.5°C–2°C/h),[1,16,17] as well as hemodialysis[18] or continuous veno-venous hemofiltration[19] (T° increase of 1.5°C–3°C/h). Since there is a lack of evidence that these techniques improve outcome, and due to the increased risk of complications, they should be used only in circumstances where rewarming using ECLS is not possible.[1,2]

WHAT IS THE ROLE OF ECLS IN ACCIDENTAL HYPOTHERMIA?

Rewarming with ECLS, primarily V-A ECMO, is indicated for patients in stage IV AH or those in stage III under specific conditions (see below).[1,10,20] Diagnosis of circulatory arrest may be difficult in profoundly hypothermic patients, and it is recommended to evaluate the carotid pulse for 1 minute for the diagnosis of CA.[1,2] CPR should not be attempted in the presence of extreme trauma, evidence of prolonged anoxia (avalanche burial > 35 minutes and obstructed airways), or, if its measurement is available, in the presence of severe hyperkalemia (see below).[1,10,11]

Immediate CPR should be performed only if CA is ascertained but should not be initiated in the presence of any vital sign. Patients with VF or asystole must undergo immediate CPR, and those with other rhythms (e.g., pulseless electrical activity), should undergo CPR if the absence of perfusion can be documented with $ETCO_2$ or echocardiography showing no cardiac contractions.[4,10] CPR should be performed regardless of the temperature unless it is lower than 13.7°C,[21] although some authors recommend initiating CPR even for lower temperatures.[4] Airway management with endotracheal intubation should be done as for usual CPR, and ventilation should be provided to maintain $ETCO_2$ in the normal range,[4]

although this is controversial.[22] Below 30°C, one to three defibrillations may be attempted.[4] Further attempts should be delayed until T° is greater than 30°C.[4] Adrenaline and other vasoactive drugs should be administered only at a temperature greater than 30°C, with intervals between doses twice that of normothermia.[4,10] There is no upper limit of time for CPR duration, and the motto "nobody is dead until warm and dead" should generally be followed.[23] Full recovery has been indeed reported after extremely long durations of CA (>8.5 hours) and CPR (6.5 hours).[1] If CPR is unsuccessful with the absence of ROSC at 32°C, one should consider termination of CPR.[1,2]

Patients in CA (stage IV) or those in stage III with unstable circulation (ventricular arrhythmias, systolic blood pressure < 90 mm Hg), or respiratory failure, should be transferred as soon as possible to a hospital able to provide ECLS.[1,2] If not possible, transfer should be done in a hospital where alternative active internal rewarming (see above) can be performed.[10] Extracorporeal blood rewarming preferentially rewarms the core of the body and provides both circulatory and respiratory support until the recovery of normal body temperature and cardiopulmonary function.[24] The first report of extracorporeal rewarming of a hypothermic patient was published in 1967. An unconscious 82-year-old female patient with mild hypothermia (33.3°C) and adequate circulation underwent 75 minutes of rewarming with a V-A circuit coupled to an oxygenator at a flow of 500–750 mL/min, with full recovery.[25] Following this initial report, extracorporeal rewarming using CPB machines progressively became the treatment of choice for severe hypothermia (<28°C) associated with CA.[24] In a retrospective analysis of 11 hypothermic CA patients (core temperature 17.5°C–26°C) treated with CPB, Walpot et al. reported in 1990 survival of seven patients in spite of a very prolonged duration of CA.[24]

Since the year 2000 and the availability of portable ECLS devices, V-A ECMO has become the gold standard for extracorporeal rewarming of patients with AH,[10] including children.[26] Ruttmann et al. published the first study comparing V-A ECMO (in 25 patients) to other extracorporeal techniques (in 34 historical controls) and found a 6.6-fold higher chance for survival with V-A ECMO rewarming. The main reason for increased success was the ability to maintain prolonged support to manage persistent cardiorespiratory failure after the rewarming period.[27] Further advantages of V-A ECMO include the ability to insert the cannulae percutaneously and peripherally and the lower requirement of systemic anticoagulation, which allows its use in hypothermic trauma patients.[28]

Implementation of V-A ECMO should be performed under continuous CPR, which can be done using a mechanical chest compression device.[1] Great care should be taken to respect aseptic conditions owing to the significant risk of secondary infections in ECMO patients.[20] The femoral percutaneous or surgical approach should be used, and the insertion of a reperfusion cannula is mandatory to prevent ipsilateral limb ischemia.[29] In trauma hypothermic patients, an algorithm suggests the performance of a FAST (focused assessment with sonography in trauma) and TEE to exclude pericardial tamponade before the insertion of the cannulae.[30] Another suggested strategy is to perform a trauma CT scan before ECMO implantation.[20] Furthermore, serum potassium must be measured, as hyperkalemia greater than 12 mmol/L (>8 mmol/L in avalanche accidents) contraindicates V-A ECMO[2] (see below).

There is no consensus regarding the speed of rewarming and the flow provided by V-A ECMO in AH. Although ECMO can provide a rewarming rate of up to 6°C per hour, a recent meta-analysis identified that neurological outcome was inversely related to the rewarming rate, possibly due to a cerebral temperature overshoot with rapid rewarming.[31] In our institution, we recommend a rewarming rate of 2°C–4°C/h and a maximal temperature gradient of 10°C between venous blood and the heat exchanger. Although higher ECMO flows have been associated with better cardiac output on return of cardiac function in experimental hypothermia,[32] the advice is to progressively increase ECMO flow up to 2.5 L/min/m^2 to limit the risk of reperfusion injury.[1] The administration of fluids is mandatory to maintain venous return, both due to absolute (cold diuresis–induced fluid losses) and relative (rewarming-induced vasodilation) hypovolemia, but great care should be taken to avoid fluid overload owing to the risk of tissue and pulmonary edema associated with rewarming and reperfusion.[20,32] Once the patient has been rewarmed to 32°C, ECMO should be discontinued in the absence of ROSC and with persistent asystole, owing to irreversible cardiac injury. In patients with ROSC, standard post-CA care should be applied.[2] We apply a protocol of targeted temperature management for 36 hours once the patient has reached 36°C, as in other forms of resuscitated CA.[33] Prolonged V-A ECMO support may be needed due to persistent cardiorespiratory dysfunction,[1] and the usual criteria for ECMO weaning should be applied as for other ECMO indications.

WHAT IS THE OUTCOME OF ECLS IN ACCIDENTAL HYPOTHERMIA?

Studies evaluating the outcome after ECLS for AH have generally indicated a favorable prognosis in terms of both survival and good neurological recovery, as well as trends toward better prognosis with ECMO in comparison to CPB.[34] Cautious interpretation of the data is however warranted given the great heterogeneity of patient populations, mechanisms of CA (purely hypothermic vs. anoxic), type of environment, and speed of cooling, as well as the frequent lack of distinction of the modalities of extracorporeal rewarming (CPB vs. ECMO).[1]

In a recent meta-analysis of 44 observational studies and 40 case reports totaling 658 patients, Saczkowski et al. reported an overall survival rate with good neurological outcome of 40.3% for patients with hypothermic CA rewarmed with an extracorporeal device (CPB 56%; ECMO 44%).[31] Pasquier et al. reviewed the clinical records of 286 patients (237 patients from published studies and 49 additional hospital unpublished cases) undergoing extracorporeal rewarming (CPB 201 patients vs. ECMO 85 patients) for hypothermic CA and found an overall neurologically intact survival in 37%

of cases (42% with ECMO and 35% for CPB).[35] Furthermore, Kosinski et al. recently presented data on 29 patients (stage IV AH 52%; stage III AH 48%) rewarmed with ECMO, of whom 45.1% were alive in good neurological condition after 1 year follow-up.[36] These recent observations indicate therefore an overall survival of about 40% following extracorporeal rewarming in AH. Importantly, excellent long-term neurological outcomes in survivors have been documented in follow-up studies up to an average of 6.7 years after the event.[37]

A critical issue raised by the aforementioned (and other less recent) studies is the striking difference in prognosis for patients with stage IV AH according to the mechanism of CA. Indeed, for CA directly imputable to hypothermia (cold exposure or immersion in cold water), survival after ECLS rewarming was significantly higher than when the cause was primarily hypoxic in nature (including avalanche burial and water submersion). For purely hypothermic CA, survival with good neurological recovery reached up to 67%[38–40] and even 73% when only witnessed CAs were considered in the analysis.[41] These findings markedly contrast with survival rates of only 23.4% and good neurological outcome of only 9.4% in conditions of hypoxic-hypothermic CA.[39] This implies that the nature of CA should be considered in the decision process to implement extracorporeal resuscitation for hypothermic CA, and two recently developed prognostic scores (Hypothermia Outcome Prediction after ECLS [HOPE] score and International Collaborators for Extracorporeal Life Support in accidental hypothermia [ICE] score) have indeed integrated the mechanism of CA, as discussed below.[31,35]

WHAT ARE PROGNOSTIC FACTORS?

The critical value of serum potassium as an indicator of poor prognosis in AH was initially identified by Schaller et al. in a series of 24 severely hypothermic patients in CA. Profound hyperkalemia (mean value 14.5 mmol/L) was especially noted in nine patients recovered from avalanche accidents, who all died.[42] The value of elevated potassium as a marker of anoxia before cooling and extensive cell death has been repeatedly demonstrated thereafter and has become a useful prognostic marker in type IV AH.[2,43] Current guidelines indicate a cut-off serum potassium of 12 mmol/L, and 8 mmol/L in case of avalanche burial, to terminate resuscitation and not initiate extracorporeal rewarming.[10]

In addition to hyperkalemia, the mechanism of CA (purely hypothermic vs. other causes) also has major prognostic significance, as previously stated. For this reason, ECLS rewarming is not recommended in patients with CA at temperatures greater than 30° since it is highly unlikely that hypothermia represents the unique cause of CA above 30°C.[41] Moreover, it is not recommended to start CPR in avalanche burial lasting more than 35 minutes in case of an obviously obstructed airway; this is due to lethal asphyxia in such cases.[1,14] Further variables associated with dismal prognosis have been reported, including severe head trauma, brain hemorrhage, asystole as the initial rhythm, male gender, higher rate of ECLS rewarming, lower pH, and higher lactate concentration.[31,34]

Two clinical scores regrouping several prognostic factors have been developed to improve outcome prediction and ease the decision to perform ECLS in stage IV AH. Saczkowski et al. proposed the ICE survival score as a weighted risk stratification tool based on asphyxiation, serum potassium, and gender, generating a score from -3 to +15 associated with a probability of survival and good neurological outcomes between 0 and 85%.[31] External validation of this score is awaited to define precisely its clinical usefulness. Pasquier et al. introduced the HOPE score, based on age, sex, admission temperature, serum potassium, asphyxia mechanism of CA, and CPR duration, to predict which hypothermic CA patients would benefit from ECMO support.[35] An online score calculator with predicted survival ranging from 0 to 100% is available (https://hypothermiascore.org). The score has been prospectively validated in a cohort of 122 patients, showing excellent discrimination, supporting that it could replace serum potassium as a triage tool to implement ECLS in stage IV AH.[44]

ARE THERE MANAGEMENT GUIDELINES FOR ACCIDENTAL HYPOTHERMIA?

General guidelines for the diagnosis, staging, rewarming strategies, resuscitation, and indication for ECLS endorsed by the European Resuscitation Council have been published in the "2015 Guidelines for Resuscitation—Section 4. Cardiac Arrest in Special Circumstances."[10] The most complete and recent evidence-based guidelines, published in 2019, for the out-of-hospital evaluation and treatment of victims of AH were developed by the Wilderness Medical Society.[14] The guidelines present key factors for hypothermia management, including the level of consciousness and physical performance, the intensity of shivering and cardiovascular stability, as well as core temperature, if available. A technical flow chart,[11] as well as a simplified "cold card,"[45] for field use have been developed, as reproduced (with permission) in Figures 49.2 and 49.3. For in-hospital ECMO teams, key aspects of these guidelines indicate that all patients with stage III and IV hypothermia should be transferred to specialized centers able to perform extracorporeal rewarming unless there are clear signs of lethal injury, frozen chest, or prolonged asphyxia (avalanche burial > 35 minutes with obstructed airways), in which case no resuscitation efforts should be undertaken. To speed up the transfer process to the hospital and be able to start ECMO, if needed, as fast as possible, it is highly recommended that hypothermic patients in stage III and IV be managed in specialized hypothermia treatment centers with an in-hospital medical coordinator.[20,28] Once in the hospital, we use, in our institution, a simplified algorithm to help decide which patient should be rewarmed with ECMO, as indicated in Figure 49.4. In case of suspected trauma, a trauma CT scan, or FAST and TEE, are recommended before starting ECMO as previously mentioned.[20,30]

WHAT ARE FUTURE PERSPECTIVES?

The management of AH is highly complex and requires strong coordination between prehospital rescuers frequently working in hostile environments, transport medical teams,

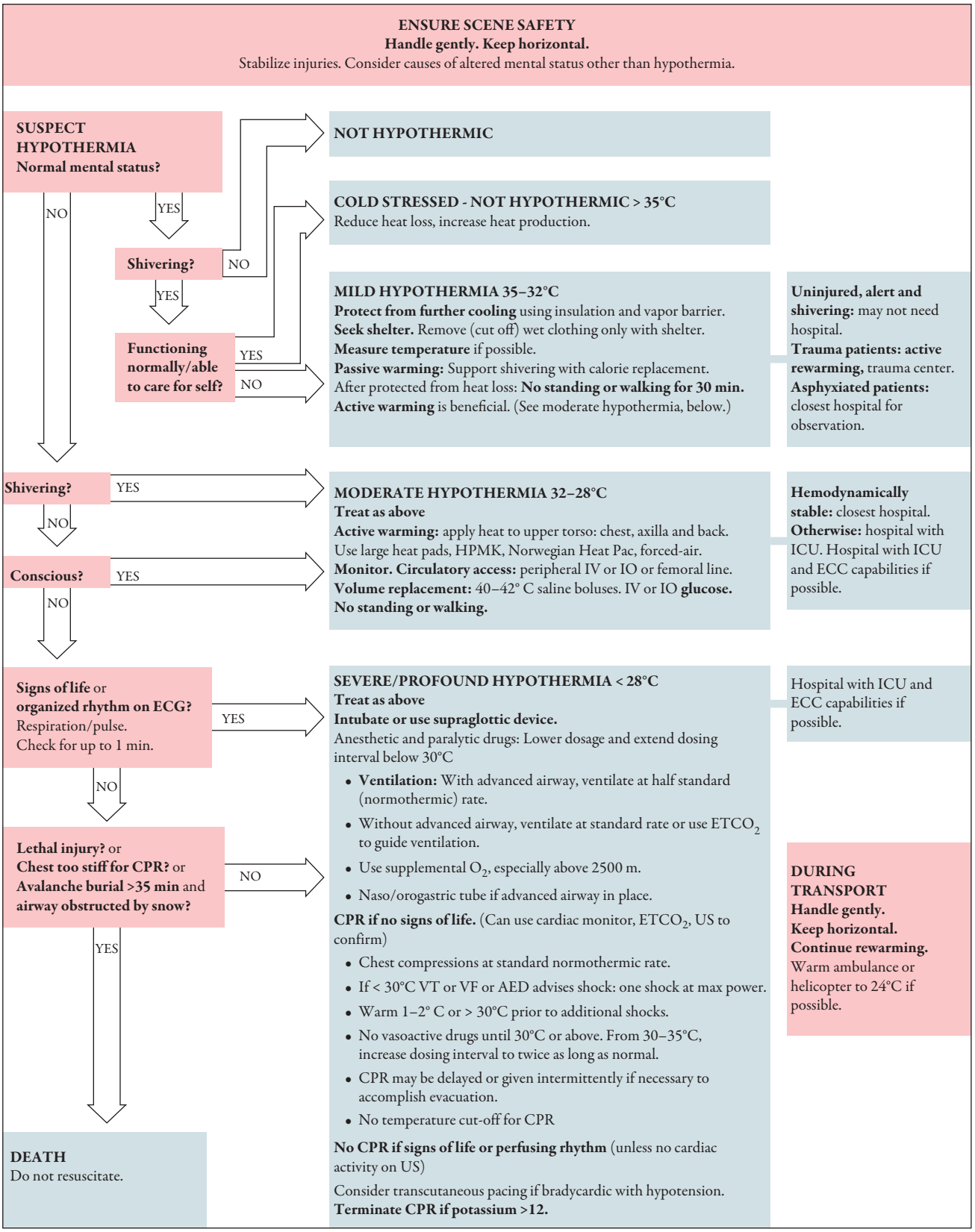


Figure 49.2 Treatment algorithm for the out-of-hospital management of accidental hypothermia.
Abbreviations: AED, automatic external defibrillator; CPR, cardiopulmonary resuscitation; ECC, extracorporeal circulation; ECG, electrocardiogram; $ETCO_2$, end-tidal carbon dioxide; HPMK, Hypothermia Prevention Management Kit; ICU, intensive care unit; IV, intravenous; IO, intraosseous; O_2, oxygen; PEA, pulseless electrical activity; US, ultrasound; VT, ventricular tachycardia; VF, ventricular fibrillation.
From Zafren et al.[11] Reproduced with permission.

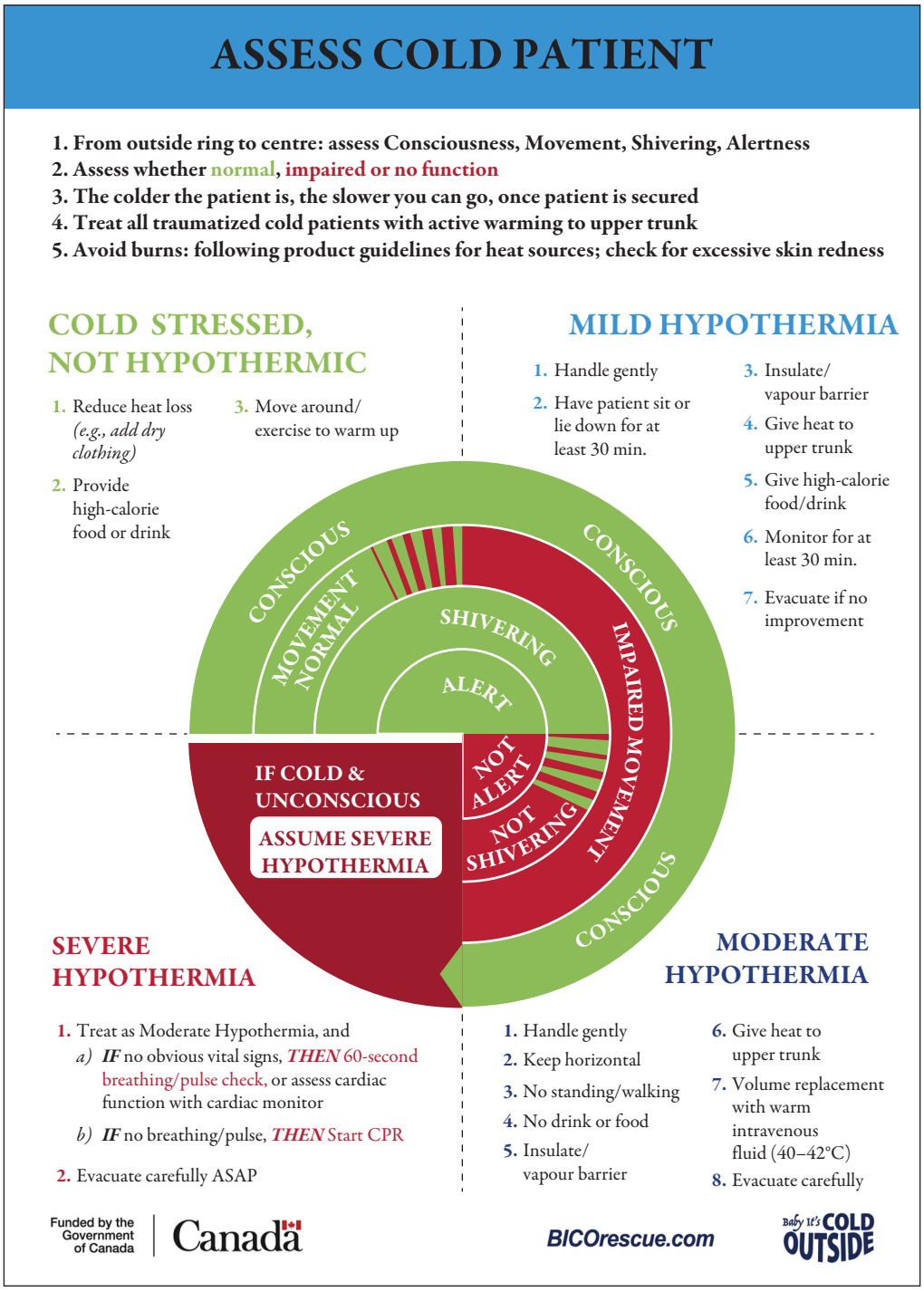


Figure 49.3 The "cold card." This card may be used by rescuers for the rapid on-site evaluation of cold-exposed patients. From Giesbrecht GG.[45] Reproduced with permission.

and in-hospital ECMO services. Furthermore, hypothermic patients often present with additional conditions such as trauma, intoxication, comorbid conditions, and asphyxia due to drowning or avalanche burial.[20] Therefore, implementation of specific treatment algorithms and protocols, together with the development of specialized hypothermia treatment centers with well-trained ECMO teams, should be a priority to improve the management of AH victims.[20,28] Also, validation of strong outcome prediction tools by concerted efforts at the international level should be a priority to improve our ability to appropriately select hypothermic patients who might benefit from extracorporeal rewarming.

With specific respect to ECMO therapy, several key aspects that could affect treatment success should be evaluated, including optimal rewarming speed, ECMO flow and oxygen delivery, type of priming solution (crystalloid vs. colloid), and anticoagulation protocols.[20] Furthermore, the development of novel surfaces in ECMO circuits to improve

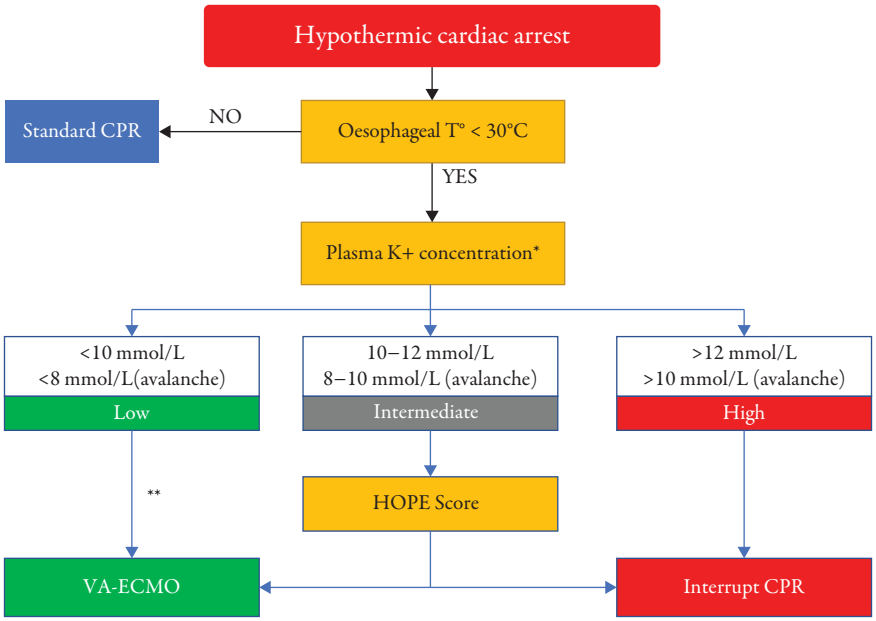


Figure 49.4 Proposed algorithm for in-hospital ECLS triage of hypothermic patients. For admission serum K^+, ECMO is NOT indicated at values above a cutoff of 12 mmol/L or 10 mmol/L in case of avalanche burial. ECMO is indicated at K^+ values below 10 mmol/L or 8 mmol/L (avalanche). We consider a "gray zone" for K^+ values of 10–12 mmol/L (avalanche 8–10 mmol/L), for which ECMO indication should be considered after additional considerations. The HOPE score may be particularly helpful in such conditions.
* For plasma K^+, only a good quality sample obtained from a central or femoral vein, or femoral artery, is acceptable.
** For patients at the low end of K^+ values, the HOPE score may also assist the decision in some circumstances (e.g., in case of known hypoxic-hypothermic arrest).

hemocompatibility and reduce the need for systemic anticoagulation[46] will be invaluable to reduce the risk of hemorrhage, most especially in hypothermic trauma patients.

Several aspects of post-CA care also need to be evaluated in the specific population of hypothermic patients. The rapid rewarming of previously hypoxic cold tissues with oxygenated blood could promote significant reperfusion injury and systemic inflammation.[32] Whether the addition of a cytokine absorption filter to the ECMO circuit could help improve prognosis in such conditions should be investigated.[47] Also, whether temperature target management needs to be implemented after hypothermic CA, at which target temperature, and for which duration are additional questions that need to be addressed in the future.[20]

DISCUSSION

The two stem cases well illustrate the problematic of hypothermic CA and the role of extracorporeal rewarming with V-A ECMO. In the first case, the patient was found severely hypothermic (temperature on the medical record was 19.9°C), comatose but with a persisting circulatory activity. This indicates severe hypothermia (<28°C), stage III according to the Swiss system. Although persisting cardiac activity may be surprising at such an extremely low temperature, it is noteworthy that the lowest reported temperature with persisting vital sign is 17°C.[1] The patient was found immersed in cold water. The situation would have been of course different in case of submersion, where asphyxia, but not hypothermia, is generally the cause of CA. Therefore, CPR should not be initiated after more than 60 minutes submersion, with possible extension (~90 minutes) in case of cold water immersion.[48]

The patient presented a witnessed CA due to VF once he was put on the stretcher. This is a typical example of so-called circumrescue collapse, well described following cold water immersion hypothermia due to the combined actions of mechanical stimulation of the heart by mobilization, temperature afterdrop related to blood volume redistribution, and hypotension secondary to peripheral blood pooling and reduced venous return.[4] Witnessed CA due to circumrescue collapse has a good prognosis, with neurologically intact survival as high as 73%.[49]

The patient was transported under continuous mechanical chest compression to the hospital, where ECMO rewarming was immediately decided. Although the total duration of CPR lasted 117 minutes, the patient survived without neurological sequelae. This is a major difference from CA of other causes, in which extracorporeal resuscitation with ECMO is not recommended for no flow duration more than 5 minutes and low flow for more than 60 minutes. Due to the reduction of cerebral metabolism in hypothermia, the decision to initiate CPR or ECMO should not be taken on the basis of low-flow and no-flow duration, and the adage "nobody is dead before warm and dead" should be applied in hypothermic CA.[23]

The patient could be successfully defibrillated once core temperature reached 28°C, with ROSC after a single shock. Of note, defibrillation should be limited to one to three attempts

at temperatures less than 30°C.[4] Following ROSC, the patient displayed unstable circulation with signs of biventricular dysfunction, requiring the maintenance of ECMO support for 24 hours before recovery of cardiac function. Cardiac dysfunction is not unusual following ECMO rewarming, which may require prolonged extracorporeal support. Diastolic dysfunction may persist after the recovery of systolic function.[50]

The second stem case underlines many of the pitfalls in the management of out-of-hospital hypothermic CA. Since many of these situations occur in a hostile environment, the rescuers' safety is a major concern, and extraction and transport of the victims may represent major technical issues.[51] It is also essential for the rescue team to have precise knowledge of the local hospital facilities with ECLS availability and to coordinate patient orientation in case of multiple victims, such as avalanche burial.[52]

The patient under discussion had a core temperature of 17°C, implying severe, stage IV hypothermia. The duration of CA could not be determined, and the patient displayed fixed mydriatic pupils with absent light reflex. The right decision was to start immediate CPR. Indeed, signs of apparent death, including fixed dilated pupils and rigor mortis should not be considered contraindications to start CPR in hypothermic patients,[4] and only major irreversible trauma, chest incompressibility, or evidence of prolonged asphyxia contraindicate resuscitation in this setting.[10] This patient had no signs of injury and was not buried, implying there was no reason to consider an anoxic etiology of his CA.

The patient was transported under mechanical chest compression to the nearest hospital with an ECLS facility. The measurement of serum potassium was unfortunately not possible due to technical issues. The decision to initiate ECMO was therefore considered while awaiting serum potassium determination. The role of serum potassium as a dichotomous triage tool has been well validated, with cutoff values for ECMO initiation less than 12 mmol/L (<8 mmol/L in case of avalanche burial). In our institution, we consider values between 10 and 12 mmol/L (and between 8 and 10 mmol/L for avalanche accidents) as a gray zone requiring multidisciplinary discussion to decide whether ECMO should be initiated (see Figure 49.4).

The problem when using serum potassium as the single determining factor for ECMO rewarming is that many hypothermic patients display normal potassium values. Therefore, there is a need for additional, clinically applicable, predictive tools to avoid overtriage owing to the financial and psychological burden of ECMO resuscitation. The recently developed HOPE score, which integrates six prognostic indicators (age, sex, temperature, serum potassium, asphyxia, and CPR duration) could be useful for this purpose, showing an excellent discriminating value to determine whether ECMO rewarming is futile or not.[36] In the patient under discussion, the HOPE score could not be calculated due to lack of initial serum potassium determination. However, we could finally obtain a potassium value of 18.7 mmol/L. ECMO was then interrupted, as such extreme hyperkalemia indicates irreversible diffuse cell death.

CONCLUSION

- Extracorporeal life support, primarily with V-A ECMO, is the gold standard for rewarming patients with stage IV hypothermia (CA) or those with stage III hypothermia and severe circulatory instability
- The prognosis of ECMO rewarming in hypothermic patients is significantly dependent on the mechanism of CA: purely hypothermic versus anoxic-hypothermic.
- In purely hypothermic CA, ECLS rewarming has an excellent prognosis, with roughly 70% survival with good neurological recovery.
- The duration of CA and CPR should not be used as criteria to initiate or not ECLS in hypothermic patients.
- Serum potassium is an excellent dichotomous predictive tool for ECLS decision in hypothermia, with cutoff values of 12 mmol/L (8 mmol/L in case of avalanche burial).
- The HOPE score is a novel predictive tool integrating several prognostic factors and may be extremely useful for the decision regarding ECMO rewarming of hypothermic patients.

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REVIEW QUESTIONS

1. A 54-year-old woman is rescued after a ski accident. On site, the patient's temperature is 30.5°C; she is conscious with altered judgment and dysarthria and slightly shivering; her blood pressure is 130/90 mm Hg. How do you classify the patient's hypothermia?

A. Stage I hypothermia
B. Stage II hypothermia
C. Stage III hypothermia
D. Stage IV hypothermia

2. A 32-year-old male patient is found in CA for unknown duration following an avalanche accident, with a core temperature of 22°C. Among the following statements, which would contraindicate immediate CPR (several answers possible)?

A. Noncompressible chest
B. Fixed, dilated pupils
C. Burial for 45 minutes with packed snow within nose and mouth
D. Asystole

3. A 47-year-old female patient is found hypothermic with a core temperature of 31°C, conscious, and shivering. What measure(s) for rewarming do you recommend?

A. Stimulate active mobilization to increase heat production
B. Rewarm externally using forced warm air
C. Internal rewarming with ECMO
D. External rewarming by applying heat on the extremities

4. Which of the following criteria contraindicate(s) ECMO rewarming for hypothermic CA?

A. A serum potassium of 9 mmol/L after cold water immersion
B. A CPR duration of 210 minutes following an avalanche accident without snow burial
C. An age greater than 65 years
D. Prolonged (>60 minutes) CA in a patient with a core temperature of 32.5°C

5. You perform out-of-hospital CPR in a 24-year-old hypothermic male patient. The heart rhythm is asystole; core temperature is 22°C; and there is no sign of asphyxia. There is a hematoma on the left cheek, but no other sign of trauma. What statement(s) is (are) correct?

A. Give epinephrine, 1 mg every 10 minutes
B. Interrupt CPR after 1 hour of persisting asystole
C. Transfer the patient to the closest hospital with ECLS facility (60 km)
D. Transfer the patient to the closest hospital to perform a brain CT scan (25 km)

6. Which is the approximate survival rate of patients with pure hypothermic, atraumatic, CA treated with ECMO rewarming?

A. About ~20%
B. About 40%
C. About 90%
D. About 70%

7. What are advantages of peripheral V-A ECMO on CPB machines for extracorporeal rewarming for hypothermic CA?

A. Greater speed of rewarming with ECMO
B. Prolonged support with ECMO after rewarming
C. Lower requirements for systemic anticoagulation
D. Better oxygenation capabilities with ECMO

8. A woman is admitted to the emergency room after the rescuers found her lying in front of her house. She is immediately intubated for severe hypoxemia (aspiration). Core temperature is 33°C. What is the stage of hypothermia with respect to the core temperature classification?

A. Cold stress
B. Mild hypothermia
C. Moderate hypothermia
D. Severe hypothermia

9. Which of the following techniques is appropriate to evaluate temperature for a patient with hypothermic CA?

A. Oral thermometer
B. Infrared thermometer
C. Rectal thermometer
D. Esophageal probe

10. Which of the following signs and symptoms is (are) not typical of mild hypothermia?

A. Shivering
B. Peripheral vasoconstriction
C. Unconsciousness
D. Severe hemodynamic instability

11. Which of the following statements is (are) true?

A. Passive rewarming techniques are effective for patients with AH stages III–IV.
B. Active external rewarming techniques are not recommended for AH stage IV.
C. Extracorporeal life support is the treatment of choice for AH stage IV or III with severe circulatory instability.
D. Peritoneal lavage showed superiority over other minimally rewarming invasive techniques.

12. Which of the following statements is correct?

A. Mechanism of hypothermic CA does not impact prognosis.
B. There is no existing score to guide the decision to implement ECLS in hypothermic CA.
C. Rescue collapse hypothermic CA has a better prognosis than unwitnessed CA.
D. Hypothermic CA with a hypoxic component has a good prognosis.

13. Which item is not included in the HOPE score for ECLS triage of hypothermic CA?

A. Age
B. Sex

C. Asphyxia mechanism of CA
D. Cardiac rhythm

14. Which of the following statements is (are) correct regarding V-A ECMO rewarming?

A. A reperfusion cannula is optional when the femoral access is used for ECMO implantation.
B. Rewarming should proceed at a rate of 10°C per hour.
C. For ECMO rewarming, central cannulation is recommended over peripheral cannulation.
D. Implantation of V-A ECMO should be performed under continuous CPR.

15. Regarding CPR for hypothermic CA, which statement is wrong?

A. Cardiopulmonary resuscitation can be interrupted in case of avalanche burial for more than 35 minutes and obstructed airways.
B. Cardiopulmonary resuscitation can be interrupted if potassium is more than 12 mmol/L after cold water immersion.
C. Cardiopulmonary resuscitation should be interrupted in unwitnessed CA and asystole.
D. Diagnosis of circulatory CA in AH may be difficult.

ANSWERS

1B
2A-C
3B
4D
5C
6D
7B-C
8B
9D
10C-D
11C
12C
13D
14D
15C

50.

ECMO SUPPORT FOR PULMONARY EMBOLISM

Maximilian Malfertheiner and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 29-year-old male patient underwent surgery for a left anterior cruciate ligament graft. The operation was performed in the ambulatory operation facility using a tourniquet. After the operation and removal of the tourniquet, the patient developed tachycardia, hypotension, and a drop in oxygen saturation (SpO_2) down to 70%. Invasive ventilation using a laryngeal mask airway (LMA) with fraction of inspired oxygen (FiO_2) of 1.0 maintained a SpO_2 of 85%. Point-of-care ultrasound using focused assessed transthoracic echo showed signs of acute right ventricular (RV) failure. Under suspicion of acute massive pulmonary embolism (PE) leading to circulatory failure, the LMA was replaced by an 8.0 endotracheal tube. The patient was brought to the emergency department, which is located in close proximity to the day surgery area, and a computed tomographic angiogram (CTA) was performed. The patient was found to have a massive saddle PE (Figure 50.1).

The patient rapidly became more hypotensive and required vasopressor support with norepinephrine. Within minutes, the patient went into cardiac arrest with multiple returns of spontaneous circulation (ROSCs). The extracorporeal membrane oxygenation (ECMO) hotline was contacted, and thrombolytic therapy was administered with 100 mg alteplase IV. The patient suffered ongoing cardiogenic shock and received 2 mg/h of norepinephrine. Due to persistent cardiogenic shock, he again went into cardiac arrest.

Extracorporeal cardiopulmonary resuscitation (ECPR) was initiated using the Lund University Cardiopulmonary Assist System (LUCAS) and percutaneous veno-arterial (V-A) ECMO cannulation. The cannulation was performed using a 23 French (23F), 55-cm, left femoral vein drainage cannula and a 17F, 23-cm femoral arterial return cannula. Further, a 7F reinforced distal perfusion catheter was placed. Cannulation was without complications besides one failed attempt of arterial puncture of the right femoral artery.

After ECMO initiation, cardiac output was still low; however, with aggressive volume resuscitation the cardiac output improved, and vasopressor requirements could be lowered significantly. Bleeding occurred at the cannulation site and into the Redon drainage of the left knee due to disseminated intravascular coagulation following thrombolytic therapy. To reconstitute hemostasis, fresh frozen plasma and fibrinogen were given. The full CTA report was obtained shortly after and showed extensive acute PE with right heart strain, multiple pulmonary infarctions bilaterally, and small pleural effusions.

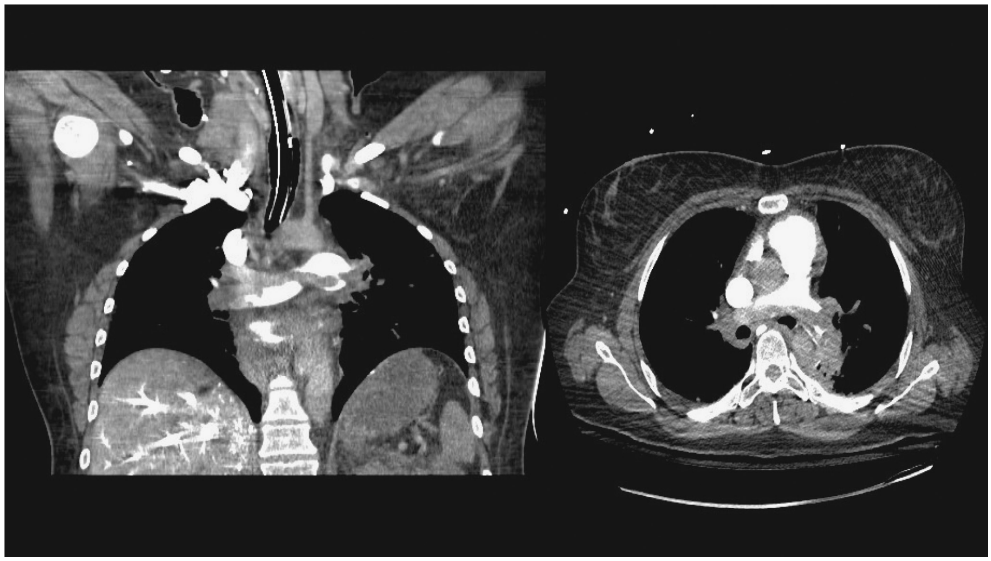


Figure 50.1 Chest CT with saddle pulmonary embolism.
From Maybauer et al., J Card Surg. 2020;35:2821-2824

The patient was transported to the intensive care unit (ICU), where he again became severely hypotensive. An epinephrine drip was commenced in addition to norepinephrine. A dose of methylene blue (2 mg/kg) and stress dose hydrocortisone 200 mg/24 h were administered. In addition, vasopressin 2.4 U/h and angiotensin II with increasing doses up to 80 ng/kg/min was started to maintain a mean arterial pressure of 65 mm Hg.

Throughout the night, the hemodynamic situation improved, norepinephrine and vasopressin could be weaned off, and the patient remained on 0.03 μg/kg/min of epinephrine and 30 ng/kg/min of angiotensin II. The patient's lactic acid level peaked overnight at 17.85 and was down to 7.46 in the morning. He developed acute kidney injury and shock liver. Throughout the night, he had persistent low-flow alarms and "chattering on ECMO," along with significant coagulopathy due to tissue plasminogen activator (tPA) administration.

The patient required 5 units of packed red blood cells (PRBCs), 500 mL of fresh frozen plasma, and 20 units of cryoprecipitates overnight and 5 units more PRBCs in the morning. He was also started on continuous renal replacement therapy (CRRT). With rising C-reactive protein, white cell count, and yellowish bronchial secretions, broad-spectrum antibiotic therapy was started to treat infarction pneumonia following PE. The left leg was noticed with a slightly increased circumferential hematoma; however, peripheral pulsation was present, and near-infrared spectoscopy (INVOSÔ, Medtronic) signals were stable and similar to the right leg. Since the blood transfusion did not match the drain output and hematoma development, the patient was brought back to the CT scan to repeat a CTA. Vasopressors were shortly increased, and the ECMO was clamped for 30 seconds to allow application of contrast with stable hemodynamics.

The CTA (Figure 50.2) showed a new aortic dissection extending from the distal aortic arch to the diaphragmatic hiatus, improved but extensive PE, worsened pulmonary hemorrhage and infarctions, increased moderate pleural effusions, moderate hemoperitoneum, large retroperitoneal (RP) hemorrhage, bilateral renal infarctions, and anasarca.

Given the CTA results, a multidisciplinary meeting with the ECMO attendings and cardiac surgeon was held, and it was concluded to keep the patient off anticoagulation for as long as possible before an embolectomy could be attempted. This goal could be achieved for 2 days more before the patient became hypoxic on ECMO, and it was decided to bring him to the operating room (OR) for emergent embolectomy.

After commencing cardiopulmonary bypass (CPB), the pulmonary artery was opened and examined. A large saddle thrombus was removed. The left and right pulmonary arteries were then examined, and large amounts of clots were removed from each side. The lungs were then squeezed, and more clot was removed (Figure 50.3). Irrigation of each artery resulted in no more clots. The pulmonary artery was closed with a 6-0 Prolene suture*. The patient was then weaned from CPB without any difficulty.

There was much better RV function, and pulmonary compliance was good. Oxygen saturations, however, were low, and V-A ECMO through the femoral cannulae was reinstated. Blake drains were placed in each pleural cavity and in the pericardial cavity. Anticoagulation was reversed, and platelets (PLTs) were given. The chest was closed, and the patient was transferred to the ICU in guarded condition.

The patient arrived from the OR on inhaled epoprostenol and intravenous milrinone; all vasopressors were off. The patient received two more units of PLTs and remained hemodynamically stable without further bleeding. ECMO flow was 4 L/min, and it was decided to hold off heparin for the next 12 hours. The following day, the patient had another CT scan, and the type B dissection and RP hematoma remained stable in size with indications for a clotted false lumen. A heparin drip at 400 U/h with an activated partial thromboplastin time (aPTT) goal of 40–50 was commenced.

Over the following two days all inotropic and vasopressor support could be weaned off and was replaced by labetalol



Figure 50.2 Left: Chest CT with type B aortic dissection. Right: Intraperitoneal and retroperitoneal hematoma. From Maybauer et al., J Card Surg. 2020;35:2821-2824



Figure 50.3 Postoperative collection of removed emboli. Of note is the comparison in size with the surgical instruments.
From Maybauer et al., J Card Surg. 2020;35:2821-2824

infusion for blood pressure control. The patient remained intubated due to pneumonia. Three days later, the patient passed an ECMO weaning trial and was brought back to the OR for decannulation and returned still intubated to the ICU. At this time, all liver enzymes had returned to normal values, and CRRT could be weaned off after a furosemide stress test. He was extubated 3 days after decannulation and was transferred to the intermediate care unit and discharged from the hospital 28 days after the event. For his aortic type B dissection, which remained stable and uncomplicated, the patient was medically managed and followed up by outpatient appointments. The knee was followed up by orthopedic surgery.

WHAT ARE THE PATHOPHYSIOLOGY AND RISK STRATIFICATION OF MASSIVE PE?

Pulmonary embolism is a frequent cardiovascular complication with a mortality reported as high as 15%.[1] Management guidelines for acute PE are available from the American Heart Association and the European Society of Cardiology/European Respiratory Society.[2,3] The guidelines define massive PE as acute PE with sustained hypotension for at least 15 minutes or need for inotropic support.[3] Clinical risk scores like the most commonly used pulmonary embolism severity index (PESI) and its simplified version, sPESI, can predict the short-term death and adverse outcome events in patients with acute PE. The PESI high-risk group has a predicted 30-day mortality of more than 10%,[4] patients with massive PE and the need for cardiopulmonary resuscitation (CPR) have a mortality reported as high as 65%.[5–7] Risk stratification in massive PE therefore should focus more on hemodynamic instability than on available scores. Low systolic blood pressure, tachycardia, respiratory insufficiency, and syncope are all associated with unfavorable outcome.

The pathophysiological changes leading to low cardiac output in massive PE are caused by pulmonary arterial obstruction causing pulmonary hypertension and further leading to altered strain of the RV causing right heart failure. These acute changes in the pulmonary circulation cause a decrease of the left ventricular preload, resulting in cardiogenic shock or even cardiac arrest.

HOW IS THE PATIENT WITH A MASSIVE PULMONARY EMBOLISM MANAGED?

The main goals of any acute treatment in massive PE are to reduce RV afterload and to restore pulmonary circulation. Systemic anticoagulation prevents further clot propagation, thus allowing the fibrinolytic system to lyse the thrombus and restore perfusion. Heparin is most commonly used for this purpose. Management of patients classified into the PESI score low-risk group is well described in the available guidelines.[2,3] If patients present with hemodynamic instability, then there is not enough time for the inert fibrinolytic system to lyse the thrombus. Primary reperfusion treatment is the treatment of choice in these patients. Systemic thrombolysis using recombinant tissue-type plasminogen activator/ alteplase is the most frequently applied treatment in hemodynamically unstable patients.[8] Accepted alternative treatments are surgical pulmonary embolectomy and percutaneous catheter-directed treatment. While surgical pulmonary embolectomy can be curative, it is logistically difficult and rarely successful for patients in cardiogenic shock.[9] Percutaneous catheter-directed treatment is logistically limited to dedicated centers, and there is still a lack of data from randomized controlled trials on the clinical efficacy and outcomes.[10]

Besides reperfusion strategies, hemodynamic and respiratory support are necessary to treat hypoxia and cardiogenic shock. Moderate (500 mL) fluid challenge may help to increase the cardiac index in some patients.[11] Furthermore, the use of vasopressors is advocated in patients with systolic blood pressure below 90 mm Hg. Norepinephrine improves RV function via a direct positive inotropic effect.

In cases of severe hypoxemia, inhalation of nitric oxide may improve the hemodynamic status and gas exchange of patients by dilation of the pulmonary vasculature and reduction in RV afterload. It may also improve oxygenation by improving ventilation/perfusion mismatch through pulmonary vascular dilation and redirection of blood flow into ventilated lung areas. However, those are temporary measures that are very helpful to buy time for procedures like ECMO cannulation; however, no benefit in regard to long-term outcome has been shown so far.[12]

WHAT ARE ANTICOAGULATION AND THROMBOLYTIC STRATEGIES FOR MASSIVE PE?

In suspected massive PE, initiation of intravenous anticoagulation with unfractionated heparin (UFH) without delay is a class I recommendation.[3] Dosing of UFH should be started with a bolus, weight adjusted with either 80 IU/kg or 5000 IU as a standardized bolus. Continuous intravenous infusion with 1000–1500 IU/h should be maintained to achieve an aPTT of 60–80 seconds or alternatively an activated clotting time (ACT) time of more than 250 seconds.

There is no evidence for a benefit of systemic thrombolytic therapy compared with heparin for the initial treatment of unselected patients with acute PE. However, a benefit is suggested for those patients with massive PE.[13] A number of

studies have evaluated the use of different fibrinolytic agents, including alteplase, urokinase, streptokinase, and telectepase. The most evidence exists for the use of alteplase in dosages of 90–100 mg given as a bolus injection or over 2 hours.[14] Systemic thrombolysis is a rescue treatment in massive PE; indication for its administration should be given as relevant bleeding complications can occur. The risk of causing intracranial bleeding from thrombolysis is small but significant (1.9%) and has a relevant impact on patient outcome.[15] Therefore, a recent hemorrhagic stroke is considered an absolute contraindication to thrombolysis. Other contraindications are recent surgery (<3 weeks), ischemic stroke (<6 months), and significant active or recent bleeding.

HOW DID EXTRACORPOREAL LIFE SUPPORT EVOLVE IN PULMONARY EMBOLISM THERAPY?

The concept of extracorporeal life support (ECLS) in the treatment of PE dates to John Gibbs in the 1930s, when he witnessed a young patient die due to massive PE.[16] In 1966,[17] reports on the successful use of CPB were published. The first scientific data on ECMO therapy for massive PE dates to 1977, when Krellenstein et al.[18] published an animal study using V-A ECMO in dogs, demonstrating improved survival with ECMO support. The first randomized controlled study on ECMO support in acute respiratory failure included[9] patients with massive PE, all with fatal outcome.[19] It took almost another 20 years until the first reports of successful treatment of PE, with technological improved ECMO devices, were published.[16,20]

HOW ARE PATIENTS WITH PE ANTICOAGULATED DURING ECLS?

Hemostatic changes induced by the ECMO circuit lead to increased risks of thrombotic events[21]; therefore, guidelines on anticoagulation for ECLS therapy recommend a target ACT of 180–220 seconds, mostly using UFH. In cases of massive PE, anticoagulation should be managed according to the PE guidelines as mentioned above. In massive PE, ACT of more than 250 seconds should be targeted. In cases of life-threatening circulatory failure also combined therapy with thrombolytic agents and ECMO can be an option, although bleeding complications are a relevant risk in these patients.

HOW ARE PE PATIENTS VENTILATED DURING ECMO?

Independently of ECMO support, it is advisable to use small volumes and low inspiratory pressures as well as low positive-end expiratory pressure (PEEP) in patients with PE. The reason for this advice are the pathophysiological consequences of mechanical ventilation on RV function.[22] Mechanical ventilation and PEEP are known to reduce venous return and RV preload. Further, the ventilator-induced rise in transpulmonary pressure leads to an increase of pulmonary vascular resistance and RV afterload.[23] Therefore, spontaneous breathing with PEEP levels that do not compromise hemodynamics is desirable.

WHAT COMPLICATED THIS CASE?

The massive saddle PE led to acute and severe respiratory failure that mandated endotracheal intubation and ventilation with FiO_2 of 1.0. The significantly reduced blood flow (preload) to the left ventricle caused cardiogenic shock and resulted in cardiac arrest. CPR was commenced, and the patient had multiple ROSCs but kept arresting. Alteplase was administered with the hope of interrupting this vicious circle, but ECMO became necessary to finally stabilize this patient. In order to facilitate CPR and ECPR, the LUCAS was used. This is a mechanical device providing automated 5-cm deep chest compressions and active decompressions back to the normal anatomical position with a frequency of 100 per minute. Mechanical chest compression devices are increasingly used during CPR and ECPR since they ensure continuous compressions of high quality and adequate blood flow during procedures such as percutaneous V-A ECMO placement. Unfortunately, this technology is not without risk. The LUCAS-related complications have been described from minor injuries like skin lesions to major injuries, such as sternal fracture and rib fractures, and up to significant complications like cardiopulmonary injury or aortic dissection.[24]

When comparing the CT scans of this patient from before and 12 hours after ECPR, the aortic dissection was a new finding that was likely related to CPR or the mechanical compressions via the LUCAS. The RP hemorrhage may also be related to the LUCAS since liver, spleen, and gastric injuries have been reported.[24] However, it should be kept in mind that also the ECMO cannulation could have caused the RP hemorrhage. Potential sources could be the failed vascular puncture attempt or the wire perforating the vein when pushed forward during chest compression with significant movements of the patient. Even though these complications are difficult to avoid during life-saving procedures and complicated conditions, they have a significant impact on the management of these patients and should trigger appropriate diagnostics when, for example, unexplained blood losses occur.

Patients with massive PE and the need for CPR per se have a mortality reported as high as 65%.[5–7] However, when complicated by aortic dissection and/or RP hemorrhage, the mortality can be significantly higher.

WHAT WAS THE RISK-BENEFIT RATIO IN REGARD TO ANTICOAGULATION IN THIS CASE?

While surgical pulmonary embolectomy can be curative, it is rarely successful for patients in cardiogenic shock. Stabilizing the patient on ECMO by weaning off the high inotropic and vasopressor support and normalizing the metabolic state improves survival chances. The risk-benefit ratio and anticoagulation must be weighed individually for the patient.

Systemic anticoagulation prevents further clot propagation, thus allowing the fibrinolytic system to lyse the



Figure 50.4 Thrombus formation within the oxygenator without the use of anticoagulants.
From Maybauer et al., J Card Surg. 2020;35:2821-2824

thrombus and restore perfusion. Further, anticoagulation is useful to prevent clotting within the ECMO circuit. In this case, there was no initial anticoagulation started due to administration of alteplase and significant transfusion requirements over the first 12 hours. With the diagnosis of type B dissection and RP hemorrhage, the multidisciplinary team had to weigh the risk of starting anticoagulation and potentially enlarging the blood volume in the false lumen of the aorta as well as expansion of the RP bleed versus not anticoagulating the patient and risking growth of the emboli. In addition, since alteplase did not fully dissolve the emboli and there was still a significant thrombus load in the pulmonary vasculature, embolectomy was the only viable treatment option. However, in order to avoid significant hemorrhage during full anticoagulation on CPB, the decision was reached to hold off on anticoagulation as long as the patient was hemodynamically stable and oxygenating well on ECMO. The procedure could be deferred for 2 days until the patient became more unstable and hypoxic. Clots were seen in the oxygenator (Figure 50.4). However, at this time point an emergent embolectomy had to be performed without an increase in the RP hematoma or the false lumen of the descending thoracic aorta.

These major complications are beyond guidelines and evidence-based practice. Individual decisions must be made for every patient based on the experience of the team involved with close monitoring and readiness to intervene at any time. Realistic estimations of the goals of care and expectations of the family members should be communicated daily.

WHAT IS THE ROLE OF ECMO THERAPY IN MASSIVE PE?

Existing data regarding the utility of ECMO in the setting of PE come from case series and single-case reports.[25–28] Indication for ECLS in massive PE can be very different depending on the scenario and the state of the patient. The following scenarios associated with massive PE and need for ECLS can occur:

1. Patient received systemic thrombolysis or embolectomy and is in ongoing cardiogenic shock
2. Extracorporeal CPR due to suspected PE before thrombolytic treatment
3. Cardiogenic shock and contraindication for thrombolytic therapy
4. Hemodynamically stable patient with severe hypoxemia

DISCUSSION

As all of the above mentioned very different scenarios have different aspects for the choice of ECMO configuration, they are discussed separately next.

SCENARIO 1

A number of case reports can be found describing the scenario of ongoing cardiogenic shock following thrombolysis.[28–32] If a patient has received systemic thrombolysis before cannulation the risk of bleeding complications has to be considered very high. As described in the stem case, diffuse bleeding from the site of cannulation, arterial or venous lines, or any preexisting wound can occur with or without major complications, such as RP bleeding or type B dissection of the aorta. In these patients, adequate resources of red blood cell transfusion should be available, as substitution of coagulation factors should be performed very cautiously. Once active bleeding is not present, systemic anticoagulation as recommended in the PE guidelines should be targeted. The ECMO support should be V-A ECMO, as circulatory support is needed. The ECMO therapy is supposed to give time for the thrombolysis to occur and allow the right heart to recover. Besides some encouraging case reports, mortality in this group of patients is still very high and reported as up to 76.5%.[26,33] The main reason for mortality is multiorgan failure or severe bleeding in these patients. One case series focused on identifying predictors of outcome and reports of monitoring the right heart function as a predictor of outcome.[27] If no sufficient thrombolysis occurs, also secondary embolectomy under ECMO support can be considered an option.[34]

SCENARIO 2

A range of therapeutic options without evidence of one being better than another is under discussion for patients with cardiac arrest due to PE. These patients can be further divided into out-of-hospital and in-hospital cardiac arrest. Relevant factors for a beneficial outcome for these patients are discussed in the ECPR chapter of this book. A crucial factor of course is the timing of cardiac arrest and initiation of resuscitation. As a consequence of the cardiac arrest, cerebral hypoxia and multiorgan failure are the most frequent reasons for death in this group of patients.

If a patient with cardiac arrest due to PE received V-A ECMO support and is stabilized, this can be used as bridge to systemic thrombolysis or surgical embolectomy. The third option would be to wait for inert thrombolytic activity and

use systemic anticoagulation alone. Until now, none of these options has been shown superior to the others.[28] Therefore, the choice of definitive treatment should be made based on logistics, local expertise, and experience with a patient-centered approach. If the patient is stable under V-A ECMO support, daily echocardiography should be performed to assess the function of the RV, and systemic anticoagulation alone might be the option with the lowest risk for complications.

SCENARIO 3

For patients in scenario 3 with ongoing cardiogenic shock and a contraindication for systemic thrombolysis, the choice of treatment options is more limited. For circulatory support, a V-A ECMO configuration is chosen, and systemic anticoagulation as recommended by PE guidelines is sought. Depending on the underlying disease, also lowering anticoagulation targets is an option. Only in experienced centers should surgical embolectomy or local thrombolysis should be considered.

SCENARIO 4

A hemodynamically stable patient with severe hypoxemia in whom the choice of ECMO support allows for respiratory support only. In the literature, V-A ECMO is reported more frequently in patients with massive PE; however, successful reports of veno-venous (V-V) ECMO exist.[35] V-V ECMO should be chosen in patients who suffer from severe hypoxemia and need only small doses of inotropes to maintain sufficient circulation. Unfortunately, there is no cutoff value to guide clinicians when V-V ECMO support is still sufficient and when V-A ECMO is needed. Comparable to the situation of patients with massive PE and hypoxemia is the situation in severe patients with acute respiratory distress syndrome (ARDS). A review of Extracorporeal Life Support Organization Registry data showed that V-V ECMO was not inferior to V-A ECMO in patients requiring pre-ECMO hemodynamic support.[36] An explanation is that hypoxemia increases the afterload of the RV and if hypoxemia is treated through ECMO, the afterload is reduced—resulting in improved circulation. As mentioned, there are no criteria to know if V-V ECMO support will be sufficient. If V-V ECMO was implanted and circulatory failure is still present, ECMO mode conversion is still an option. The ECMO mode can either be switched from V-V to V-A or possibly and addition of an arterial cannula for a veno-veno-arterial configuration. Upgrade to a veno-arterial-venous hybrid mode is of course also possible from initial V-A ECMO. This could be necessary if severe hypoxemia is still relevant after circulatory support with V-A ECMO.

Regarding the configuration of ECMO cannulation, there is no clear stipulation. The majority of reported cases were cannulated via the femoral vein and femoral artery, both cannulae either on one side or on opposite sides. For V-V ECMO, a femoro-jugular approach is most common.

For the interaction of circulatory failure and ventilation, it should be mentioned that high PEEP is not recommended in massive PE as PEEP causes an increased RV afterload secondary to the rise of pulmonary vascular resistance. Therefore, in treatment of severe hypoxemia in PE, ECMO support should be considered earlier than in ARDS patients.

CONCLUSION

Veno-arterial and V-V ECMO are rescue options in massive PE.

Veno-arterial ECMO is the most frequently used configuration for cardiocirculatory support in patients with PE.

Timing, mode, and configuration of extracorporeal support have to be made on an individualized patient-centered basis.

ECMO therapy has to be seen in conjunction with other available treatments in massive PE.

ECMO can be a bridge to postponed embolectomy in patients with PE and bleeding complications.

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REVIEW QUESTIONS

1. A 43-year-old female patient presents to the emergency department with acute dyspnea and suspected PE. She undergoes witnessed cardiac arrest in the emergency department. What is the treatment of choice during ongoing CPR?

   A. Bolus injection of alteplase in a dosing of 100 mg.
   B. Immediate bolus of 5000 UI of UFH and percutaneous catheter-directed treatment.
   C. Implementation of V-A ECMO support for ECPR.
   D. All of the above options are feasible in a rescue situation depending on local experience and availability of the treatment option.

2. Which of the following statements is incorrect?

   A. Computed tomography of the chest is considered the gold standard for diagnosis of PE.
   B. Systemic thrombolytic therapy is superior to UFH in massive PE.
   C. Compared to systemic thrombolytic therapy, V-A ECMO significantly reduces mortality in patients with massive PE.
   D. In massive PE, V-A and V-V ECMO can be considered treatment options.

3. Which of the following statements on mechanical ventilation in massive PE is correct?

   A. High peak inspiratory pressure reduces pulmonary vascular resistance.
   B. To improve oxygenation and increase RV preload, PEEP values greater than 15 mbar should be targeted in patients with PE.
   C. High PEEP levels are known to reduce venous return and RV preload.
   D. The FiO_2 should always be at 1.0 to reduce pulmonary vascular resistance.

4. Which of the following statements on anticoagulation in massive PE is incorrect?

   A. A bolus of 5000 UI of UFH followed by continuous infusion with 1000–1500 IU/h can be recommended.
   B. Alteplase in a dosage of 90–100 mg can be given as a bolus or as an infusion over 2 h.

C. The risk of causing intracranial bleeding from thrombolysis is small (<2%).
D. Following systemic thrombolysis, UFH infusion should be stopped for 24 hours.

5. Which of the following scenarios should be considered an absolute contraindication for ECMO support?

A patient with massive PE, ongoing CPR for 30 minutes, and alteplase bolus 10 minutes before ECMO cannulation.
B. A 73-year-old patient with a history of ischemic stroke (8 months ago) and massive PE
C. A 56-year-old women with stage 4 liver cirrhosis and massive PE resulting in cardiac arrest
D. A patient with a body mass index greater than 40 kg/m^2

ANSWERS

1D; 2C; 3C; 4D; 5C

51.

EXTRACORPOREAL CARDIOPULMONARY RESUSCITATION IN ADULTS

Jan Bělohlávek and Jana Šmalcová

STEM CASE AND KEY QUESTIONS

A 66-year-old male, with no significant medical history, called emergency medical services (EMS) for himself for an overall worsening, precollapse state at 9:54 AM. He communicated normally to the EMS operator and was able to provide his address. On EMS crew arrival, he was still in contact, responding; however, he was obtunded and complaining of faintness and chest discomfort. At 10:14 AM, he suddenly lost consciousness and developed cardiac arrest (CA). Pulseless electrical activity (PEA) was the first recorded rhythm; no pulses were palpable on carotid arteries. Cardiopulmonary resuscitation (CPR) was immediately initiated; he was put on the Lund University Cardiopulmonary Assist System (LUCAS), and the CA center was called in the 22nd minute of CA. He did not responded to CPR; he had 3 mg epinephrine and still in PEA and bilateral mydriasis; his $EtCO_2$ was 19 mm Hg. The cardiac center was asked to admit this patient under ongoing CPR for possible extracorporeal CPR (ECPR).

HOW WOULD YOU RESPOND?

- A. You tell them "YES, come."
- B. You refuse: "Call me after you have stable return of spontaneous circulation (ROSC)."
- C. You recommend: "Two more milligrams of epinephrine, heparin 5000 IU IV, aspirin 250 mg IV, and call again in 10 minutes."

Based on current European Resuscitation Council (ERC) guidelines, all responses are actually correct. However, the patient was accepted and admitted 42 minutes into cardiac center and was unresponsive in deep coma, with a reactive midmydriasis, slow PEA on electrocardiogram (ECG); his near-infrared spectroscopy (NIRS) on admission was 20%, and he had a pH of 6.8 and lactate of 14 mmol/L.

WHAT WOULD YOU DO NEXT?

- A. You continue standard CPR.
- B. You stop CPR.
- C. You start extracorporeal membrane oxygenation (ECMO) cannulation.

Again, all responses are viable options and correct. Nonetheless, a consensual decision was to continue with ECPR. The patient was admitted to the catheterization laboratory (cath lab) and was cannulated on the cath lab table. Femoro-femoral veno-arterial (V-A) ECMO was launched within 7 minutes after admission (e.g., in the 49th minute of CA). Other arterial access was promptly established, and coronary angiography was performed. A borderline proximal left anterior descending coronary artery (LAD) lesion and a right coronary artery (RCA) proximal occlusion was found (Figure 51.1). Primary percutaneous coronary intervention (PCI) was successfully performed, and the RCA was stented with a drug-eluting stent (Figure 51.2).

Following PCI, the patient was hemodynamically stable, with no need for catecholamine support; he reacted to painful stimuli and had reactive pupils. NIRS had increased to 80%, and analgosedation was needed. On bedside echocardiography, he had moderate bilateral ventricular systolic dysfunction. He also had hemoptysis with frequent need for endotracheal suction. He had a left pulmonary contusion on x-ray.

HOW WOULD YOU PROCEED NEXT?

- A: Transfer to the intensive care unit (ICU); provide deep sedation, hypothermia for 24 hours, bronchoscopy

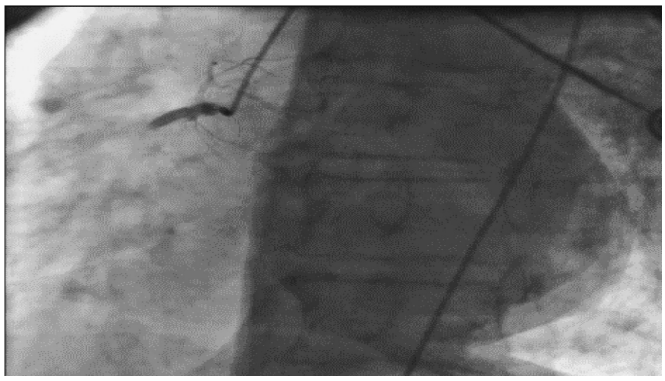


Figure 51.1

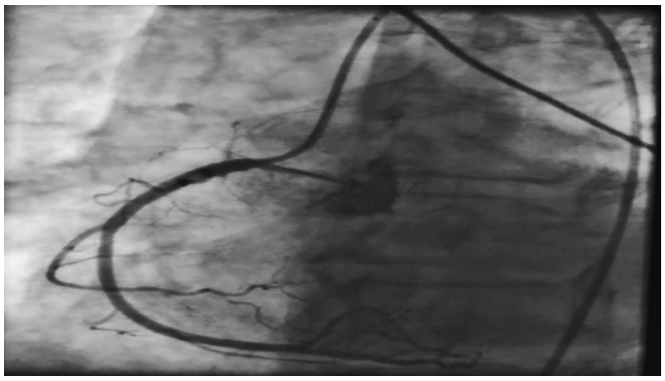


Figure 51.2



Figure 51.4

- B: Utilize normothermia and light sedation; try to wean mechanical ventilation
- C: Transfer to whole-body computed tomography (CT)

We consider again all the above scenarios appropriate, but the patient was kept in normothermia and was only lightly sedated; he was weaned from mechanical ventilation and the same day evening extubated to full consciousness. He continued to have mild hemoptysis, was hemodynamically stable, and ECMO weaning was initiated. However, the next day he suffered hemodynamic collapse and needed high-dose vasopressors and inotropes to maintain spontaneous circulation; full ECMO support was necessary again. Based on new echocardiography, a computed tomographic angiography (CTA) was performed and confirmed a massive bilateral pulmonary embolism (Figure 51.3).

HOW WOULD YOU PROCEED IN THIS SITUATION?

- A. Cardiac surgery consult and surgical embolectomy
- B. Reduced dose thrombolysis
- C. Only heparin, conservative approach

Again, all these scenarios are acceptable and possibly correct. However, the patient was kept heparinized on ECMO with a target activated partial thromboplastin time of 70–80 seconds. The next day, he was hemodynamically stable again with minimal doses of catecholamines, but with bilateral lung infiltrates and pleural effusions on CT (Figure 51.4) and hypoxia on V-A ECMO with Harlequin syndrome.

He was switched to veno-venous (V-V) ECMO via 27 French (27F) Avalon cannula inserted into the right internal jugular vein, and bilateral pleural punctures were performed. He was slightly improving, and on day 13 of his stay, V-V ECMO was discontinued. He was exhausted and malnourished, and finally after 45 days was discharged home fully awake with normal neurological status.

This case demonstrates how ECPR is sometimes misleading and complex. We hypothesize that the primary cause of CA was not the coronary obstruction as deemed initially (possibly caused by coronary artery dissection and occlusion during mechanical chest compressions; details of coronary angiography demonstrating this were not shown), but the pulmonary embolism itself. In this regard, the beginning of CA with initial rhythm of PEA is typical for PE, not for acute coronary syndrome (ACS). The typical drama of the presented ECPR case covered the clinical presentation and combined with the complicated course of the illness itself together with CPR sequelae (pulmonary contusion, hemoptysis, pleural effusions) made it almost impossible to diagnose the initial primary cause of CA.

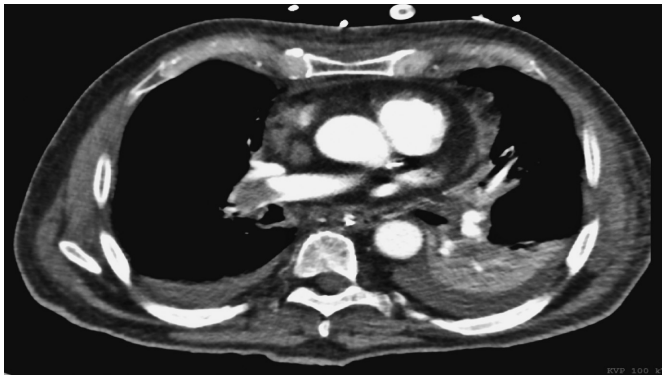


Figure 51.3

HOW IS ECPR DEFINED?

Extracorporeal CPR actually is indicated for the use of extracorporeal life support (ECLS) in patients who remain in CA despite prolonged conventional CPR or when intermittent ROSC occurs but repetitive CA reoccurs. It is essential that ECPR is used in refractory CA, where the chance of obtaining and sustaining ROSC is low. The definition of refractory CA, however, varies from 10 minutes[1] to 30 minutes[2] of CPR without sustained ROSC. Clinically, it is very difficult to define an optimal time span when refractory CA suitable for ECPR should be considered. Consensually, both for in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA), the time of approximately 15 minutes of CPR might seem to be reasonable.[3]

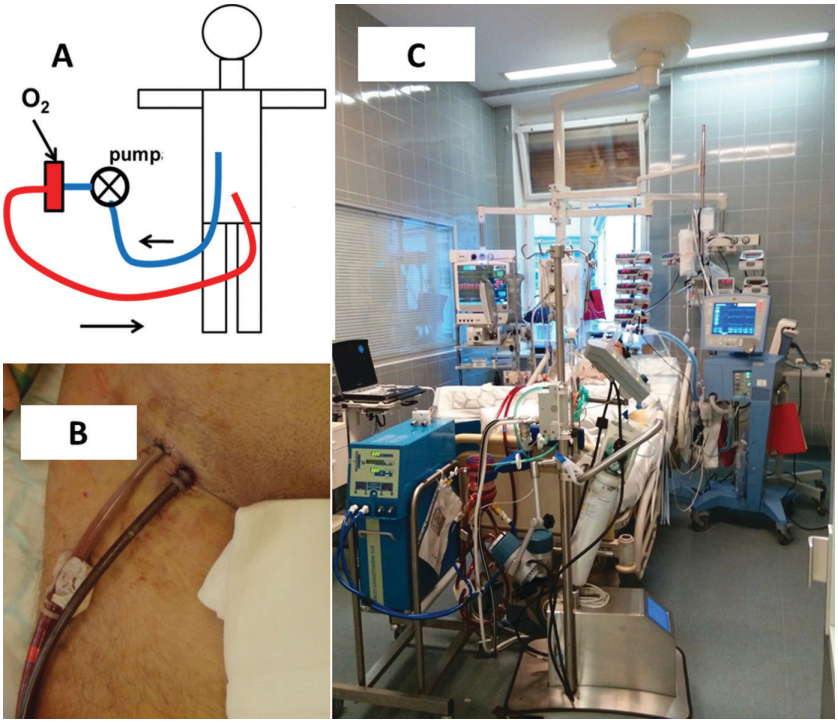


Figure 51.5

Extracorporeal CPR provides mechanical support/replacement for failed circulation or gas exchange, whatever the reason for CA was. The setting is usually the femoro-femoral V-A ECLS/ECMO because of easy percutaneous or surgical implantation (Figure 51.5).

WHAT ARE THE MAIN ORGANIZATIONAL ISSUES RELATED TO ECPR IMPLEMENTATION?

Extracorporeal CPR is usually provided in facilities with established and functioning ECMO teams. The ECMO team consists of devoted professionals from intensive care, cardiology, cardiac surgery, and other specializations collaborating with specialized nurses and perfusionists. ECMO team members are well trained in CPR, but they are usually not the first responders to CA. In-hospital coordination with the CPR team must be established, and, optimally, a protocol for activation of the ECMO team in case of ongoing CPR should be implemented in a 24/7 manner. Specialists in ECPR must be well trained in V-A cannulation and vascular ultrasound, circuit and hemodynamic management, and early postresuscitation care. Training in the use of extracorporeal devices, preferably in close collaboration with perfusionists, is mandatory. An ECLS-trained physician, perfusionist, and possibly the nurse should provide 24-hour coverage for ECLS patients. A trained interventionalist must also be available for distal perfusion cannula placement to prevent limb ischemia.

Routine intensive care must be adjusted to ECMO use, that is, ICU nurses should be trained in basic ECLS and circuit troubleshooting and management. The nurse-to-patient ratio during the postresuscitation phase should be at least 1:1, in selected very unstable patients even 2:1, depending on the local regulations or resource availability (see below). The specialist team, besides ECLS device and circuit management, might also be responsible for managing equipment and supplies, regular service organization, daily rounds, education, patient database administration, and quality control.[4] Neurological, psychiatric, psychological, rehabilitation, and palliative care is of paramount importance in units providing ECPR.

In-hospital logistics must also be established. ECPR for IHCA is usually provided in the emergency department, ICUs, or operating/catheterization rooms. For OHCA, the cath lab and emergency department are typical places where patients with refractory OHCA are brought to undergo ECPR.[5–7] However, out-of-hospital ECPR for OHCA has also been reported, mainly in France and Germany.[8–10] Finally, the ECMO team has to be trained for both in-hospital and interhospital transport of ECLS patients. However, ECPR cases are usually not suitable for remote retrieval.

WHAT IS A TYPICAL ECPR SCENARIO?

Extracorporeal CPR is usually performed in tertiary cardiovascular centers providing advanced intensive care, including a wide range of organ support. Specialties involved include cardiology, emergency departments, general intensive care, and cardiac surgery. Complementary services obligatory for ECPR are biochemistry with emergently available laboratory tests (arterial blood gas, lactate, hemoglobin, glycemia, and mineral tests, and all need to be available also at the bedside or within the place where ECPR is performed); radiology with the ability to perform both noninvasive and invasive techniques, including vascular ultrasound and x-ray diagnostics, vascular embolizations, CT imaging used to adopt

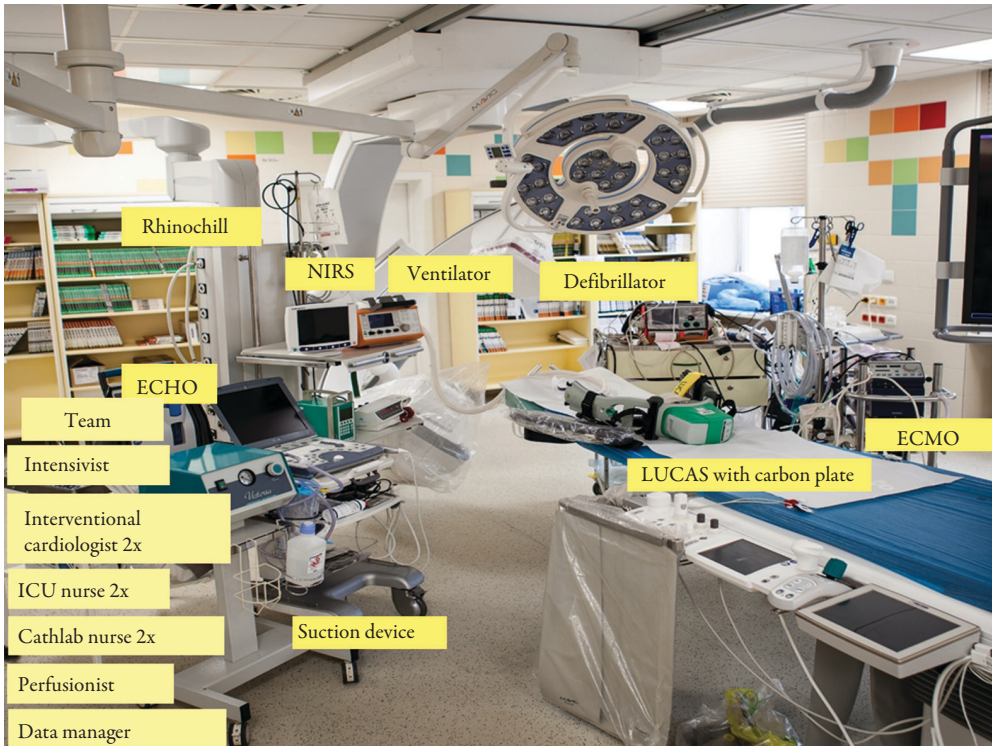


Figure 51.6

adjustments specific for ECMO patients[11,12]; blood bank; and 24/7 coronary angiography and PCI. Gastroenterology, neurology with neurosurgery consults, general surgery, pulmonology, and palliative care are also an integral part of widely approached ECPR service.[4]

Where ECPR is instrumented, readily available equipment should include ECMO cannulation sets, ECMO cannulae (15F to 21F cannulae for arterial access and 19F to 29F cannulae for venous access), catheterization wires, catheterization sheets useful also for distal perfusion, stopcocks, basic surgical instruments required for open access to femoral vessels, and other routine material used for invasive procedures like sterile dressings, drapes, adequate lights, and more. A preassembled ECLS machine, either dry or wet primed (in high-volume centers) should be available 24/7 at the place where ECPR is provided. Regular checks for technical and battery status are mandatory. The team has to be trained to deploy the device for full use within 5–10 minutes from decision to proceeding with ECPR. A picture of a cath lab prepared for admitting a patient under ongoing CPR is demonstrated in Figure 51.6; similar preparation applies for other usual locations where ECPR is being performed (i.e., emergency department, ICU).

WHAT IS THE IMPORTANCE OF INDIVIDUAL ROLES WITHIN THE ECPR TEAM?

Intensivist: ECPR Coordinator

The intensivist plays a key role in coordinating ECPR. This person is usually the leader of CPR, coordinator of ICU nurses, and perfusionist and provides data for a data manager. The intensivist is responsible for and provides initial evaluation on admission (brief physical and echocardiography examinations); brief history retrieval; care for the airways; continuous neurological and hemodynamic assessment; control of the laboratory values, and ventilation adjustment and ECLS blood and sweep gas flow accordingly in conjunction with the perfusionist. This person communicates with the cannulating physician and stops the chest compressions when ECLS is launched.

Cannulating Person (Interventional Cardiologist, Intensivist, or Surgeon)

The cannulating person (interventional cardiologist, intensivist, or surgeon) is responsible for vascular access establishment using blind or ultrasound-guided cannulation. The cannulating person performs angiography to confirm adequate vessel puncture (if performed in the cath lab) and implants the ECMO cannulae into the proper vessel. ECMO wires and cannulae positions are frequently checked and have to be tightly secured in place so they are not dislodged. Adequate positions of the sheets positions in the femoral vein and artery on an s-ray picture are outlined in Figure 51.7.

Perfusionist

The perfusionist deploys the ECLS machine, primes with fluid if not preprimed, and prepares the extracorporeal circuit for connection to cannulae. The perfusionist is ultimately responsible for a well-functioning ECLS system, air and oxygen delivery, and adequate blood flow and detects

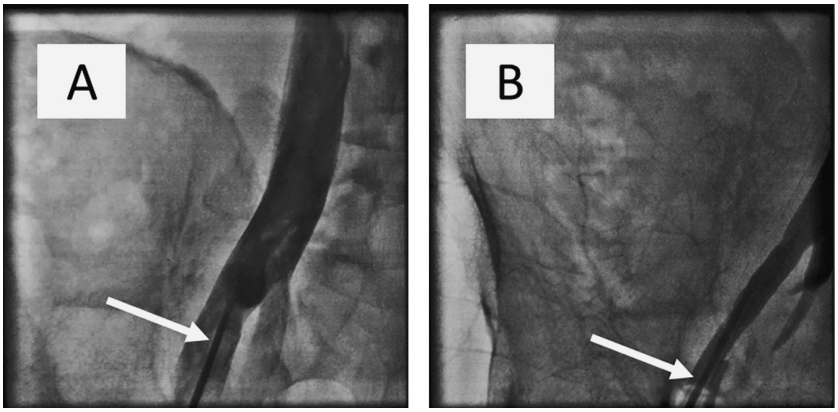


Figure 51.7

possible technical and clinical complications, like hypovolemia (decreased ECLS blood flow and circuit chattering). This person overviews the blood gases, hemoglobin, and coagulation parameters for early bleeding detection. The perfusionist assists the cannulating person with clamping and declamping of the circuit and secures the circuit after establishment. After initial patient stabilization, the perfusionist removes the stopcocks from the circuit to prevent circuit access and inadvertent air embolization or detachment.

ICU Nurses

Intensive care unit nurses generally provide assistance to the intensivist, help to establish invasive blood pressure monitoring, prepare the central line for drug administration, regularly draw blood gases and other specimens, and take care of the airways, including regular suctioning from the secured endotracheal cannula.

Cath Lab Nurses

Cath lab nurses provide assistance to the cannulating person(s); provide adequate wires and sheaths; and assist during subsequent angiography diagnostics and eventually during the PCI.

Data Manager

The data manager is responsible for all data retrieval, mainly during the initial CPR and ECLS attachment. ECPR is a very dynamic situation, and proper data storage is essential. Based on a prespecified protocol, relevant data are being retrieved and provided by the intensivist or other physicians or nurses during ECPR. A sample data form being used during admission is depicted in Table 51.1.

WHAT ARE THE POSSIBLE MAJOR COMPLICATIONS DURING IMPLANTATION AND INITIATION?

Serious complications may occur during initial stages of ECPR implementation. Unsuccessful cannulation itself may occur, usually with fatal consequences for a patient who dies of refractory CA. Surgical exploration of the groin is an alternative, with obstructive atherosclerotic femoral/iliac artery disease precluding even the surgical approach. Alternative approaches should be immediately tried if femoral cannulation is not possible. Usually, arterial cannulation is troublesome, and axillary or even a central approach may be established. However, prolonged low-flow times are associated with poor neurological outcome or death.[13,14] Vessel tear or rupture may become a fatal complication, which must be avoided by a very careful technique during all stages of cannulation.

Complications related to initial CPR may rapidly progress during the ECPR, that is, barotrauma or thoracic or upper abdominal bleeding (liver or spleen injury). Figure 51.8 depicts typical complications diagnosed in ECPR patients.

WHAT ARE LABORATORY AND OTHER IMPORTANT DIAGNOSTICS?

Frequent laboratory examinations are of paramount importance in ECPR. On admission, initial examination excludes severe blood ion imbalances, helps to assess organ functions, and allows thorough monitoring, mainly the lactate, blood gases, and hemoglobin evaluations. Not only at ECLS start, but also further lactate values[15] and other variables (hemoglobin) may correlate with outcome in ECPR. It is usual practice to have blood gases monitored every 15 to 30 minutes after connecting a patient to ECLS as the changes induced by ECLS may be very dynamic.

Morphologically, coronary angiography usually follows institution of ECLS; if the cause is not evident, then pulmonary angiography or aortography may proceed, assuming that other causes like pericardial tamponade/massive pulmonary embolism have already been excluded by echocardiography. Whole-body or at least brain and chest/abdominal CT diagnostics follow. When ECPR is provided in the emergency department, whole-body CT may be the first diagnostic tool, and eventually coronary angiography may follow based on initial ECG pattern.

Table 51.1 ADMISSION PARAMETERS IN ECPR

BRIEF MEDICAL HISTORY DATA

- ☐ CHF (NYHA II, III, IV)
- ☐ CAD ☐ Post MI ☐ Post PCI ☐ Post CABG
- ☐ Valvular disease
- ☐ Post valvular replacement
- ☐ Pacemaker ☐ ICD
- ☐ Arrhythmias in past medical history
- ☐ History of cardiac arrest
- ☐ Arterial hypertension
- ☐ Post stroke/TIA
- ☐ Epilepsy
- ☐ DM ☐ On diet ☐ On insulin
- ☐ Asthma, COPD
- ☐ CKD, chronic dialysis
- ☐ Liver cirrhosis
- ☐ History of malignancy
- ☐ Immunodeficiency ☐ AIDS
- ☐ Alcoholism ☐ Intravenous drug abuse
- ☐ CPC 1 before cardiac arrest
- ☐ Other

PARAMETERS ON ADMISSION

Date:..... Time:.....

☐ Place of admission: Emergency department ☐ YES ☐ NO

Cath lab ☐ YES ☐ NO

Other.....

☐ Physical exam on admission:

☐ Abnormalities ☐ Head ☐ YES ☐ NO Describe.....

☐ Chest ☐ YES ☐ NO Describe.....

☐ Abdomen ☐ YES ☐ NO Describe.....

☐ Extremities ☐ YES ☐ NO Describe.....

☐ "Sun sign" ☐ YES ☐ NO Describe.....

Other?.....

☐ Weight.....kg ☐ Estimate Height.....cm ☐ Estimate

Hearth rhythm:

☐ Asystole ☐ VF ☐ VT ☐ PEA ☐ Sinus

☐ Other.....

☐ ROSC? (defined as palpable pulse on great arteries) ☐ YES ☐ NO

☐ Ongoing massage? ☐ YES LUCAS: ☐ YES ☐ NO

AUTOPULSE ☐ YES ☐ NO

☐ NE

☐ Neurological status:

☐ Glasgow Coma Score .....

☐ Pupils izocoric ☐ Pupils anizocoric Left .....mm Right.....mm

☐ Mydriasis ☐ Reaction to light ☐ YES ☐ NO

☐ corneal reflex ☐ YES ☐ NO

Table 51.1 CONTINUED

☐ **NIRS - hemispheres (rSO_2%)** ☐ **right.....** ☐ **Left.....**

☐ **Body temperature (optional) (°C) .....** **Place measured.....**

☐ **Any signs of spontaneous breathing activity?** ☐ **YES** ☐ **NO**

☐ **Any spontaneous movements?** ☐ **YES** ☐ **NO**

☐ **First available blood pressure and pulse:**

Time:.....mm Hg:..... Pulse...../min

☐ **Peripheral O_2 saturation: .....%** ☐ **not measurable**

☐ **$EtCO_2$.....mm Hg/kPa**

☐ **First 12-lead ECG Time.....**

☐ **Normal** ☐ **STEMI** ☐ **ST depressions** ☐ **LBBB** ☐ **RBBB**

☐ **Other: .....**

☐ **Echocardiography:** ☐ **NO** ☐ **YES time .....**

LV contractions ☐ **YES** ☐ **NO**

LV EF estimate: ☐ **55% and more** ☐ **45-54%** ☐ **35- 44%** ☐ **34% and less**

RV dilatation: ☐ **YES** ☐ **NO**

Pericardial effusion: ☐ **YES** ☐ **NO**

Ascending aorta normal: ☐ **YES** ☐ **NO**

ECLS started: ☐ **YES** **Time.....Blood flow:.....L/min**

☐ **NO**

Cannulae: **Arterial:** **Place.....Diameter:.....F**

Venous: **Place.....Diameter:.....F**

Distal limb perfusion: ☐ **YES** ☐ **NO**

<u>After launching ECLS:</u> **Time:.....**

MAP (mean arterial pressure).....mm Hg

Peripheral O_2 saturation:.....% ☐ **Not measurable**

NIRS hemispheres (rSO2%) ☐ **Right.....** ☐ **Left.....**

Circulatory status: ☐ **Pulsatile flow (defined as pulse pressure 15 mm Hg or more)**

☐ **Nonpulsatile flow**

Medications during initial treatment on emergency department/cath lab:

☐ **Infusions** ☐ **YES mL:.....** ☐ **NO**

☐ **Epinephrine.....mg** ☐ **Norepinephrine.....mg** ☐ **Atropine....mg** ☐ **Amiodarone.....mg**

☐ **Magnesium .....mg** ☐ **Calcium ..... mL** ☐ **Bicarbonate .....mL**

☐ **Sedation.....**

☐ **Relaxation**

☐ **Other.....**

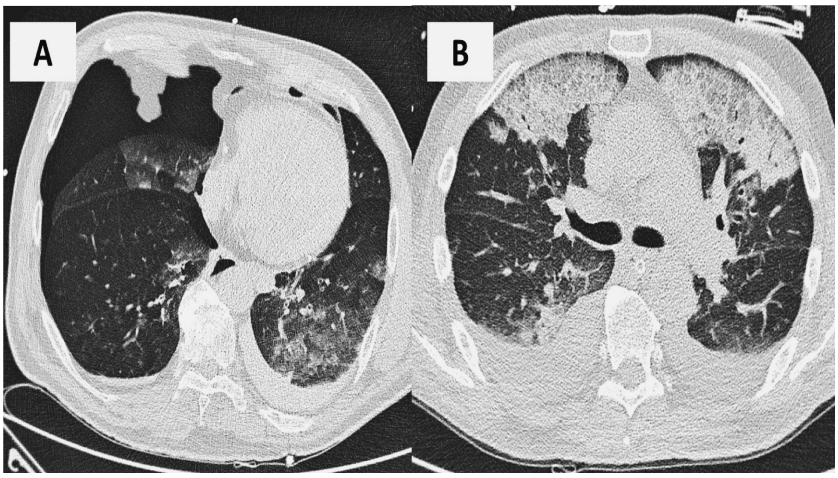


Figure 51.8

WHAT TYPE OF POSTRESUSCITATION CARE AND MONITORING IS NEEDED?

Veno-arterial ECMO requires a different approach in monitoring compared to usual ICU monitoring. Blood pressure must always be monitored invasively, as cardiac function frequently may become non- or low pulsatile. Pulsatility is defined as a pulse pressure over 15 mm Hg.[16] The right radial artery is preferred for blood pressure monitoring and blood gas examination. It reflects the blood flow in the aortic arch, and specimens drawn from the right radial artery represent blood entering the right carotid artery and thus the brain. When interpreting monitored data, one must consider the presence of a combination of spontaneous and extracorporeal circuits and influence by the ratio of these two circuits. In this regard, also cerebral and peripheral tissue NIRS may help in not monitoring only the brain and peripheral perfusion but also providing an insight into hemodynamic status.[17,18]

The presence of pulsatility has to be cautiously monitored as development of a low- or nonpulsatile flow in severely impaired left ventricular function may potentially cause pulmonary edema or left ventricular thrombosis. These severe complications of V-A ECMO may need left ventricular venting by means of a percutaneous approach (intra-aortic balloon counterpulsation or left ventricular unloading by, e.g., an Impella device) or even a surgical vent.[19] Target temperature management is generally easy on ECLS; central temperature must be monitored, usually by means of a bladder probe. Ventilatory parameters are adjusted based on the presence or absence of pulmonary edema or acute respiratory distress syndrome. In patients on V-A ECMO with pulmonary failure, it must be ensured that the blood flowing across the aortic valve is well oxygenated to provide enough oxygenation for coronary arteries and avoid coronary ischemia.

WHY IS ICU NURSING CARE IMPORTANT?

Nursing care for ECPR patients is extremely demanding. Continuous bedside presence of the nurse is crucial. Nurses have to be well trained in critical scenarios like sudden blood pressure drop, cannula site bleeding, circuit twitching, oxygenator or pump failure, to name a few (see Table 51.2). During admission of an ECPR patient to the ICU, the presence of usually two or three nurses, an intensivist, and a perfusionist is needed. The patient is very carefully moved to an ICU bed, with special care of indwelling cannulae. At our institution, an antidecubital mattress is always used. Patients are frequently very unstable and may not tolerate any movements or turnovers. Patients are continuously monitored with ECG, invasive blood pressure from the right radial artery, oxygen saturation, $EtCO_2$, and NIRS from both hemispheres and lower extremities. Neurological status, including pupillary diameter, is being checked very frequently and recorded hourly. Fluid balance is of paramount importance to keep enough volume for effective ECMO flow and to avoid inadvertent volume overload. A urinary catheter is used for core temperature measurement within the target temperature management. All indwelling catheters are aseptically covered and secured tightly to avoid dislodgement during the movement with the patient.

Bedside blood gas, glucose, mineral, lactate, and hemoglobin determination is of great benefit and should be immediately available. The nurse performs laboratory examination at predetermined intervals or with a sudden change in the patient's status.

The care for an ECPR patient also bears many administrative consequences that are demanding for nursing time. Therefore, it is desirable to complete nursing documentation at the bedside to have continuous supervision on a patient's status and to be able to react immediately to any hemodynamic or other changes.

The best model we use is to have a primary nurse taking care of a patient and one or two other assisting with blood samples, dilution of medication, and request forms preparation like for lab test etc.

HOW IS WEANING FROM ECLS PERFORMED AFTER ECPR?

During weaning from ECLS, extracorporeal blood flow is being decreased and spontaneous heart function is closely monitored. Several echocardiographic evaluations per day are usually performed to assess cardiac output and cardiac filling.

Table 51.2 VITAL SIGNS DURING FIRST 2 HOURS AFTER ADMISSION

DATE / PARAMETER	TIME OF ADMISSION	+ 15 MIN	+30 MIN	+45 MIN	+1 H	+1 H 15 MIN	+1 H 30 MIN	+1 H 45 MIN	+2 H
NIRS R (%)									
NIRS L (%)									
Pupillary diameter, R/L (mm)									
Temperature (°C)									
Invasive blood pressure (s/d/m)									
Pulse									
O_2 saturation									
$EtCO_2$									
Blood gases including hemoglobin to draw									
ECLS flow (L/min)									
Norepinephrine dose (μg/kg/min)									
Dobutamine dose (μg/kg/min)									

Abbreviations: CAD, coronary artery disease; CHF, chronic heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CPC, cerebral performance category; DM, diabetes mellitus; ECG, electrocardiography; ECLS, extracorporeal life support; EF, ejection fraction; $EtCO_2$, end-tidal CO_2; F, French; ICD, implantable cardioverter defibrillator; L, left; LBBB, left bundle branch block; LV, left ventricle; MAP, mean arterial pressure; MI, myocardial infarction; NIRS, near-infrared spectroscopy; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; R, right; RBBB, right bundle branch block; RV, right ventricle; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic attack; VF, ventricular fibrillation; VT, ventricular tachycardia.

Similarly, close neurological monitoring and prognostication must be executed. Daily clinical examination, neuron-specific enolase determination, and electroencephalography belong to routine multimodality assessment.[20] Patients after prolonged CPR may suffer both irreversible cardiac and neurological damage. In patients with favorable neurological outcome, sustained severe cardiac dysfunction may lead to long-term mechanical circulatory support or heart transplantation. In severe neurological damage, early brain death diagnostics followed by organ donorship may be considered. Based both on Extracorporeal Life Support Organization (ELSO) Registry data and our experience, ECMO support duration in ECPR usually lasts 60–70 hours.[21]

WHAT ARE ETHICAL ISSUES IN ECPR?

Extracorporeal CPR is currently considered to be an important advance in the treatment of refractory CA. It seems to

be ethically appropriate to use ECPR when there is a realistic likelihood of clinical benefit, clinicians have adequate training and expertise, and institutions will provide subsequent care.[22]

However, inevitably, ECPR may be associated with potential harm. Treating patients with prolonged CA aiming at improved survival with a good neurologic outcome may cause increased rates of coma or vegetative state.[23] An undesirable "bridge to nowhere" has also been described following ECPR: It applies to a scenario when the patient awakes but is not weanable from ECLS, is not a transplant candidate or a destination therapy candidate, and is not able to leave the ICU/hospital.[24] Prolonging the time to death in patients with unfavorable outcome causes harm to both patients and their relatives. Consequently, the eventuality of "turning off" the device may be a rather stressful decision for both the team and the family members. Therefore, regular benchmarking, outcome data analysis, and feedback to the team should be provided to ensure high-quality care is being provided with an expected favorable outcome comparable to available registry data.[25–27]

DISCUSSION

Cardiac arrest bears a poor prognosis. However, in subgroups of patients with shockable rhythms, witnessed collapse, high-quality CPR, and postcardiopulmonary resuscitation care with advanced intensive care including target temperature management; early coronary reperfusion; treatment of electrolyte disorders, seizures, and pneumonia, a neurologically favorable outcome in 25%–30% of CA victims can be achieved.[28,29] Importantly, other interventions (i.e., reduction in no-flow time by early bystander CPR, dispatch center–directed telephone assistance to bystander CPR, early defibrillations using automated external defibrillators, adequate compression depth and rate of CPR, compression-to-ventilation ratios, adequate oxygenation, catecholamines for cardiac output modulation, thrombolysis, and early PCI) have been adopted into routine care and tested with a goal to improve CA outcome.[30] Mechanical chest compression devices have also been tested in large studies; however, they were not more efficient in achieving better overall outcome compared to high-quality manual chest massage.[31,32] The main aim of resuscitation is always the earliest possible ROSC. Prolonged CA, CA without ROSC, and CA needing multiple defibrillations are associated with dismal prognosis.[33,34] In patients without ROSC, the chance of survival when transport to the hospital occurs during CPR is low, that is, far less than 4%.[35,36]

Substituting failed spontaneous circulation by an extracorporeal device seems to be an attractive approach in refractory CA. This concept, using an extracorporeal pump for artificial circulation, is not new[37,38] and has initially been implemented in moribund patients, still with reasonable survival. Fifty-four studies with 675 patients in CA treated by percutaneous cardiopulmonary bypass between 1966 and 2005 were analyzed and found a survival to discharge of 42% (interquartile range 15.4%, 75%); however, these analyses might have been biased by underreporting poor outcomes.[39] Despite various critiques, initial reports and advances in technology, availability of miniaturized simple ECLS/ECMO devices useful for transporting patients, compatible extracorporeal circuits, novel percutaneous cannulae suitable for rapid implantation, and pertinent efforts to improve outcomes in CA allowed to use extracorporeal mechanical support technique during CPR (i.e., to develop the concept of ECPR).

Ultimately, ECPR was embedded into European Resuscitation Council Guidelines 2015 as a rescue therapy for those patients in whom initial advanced life support measures are unsuccessful or to facilitate specific interventions (e.g., coronary angiography and PCI or pulmonary thrombectomy for massive pulmonary embolism).[40] The American Heart Association guidelines were more cautious regarding the recommendation of ECPR because of the ongoing paucity of available data.[41] A meta-analysis compared ECPR to conventional CPR and proved a favorable effect on 3- to 6-month survival and good neurological outcome in ECPR subjects. However, the effect of ECPR on survival to discharge in OHCA has not been clearly shown, indicating a need for strict indication criteria for implementation of ECPR in such a setting.[42,43] Several other publications reported reasonably good results when an established ECPR program is in place.

A large registry report described trends in survival and patient demographics for ECPR patients in the international ELSO database over the past 12 years, and identified factors associated with changes in survival.[25] In this comprehensive report, 1796 patients who received ECPR between January 2003 and December 2014 were divided into three 4-year cohorts (cohort 1, 2003–2006; cohort 2, 2007–2010; cohort 3, 2011–2014) and compared. Annual ECPR episodes increased more than 10-fold, from 35 to over 400 per year, with respective survival to hospital discharge of 29% overall (27% cohort 1, 28% cohort 2, 30% cohort 3; $P = .71$). Age, body weight, and documented comorbidities increased over time; reduction in complications associated with ECMO usage was noted. Importantly, despite changing the patient profile, survival remained the same over the time period examined. In two reports on refractory ventricular fibrillation (VF)/ventricular tachycardia (VT) OHCA transported to the cardiac catheterization laboratory and treated by ECMO and PCI if appropriate, a Minnesota group showed a high prevalence of coronary artery disease (84%), including acute thrombotic lesions (64%) and a high incidence of multisystem organ failure, but high functionally intact survival (48%).[44,45]

Recent meta-analyses evaluated the contribution of ECPR mainly in terms of neurological outcome: An analysis of 13 studies encompassing 3098 patients showed ECLS was associated with a significantly improved 30-day survival of 13% compared to patients without ECLS, number needed to treat (NNT) 7.7, and also a higher rate of favorable neurological outcome at 30 days, absolute risk difference 14%, NNT 7.1. Propensity matching (five studies, 438 patients) showed similar results.[46] Similarly, the other one meta-analysis evaluating 17 studies demonstrated improved survival (odds ratio [OR] 0.40 [0.27–0.60]) and a better neurological outcome (OR 0.10 [0.04–0.27]) over conventional CPR. Characteristics associated with improved survival in ECPR included an initial shockable rhythm and shorter low-flow time.[47]

Importantly, a recent large retrospective study in five European centers evaluated ECPR in a total of 423 patients: ECPR was initiated for OHCA in 258 (61%) patients. Time from arrest to ECMO implementation was 65 minutes. Eighty patients (19%) had favorable neurological outcome, and ICU survival was 24%. The favorable neurological outcome rate was lower (9% vs. 34%, $P < .01$) in OHCA versus IHCA and was significantly associated with a shorter time from collapse to ECMO. The application of stringent ECPR criteria ($n = 105$) resulted in 38% of patients with favorable neurologic outcome demonstrating a potential for excellent outcome with appropriately used ECPR.[48]

CONCLUSION

- Extracorporeal CPR for both in-hospital and out-of-hospital refractory CA may offer a chance for survival for patients who would otherwise die.
- Extracorporeal CPR is extremely demanding logistically and financially and brings an additional burden for the ICU staff, mainly the nurses.
- Careful selection of patients, adequate prognostication, and avoidance of unnecessary prolongation of futile care are of major importance.

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REVIEW QUESTIONS

1. ECPR stands for

   A. Extraordinary cardiopulmonary resuscitation
   B. Extracorporeal cardiopulmonary resuscitation
   C. Early cardiopulmonary resuscitation

2. A 48-year-old male suddenly collapses while waiting for the bus. Bystanders start CPR, the dispatch center is activated, and an EMS crew is on site after 7 minutes. The First recorded rhythm is VF, three defibrillations delivered, but VF is ongoing. CPR is continued for the next cycle, but the patient is still in VF; the cardiac center is asked for ECPR.

   A. The patient is a good ECPR candidate.
   B. Another two or three cycles of CPR should be performed before considering ECPR.
   C. Thrombolysis should be considered.

3. Refractory CA is defined as

   A. Cardiac arrest with asystole as a presenting rhythm
   B. Cardiac arrest resistant to usual CPR efforts with ongoing VT
   C. Cardiac arrest resistant to conventional CPR

4. A 55-year-old woman is found lying in a restaurant restroom; EMS is called. On arrival, the patient is in asystole on ECG and has wide mydriasis. CPR is started; after 15 minutes of ongoing CPR and 3 mg of epinephrine administered, ECPR is requested.

   A. Unwitnessed asystole is a poor prognostic marker, but ECPR should be considered.
   B. Unwitnessed asystole is a poor prognostic marker, and ECPR should not be considered.
   C. Unwitnessed asystole is a poor prognostic marker; only conventional CPR can improve the outcome.

5. Intermittent ROSC in a patient with witnessed collapse and VF is an optimal indication for ECPR:

   A. False
   B. True
   C. Only if at least 5 mg of epinephrine have been administered

6. Cardiac arrest/CPR time of at least 15 minutes without ROSC is consensually considered to be a threshold for eventual ECPR implementation:

A. Applies only for OHCA
B. Applies only for IHCA
C. Applies for both OHCA and IHCA

7. ECPR should be performed in every hospital.

A. No; small hospitals are suitable due to understaffing.
B. No; small hospitals with an established V-V ECMO program are suitable.
C. No; only high-volume ECMO centers should also perform ECPR.

8. ECPR cannulation should be provided in the

A. ICU or operating room
B. Catheterization laboratory or emergency department
C. All above locations are suitable

9. The patient had undergone ECPR for PEA, is stable, and has normal coronary angiography.

A. Whole-body CT, including pulmonary angiography, should be performed.
B. Further post-CPR care should be provided in the ICU.
C. ECPR for PEA should not be performed.

10. Low-flow time is considered a strong predictive factor for ECPR efficiency.

A. Yes, but assuming no-flow time is negligible.
B. Yes, but low-flow time over 60 minutes is associated with poor outcome.
C. Yes, both the above statements are true.

ANSWERS

1.B, 2.A, 3.C, 4.B, 5.B, 6.C, 7.C, 8.C, 9.A, 10.C

52.

BRIDGING FROM ECMO TO DURABLE LEFT VENTRICULAR ASSIST DEVICE

A. Reshad Garan, Koji Takeda, and Daniel Brodie

STEM CASE AND KEY QUESTIONS

A 45-year-old man was admitted to the hospital with new-onset shortness of breath and was found to have pulmonary edema on chest radiograph. An electrocardiogram revealed sinus tachycardia without evidence of ischemia. A transthoracic echocardiogram revealed enlarged left ventricle (LV) and right ventricle (RV) with normal wall thickness and evidence of severe LV global hypokinesis. Coronary angiography demonstrated normal coronary arteries, and workup for etiology was largely unrevealing. Pulmonary artery (PA) catheterization was notable for pulmonary venous hypertension with low cardiac output. He was aggressively diuresed, but due to hypotension he was intolerant of β-blockers or vasodilator therapy. In the setting of worsening renal function, milrinone infusion was initiated with good effect, and he was discharged with close follow-up with a cardiologist.

Over the course of 2 months, he became progressively limited in his exercise tolerance and presented to the hospital in the setting of respiratory distress. Repeat PA catheterization revealed markedly elevated filling pressures and persistently low cardiac output despite milrinone therapy. An intra-aortic balloon pump (IABP) was inserted, with initial improvement in his cardiac output and mild reduction of the intra-cardiac filling pressures. Despite this, he had worsening hypotension, elevated arterial lactate, and diminishing urine output with acute kidney injury.

Extracorporeal life support (ECLS) was initiated in a veno-arterial (V-A) configuration via the femoral vein and artery, improving his mean arterial pressure and urine output. However, after 12 hours of combination VA-ECLS and IABP support, he had worsening respiratory distress and was endotracheally intubated. The following day, a second inflow cannula (blood drained back to the circuit) was inserted via thoracotomy into the LV apex, and the outflow cannula was moved from the femoral artery to the right axillary artery, where it was inserted via a graft, and the IABP was removed. After several days of diuresis and weaning of the ventilatory support, the femoral venous cannula was removed. The patient began to ambulate and was treated with antibiotics for pneumonia.

After 1 week of antibiotic treatment, optimization of his intracardiac filling pressures, and recovery from acute kidney injury, he underwent implantation of a durable LV assist device (LVAD) and short-term RV assist device (RVAD) in a configuration of right femoral vein to PA via a graft to the PA and removal of the LV apical and axillary ECLS cannula. The following day, the patient required reexploration of the chest in the setting of significant chest tube bleeding associated with hypotension, requiring vasopressors and resulting in recurrence of acute kidney injury. Over the next week, vasopressors were weaned off, and the kidney injury resolved. One week after that, the RVAD was removed. The patient was discharged from the intensive care unit, and, after 2 weeks of further recovery on the surgical ward, he was discharged to physical rehabilitation, having spent a total of 62 days in the hospital.

HOW COMMON IS BRIDGING FROM ECLS TO DURABLE LVAD?

Currently, over 26 million people worldwide have congestive heart failure, and this disease is estimated be one of the costliest conditions in developed nations.[1,2] Roughly half of heart failure patients have preserved LV ejection fraction, while the other half have systolic heart failure with reduced ejection fraction. Cardiac transplantation remains the gold standard for end-stage systolic heart failure, but LVADs have emerged as another viable option for patients with stage D refractory heart failure.[3]

Durable LVADs are fully implantable blood pumps that support the failing LV. Due to the shortage of donor organs, LVADs emerged as a means to support the patient with advanced heart failure while awaiting a transplant. However, LVADs have also demonstrated benefits to survival and quality of life for patients who are not transplant eligible; this use is known as the destination therapy indication for device implantation.[4] As a result, the number of durable LVAD implants has risen dramatically over the past decade, and this therapy will likely continue to grow as device technology improves further.[5]

While the best outcomes with LVAD implantation are typically achieved with ambulatory patients with class IV heart failure, a subset of patients are considered for this therapy after an acute presentation in cardiogenic shock (CS). Temporary mechanical circulatory support devices, including

Table 52.1 INTERMACS PROFILES AND PATIENT EXAMPLES

PROFILE	DESCRIPTION	PATIENT EXAMPLE
1	Critical cardiogenic shock	Required VA-ECMO and inotrope/vasopressor
2	Progressive decline on inotropic support	Stabilized by IABP with low dose inotrope
3	Stable but inotrope dependent	Ambulatory on chronic inotropic therapy
4	Resting symptoms home on oral therapy	Low dose neuro-hormonal blockade with resting dyspnea
5	Exertion intolerant	Dyspnea with any level of exertion
6	Exertion limited	Dyspnea with more than minimal exertion
7	Advanced NVHA Class III symptoms	Dyspnea with more than mild exertion

Patients supported by VA-ECMO would typically be classified as INTERMACS profiles 1 with the poorest overall outcomes among the INTERMACS profiles.

ECLS, have been used to stabilize patients in CS. For those who do not exhibit the potential for ventricular recovery, via either revascularization or medical therapy, LVAD implantation is often considered.

More than 25,000 durable LVADs have been implanted in the United States alone, and the majority have been continuous flow devices.[5] The mean duration of LVAD support is currently 20 months, and 1- and 5-year survival has been reported to be 83% and 46%, respectively.[5] Of these, 14% have been implanted in patients in Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile 1 (i.e., critical CS; Table 52.1), and this proportion has been consistent across the past decade. However, it is notable that an increasing proportion of LVAD recipients have had preoperative temporary mechanical circulatory support (from 25% to 31% most recently), yet only a minority of these patients have had preoperative ECLS, although this proportion is also increasing (from 1.9% to 2.5% most recently).[5] There is significant variability in practice, with some centers implanting more than 10% of their durable LVADs in patients supported by ECLS.[6]

WHO ARE THE PATIENTS THAT ARE BRIDGED?

The most common cardiac disease states requiring support with ECLS prior to durable LVAD implantation are acute myocardial infarction (AMI), acute decompensation of chronic heart failure (ADHF), and fulminant myocarditis (FM).[7] While AMI and FM patient populations represent acute and unpredictable pathologies, patients with chronic heart failure have considerably improved outcomes when they do not deteriorate into CS prior to LVAD implantation and require ECLS for stabilization. However, the patient with advanced chronic heart failure may deteriorate acutely in the setting of arrhythmia or infection, among other complications. In all scenarios, ECLS is typically reserved for the most profoundly compromised patient in an effort to stabilize their condition. Early implementation of ECLS in the setting of CS offers the best opportunity to reverse end-organ dysfunction, which can reduce the risk of LVAD implantation.[8]

Of these patient subtypes, AMI and FM are more likely to recover from significant hemodynamic compromise, and many will not require durable LVAD to survive.[9–11] However, those with ADHF are less likely to recover except in the setting of an easily reversible cause (e.g., rapid atrial fibrillation), and survival typically requires LVAD implantation.[12,13] As a result, patients bridged from ECLS to durable LVAD are most commonly those with ADHF.[7] Regardless of the etiology of CS, many centers will typically attempt to assess the patient's ability to wean from temporary circulatory support devices. Center-specific methodology for formal assessment of the ability to wean from support have been reported and rely on echocardiographic[14] and hemodynamic[10,13] evaluation during deliberate reduction in the degree of circulatory support provided by ECLS.

When the patient supported by ECLS is determined to be dependent on mechanical circulatory support, formal assessment of their candidacy for durable LVAD implantation is typically performed. Those centers that do not have the capability to implant durable LVADs often partner with those that do, so that an ECLS-dependent patient may be transferred to a center for LVAD implantation when appropriate.[15]

HOW DO OUTCOMES WITH ECLS BRIDGING COMPARE TO OTHER DURABLE LVAD RECIPIENTS?

Typically, the best outcomes are achieved with LVAD implantation when performed on ambulatory patients with advanced heart failure. However, a substantial proportion of patients are considered for this surgery when they are in CS. For patients with advanced chronic heart failure, there remains a risk of decompensation into CS prior to LVAD implantation, which often results in end-organ failures, substantially increasing the risk of device implantation.[8] To avoid irrecoverable end-organ failures, some have advocated for early ECLS initiation in the setting of CS to stabilize ADHF patients in an effort to bridge them to durable LVAD.[16] The short-term mortality of ADHF patients requiring ECLS for stabilization is approximately 50%, with the vast majority requiring durable

LVAD or cardiac transplant to survive.[12,13,17] For those with acute pathologies such as AMI who require stabilization with ECLS, the overall outcomes are similar to ADHF patients,[18–20] though most survivors will experience ventricular recovery and not require durable LVAD or transplant.[10]

Not surprisingly, patients in INTERMACS profile 1 have the highest mortality among LVAD recipients.[21] As the use of short-term circulatory support devices increases,[22] an increasing number are being supported by such devices prior to durable LVAD implantation.[5,23] This class of devices includes the IABP, percutaneous LVADs (e.g., the TandemHeart, LivaNova, Pittsburgh, PA; and Impella, Abiomed, Danvers, MA), short-term surgically implanted ventricular assist devices (e.g., CentriMag, Chicago, IL biventricular assist device), and ECLS. Patients with short-term devices have not been found to experience worse outcomes than those in similar INTERMACS profiles without devices, with the exception of ECLS-supported patients, who represent the highest risk cohort and not surprisingly have the worst overall outcomes.[24] Long-term outcomes of patients bridged from ECLS to durable LVAD have been variable, with 1-year survival ranging from 43% to 70% in selected series, notably worse than the remainder of LVAD recipients.[5,6,13,25]

WHAT IS THE APPROPRIATE PERIOD OF TIME FOR ECLS SUPPORT PRIOR TO DURABLE LVAD IMPLANTATION?

In general, the amount of time supported by ECLS should be minimized prior to durable LVAD implantation to reduce the risks associated with this surgery. However, most patients supported by ECLS have some degree of end-organ dysfunction prior to initiation of this therapy, and recovery of end-organ function is critical in reducing the risk of durable LVAD implantation. For example, renal and liver function typically improve to some degree with ECLS support in these patients,[8] and ECLS is often used to assess the ability of end organs to recover prior to LVAD implantation.[16] Hence, the optimal timing of LVAD implantation for the ECLS-dependent patients typically balances end-organ recovery against the potential hazards associated with prolonged ECLS support, including bleeding, infection, and complications associated with immobility or sedation. In one study of ECLS patients bridged to durable LVAD, the survival following LVAD implantation was markedly improved for patients who had been transitioned from ECLS to LVAD in 14 days or less.[8]

HOW CAN THE RIGHT VENTRICULAR FUNCTION BE ASSESSED WHILE RECEIVING ECLS SUPPORT?

One potential hazard of implanting durable LVADs in patients supported by ECLS is the risk of RV failure following the transition. While ECLS does not directly support the RV, it shunts blood away from the right heart, thereby decompressing it and potentially masking the degree of RV dysfunction, if present. If the patient has not been evaluated for durable LVAD implantation with careful assessment of the RV prior to initiation of ECLS support or if RV function has deteriorated, it may be difficult to evaluate this once ECLS is initiated because of the inability to wean hemodynamic support for one ventricle in isolation with ECLS. Similarly, transthoracic echocardiographic assessment of the RV may be somewhat misleading in the presence of ECLS when a considerable portion of RV preload is diverted away from the ventricle. Indeed, higher rates of RV failure are observed in patients bridged to durable LVAD from ECLS.[6] Whether this is due to the severity of the patients' overall condition or the inability to carefully assess the RV remains unknown.[25]

ARE THERE TECHNICAL DIFFERENCES FOR LVAD IMPLANTATION IN THE ECLS-SUPPORTED PATIENT?

While the technical aspects of durable LVAD implantation are not altered by the preoperative presence of ECLS, the perioperative management may differ. For example, some authors have advocated for implantation of the durable device using ECLS support in lieu of cardiopulmonary bypass for this patient population. This approach has been associated with similar survival but overall fewer postoperative bleeding complications.[26] Others have observed a trend toward a lower rate of RVAD use when this strategy is employed.[27] Maintaining ECLS support throughout the perioperative period provides support for the RV but may raise the risk of LVAD thrombosis as blood flow through this device is reduced by the presence of ECLS.

IS LEFT VENTRICULAR VENTING NECESSARY PRIOR TO DURABLE LVAD IMPLANTATION?

It is well described that peripherally inserted ECLS increases afterload, which may result in pressure overload of the failing LV.[28] Sequelae may include intracardiac or aortic root thrombus formation and pulmonary edema, both of which raise morbidity and mortality associated with this support.[29] ECLS also increases cardiac work, potentially impeding recovery of ventricular myocardium, which is a significant concern in recoverable phenotypes of CS like AMI.[28] This consideration is less of a priority in disease states with a low likelihood of ventricular recovery, like ADHF patients, where the primary focus is instead minimizing complications while bridging to durable LVAD.

Many centers employ a venting strategy with aortic counterpulsation. In a large series of patients with chronic heart failure and CS supported by ECLS, two-thirds had a concomitant IABP to avoid pressure overload. This device provides a benefit for ECLS-supported patients in reducing the risk of overt pressure overload manifested, for example, by the development of pulmonary edema.[30,31] Other centers have used a microaxial percutaneous LVAD (e.g., Impella) with ECLS to reduce the risk of pressure overload of the LV. Use of this device was associated with improved survival and higher rates of successful bridge to the next support device or ventricular recovery in a propensity-matched cohort compared to ECLS-supported patients without this device.[9] A recent meta-analysis

also demonstrated that concomitant use of either of these devices with ECLS was associated with improved survival.[32]

DISCUSSION

Substantial variability exists in the practice of bridging the CS patient to durable LVAD. Many centers employ a strategy of multiple bridging stages prior to durable LVAD; this typically involves a move to an invasive short-term surgical ventricular assist device (e.g., CentriMag biventricular assist device support) or a hybrid configuration as an intermediate step between ECLS and durable LVAD.[33,34] Such patients may have better long-term outcomes, although there is considerable possibility for this observation to be related to selection bias.[13] As an alternative to the multiple-stage bridging strategy, others have advocated for avoidance of ECLS altogether in the shock population. For example, in a highly selected patient population of patients with CS following AMI, direct implantation of a durable LVAD has been performed with good results.[35,36] Other centers may choose to bridge CS patients stabilized with ECLS directly to transplant as this population often is considered the highest priority for transplant.[37]

One potential benefit to the strategy of an intermediate stage between ECLS and durable LVAD is the facilitation of patient mobilization when cannulae are moved from the femoral vessels to a central position, although femoral cannulation does not itself preclude mobilization, including ambulation.[38] Indeed, patient mobility is a key factor in optimizing patient outcomes with ECLS and is critical in improving outcomes with durable LVAD implantation.[38] Another potential benefit is the ability to support patients for longer periods of time with these configurations in order to allow more time for recovery from end-organ failures related to the shock state.

Another important consideration for the patient who is anticipated to require a longer period of ECLS support prior to transition to durable LVAD is invasive mechanical ventilation. ECLS itself should not be viewed as a barrier to endotracheal extubation; in the appropriately selected patient, avoidance of invasive mechanical ventilation may decrease the risks of pneumonia and complications associated with prolonged sedation. Additionally, patients free of sedation and invasive mechanical ventilation are likely to be able to participate more meaningfully in conversations about medical decision-making, which is preferred over requiring the patient's healthcare proxy or surrogate to make critical decisions for the patient. Indeed, some centers have employed a strategy in selected ECLS patients of maintaining them awake and free of invasive mechanical ventilation to avoid the complications noted above. Such patients have experienced superior outcomes when bridging to durable LVAD, though there is clear selection bias at play here.[39]

Given the acuity of illness of many ECLS-supported patients, it is not surprising that many of these patients will not be candidates for durable LVAD implantation. This is particularly true if end-organ failures cannot be recovered with ECLS support. Given the high likelihood of dependence on mechanical circulatory support for some patients being considered for ECLS,[12,13] the candidacy for durable LVAD is often considered in the decisions to initiate ECLS. Ideally, for someone deemed unlikely to experience ventricular recovery and wean from mechanical circulatory support, ECLS should not be initiated if there are strict contraindications to durable LVAD implantation (e.g., anoxic brain injury) in order to avoid the so-called "bridge-to-nowhere" situation.[40] However, there are other options for bridging the ECLS-dependent patient when certain contraindications for durable LVAD therapy exist. For example, a patient with severe RV dysfunction may not be a candidate for durable LVAD implantation but may be considered for cardiac transplantation or total artificial heart implantation, although fewer centers are capable of implanting the latter therapy.

CONCLUSION

- Extracorporeal life support may be used to stabilize patients with CS from a variety of cardiovascular pathologies.
- Those patients who are unable to wean from ECLS should be considered for durable LVAD implantation.
- Bridging from ECLS to LVAD involves higher levels of risk than implantation of this device in other patient populations.
- In particular, minimizing time on ECLS support prior to durable LVAD implantation and configurations that allow for patient mobilization may help to reduce these risks.

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REVIEW QUESTIONS

1. Compared to patients requiring VA-ECMO after AMI with CS, patients with chronic heart failure who present with CS and require ECLS for stabilization are more likely to have ventricular recovery sufficient to allow weaning from circulatory support altogether.

   A. True
   B. False

2. Which of the following statements is true?

   A. Compared to patients with CS supported by other forms of short-term circulatory support devices prior to durable LVAD implantation, patients supported by ECLS prior to durable LVAD implantation have higher mortality.
   B. Compared to patients with CS supported by other forms of short-term circulatory support devices prior

to durable LVAD implantation, patients supported by ECLS prior to durable LVAD implantation have lower mortality.

C. Compared to patients with CS supported by other forms of short-term circulatory support devices prior to durable LVAD implantation, patients supported by ECLS prior to durable LVAD implantation have similar mortality.

D. Compared to patients with CS in INTERMACS profile 1 who are not supported by short-term circulatory support devices prior to durable LVAD implantation, patients supported by short-term circulatory support devices prior to durable LVAD implantation have lower mortality

3. Compared to other patients without ECLS prior to durable LVAD implantation, patients supported by ECLS prior to durable LVAD implantation are more likely to experience RV failure in the postoperative period.

A. True
B. False

4. A patient with dilated cardiomyopathy presents with worsening renal failure, elevated filling pressures, and a low cardiac index. Dobutamine is initiated, and his condition stabilizes. On weaning the dobutamine, he has recurrent worsening of his renal function and cool extremities, and he is determined to be inotrope dependent. If he were to be evaluated for durable LVAD implantation, what INTERMACS profile would he be considered?

A. 1
B. 2
C. 3
D. 4

5. A patient with a history of hypertension presents with acute anterior wall myocardial infarction 6 hours after the onset of chest pain. Despite revascularization with percutaneous coronary intervention, she develops CS, and ECLS is used to support her. Each time ECLS flows are reduced, she becomes profoundly hypotensive, and she is evaluated for durable LVAD implantation. In addition to ECLS with 4 L/min of circulatory support, she requires moderate doses of vasopressors and inotropes to maintain end-organ perfusion. In her current condition, she would be considered which INTERMACS profile?

A. 1
B. 2
C. 3
D. 4

53.

ECMO IN THE MANAGEMENT OF HEART TRANSPLANTATION

Lucy W. Mwaura and Alain Vuylsteke

STEM CASE AND KEY QUESTIONS

A 48-year-old man (60 kg, 165 cm, body surface area 1.66 m^2) was admitted to the intensive care unit (ICU) with acute decompensated heart failure. This patient had previously been assessed by the heart failure team in the context of chronic heart failure appearing 18 years after a mechanical aortic valve replacement. The patient was treated with warfarin, ramipril, aspirin, and pravastatin.

On arrival, the patient was in sinus tachycardia (heart rate at 116 beats/min). His systemic blood pressure was recorded at systolic pressure 74 mm Hg/diastolic pressure 50 mm Hg (mean arterial pressure [MAP] of 61 mm Hg). He was clinically fluid overloaded with pitting edema in both legs, and his central venous pressure (CVP) was 25 mm Hg.

Bedside echocardiography revealed a well-functioning mechanical aortic valve. The function of both left and right ventricles were reported as poor, with the left ventricular ejection fraction (LVEF) estimated at 20%. A chest radiograph showed bilateral pulmonary edema. Inotropic therapy was commenced (dopamine at 5 μg/kg/min and noradrenaline at 0.03 μg/kg/min). Furosemide infusion was started at 10 mg/h. Ventilation was supported noninvasively with an increased concentration of inspired O_2.

Blood tests sampled revealed a raised level of serum creatinine (148 mmol/L) and potassium (5.8 mmol/L), with a low level of sodium (128 mmol/L). The blood formula was normal (hemoglobin 108 g/dL, white blood cells at 11.4 × 109/L, and the platelet count of 290,000). Coagulation was deranged with an international normalized ratio (INR) reported at 2.8. Blood lactate level was measured at 3.2, and liver function tests were deranged (albumin 14 g/L, alkaline phosphatase 235 U/L, alanine aminotransferase 97 U/L, bilirubin 24 μmol/L).

A right heart catheter was placed, and the cardiac output was measured by thermodilution (CO 2.2 L/min, CI 1.3 L/min/m^2). The other measurements were calculated as follows: systematic vascular resistance 1200 dynes, pulmonary vascular resistance 480 dynes, and the transpulmonary gradient 10 mm Hg).

The patient remained hypotensive, justifying the addition of an increased dose of an infusion of adrenaline at 0.04 μg/kg/min and enoximone at 10 μg/kg/min (without a loading dose).

In the presence of continued oliguria, rising blood lactate levels, and persistently low cardiac output, an intra-aortic balloon pump (IABP) counterpulsation device was inserted.

The shock team met, and veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) was the most suitable form of additional circulatory support if deemed necessary.

The patient's renal function continued to deteriorate over the following 48 hours, and he developed stage 2 acute kidney injury with persistent low urine output despite furosemide infusion. The creatinine and potassium blood levels continued to rise, and fluid restriction proved to be impossible. Continuous veno-venous hemofiltration (CVVH) was initiated.

The patient's blood pressure decreased after initiation of CVVH and was further impaired by recurrent short runs of ventricular tachycardia that would self-revert back to sinus rhythm. Amiodarone was administered intravenously, and a continuous infusion was started.

The patient was now categorized as profile 1 in the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS class 1), and this justified instituting V-A ECMO without delay.

The patient was transferred to the operating theater, where general anesthesia was administered with standard monitoring that included electrocardiography, end-tidal carbon dioxide, oxygen saturation by pulse oximetry, CVP via right internal jugular vein central venous catheter, pulmonary pressure monitoring via a Swan-Ganz catheter, cardiac output monitoring by thermodilution, and left and right ventricular assessment by transesophageal echocardiography. Induction was uneventful, and inotropes were titrated to maintain reasonable hemodynamic parameters.

A 25-gauge drainage cannula was inserted under ultrasound and fluoroscopic guidance in the right femoral vein, and a 19-gauge arterial return cannula was inserted in a side graft attached surgically to the right axillary artery.

Anticoagulation was maintained with unfractionated heparin and monitored by activated partial thromboplastin time.

Veno-arterial ECMO flows of 4 L/min were obtained.



Figure 53.1 CVVH attached to VA ECMO circuit.

The patient returned to the ICU sedated and mechanically ventilated. IABP support and adrenaline infusion were continued while a plan was set to progressively decrease dopamine and noradrenaline infusions.

Great care was given to ensure the left ventricle continued to eject, and an echocardiogram was obtained to ensure the mechanical aortic valve was still opening. Staff at the patient's bedside were instructed to ensure pulsatility at all times by monitoring closely the pulse pressure in both pulmonary and systemic circulations.

Continuous veno-venous hemofiltration was directly attached to the ECMO circuit and continued while the patient was on ECMO (Figure 53.1).

Veno-arterial ECMO was managed according to our local protocols.[1] The patient was awakened, and the endotracheal tube was removed the following day. CVVH was discontinued after 5 days as renal function had recovered. The patient was actively engaged in rehabilitation and physiotherapy, with daily exercise, including walks. Blood tests informing on renal and liver function indicated a return to normality. There was no evidence of ongoing infection.

A multidisciplinary team agreed that the most suitable option for this gentleman was to be offered a heart transplant, and he was placed on the urgent waiting list.

Veno-arterial ECMO support was complicated by blood loss around the site of the arterial access, requiring multiple transfusions and repeated surgical hemostasis. This was compounded by thrombocytopenia, which was deemed not to be induced by heparin.

Ten days after initiation of V-A ECMO support, orthotropic heart transplantation was performed. The intervention required extensive dissection, and the patient received multiple units of red blood cells, fresh frozen plasma, and platelets. The total ischemic time for the donor heart was 160 minutes. Steroids and antithymocyte globulin were administered as immunosuppressive therapy. It proved difficult to separate the patient from cardiopulmonary bypass without a high level of pharmacological inotropic and vasopressor support. Transesophageal echocardiography revealed impaired right ventricular free wall movement and moderately impaired left ventricular function.

A high level of oxygen was required to maintain systemic oxygen levels despite mechanical ventilation.

In the presence of the high level of support, the team agreed that V-A ECMO should be reinstituted to facilitate cardiac recovery. On this occasion, V-A ECMO was achieved by using a 22 French (22F) return cannula inserted in the ascending aorta and a 34F venous drainage cannula inserted in the right atrium. A 20F cannula was placed in the pulmonary vein to ensure appropriate decrease of left ventricular volume. The cannulae were exposed, though the sternotomy and the surgical incision were covered with an occlusive dressing.

On the third day following heart transplant, the patient was transferred to the operating theater and was successfully weaned from V-A ECMO support and required only a small dose of inotropic support. The patient made a good recovery and was discharged from the ICU 15 days following heart transplant.

WHAT CLASS OF HEART FAILURE WAS THIS PATIENT SUFFERING FROM?

A comprehensive history confirmed that the patient had suffered from increasing dyspnea that was present at rest (New York Heart Association [NYHA] class IV).[2] Medical therapy was ineffectual, and signs of hypoperfusion (increasing lactate level, acidosis, and deranged renal and liver function) had progressively set in (INTERMACS class 2).[3]

WHEN IS V-A ECMO APPROPRIATE TO SUPPORT ADULT PATIENTS WITH CARDIAC FAILURE?

The guidelines of the Extracorporeal Life Support Organization suggest that V-A ECMO is indicated in persistent cardiogenic shock unresponsive to conventional management, including intravascular expansion, inotropes, vasoconstrictors, and IABP.[4]

Refractory cardiogenic shock can occur following acute myocardial infarction, open heart surgery, peripartum cardiomyopathy, or in decompensated chronic heart failure.

In these situations, V-A ECMO can be used as a bridge to decision (when the team is unsure of what is the best option for the patient because elements of the history are missing); as a bridge to recovery (e.g., after revascularization following acute myocardial infarction or after cardiotomy); or as a bridge to implantation of a longer lasting mechanical circulatory support (MCS) or as a bridge to heart transplant.

WHAT ARE SOME OF THE BENEFITS OF V-A ECMO AS A RESCUE DEVICE FOR CARDIOGENIC SHOCK?

Veno-arterial ECMO is easily deployed, and some configurations can be initiated in an emergency situation at the patient's bedside. In these situations, cannulae can be inserted percutaneously under ultrasound guidance. V-A ECMO provides biventricular support and gas exchange.[4]

In this patient, who had had a previous sternotomy with a mechanical valve in place, V-A ECMO was considered appropriate as it reduced the risks associated with resternotomy as well as prosthetic valve thrombus formation as long as the left ventricle was left to eject.

In the case presented, a mixed approach was selected to facilitate rehabilitation and physiotherapy for the patient while he awaited heart transplant. Femoral arterial access usually limits patient mobility to a great extent; therefore, a surgical insertion of the return cannula in the axillary artery was preferred.

WHAT ARE THE DIFFERENT WAYS IN WHICH V-A ECMO CAN BE ESTABLISHED?

Veno-arterial ECMO supports the heart by pumping oxygenated blood directly in the arterial circulation. The pump generates higher pressure than the patient's own blood pressure, allowing the blood to flow from the vein to the artery. The blood bypasses both heart and lungs.

This system provides pump support and supports failed lungs by providing the required gas exchange. Different cannulation sites can be used to achieve this; V-A ECMO can be either central or peripheral.

Peripheral V-A ECMO is commonly established by draining blood from a 21F–25F cannula inserted in the femoral vein and the return 17F–21F cannula inserted into the femoral artery.[4] It can also be established with the drainage cannula in the femoral vein and the return cannula in the subclavian artery.

There is a high risk of limb ischemia with cannulation of the femoral artery, and a reperfusion cannula should be inserted to promote distal limb perfusion.

Central V-A ECMO involves a venous cannula directly inserted into the right atrium and the return cannula in the ascending aorta; this is done following sternotomy. This circuit allows blood to flow in line with the patient's circulation. Its advantages include higher flow rates, anterograde flow through the arch, and less risk of upper body hypoxemia; it avoids lower limb vascular complications.

WHAT ARE THE PRINCIPLES OF MANAGING A PATIENT FOLLOWING INSTITUTION OF V-A ECMO AND RISKS THAT ARISE?

The aim of V-A ECMO as a bridge to transplant is to ensure organ perfusion when the heart is unable to do so. This is easy in principle; its practical application is fraught with difficulties. One key issue among many is the need to ensure continued left ventricular ejection to avoid the risk of intracardiac thrombus formation and pulmonary congestion.[5]

During peripheral V-A ECMO, high ECMO flow rates in the setting of worsening left ventricular function result in an increase in left ventricular afterload. This results in left ventricular distention, with resulting pulmonary edema.[6] It is important to ensure that left ventricular ejection is maintained and left ventricular distension is avoided after establishing the patient on V-A ECMO.[4,5]

This can be achieved by multiple means, which in themselves introduce secondary risks:

- Use of inotropic agents to ensure adequate pump function to overcome pressure generated by blood returned into the arterial circulation.[5] These can alter other organ perfusion and function and might affect their recovery after transplantation.
- Ensuring continued ejection requires constant monitoring. This can be provided by a Swan-Ganz catheter to monitor pulmonary artery pulsatility. This increases the risk of pulmonary hemorrhage and infection. The inappropriate use of thermodilution in the presence of a large right-to-left shunt can also lead to erroneous pharmacological adjustments.
- Use of IABP during V-A ECMO reduces the left ventricular afterload and increases both coronary and cerebral perfusion. This increases the risk of limb ischemia or dislodgment of aortic plaque, which may embolize in various vascular beds.

Despite all the above measures, if cardiac function remains poor with reduced ejection, left ventricular vents can be inserted to prevent overdistension of heart chambers and reduce the risk of thrombus formation.[1] These cannulae can be inserted either percutaneously via a transfemoral septal cannulation of the left atrium or surgically by direct cannulation of the left ventricle by a single-lumen cannula via either sternotomy or thoracotomy. Such catheters carry the risk of dislodgment, disconnection, bleeding, and infection.

Other considerations when managing a patient on V-A ECMO include

- Systemic heparinization, with associated risks, such as retroperitoneal hematoma, pericardial hemorrhage, bleeding around the cannulation site, heparin-induced thrombocytopenia, among others.
- A reduction in MAP to maintain adequate ECMO flows and normalize acid-base balance and lactate levels results in a decrease in the patient's blood pressure. Hence, a fine balance should exist where sufficient ECMO flows are balanced against the patient's intrinsic blood pressure to maintain left ventricular ejection.

Veno-arterial ECMO is solely a bridge to another step and should never be used in the absence of a potential treatment to reverse the heart failure.

After the presented patient was established on peripheral V-A ECMO at a flow of 4 L with sweep gas adjusted to achieve normocapnia, both dopamine and noradrenaline infusion were discontinued. Unfractionated heparin was administered as an infusion. A transthoracic echo confirmed there was no ventricular distension, and left ventricular ejection was aided with an infusion of adrenaline set at 0.05 μg/kg/min.

WHAT IS THE OUTCOME OF PATIENTS BRIDGED FROM V-A ECMO TO HEART TRANSPLANT?

Published case reports and retrospective studies showed inferior outcome when V-A ECMO was used as a direct bridge to heart transplantation, with a higher early posttransplant mortality rate.[7–11] A recent retrospective analysis of United Network for Organ Sharing database suggest better patient outcome when V-A ECMO is used as a bridge to bridge therapy prior to heart transplantation.[12]

Despite this, V-A ECMO remains a useful rescue therapy in patients with acute cardiogenic shock and is a valuable MCS acting as a bridge to decision-making for INTERMACS class 1 and 2 patients, who would otherwise not survive.

WHAT IS PRIMARY GRAFT DYSFUNCTION? WHAT IS THE ROLE V-A ECMO PLAYS IN MANAGING PRIMARY GRAFT DYSFUNCTION FOLLOWING HEART TRANSPLANT?

The International Society of Heart and Lung Transplant defines primary graft dysfunction as left, right, or biventricular dysfunction that occurs following heart transplant without any other discernible cause, including hyperacute rejection, pulmonary hypertension, or a known surgical complication.[13]

The presented patient remained hemodynamically unstable despite maximum inotropic and vasopressor support after heart transplant. He was transitioned from cardiopulmonary bypass to central V-A ECMO at flows of 2.5–4 L to facilitate myocardial recovery while maintaining perfusion to other organs.

The role of V-A ECMO in managing primary graft dysfunction includes the following:

- Promotion of myocardial recovery by reducing the venous return. This results in a reduction in the left ventricular end-diastolic volume and end-diastolic pressure, which in turn reduces the left ventricular transmural stress, allowing myocardial recovery.
- Minimizing the work done by the heart during the recovery period, V-A ECMO allows down-titration of inotropes and vasopressors, hence reducing the amount of noxious drugs required.
- Finally, during this acute period, V-A ECMO ensures adequate organ perfusion is maintained.

The challenges involved in managing a patient on V-A ECMO were discussed previously in this chapter.

WHAT ARE THE KEY STEPS TO FOLLOW WHEN WEANING A PATIENT OFF V-A ECMO SUPPORT?

Weaning from V-A ECMO after heart transplant occurs when there is evidence of improved graft function. This is evidenced by a continuous pulsatile waveform, hemodynamic stability with minimal doses of catecholamines, and a recovery of both pulmonary function and metabolic derangement.

The majority of weaning strategies are based on ECMO flow reduction. Various protocols and predictors of successful weaning, such as the use of Doppler echocardiography, have been described,[14] but none is more important than the cardiac surgical team's experience and judgment.

We suggest a simple algorithm:

- Step 1: Decrease flow

  Echocardiography should be used to evaluate the right and left ventricle and demonstrate recovery of myocardial function (LVEF > 25%, aortic velocity time integral > 12 cm).[14]

  Pump flow can then be reduced to 60%, then 30% of original flow. Anticoagulation is required if ECMO flow is less than 2 L, and this can only be maintained for short period of time.

  Critical note: Gas flow to the oxygenator on the ECMO should never be stopped on V-A ECMO patients.

- Step 2: Stop pump (should be done in the operating room)

  A clamp should be applied as close to the patient as possible. This is a one-way process as ECMO cannot be reinstated as thrombi will have built up in the cannulae.

- Step 3: Removal

  A venous cannula that was percutaneously inserted can be removed by a gentle pull with skin closure with a standard mattress stitch around the cannula site.

Arterial cannula removal should ideally be done under vision and direct surgical repair.

WHAT ARE SOME OF THE COMPLICATIONS ASSOCIATED WITH V-A ECMO?

Some of the complications associated with V-A ECMO use include the following:

- Complications related to cannula insertion: Bleeding and vascular injury with formation of retroperitoneal hematoma, sepsis, and thrombosis.[15]

- Lower limb ischemia: Common with peripheral V-A ECMO arterial cannulation and has been shown to be associated with poor patient outcome.[16] Incidence can be reduced by cautious arterial cannula sizing and cannulation, use of a small antegrade limb reperfusion cannula, and increased monitoring and vigilance for any limb changes that may occur after the femoral vessels are cannulated.[17]
- Pulmonary thrombosis: V-A ECMO bypasses the cardiopulmonary circulation, hence there is a risk of decreased blood flow in the pulmonary vessels with formation of pulmonary thrombi.
- Left ventricular thrombus: As described previously, the increase in afterload associated with peripheral V-A ECMO can result in left ventricular distension with blood stasis and thrombus formation, especially when the ejection fraction is poor. This can be avoided by inserting ventricular vents to offload the left ventricle. Another solution to the poorly ejecting heart would be to convert the patient from peripheral to central V-A ECMO with the addition of surgically inserted ventricular vents.[15]
- Harlequin syndrome: The syndrome occurs when the patient's intrinsic gas exchange is impaired, and the left ventricle output is high relative to the retrograde ECMO output. This results in part of a patient's circulation being supplied by poorly oxygenated "native" blood and the rest by oxygenated blood from the ECMO circuit. This is common when the return cannula is in the femoral artery, resulting in a significant risk of hypoxia to the brain, heart, and upper limbs.[1]
- Acute kidney injury from nonpulsatile arterial flow

Extracorporeal membrane oxygenation used in the post-transplant period has no detrimental effects on graft function when used for primary graft dysfunction. Long-term ECMO survivors have similar survival rates to heart transplant recipients who did not experience graft dysfunction.[18–20]

DISCUSSION

THE EVOLVING USE OF V-A ECMO IN HEART TRANSPLANT

Traditionally, V-A ECMO was mainly used in children awaiting heart transplant who required MCS, but studies have shown inferior survival among children bridged to transplant with V-A ECMO and higher long-term survival among patients bridged with ventricular assist devices (VADs).[11,21,22] In the adult population, there are reported case reports of patients who have been successfully bridged to heart transplant from V-A ECMO.[23–25] Larger retrospective analyses have shown inferior results in heart transplant patients bridged with V-A ECMO compared to those bridged with LVAD and the nonbridged recipients[8,9,26,27] (see Table 53.1).

Veno-arterial ECMO is used infrequently as a direct bridge to heart transplant; these patients are prioritized on the transplant list.[28]

ROLE OF V-A ECMO USE BEFORE HEART TRANSPLANT

Patients with advanced heart failure (NYHA class III and VI symptoms) have been classified into seven classifications as per the INTERMACS Registry.[3]

Veno-arterial ECMO is largely indicated for INTERMAC class 1 patients "crash and burn" as these patients have life-threatening hypotension that is unresponsive to inotropic or vasopressor therapy.[29] V-A ECMO can then be used as a bridge to decision, to VAD (discussed elsewhere in this book), or to transplant.

Table 53.1 **OUTCOME OF HEART TRANSPLANT PATIENTS BRIDGED WITH V-A ECMO COMPARED TO THOSE BRIDGED WITH LVAD AND NON-BRIDGED RECIPIENTS**

AUTHOR, YEAR (REFERENCE)	TYPE OF STUDY	STUDY POPULATION	OUTCOME
Jasseron et al., 2016 (27)	**Retrospective**	**866** **80 V-A ECMO**	**1-year survival: 52.2% V-A ECMO vs. 75.5% comparison group**
Zalawadiya et al., 2017 (8)	**Retrospective**	**157 V-A ECMO**	**1-year survival: 57.8%** **For those surviving 30 days,** **1-year survival 82.3%** **5-year survival 76.2%**
Fukuhara et al., 2018 (9)	**Retrospective**	**25,168** **107 V-A ECMO (0.4%)** **6148 VAD (24.4%)**	**90-day survival:** **73.1% V-A ECMO vs. 93.1% VAD group** **3-year survival:** **67.4% V-A ECMO vs. 82.4% in VAD group**
Poptsov et al., 2019 (31)	**Retrospective**	**182 V-A ECMO**	**90-day survival: 84.2% V-A ECMO vs. 90% without MCS** **1-year survival: 83.3% V-A ECMO vs. 91% without MCS**

MCS, mechanical circulatory support; VAD, ventricular assist device.

Specific considerations arise when using V-A ECMO as a bridge to heart transplant.

Who?

There is no evidence that any patient will benefit from V-A ECMO as a direct bridge to transplant in comparison to other modes of mechanical support. V-A ECMO might be the best choice in relation to the following:

- To buy time in patients for whom it is yet unknown if transplantation or long-term mechanical support is the appropriate option (physical, psychological, or social uncertainties).
- Patients presenting with hemodynamic collapse or profound biventricular dysfunction perhaps precipitated by intractable arrhythmias: These are the unstable INTERMACS 1 and 2 class patients.
- Patients with advanced stages of heart failure in whom durable LVAD is not practical, such as those with anatomical contraindication to LVAD use.[30]
- Patients in geographical locations where surgical insertion of mechanical support is not possible. V-A ECMO might be used to allow transfer to a specialist center.

When?

Veno-arterial ECMO as a bridge to transplant should be neither too late nor too early! It should be in place before multiorgan dysfunction sets in.[29] Studies have shown worse outcome in patients with a higher acuity of illness score, renal dysfunction, liver dysfunction, or on mechanical ventilation who are bridged from V-A ECMO to transplant.[7,9,12,31]

A clear management plan should be in place without delay after starting V-A ECMO.

Starting V-A ECMO initiates an ineluctable countdown toward complications and organ failure. Stabilizing and improving other organ perfusion is required before heart transplant as patients in critical status pretransplant have been found to have worse outcomes.[7,9,12]

Veno-arterial ECMO is time limited to the high number of inherent complications, and those patients should have the highest priority for the allocation of organs.[28]

Where?

Management of patients with heart failure supported with V-A ECMO is complex and requires a team approach that is available in large cardiac centers with a wide range of multidisciplinary medical and nonmedical expertise.

ROLE OF V-A ECMO FOLLOWING HEART TRANSPLANT

Veno-arterial ECMO is useful for the management of severe primary graft dysfunction after heart transplant. The International Society of Heart and Lung Transplant published consensus guidelines in 2014 defining severe primary graft dysfunction as dependence on left, right, or biventricular mechanical support within 24 hours of cardiac transplantation.[13] Mild and moderate primary graft dysfunction represents a less severe form of graft dysfunction that can be managed by inotropes and vasoactive medication.

The incidence of graft dysfunction varies from 2% to 30%.[18,39,32–34] When it occurs, it is associated with a high mortality rate and has been associated with up to 40% of deaths within 30 days after heart transplant.[34,35]

The pathogenesis of primary graft dysfunction is multifactorial, involving donor, recipient, and procedural related factors. This includes ischemia-reperfusion injury on the donor heart, donor heart preservation techniques, and hormonal imbalances in the brainstem of the dead donor, resulting in various electrolyte and metabolic imbalances.[36,37] In the recipient, preexisting MCS and prolonged cross-clamp time may result in a vasoplegic state.[38]

This leads to the donor heart being unable to meet the circulatory requirements of the recipient posttransplant.

Mechanical circulatory support such as V-A ECMO or temporary VAD is indicated in severe cases of primary graft dysfunction. De Roo et al. found that prompt V-A ECMO initiation in cases of severe primary graft failure promotes myocardial recovery and reduces the mortality rate.[39] A delay in initiation of MCS where primary graft dysfunction is suspected results in periods of end-organ hypoperfusion and worse patient outcome.

In their retrospective study, Takeda et al. compared V-A ECMO use in severe primary graft dysfunction to temporary VAD and found V-A ECMO to be superior; it is associated with fewer device-related complications, lower mortality, and higher graft recovery rate.[40]

Best evidence suggests V-A ECMO should be first-line therapy when considering MCS for patients with severe graft dysfunction after heart transplant. Long-term survival has been found to be similar among patients with primary graft dysfunction treated with ECMO support compared to those who do not develop primary graft dysfunction.[19,20,33,39–41]

CONCLUSIONS

- The use of V-A ECMO as a bridge to cardiac transplant is rare in adults, and its use is limited to INTERMACS class 1 and 2 patients.
- The use of V-A ECMO as a bridge to heart transplant is associated with poorer outcomes compared to the use of continuous flow LVADs.
- Starting V-A ECMO initiates an ineluctable countdown toward complications and organ failure.
- The use of V-A ECMO for severe primary graft dysfunction improves survival with comparable long-term survival to that of patients who do not develop primary graft dysfunction.

- Management of patients with advanced heart failure is complex and should involve a multidisciplinary team in specialized cardiac enters.
- Veno-arterial ECMO should be exclusively reserved for those patients with potentially recoverable heart failure or eligible for either transplant or long-term device support.

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REVIEW QUESTIONS

1. Which of the following is not an indication for heart transplantation?

A. Advanced heart failure secondary to ischemic heart disease
B. End-stage heart failure secondary to congenital heart disease
C. Diastolic dysfunction due to restrictive or hypertrophic cardiomyopathy
D. Low cardiac output state secondary to ruptured aortic aneurysm

2. Which of the following potential physiological effects is not achieved when using peripheral V-A ECMO?

A. Increased myocardial wall stress and oxygen demand
B. Reduced left ventricular end-diastolic volume
C. Reduced coronary perfusion pressure
D. Impaired ventricular recovery and worsening of myocardial injury

3. Which of those will not contribute to left ventricular decompression?

A. Left ventricular venting
B. Distal perfusion catheter in femoral-femoral V-A ECMO
C. Intra-aortic balloon counterpulsation
D. Atrial septostomy

4. Which of the following statements is incorrect?

A. Peripheral cannulation of the femoral artery during V-A ECMO is associated with increased risk of limb ischemia.
B. Insertion of a distal reperfusion cannula in the limb with femoral return cannula reduces the risk of limb ischemia.
C. During V-A ECMO support, insertion of an IABP reduces afterload and increases cerebral and coronary perfusion.
D. During V-A ECMO blood flows from the oxygenator to a pump that returns the blood into the arterial circulation.

5. A patient presents with decompensated acute-on-chronic heart failure and is fluid overloaded. The patient is admitted to the cardiac ICU for inotropic support. Which of these is not a contraindication to initiation of peripheral V-A ECMO as a rescue MCS if he was to deteriorate?

A. Cardiogenic shock with biventricular failure
B. Severe aortic regurgitation
C. Intracerebral hemorrhage
D. Severe multiorgan failure

6. Central V-A ECMO is instituted for primary graft dysfunction following heart transplant. Which of these is not an advantage of central V-A ECMO?

A. Delivers better flow rates than peripheral V-A ECMO
B. Prevents need for resternotomy when weaning from V-A ECMO support
C. Allows antegrade flow through the arch without admixing with deoxygenated blood
D. Avoids lower limb vascular complications

7. One of these is not associated with poor outcomes among patients bridged to heart transplant from V-A ECMO support?

A. Higher levels of APACHE 1V score
B. Pretransplant need for mechanical ventilation
C. Use of central versus peripheral V-A ECMO
D. Renal dysfunction

8. A 48-year-old man with ischemic cardiomyopathy is on rescue peripheral V-A ECMO support following an episode of acute decompensation triggered by refractory ventricular tachycardia; while on V-A ECMO support he develops pulmonary edema. Which one of these is not acceptable as a means to reduce pulmonary edema?

A. Increase flows on the V-A ECMO circuit
B. Administer diuretic therapy
C. Consider insertion of Impella device to offload the left ventricle
D. Administer low-dose inotrope

9. All the following statements are correct except

A. INTERMACS class 1 patients may benefit from insertion of a first-line device such as V-A ECMO for stabilization.

B. The literature shows superior outcome with early V-A ECMO use compared to VAD use for managing severe primary graft dysfunction.
C. Patients with advanced heart failure and a poor short-term prognosis are given priority in heart transplant allocation scheme.
D. Among children, V-A ECMO support is superior to a continuous flow VAD as a direct bridge to heart transplant.

10. All are complications associated with V-A ECMO except

A. Left ventricular thrombus formation
B. Cannula site infection
C. Pulmonary hemorrhage
D. Pulmonary edema

ANSWERS

1D, 2B, 3B, 4D, 5A, 6B, 7C, 8A, 9D, 10C

54.

WEANING AND LIBERATION FROM V-A ECMO

Arpan Chakraborty, Dipanjan Chatterjee, and Kunal Sarkar

STEM CASE AND KEY QUESTIONS

A 52-year-old male, smoker, type 2 diabetes mellitus presented with an acute inferior wall myocardial infarction at another hospital. Primary angioplasty was attempted, but the right coronary artery origin could not be engaged. Meanwhile, he became hypotensive and was started on noradrenaline. His pH was 7.11 with cold peripheries and metabolic acidosis. He was shifted to our hospital with steep inotropes after 12 hours of myocardial infarction. He also was in cardiogenic shock with acute kidney injury (AKI). On arrival, he suffered sudden bradycardia with further hypotension and was subsequently intubated and ventilated. His lactate level was 8.4 mmol/L. Peripheral veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) was initiated through the percutaneous femoro-femoral route. The venous cannula used was a 24 French (24F) cannula, and the arterial cannula was an 18F cannula. Distal perfusion was achieved by a 6F sheath in the femoral artery (Figure 54.1). The flow achieved was 3.5 L/min with a mean arterial pressure (MAP) of 70 mm Hg. The AKI did not resolve, and continuous renal replacement therapy was started through a separate temporary dialysis catheter.

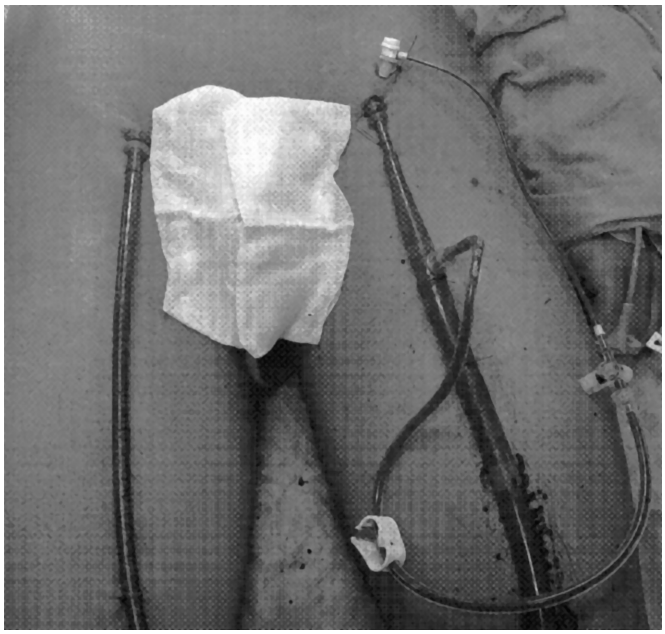


Figure 54.1

His liver enzymes rose to more than 5000 U/L and the international normalized ratio (INR) was 2.5.

Echocardiography showed ejection fraction (EF) of 35% with severe right ventricular (RV) dysfunction with tricuspid annular plane systolic excursion (TAPSE) of 6 mm. His sensorium started to improve from the second day, and near-infrared spectroscopy (NIRS) showed adequate numbers. He remained anuric and received regular sustained low-efficiency dialysis (SLED). On the fourth day, his liver enzymes declined to 500 U/L, and the INR became normal. Repeat transthoracic echocardiography (TTE) showed aortic velocity time integral (VTI) of 12 mm, and TAPSE improved to 10 mm. So, we decided to start weaning from V-A ECMO at a rate of 0.5 L/10–15 min. At a flow of 2 L/min, his MAP dropped to 50 mm Hg, and central venous pressure (CVP) increased to 20 from 11 cm of H_2O (preweaning). We abandoned weaning and went back to 3.5 L/min flow.

The next day (day 5), we started milrinone infusion at 0.5 μg/kg/min in addition to noradrenaline to maintain an MAP of 70 mm Hg and pulse pressure more than 20 mm Hg. On day 6, we reduced flow to 0.3 L/10 min up to an idle flow of 1 L/min. We inserted a bridge to facilitate trial off. TTE showed aortic VTI was more than 14 mm, and TAPSE was more than 12 mm. We clamped the cannulae and opened the bridge for trial off and continued for the next 3 hours with hourly arterial blood gases (ABGs) and monitoring of hemodynamics. In 15- to 20-minute intervals, the circuit was declamped, and cannulae were flushed. Heparin infusion was increased during trial off, and serial activated clotting time (ACT) measured at hourly intervals to keep it greater than 200 seconds. After 3 hours of trial off, the patient was taken to the operating room for decannulation by the surgical team. Doppler ultrasound was checked in both lower limbs after removal of the cannulae. After 2 days of decannulation, he was extubated, and inotropes were tapered gradually. He was on regular dialysis until his urine output improved in the third week of his hospital stay. He was discharged on day 24.

WHAT ARE THE INDICATIONS FOR V-A ECMO?

Veno-arterial ECMO may be used to rescue patients with refractory cardiogenic shock.[1–10] The main indication for V-A ECMO may be medical cardiogenic shock, including that associated with acute myocardial infarction, fulminant

myocarditis, acute-on-chronic systolic and diastolic heart failure, drug intoxication, hypothermia, and acute circulatory failure due to intractable arrhythmia.[1–7] V-A ECMO may also be used for patients with postcardiotomy cardiac failure or after cardiac or pulmonary transplantation or cardiac arrest requiring cardiopulmonary resuscitation.[1,4,8] V-A ECMO may be used in some particular situations for patients with pulmonary embolism, sepsis-associated cardiomyopathy, and pulmonary hypertension.[1–10]

Veno-arterial ECMO is used as a bridge to myocardial recovery and cardiac transplantation. It may also be used as a "bridge to a bridge," that is, before implantation of a ventricular assist device (VAD). No randomized controlled trials have compared V-A ECMO to other mechanical support systems in patients with cardiogenic shock. However, several nonrandomized studies suggested that the early use of ECMO offers a survival advantage in such circumstances.[1–12] After a few days of mechanical circulatory support (MCS), the device can sometimes be successfully removed if the patient has partially or fully recovered from the condition that required the use of ECMO. However, to date, only a few studies have reported strategies for weaning from V-A ECMO.[13–16] The percentage of patients with refractory cardiogenic shock who are successfully weaned from ECMO varies from 31% to 76%, depending on the underlying cause of cardiogenic shock and the definition of successful weaning.[10–16] Indeed, the definition of successful weaning varies in the reported studies. Moreover, weaning does not signify survival because 20%–65% of patients weaned from V-A ECMO support do not survive to hospital discharge.

WHAT IS THE DEFINITION OF WEANING?

Weaning is considered successful if the patient survives for longer than 48 hours after ECMO explantation.[6–8] We defined patients successfully weaned from V-A ECMO as those having ECMO removed and not requiring further mechanical support because of recurring cardiogenic shock over the following 30 days.[13,16] This last definition seems to be the most clinically acceptable to us. We discuss the various factors influencing survival and successful weaning from V-A ECMO in addition to weaning approaches proposed in the current literature.

WHEN IS WEANING FROM VA-ECMO ATTEMPTED?

According to the Extracorporeal Life Support Organization (ELSO) guidelines, hepatic function should have recovered prior to any attempt to wean patients from V-A ECMO, irrespective of the findings of cardiac assessment.[17]

It is not wise to attempt weaning in the first 72 hours after V-A ECMO implantation because damaged organs need time to recover. However, the duration of ECMO may be shorter in cases of drug intoxication, and V-A ECMO weaning may be attempted earlier.[18–20] In most studies, the mean duration of support was at least of 3.3 plus/minus 2.9 days and was even 8.0 plus/minus 6.0 days in one study.[21] This time period is also necessary to allow the recovery of a potentially "stunned" myocardium.

It is not necessary to wait for the recovery of renal function. Restoration of acute renal injury after cardiogenic shock can take up to 4 weeks after the improvement of cardiac output, by which time significant decreases in elevated filling pressures may have occurred.[21,22] Other considerations include the pre-ECMO status (age, comorbidities, cardiopulmonary resuscitation) and the etiology of cardiocirculatory dysfunction, which must be compatible with myocardial recovery (acute myocarditis, acute myocardial infarction, postcardiotomy, drug intoxication, septic cardiomyopathy).

Veno-arterial ECMO should not be removed if the patient has not recovered from the condition for which V-A ECMO implantation (high volume overload and high doses of inotropic agents) was done. Volume overload must be managed by diuretics or hemofiltration. Doses of inotropic agents should be decreased to a minimum. Furthermore, pulmonary edema must be resolved, and pulmonary oxygenation of the blood must not be compromised.[17]

The PaO_2/FiO_2 (fraction of inspired oxygen) ratio should be more than 200, and the oxygen fraction delivered by the extracorporeal circuit should be 21% and that delivered by the ventilator circuits should be less than 60%.[23] These measurements should be made with an ECMO flow rate of less than 1 L/min and a sweep gas flow rate of 1 L/min. However, the editor of this book annotated that his and many other institutions never reduce the FiO_2 in the V-A ECMO circuit and keep the sweep flow on 2 L/min with FiO_2 of 1.0 in order to avoid any potential risk of differential hypoxemia. One should keep in mind that weaning from V-A ECMO is primarily about cardiovascular recovery and contractility of the patient's heart and the reduction of flow and potential increase in filling pressures and that weaning of FiO_2 is of more importance for weaning from V-V ECMO. When reducing the flow to less than 2 L/min, additional heparin must be given to avoid clotting from low-flow events, especially if the weaning process goes on over extended time periods. Some institutions prefer to clamp the cannulae for 2 minutes after administration of an anticoagulant to evaluate filling pressures and hemodynamics in order to avoid the use of a bridge.

In case of persistent severe respiratory failure despite cardiac recovery, V-A ECMO should be switched to V-V ECMO.[15]

Factors indicating cardiac recovery, and thus patients who can be potentially weaned from ECMO, include an increase in blood pressure and return of pulsatility or an increase in the pulsatility of the arterial pressure waveform.[17] The patient should be considered hemodynamically stable; that is, the patient should have a baseline MAP of more than 60 mm Hg in the absence or at low doses of vasoactive agents and should have a pulsatile arterial waveform maintained for at least 24 hours.[3]

WHAT ARE THE PREDICTORS OF SUCCESSFUL WEANING?

Pulse Pressure

Pulse pressure appeared to be the only clinical factor associated with weaning success.[13,15,24] In a study assessing 51 patients,

among the 38 patients undergoing a decrease of ECMO flow, mean pulse pressure was higher in the successfully weaned group (52 ± 12) versus (39 ± 15) mm Hg in others.[5] Pappalardo et al. also reported a mean pulse pressure of 59 (53–69) mm Hg in the 49 successfully weaned patients. However, no clinically relevant predictive threshold could be identified.[15]

Biomarkers

Cardiac and vascular biomarkers were shown to be associated with outcome in patients with heart failure.[25] Reflecting on pathological processes happening in the heart, they may be useful to predict cardiac recovery and to help to identify V-A ECMO patients who would recover. Luyt et al. examined whether biomarkers could predict cardiac recovery in 41 patients receiving V-A ECMO.[25] They analyzed circulating concentrations of the N-terminal fragment of the B-type natriuretic peptide, troponin Ic, the midregional fragment of the pro–atrial natriuretic peptide, pro-adrenomedullin, and copeptin on the first day of ECMO and at days 3 and 7. There was no difference in the absolute values of these biomarkers or in their kinetics during the first week between patients who were weaned from ECMO and those who were not.

A few studies suggested that lactate and lactate clearance could help ECMO weaning.[26] Li et al. evaluated lactate at baseline and within 6 and 12 hours in inpatients under V-A ECMO for a refractory postcardiotomy cardiogenic shock. Mean lactate concentration (odds ratio [OR] 1.1, 95% CI 1.0–1.2, $P < .001$ in the 6-hour model and OR 1.2, 95% CI 1.1–1.4, $P < .001$ in the 12-hour model) and lactate clearance (OR 0.5, 95% CI, 0.3–0.9, $P = .001$ in the 6-hour model and OR 0.1, 95% CI 0.02–0.3, $P = .001$ in the 12-hour model) were significantly associated with hospital mortality and unsuccessful weaning.[26]

WHAT ABOUT ECHOCARDIOGRAPHIC PARAMETERS?

In cardiogenic shock patients assisted by V-A ECMO, echocardiographic assessment is of utmost importance to manipulate the degree of extracorporeal blood flow and concomitant supports, such as mechanical ventilation, fluid loading, and inotropic therapy.[13,15,27,28]

As comprehensive and dynamic echocardiographic measurements are mandatory to manage patients with cardiogenic shock assisted by ECMO, it seemed logical to assess the ability of echocardiographic parameters to predict successful weaning.[27,28] Thus, Aissaouiet al. assessed the ability of echocardiographic variables to predict successful weaning in 51 patients receiving V-A ECMO.[13] High values of parameters assessing systolic left ventricular (LV) function, such as aortic VTI, LVEF, and lateral mitral annulus peak systolic velocity were associated with successful weaning. The Doppler parameters reflecting LV filling pressures (i.e., mitral E and TDI Ea velocities and E/Ea) did not differ significantly at each ECMO flow level and were not predictive of weaning outcome, suggesting that preload conditions were comparable for the two groups.[13]

Precise RV assessment, except for RV dilation, has rarely been investigated. Interestingly, in a recent study assessing 46 patients, successfully weaned patients had smaller RV dimensions, better RVEF, and higher RV area change and magnitudes of RV strain.[29] The value of TAPSE and the severity of tricuspid regurgitation did not differ between the two groups. Of note, three-dimensional RVEF had the highest area under the curve (0.90, $P < .001$) for weaning success, with a cutoff value at 24.6% in this series.[29]

Thus, current data suggest that echocardiography is an important tool to determine both the recovery of LV and RV function and the readiness of patients for weaning from ECMO support, whereas early measurements of cardiac biomarkers are not useful for identifying those who will recover.

HOW ARE HEMODYNAMICS ASSESSED DURING THE WEANING ATTEMPT?

Hemodynamic assessment may be useful during the weaning trial in teams using the tool for critically ill patient monitoring. The pulmonary arterial catheter measurements give important information regarding the preloads of the RV and LV. For patients to be considered for V-A ECMO weaning, hemodynamic variables with the pump off should be as follows: cardiac index greater than 2.4 L/min/m^2, MAP greater than 60 mm Hg, pulmonary capillary wedge pressure less than 18 mm Hg, and CVP less than 18 mm Hg.[30]

WHAT IS THE ROLE OF MICROCIRCULATION?

Akin et al. recently reported in a study on 13 patients that the assessment of the sublingual microcirculation functional parameters, such as the total vessel density and perfused vessel density, may be of worth alongside weaning from V-A ECMO.[31] Patients who were not weaned from V-A ECMO had clear deterioration in total small- and large-vessel densities. In contrast, in weaned patients, there was no or minimal alterations in microcirculation. A comparison of the microcirculatory parameters with echocardiographic parameter values showed good correlation. Such measurements may be attractive and complementary but are not available in many centers due to questionable reproducibility and sensitivity to artifacts.

WHAT IS THE PURPOSE OF WEANING TRIALS?

Weaning trials are essential to assess the behavior of the LV during increases in preload and to determine whether ECMO can be removed. Load conditions can be modified by varying the flow of the ECMO centrifugal pump. When ECMO flow is decreased, preload is increased, and afterload is decreased.[32] Aissaoui et al. varied ECMO flow and examined hemodynamic variables of the failed LV in 22 patients receiving V-A ECMO. With this approach, they found significant variations between patients who were successfully weaned and those who were not. Indeed, increased preload and decreased afterload were associated with increased systolic function

in patients who survived weaning. These changes in systolic variables that occurred during modifications to ECMO flow identified a load-dependent contractile reserve, following the Frank-Starling law. The presence of this contractile reserve was associated with successful weaning.[32]

A weaning trial is also very important to evaluate RV function because the ECMO circuit creates negative pressure and drains venous blood from the right atrium. In these conditions, it is difficult to determine RV function in maximal ECMO flow.[32] A reduction in ECMO flow results in an increase in preload and enables RV function to be assessed.

Cavarocchi et al. assessed the behavior of both ventricles during decreased ECMO support, volume loading, and inotropic support in 21 patients.[14] They showed that a weaning trial involving LV and RV assessment by transesophageal echocardiography (TEE) could accurately predict both successful weaning from ECMO and successful lLV assist device (LVAD) implantation without the occurrence of RV heart failure. The assessment of RV function is very useful specifically in two cases: for patients receiving ECMO for postcardiotomy shock after heart transplantation and for those receiving ECMO prior to VAD implant surgery. Ideal candidates for LVAD placement are those who have isolated LV failure with reasonably recovered RV function. Failure to identify significant coexisting RV dysfunction may significantly increase the risk of postoperative morbidity and mortality in patients undergoing LVAD placement after ECMO and requires prolonged use of inotropic agents, biventricular support, or extracorporeal support.[33]

WHAT ARE THE STRATEGIES FOR CARRYING OUT ECMO WEANING TRIALS?

Two echocardiographic strategies for carrying out an ECMO weaning trial have been reported in the literature: The first strategy involves TTE,[13] and the second involves hemodynamic transesophageal echocardiography (hTEE).[14]

In the TTE study conducted by Aissaoui et al., an ECMO weaning trial was undertaken daily if the following occurred:

1. The patient was considered hemodynamically stable; that is, if the patient had a baseline mean blood pressure of greater than 60 mm Hg in the absence or at low doses of vasoactive agents and a pulsatile arterial waveform maintained for at least 24 hours; and
2. Pulmonary oxygenation of the blood was not compromised.[13]

The ECMO flow was decreased to 66% of the initial flow rate for 10–15 minutes. It was then decreased to 33% for 10–15 minutes and then to a minimum of 1–1.5 L/min for another 10–15 minutes.

If mean arterial blood pressure dropped significantly and was constantly less than 60 mm Hg during the trial, ECMO flow was returned to 100% of the initial flow, and the trial was stopped. Doppler echocardiography was repeated at each ECMO flow rate. The removal of ECMO was considered if the patient had no end-stage cardiac disease, was partially or fully recovered from the initial cardiac dysfunction, tolerated the full weaning trial, and had a LVEF of more than 20%–25% and aortic VTI of more than 10 cm under minimal ECMO support.

In the TEE study conducted by Cavarocchi et al., the weaning trial consisted of four stages and involved hTEE.[14] In the first stage, baseline LV and RV volume and function were assessed on full-flow ECMO support. During the second stage, ECMO flow was gradually decreased in increments of 0.5 L/min to half of the original flow rate (stage 2). Throughout the weaning protocol, LV and RV function and hemodynamic responses (heart rate and blood pressure) were monitored continuously to assess ventricular volume and function. If LV or RV distension or significant hypotension occurred, the weaning trial was stopped, and the ECMO support was returned to full flow. Stage 3 consisted of monitoring hemodynamic responses during both volume challenge with 5% albumin (10 mL/kg) and a reduction of ECMO flow to a minimum rate of 1.2–1.5 L/ min. Volume loading was used to achieve an appropriate preload. During the last stage (stage 4), LV and RV function was assessed during the infusion of inodilators (dobutamine and/or milrinone). These drugs were used to assess RV function in patients with LV dysfunction under consideration for LVAD placement. The definitive removal of the ECMO circuit was considered if both LV and RV functions recovered. If LV dysfunction persisted without RV failure, LVAD implantation was considered. An external RVAD placement was considered in cases of isolated, persistent RV dysfunction. For biventricular dysfunction, total artificial heart replacement was considered if the patient was a candidate for heart transplantation.

Our institute follows the following weaning plan:

1. Wean the pump flow by 10 mL/kg/h. Continue to wean until minimum flow is reached. Absolute minimal flow is known as idle flow, and it is 10 mL/kg/min. With any change, one should evaluate for 1 up to 3 hours. Reduce the blood flow proportional to the decrease in blood flow.
2. Once the patient is on minimum support, upgrade the ventilator setting to moderate level. Start small-dose inotropes if required.
3. Reduce the ECMO FiO_2 to 60%. Keep the patient on idle flow for 2 hours. ACT should be maintained at 200 seconds or greater as pump flow is weaned.

WHAT IS TRIAL OFF?

Trial off is to disconnect the patient from ECMO for a few hours without removing the cannulae.

Criteria for Trial Off

On idle ECMO flow, there is minimal inotropic support (inotrope score less than 10) and minimal ventilator support for 2 hours, monitoring the following:

- Maintaining hemodynamics with a MAP of 70 and pulse pressure more than 30
- Tissue perfusion—$ScvO_2$ more than 70, lactate less than 2 mmol/L, and urine output maintained as before (1–2 mL/kg/h) weaning
- Echocardiography—improved EF, no or minimal mitral regurgitation, VTI of more than 10, TDSa at lateral mitral leaflet of more than 6 cm/s

Method of Trial Off

- Keep the moderate ventilator setting and continue low-dose inotropes.
- Clamp the cannulae—go artery-bridge-vein (ABV) (i.e., clamp artery first, then open the bridge, then clamp the vein).
- Disconnect gas from oxygenator.
- Stop ultrafiltration.
- Do ABG 10 minutes after the trial off starts and repeat after 1 hour and then after 2 hours of trial off and in between if required.
- Do ACT of patient and circuit separately every 30 minutes as both are not connected now.
- Flush the cannula every 10 minutes for 15 seconds.
- To flush the cannulae:
  - First do VBA (vein, bridge, artery), release the vein first, clamp the bridge, and release the artery.
  - Wait for 15 seconds.
  - Then reclamp in ABV fashion
- Do not collect ABG when flushing.
- Time for trial off to be undertaken is 2–3 hours.
- If the trial off is successful, the patient will go for decannulation.
- If not successful, the patient will go back to full ECMO flow for the next 24 hours.
- If the decannulation is going to take time, continue idle flow.

HOW IS TTE ASSESSED VERSUS TEE?

The weaning assessment requires repeated measurements to be recorded over several days. Echocardiographic variables of LV flow (aortic velocity time integral; Figure 54.2), LV systolic function (LVEF and lateral mitral annulus peak systolic velocity; Figure 54.3), and RV diameters (Figure 54.4) can be used to predict successful weaning. These parameters are factors that are simple and easy to acquire with TTE. For these reasons, the transthoracic approach is a good option because it can be easily repeated many times.[27] In case of poor echogenicity, TEE can be used.[14]

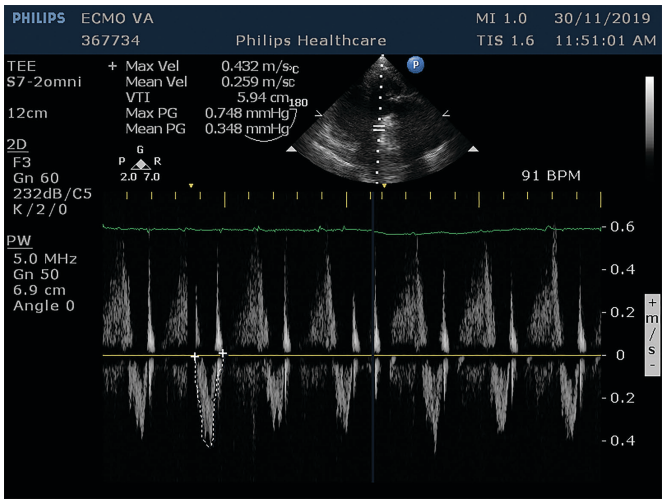


Figure 54.2

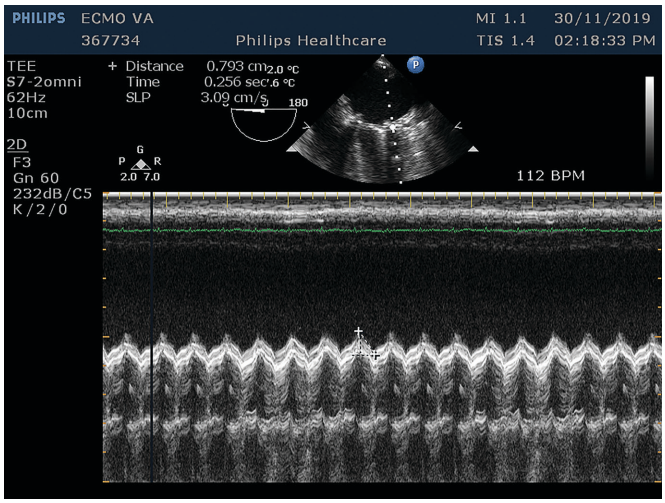


Figure 54.3

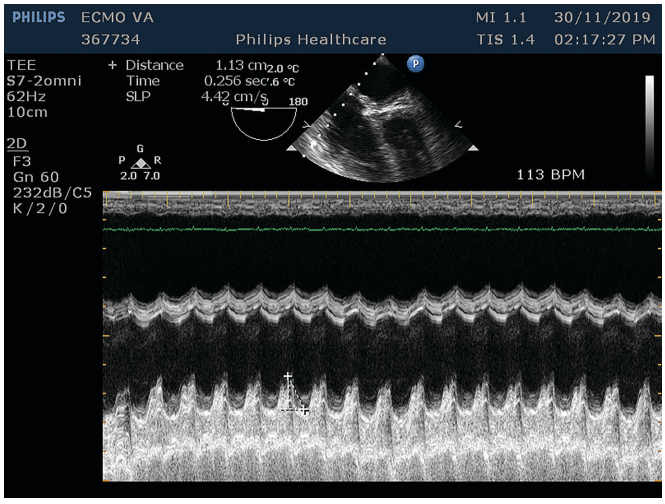


Figure 54.4

WHAT IS THE ANTICOAGULATION STRATEGY DURING THE WEANING ATTEMPT?

Extracorporeal membrane oxygenation weaning and weaning trials are associated with a risk of thromboembolic complications due to blood stagnation during the reduction of ECMO flow. ELSO recommends that anticoagulant drugs should be continued during the trial, and that the blood lines and access cannulae with the bridge should be periodically unclamped to avoid stagnation.[17] The activated partial thromboplastin time (aPTT) should be between 1.5 and 2.5 times the normal value.[17,34] Our institute performs ACT at 30-minute intervals during trial off and maintains it around 200.

WHICH AIDS CAN BE USED TO OPTIMIZE WEANING?

Some medications were used to facilitate weaning from V-A ECMO.[35] Levosimendan was assessed in six V-A ECMO patients, with the hypothesis that its remaining effects could favor weaning from ECMO. This inodilator drug was infused in patients 24 hours before the planned weaning. In this small study, the use of levosimendan was associated with an increased rate of successful weaning[35]; however, the sample size was very small.

The use of an intra-aortic balloon pump may improve survival in ECMO patients.[8] In a recent study conducted by Petroni et al., the use of an intra-aortic balloon pump in patients receiving V-A ECMO restored pulsatility, decreased LV afterload, and was associated with small LV dimensions and low pulmonary artery pressure.[36] No study has assessed the value of intra-aortic balloon pumps during V-A ECMO weaning.

WHAT IS PUMP-CONTROLLED RETROGRADE TRIAL OFF?

Pump-controlled retrograde trial off (PCRTO) relies on the retrograde flow of blood through the ECMO circuit to maintain circuit integrity and allows a longer trial off from V-A ECMO support without circuit clot formation or significant patient hemodynamic compromise. This technique avoids the insertion of an arterial-venous (A-V) bridge and the need to clamp the circuit. In PCRTO, appropriate mechanical ventilation is established based on the lung mechanics. The sweep gas is disconnected, and the trial off is commenced. At the start of the trial off, the flow probe is reversed, and the pump revolutions per minute (RPM) is reduced. As the pressure generated by the pump falls below the systemic arterial pressure, a state of retrograde flow is induced. The RPM is further reduced until a retrograde flow of approximately 120 mL/min is achieved. The pump is acting as a brake to stop excessive retrograde flow with systemic steal of blood and the risk of increased pulmonary blood flow. ACT is kept between 200 and 220 seconds.[37] In our experience, despite further heparinization, the presence of the A-V bridge to allow the recirculation of the ECMO, and the routine flushing of the cannulae, the circuit still has a maximum "integrity" time of 2 hours before starting to clot, and in some patients despite apparent adequate anticoagulation (as measured by ACT), the circuit clots very quickly. By removing the bridge completely and relying on retrograde flow to maintain circuit integrity, a long trial off from ECMO support can be achieved without significant hemodynamic compromise and reduced risk of clot propagation.[37]

HOW ARE THE VENOUS AND ARTERIAL ACCESS DECANNULATED?

Removal of a Venous Cannula

All venous cannulae can be removed using a simple aseptic technique. This can be done in an awake and cooperative patient and does not require sedation. A team is required to ensure that resuscitation measures can be established without delay in case of a problem. The operator requires an assistant. The team needs to plan for possible issues. Personal protective equipment should be used by all team members as there is a high risk of blood splash while removing a long indwelling cannula. Patient positioning is crucial to avoid deterioration during the process of removing the cannula. For example, keeping a patient in the supine position for a long period of time may cause distress and ventilatory issues. The operator must be aware of the risk of air embolism (which could be entrained into the patient's own circulation with devastating consequences), and positive pressure needs to be applied when the cannula is withdrawn. The area around the venous cannula should be infiltrated with local anesthetic and a horizontal mattress suture placed in the cannulation wound (Figure 54.5). A conscious patient is then asked to perform a Valsalva maneuver to prevent air embolism, the tubing is clamped, the cannula is smartly withdrawn by an



Figure 54.5

assistant, and the suture is tied. No manual pressure should be applied to the skin as the lips of the wound will usually close the track and avoid bleeding. Pressure might occlude the vein and lead to the formation of a thrombus. If the patient is sedated and fully ventilated, positive pressure ventilation will prevent an air embolism. Note that the vein can be immediately recannulated for a central line (or a new ECMO cannula if it does not work out as planned) via a separate skin puncture. Vein avulsion has been described, and the operator should evaluate a possible cause of cannula retention rather than use brute force. Our institute routinely sedates and paralyzes patients during removal of a venous cannula. We perform early Doppler studies to exclude deep venous thrombosis after decannulation.

Removal of an Arterial Cannula

Cannulae inserted surgically should be removed surgically. Percutaneous arterial cannulae can be removed manually, with subsequent compression of the artery. However, we do not advocate this, and surgical removal in the operating room is preferred in all situations. As advocated by Yeo et al., percutaneous removal of the arterial cannula should be attempted once heparin has been stopped for 30–60 minutes.[38] Manual compression at the site of vascular puncture should be maintained for 1 hour to stop bleeding. Further compression may be required in case of persistent bleeding. We perform early Doppler studies to exclude any thromboembolic occlusion after decannulation.

WHAT ARE THE FACTORS PREDICTING DEATH IN WEANED PATIENTS?

Successful weaning from ECMO does not signify patient survival. Death-associated factors reflect the severity and progression of multiorgan failure at the time of ECMO implantation. Several studies have assessed predictors of death after ECMO weaning in particular situations or settings, mainly in postcardiotomy shock and out-of-hospital cardiac arrest. Factors associated with death after weaning include door to V-A ECMO implantation time (i.e., the elapsed time between cardiogenic shock and ECMO), cardiopulmonary resuscitation time, poor renal and liver function, high lactate levels, diabetes mellitus, obesity, and SOFA score.[8,11,39] These should be considered prior to weaning from ECMO.

DISCUSSION

Only a few studies have examined outcome predictors following ECMO implantation, and most of these studies evaluated very early predictors of unsuccessful outcomes. Chen et al.[40] observed that five factors evaluated during the 96 hours following ECMO initiation were associated with poor outcomes: pulmonary dysfunction, peak lactate 3 mmol/L, systemic infection, renal dysfunction, and peak creatine kinase 10,000 U/L. Smedira et al.[41] reported that successful withdrawal from ECMO was associated with intra-aortic balloon pump use and fewer infectious complications and organ failures. Still, all those studies were not specifically designed to identify which patients could be successfully weaned. Indeed, detailed weaning strategies following ECMO initiation for refractory cardiogenic shock have never been reported. In most series described to date, weaning trials were not attempted during the first 24–72 hours after ECMO implantation and consisted of gradually decreasing pump flow to 0.5–1.5 L/min for 1–10 minutes while evaluating cardiac contractility and cardiac index.

However, none of those studies analyzed the predictive capability of the criteria they used for deciding ECMO withdrawal. Among the parameters monitored, those evaluating LV systolic function (TDSa, LVEF) and LV flow (aortic VTI) had the highest predictive values for successful weaning. LVEF and aortic VTI were higher at 100% ECMO flow for the group of ultimately weaned patients and increased significantly as ECMO flow was lowered, mostly because of increased preload and decreased afterload at the lowest assistance level. This effect was more apparent for weaned patients, who therefore displayed greater contractile reserves when challenged by the weaning trial. On the contrary, TDSa was only modestly altered by flow reduction, suggesting its relative preload and afterload independence. Lower ECMO flow before the weaning trial was also associated with successful weaning, reflecting reduced need for mechanical assistance in these patients.[13] Last, Doppler parameters reflecting LV filling pressures (mitral E and TDI Ea velocities and E/Ea) did not differ significantly at each ECMO flow level, suggesting that preload conditions were comparable for the two groups and not predictive of weaning outcome. Therefore, markers of systolic (vs. diastolic) LV function were better predictors of ECMO weaning success.

Aissaoui et al. evaluated a mixed population of patients who had received peripheral and/or central ECMO support following medical, postcardiotomy, or posttransplantation cardiogenic shock. Detailed evaluation of each of these specific populations should be the focus of future studies. Since weaning was not attempted in all 38 patients who tolerated maximal ECMO flow lowering, it cannot be excluded that some of the five nonweaned patients who had aortic VTI of 10 cm and LVEF of 20%–25% would in fact have tolerated weaning if they had been offered the option.[13]

Insufficient LV unloading is likely to inhibit successful weaning from V-A ECMO. Colombier et al. analyzed patients with V-A ECLS and intra-aortic balloon pump for refractory cardiogenic shock and subsequently benefiting from Impella implantation between 2011 and 2015. Median time between V-A ECLS and Impella implantation was 84 hours. The Impella median support duration was 8 days. ECLS and Impella were weaned simultaneously in 26% of patients, 33% were switched to long-term assistance, and 10% were transplanted. Overall, day 30 survival was 53%. Chronic heart failure with reduced EF was an independent risk factor for 30-day mortality. Though the Impella and V-A ECLS combination is a promising tool for LV unloading, for weaning V-A ECLS or testing the RV before a switch to LVAD support.[42]

Shamir Vally et al. suggested that levosimendan might be associated with a beneficial effect on V-A ECMO weaning in

patients in the intensive care unit. The main indications for initiation of V-A ECMO treatment were postcardiotomy cardiogenic shock in 49 cases (32.7%) and postacute myocardial infarction cardiogenic shock in 44 cases (29.3%). The difference in mortality among propensity-matched patients failed to reach statistical significance. Out of 103 patients, 73 were successfully weaned from V-A ECMO (70.9%). After propensity score matching, exposure to levosimendan was the only remaining factor associated with a significant reduction in V-A ECMO weaning failure rates.[43]

Atsushi Sugiura et al. aimed at a multicenter study in Japan to determine predictors of successful weaning during treatment with V-A ECMO and percutaneous coronary intervention (PCI) for acute myocardial infarction complicated by cardiac arrest.[44] The independent predictors of successful weaning were post-PCI TIMI flow grade, MAP at 4 hours, and serum lactate at 24 hours. In addition, this study found that patients who were weaned successfully exhibited a faster and more substantial recovery in LVEF, while LV function was not recovered at 24 hours after initiation of ECMO in patients who subsequently failed to wean from ECMO. As the patients with cardiac arrest due to acute myocardial infarction on V-A ECMO desirably need early prediction to wean or timely implementation of a VAD to preserve the potential for heart transplantation, this study stands different from previous studies on weaning prediction. Vincentelli and colleagues' aim of this study was to evaluate the outcome of the patients successfully weaned from ECMO after cardiac recovery. Early deaths (<3 months) were due to septic shock ($n = 4$), brain death ($n = 4$), multiple-organ failure ($n = 8$), and therapeutic limitations ($n = 4$). Late deaths (>2 years from ECMO weaning) were due to septic shock ($n = 4$) and heart graft failure. Older age, a longer duration of support, stroke, and postcardiotomy shock were associated with poor outcome.[45]

CONCLUSION

- Hepatic function should first recover.
- Patients with end-stage cardiac disease cannot be taken off ECMO. Indeed, the etiology of cardiocirculatory dysfunction must be compatible with myocardial recovery.
- For successful weaning, the patient should be hemodynamically stable and the PaO_2/FiO_2 ratio should be greater than 200.
- Weaning trials with progressive reduction in ECMO may go to an idle flow of 1–1.5 L/min.
- ECMO removal should be considered if the patient does not have end-stage cardiac disease, tolerates the full weaning trial, and has an LVEF of 20%–25% or greater, an aortic VTI of 10 cm or greater, and a lateral mitral annulus peak systolic velocity of 6 cm/s or greater under minimal ECMO support.

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REVIEW QUESTIONS

1. The success of weaning is defined as

   A. The patient is off V-A ECMO for 24 hours.
   B. Veno-arterial ECMO is off but cannulae are not removed.
   C. Veno-arterial ECMO is removed and not required for 1 month.
   D. Veno-arterial ECMO is running at 1 L/min.

2. A weaning trial should be started with the following except

   A. After at least 48–72 hours
   B. After hepatic function recovers
   C. After kidney function recovers
   D. After oxygenation recovers

3. A trial off is defined as

   A. Veno-arterial ECMO off, cannulae not removed
   B. Veno-arterial ECMO running at 1 L/min
   C. Veno-arterial ECMO off, decannulated
   D. Veno-arterial ECMO flow reduced to 10 mL/kg/min

4. Idle flow is known as

   A. Veno-arterial ECMO flow at 1 L/min
   B. Veno-arterial ECMO off, circuit flowing through a bridge
   C. Veno-arterial ECMO flow reduced to 0.5 L/10 min
   D. Veno-arterial ECMO flowing retrogradely

5. For patients to be considered for V-A ECMO weaning, hemodynamic variables with the pump off should be as follows except

   A. Cardiac index greater than 2.4 L/min/m^2
   B. Mean arterial pressure less than 50 mm Hg
   C. Pulmonary capillary wedge pressure less than 18 mm Hg
   D. Central venous pressure less than 18 mm Hg

6. ECMO removal should be considered in all except

A. End-stage cardiac disease and tolerates the full weaning trial.
B. Has a LVEF of 20%–25% or greater
C. An aortic VTI of 10 cm or more
D. Lateral mitral annulus peak systolic velocity of 4 cm/s or greater under minimal ECMO support

7. Trial off can be accomplished by

A. Clamp the vein, the clamp artery, then open the bridge.
B. Clamp the artery first, then open the bridge, and then clamp the vein.
C. Clamp the vein, then open the bridge, then clamp the artery.
D. Clamp the artery first, then clamp the bridge, and then clamp the vein.

8. Flushing the cannulae during trial off can be accomplished by

A. Release the vein first, clamp the bridge, and release the artery.
B. Release the artery, then release the vein, and then clamp the bridge.
C. Release the artery, then release the bridge, and then release the vein.
D. Clamp the bridge, then release the vein, followed by the artery.

9. The difference of weaning for V-A ECMO from V-V ECMO applies to all except

A. The duration is usually short.
B. Bridge is not required.
C. Anticoagulation strategy needs to be changed.
D. Flushing of the cannulae is done.

10. Regarding PCRTO, all are correct except

A. Pump runs in reverse direction
B. ACT should be 180–200
C. Bridge is mandatory
D. Chance of air embolism increases

11. Highest predictive value of successful weaning includes all except

A. Left ventricle ejection fraction
B. TDSa of mitral annulus
C. Aortic VTI
D. Left ventricular dimensions

12. For difficult weaning from V-A ECMO, which of the following can be used?

A. IABP and Impella
B. Levosimendan
C. Ventricular assist device therapy
D. All of the above

13. Weaning from V-A ECMO can be difficult due to all except

A. Ineffective LV unloading
B. Gross volume overload
C. Poor lung function
D. Acute myocardial infarction with cardiac arrest

14. Regarding PCRTO all are true except

A. Gives longer trial off time
B. Maintains circuit integrity
C. Requires lower heparinization
D. Cannula flushing will be easier

15. The factors predicting death in weaning ECMO patients are all of the following except

A. Multiorgan dysfunction on ECMO
B. Postcardiotomy shock
C. High lactate level
D. The time elapsed between cardiogenic shock and initiation of ECMO

16. The tools for RV assessment are the following except

A. Tricuspid annular plane systolic excursion
B. Three-dimensional RVEF
C. Right ventricular wall thickness
D. Right ventricular myocardial performance index

17. All are true regarding decannulation except

A. Air embolism can happen during venous decannulation.
B. Air embolism can happen during arterial decannulation.
C. Surgical decannulation is preferred in arterial access.
D. A long duration of compression is avoided in venous access removal.

18. Regarding anticoagulation during weaning, all are true except

A. Heparin infusion should be continued during trial off.
B. Cannulae and bridge should be periodically flushed.
C. PCRTO requires higher heparinization.
D. Target aPTT is between 1.5 and 2.5 times.

19. Factors which can prevent air embolism during decannulation of venous access is

A. Positive pressure ventilation with paralysis and sedation
B. Compression for long duration
C. Head-up position
D. Taking long deep breaths

20. All are true regarding the bridge, except:

A. It is a connection between venous and arterial circuit.
B. It is applied as close as possible to the patient.
C. It is kept open during idle flow.
D. It is not applied during retrograde trial off.

21. All the following statements are true except

A. Veno-arterial ECMO supports both the RV and the LV.
B. Ventricular assist device therapy is applied when predominantly the LV is dysfunctional.
C. Good RV function is a prerequisite for starting VAD.
D. Poor RV function in V-A ECMO is managed by an intra-aortic balloon pump.

ANSWERS

1C The 30-day mark has been given for not requiring any mechanical support for recurrent cardiogenic shock.

2C The kidney needs 4–6 weeks to recover following cardiogenic shock.

3A Trial off is 2–3 hours in duration, keeping the cannulae in.

4A Idle flow is considered 1–1.5 L/min before going for trial off.

5B For successful weaning, MAP has to be more than 60 mmHg.

6B TDsa of the lateral mitral leaflet has to be more than 6 cm/s under minimal support.

7B Follow the ABV fashion (artery-bridge-vein) during commencing trial off.

8A Follow the VBA fashion (vein-bridge-artery) during flushing the cannulae.

9B A bridge is usually required for trial off to maintain circuit integrity in V-A ECMO.

10C A bridge is not required as the pump flows in the reverse direction in PCRTO.

11D Diastolic parameters are not very sensitive for prediction of ECMO weaning.

12D All the aids can help for effective weaning from V-A ECMO.

13D Veno-arterial ECMO is frequently used in cardiac arrest after acute myocardial infarction with good outcome.

14D As the pump is flowing, cannula flushing is not required separately.

15 B Even though the outcome is poor postcardiotomy, it is not a predictor of death.

16C Right ventricular wall thickness is not a parameter for functional RV assessment.

17B Air embolism does not happen in removing arterial access due to high pressures.

18C Pump-controlled retrograde trial off does not require higher heparinization due to the flowing circuit.

19A Venous decannulation is best done in the paralyzed and sedated patient if still requiring intubation and ventilation, even though it can also be safely done in the awake and extubated patient who is performing a Valsalva maneuver.

20C The bridge is open during trial off, not during idle flow of 1 L/min.

21D An intra-aortic balloon pump is used for inadequate LV unloading.

ECMO IN THE TRAUMA PATIENT

55.

ECMO FOR HEMORRHAGIC SHOCK AFTER BLUNT TRAUMA

Justyna Swol

STEM CASE AND KEY QUESTIONS

A 27-year-old female was hit by a truck and suffered blunt chest and abdominal trauma and underwent subtotal amputation of her left lower extremity. At the scene, she was in a hemodynamically unstable condition. Her Glasgow Coma Scale score was 8 at arrival of paramedics. Initial vital signs on scene were heart rate (HR) 144 beats/min, blood pressure (BP) 85/50 mm Hg, respiratory rate (RR) 28 breaths/min, O_2 saturation 88%, and body temperature 36.2°Celsius. The patient was intubated, with temporary desaturation to 84%. Endotracheal bleeding was observed during intubation. Waveform capnography and end-tidal CO_2 confirmed placement of the endotracheal tube.

The patient was admitted to the hospital with a tourniquet on her leg. On arrival in the emergency department, a bolus of crystalloid was started, and her blood pressure was 70/40 mm Hg and heart rate was 128 beats/min. The initial arterial blood analysis showed anemia, with a hemoglobin level of 4.9 g/dL, acidosis with a pH of 6.99, a $PaCO_2$ of 65 mm Hg, a base excess (BE) of -10, and a PaO_2/FiO_2 (fraction of inspired oxygen) ratio of 70. A focused assessment with sonography in trauma (FAST) detected bilateral hemothorax and a ruptured spleen (hemoglobin 3.8 g/dL). Lung parenchyma bleeding was suspected after chest tube insertion. A physical examination revealed no head or neck injury. The Injury Severity Score (ISS) at admission was 57.

The patient crashed and suffered circulatory arrest. Extracorporeal life support (ECLS) was indicated to restore the circulation. As a blood transfusion was initiated, the right femoral vessels were cannulated veno-arterially during cardiopulmonary resuscitation (CPR) for veno-arterial (V-A) ECLS. A 15 French (15F) cannula was inserted into the femoral artery, and a 21F cannula was inserted into the femoral vein. Once the tubes were connected to the ECLS, after a few minutes the circulation was restored, hypercarbia was corrected, and oxygenation improved.

The patient received a massive transfusion, including 25 units of packed red blood cells (PRBCs), 40 units of fresh frozen plasma (FFP), 10 units of platelets, and 4 units of cryoprecipitate. No heparin was given except for priming the ECLS circuit. The patient was subsequently transferred to the operating room. Emergency laparotomy with intra-abdominal packing was performed for the purpose of damage control. The injured left lower extremity was stabilized with external fixation. The perfusion of the injured leg was sufficient. An 8F cannula was inserted distal to the arterial extracorporeal membrane oxygenation (ECMO) cannula to secure perfusion of the right leg. Intraoperatively and during the first 3 days after ECMO cannulation, the patient received 5 units of PRBCs, 4 units of FFP, 2 units of platelets, and 2 units of cryoprecipitate. Tranexamic acid was given continuously for 24 hours.

The intra-abdominal packing was removed 48 hours after trauma without further bleeding complications. The patient deteriorated the next day and developed multiorgan failure (renal, pulmonary, and liver dysfunction). A complete secondary computed tomographic (CT) scan indicated extensive lung contusion of both lungs with hemopneumothorax and pneumomediastinum as well as a fracture in the right first rib. The compliance of the lung worsened, and the PaO_2/FiO_2 ratio was 80. Oxygenation did not improve after prone positioning for 12 hours (Table 55.1). The next arterial blood gas analysis via right radial artery revealed the following: pH 7.12, $PaCO_2$ 72 mm Hg, and PaO_2 65 mm Hg (FiO_2 1.0). Postoxygenator PaO_2 was 415 mm Hg.

The ECLS configuration was extended to veno-arterial-venous (V-AV; with an additional 19F return cannula inserted into the right jugular vein). Oxygenation improved, and the ventilator settings were set to lung protective (4 mL/kg body weight). During the next 48 hours, the ejection fraction improved to 50%, allowing consideration of removal of the arterial cannula and conversion to veno-venous (V-V) ECLS. ECLS was run in a V-V configuration until the lung recovered. The patient was extubated on day 14 posttrauma and was weaned from ECLS on day 18.

Acute renal failure persisted, and continuous renal replacement with V-V hemofiltration was needed for 12 days total. Finally, the patient recovered and was discharged on day 42 after trauma with left leg disability for rehabilitation.

WHAT INJURIES DID THE PATIENT SUFFER FROM THE ACCIDENT?

Car accidents involving pedestrians result in fatalities because of the vehicle's size and weight. The injuries of this patient resulted from a pedestrian-versus-truck collision. Multiple

Table 55.1 ECLS AND IMV SETTINGS DUE TO THE TEST MEASURES IN ARTERIAL BLOOD GAS DRAWN FROM THE RIGHT RADIAL ARTERY[a]

	TIME	8:00 PM	9:00 AM	11:00 AM	2:00 PM	6:00 PM
Arterial blood gas arteria radialis right	pH	7.31	7.28	7.12	7.35	7.32
	PO_2 mm Hg	80	55	65	115	98
	PCO_2 mm Hg	42	64	72	58	50
	BE	3	4	2	3	3
	HCO_3^-	29	27.2	28	32	30
	PaO_2/FiO_2	100	68.75	65	115	122.5
ECLS/IMV settings changed due to the arterial blood gas analysis						
ECLS setting	Configuration	Veno-arterial	Veno-arterial	Veno-arterial	Veno-arterial-venous	Veno-arterial-venous
	Blood flow, L/min	2.2	2.5	2.5	Arterial 1.8	1.5
					venous 2.2	2.2
	Sweep gas, L/min	6	8	10	7	6
IMV setting	Positive end-expiratory pressure	12	14	14	14	12
	Pinsp	28	32	32	30	28
	Tidal volume, mL	320	380	400	380	340
	FiO_2	0.8	1.0	1.0	0.8	0.6

[a]The IMV settings were calculated for a female patient with an actual body weight of 78 kg and height of 172 cm. Ideal body weight (IBW) was calculated as 63 kg. Tidal volume for lung-protective ventilation was calculated (IBW × 6 mL/kg IBW) as 378 mL. Ultraprotective ventilation with 5 mL/kg IBW and 315 mL tidal volume was aimed for due to the severe lung injury pattern.

injuries were expected. The patient suffered severe blunt chest and abdominal trauma and penetrating injury of the lower extremity, resulting in bleeding shock due to multiple organ injuries (lung parenchyma bleeding, hemothorax, spleen rupture, and subtotal amputation of the lower extremity). Blunt force injuries are a subset of thoracic injuries and include injuries to the tracheobronchial tree, pleural space, and lung parenchyma (Table 55.2). The early identification of these injuries during initial assessment and resuscitation are essential to reduce the associated morbidity and mortality rates (Table 55.3). The management of airway injuries includes definitive airway control with the identification and repair of tracheobronchial injuries. The management of pneumothorax and hemothorax includes pleural space drainage and ongoing hemorrhage control. Furthermore, the use of FAST point-of-care ultrasound is recommended for the detection of intra-abdominal bleeding.

Surgical treatment for trauma typically follows the Advanced Trauma Life Support guidelines. The ISS is used to record the severity of the injury. It is the only anatomical

Table 55.2 ETIOLOGY OF THE CHEST INJURIES

ACCIDENTS LEADING TO THORACIC INJURY	MECHANISMS AND FORCES LEADING TO MYOCARDIAL AND/OR LUNG INJURY	CAUSES OF PENETRATING INJURIES
- Fall from more than 3 m - Thrown out of a vehicle - Death of another passenger - Vehicle hit a pedestrian, cyclist, or motorbike driver - High-speed car or motorbike accident - Strong vehicle deformity with missed or released airbags - Passenger trapped in the vehicle - Buried by an avalanche or landslide - Violent pressure - Assault - Industrial accidents - Blast injury, high energy, shock waves from explosion	- Rapid deceleration - Compression (under or between heavy objects) - Sudden compressional force squeezing the chest - Steering wheel crush - Dashboard crush - Massive general crush injury - Severe hyperflexion of the thoracic cage	- Gunshots - High-velocity missile wounds - Stab wounds (knife) - Impaled objects - Motor vehicle collisions - Falls

Table 55.3 CLASSIFICATION OF CHEST INJURY PATTERNS

SKELETAL	HEART AND GREAT VESSELS	PULMONARY	MEDIASTINAL DIAPHRAGMATIC
Flail chest	Contusio cordis	Tracheobronchial tree rupture	Diaphragm rupture
Rib fractures	Pericardial tamponade	Pleural space injury	
Sternum fracture	Aortic dissection	Lung parenchyma	
Clavicle fracture	Great vessel injury	Pneumothorax	
Spinal cord fracture		Hematothorax	
		Tension pneumothorax	

scoring system in use, and it correlates linearly with mortality, morbidity, hospital stay, and other measures of severity. The ISS is derived from the Abbreviated Injury Scale, which includes an anatomically based consensus of the global severity scoring system that classifies each injury in every region of the body according to its relative severity on a 6-point ordinal scale.

WHAT IS THE PRIMARY LIFE-THREATENING CONDITION AND THE IMMEDIATE NECESSARY WORKUP?

This patient was in a severe shock state. The immediate, initial priority should be identifying and addressing the cause(s) of the patient's shock. Hypotension was existing already on the scene, particularly with a shock index (systolic HR/BP) greater than 1, and finally associated with cardiac arrest due to the bleeding shock.

Hemorrhage and coagulopathy play a central role as main preventable causes of death after trauma.[1] Bleeding can be caused by isolated or multiple blunt and penetrating injuries. It may cause hemodynamic redistribution that compromises blood flow to some vital organs. Furthermore, hypoxemia caused by lung injury also limits the effectiveness of hypotensive resuscitation by augmenting the attendant shock state. Mass bleeding due to intra-abdominal or thoracic injury and subtotal limb amputation led to circulatory arrest in the reported patient.

Cardiopulmonary resuscitation and mass transfusion were required. Cardiac arrest after trauma is associated with a less than 10% survival rate despite the most advanced resuscitation techniques.[2] The efficacy of CPR in a patient with profound hypovolemia due to hemorrhage was reduced, and the speed of exsanguination limited the effectiveness of standard CPR in major trauma.[2] In this life-threatening condition, extracorporeal CPR was initiated to restore circulation. In recent years, ECLS has also been used in severely injured trauma patients with cardiopulmonary failure and coexisting bleeding shock.[3]

WHAT IS THE RATIONALE FOR ECLS USE IN CIRCULATORY FAILURE DESPITE BLEEDING?

Veno-arterial ECLS may be an effective type of support in acute hemodynamic arrest with the sole purpose of supporting or restoring the circulation as a result of massive hemorrhage. The rationale for using V-A ECLS in trauma patients is to support cardiopulmonary function, providing adequate systemic perfusion and therefore avoiding consequent multiorgan failure and permitting organ recovery.[3,4] The benefits of rewarming, acid-base correction, oxygenation, and circulatory support must be weighed individually against the risk of hemorrhage or bleeding control possibilities. Utilizing a heparin-coated ECLS system and heparin-free support to avoid systemic anticoagulation is a valuable option to support severe trauma patients when conventional therapies are insufficient. It is feasible and effective in providing hemodynamic support and blood gas exchange.[3] V-A ECLS cannot treat the underlying disease, but it allows us time for a massive transfusion (to treat consumption coagulopathy) and for a radiological intervention or surgical procedure (to control the bleeding source).[4] Damage control surgery is performed to control both hemorrhage and contamination with planned reexploration. This subsequently allows focus on reversing the physiologic insult prior to completing a definitive repair.

WHICH FURTHER ORGAN DYSFUNCTIONS ARE TO BE TREATED AND HOW?

Major trauma patients suffer from systemic inflammatory response syndrome in the early posttraumatic phase, are hemodynamically unstable, and have a high risk of multiorgan failure. Acute respiratory failure (ARF) is the commonest form of organ failure following traumatic injury. It is the physiological consequence of alveolar hemorrhage and pulmonary parenchymal destruction. Patients with major trauma necessitating the transfusion of PRBCs may be at an increased risk for acute respiratory distress syndrome (ARDS).[5] The clinical symptoms of ARF, including respiratory distress with hypoxemia and hypercarbia, peak approximately 72 hours after injury. The diagnosis of acute parenchymal lung injury is usually confirmed by thoracic CT. The general strategies used to improve pulmonary function and gas exchange include balanced fluid resuscitation to targeted volume-based resuscitation end points and prone positioning therapy.

Even though the reported patient was on ECLS, oxygenation was not ensured. In the presence of pulmonary failure during V-A ECLS, blood to the upper body will be hypoxemic, which remains a dangerous condition for brain saturation. Differential oxygenation between the upper and lower body parts is also known as Harlequin syndrome or North-South syndrome. In this case, secondary venous return to the right atrium via the internal jugular vein can maintain upper body oxygenation. The V-AV hybrid mode, which combines V-A and veno-venous (V-V) support, was performed in the

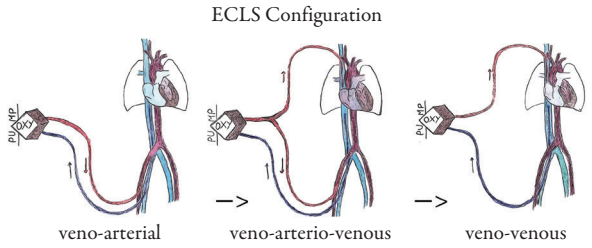


Figure 55.1 ECLS configuration change from veno-arterial to veno-arteriovenous to veno-venous.

described case due to combined cardiopulmonary failure (Figure 55.1). Once cardiac function recovers, the conversion to V-V ECLS for respiratory support can be considered.

Additional extracorporeal devices, such as a hemofiltration machine for continuous renal replacement, can be attached in parallel to the ECLS circuit or as a separate vascular access.

Improvements in lung function and gas exchange should be monitored, but the optimal weaning strategy during V-V ECLS remains unknown. The main adjustments are blood flow on the ECLS device, sweep gas flow, and sweep gas fraction of delivered oxygen.

Veno-venous ECLS allows the reduction of invasive mechanical ventilation (IMV) settings in order to provide improved lung protection. There is increasing experience in the practice of liberation from IMV during ECLS in trauma patients who may benefit from weaning before ECLS decannulation.[6,7]

WHAT IS THE ROLE OF ECLS IN THE TREATMENT OF ACUTE RESPIRATORY FAILURE?

Guirand et al.[8] reported that the use of ECLS in the trauma population had a survival benefit in patients with severe refractory hypoxic respiratory failure. This is the only cohort study that compared the outcome of V-V ECLS versus mechanical ventilation in adult trauma patients with ARF. Bosarge et al.[9] compared the early initiation of ECLS for the management of severe ARDS versus a historical control, immediately preceding the use of ECMO for trauma patients and concluded that ECLS should be considered at the early onset of severe ARDS in order to improve survival. Several recent studies on the application of ECLS in trauma patients and data from the largest registry of critically ill trauma patients receiving ECLS reported survival rates of 65%–79%, similar to those in other Extracorporeal Life Support Organization Registry cohorts.[10,11]

The American Association for the Surgery of Trauma Critical Care Committee developed a clinical consensus to guide the specific considerations for ECLS use in trauma patients.[10] The criteria for the initiation of ECLS include the presence of severe ARDS or ARF (PO_2/FiO_2 ratio < 100), with severe hypoxemia or inability to ventilate and refractory to conventional therapy; in particular, paralytics and prone positioning are recommended to be attempted prior to the initiation of ECLS.[10]

DISCUSSION

In blunt trauma caused by motor vehicle and pedestrian crashes, injuries are mostly related to the chest, abdominal organs, or/and extremities. The accurate identification of a patient at high risk for major chest trauma is essential to avoid over- and undertriage (Tables 55.2 and 55.3). Patients who have massive but potentially survivable injuries may die from complications of hypovolemia, hypoxemia, hypothermia, metabolic acidosis, and coagulopathy.[1]

The evidence for improved outcomes after ECLS support in trauma is increasing.[8–17] ECLS may be indicated in refractory acute respiratory or cardiac failure in selected trauma patients. Extracorporeal support provides adequate circulation and gas exchange, but it usually requires adequate anticoagulation to prevent clotting in the circuit tubes and oxygenators. Platelet dysfunction may also be an adverse effect of ECLS. Therefore, trauma-related bleeding conditions and coagulopathies have been considered contraindications for the use of ECLS.

However, the rationale for ECLS use in circulatory arrest and bleeding is based on beneficial hemodynamic support adjusting hypoxemia, hypothermia, and metabolic acidosis, which must be weighed individually against the risk of hemorrhage.[2,3] It is important to understand that ECLS is not a therapy for coagulopathy. Immediate hemodynamic support with ECLS might be bridging to buy time to stabilize the patient and to gain surgery or radiological intervention for bleeding control. ECLS with a heparin-bonded circuit offers supplemental support for selected massively injured patients while their primary injuries are being evaluated and treated.[18,19]

Recently, several case reports and case series have reported successful outcomes after ECLS support for respiratory and circulatory support in hemorrhagic conditions.[2–4,18] Cannulation during circulatory shock is feasible, and ECLS should not be considered as an absolute contraindication for bleeding conditions until it allows bridging of the response to coagulopathy treatment or definitive control of the source of bleeding.

On the other hand, there is evidence from a multicenter database for examining outcomes when ECLS is used for pulmonary support in patients with blunt thoracic trauma.[8,9,11–15,17] There was a paradigm shift that took place during the last decade. V-V ECLS was neither a contraindication nor a rescue treatment in adult trauma patients with severe hypoxemic respiratory failure, even in the presence of coagulopathy. ECLS has been safely implemented in adult trauma patients with multiple injuries and severe pulmonary failure. Early decisions and ECLS cannulation may lead to improved oxygen delivery, diminished ventilator-induced lung injury, and improved survival.[8,9]

CONCLUSIONS

- The early deployment of ECLS to preserve systemic organ perfusion and tailored anticoagulation protocols may outweigh the risk of associated bleeding.

- Alternative anticoagulants and heparin-free periods may be well tolerated in trauma patients with a high risk of hemorrhage.
- The use of ECLS to resuscitate patients with traumatic respiratory distress has proven to be safe and effective when conventional therapies have been exhausted.
- The use of ECLS for respiratory support in trauma patients may provide survival benefits.

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REVIEW QUESTIONS

1. Which statement regarding the use of ECLS is appropriate?

   A. Veno-arterial ECLS provides gas exchange and circulatory support.
   B. In severe hypoxemia, V-A ECLS is more suitable for oxygenation than V-V ECLS when cardiac function is sustained.
   C. The patient always needs anticoagulation.
   D. Bleeding is frequent and always associated with a fatal outcome.

2. The following are appropriate statements regarding extracorporeal support in severely injured patients (major trauma) except:

   A. At least two cannulae are required for pulmonary support.
   B. Thrombocytopenia is a common complication during ECLS support.
   C. Extracorporeal life support can be continued during patient transportation.
   D. Patients must remain deeply sedated and paralyzed when receiving mechanical ventilation during V-V ECLS.

3. Veno-arterial ECLS offers a supplemental extracorporeal technique during CPR due to trauma-related circulatory arrest. This modality is superior to conventional modalities for which of the following reasons?

   A. Rewarming option to prevent or correct hypothermia
   B. Provide circulatory support
   C. Lung-protective ventilation
   D. Fast access for a blood transfusion, volume and coagulation agent infusion

4. Patients suffering blunt trauma have a high risk of bleeding complications and hemodynamically unstable conditions. ECLS should not be considered in which of the following clinical conditions?

   A. Traumatic brain injury due to disseminated small bleeding and increased intracranial pressure
   B. In the presence of irreversible conditions known to be futile and incompatible with life
   C. Injury to the bronchial tree and hemorrhagic shock due to lung parenchymal bleeding

D. Bleeding shock due to pelvic injury and the need for further radiological interventions or surgical procedures

5. Extracorporeal support for trauma is a balancing act between the continuous risk of bleeding and the need for anticoagulation. The need for an intermediate heparin-free ECLS run may be considered in several situations except in the case of which of the following?

A. Veno-venous ECLS for respiratory support in cases of severe hypoxemia related to massive transfusion and hemorrhagic shock
B. Veno-venous ECLS for respiratory support following traumatic brain injury with intracerebral bleeding
C. Veno-arterial ECLS for circulatory support in lung parenchymal bleeding resulting in circulatory arrest and inadequate gas exchange
D. Veno-venous ECLS in ARF due to diffuse bilateral pulmonary contusions in blunt chest trauma with no further co-injuries or coagulopathy

ANSWERS

1. A) Veno-arterial ECLS provides gas exchange and circulatory support.
2. D) Patients must remain deeply sedated and paralyzed receiving mechanical ventilation during V-V ECLS.
3. B) Provide circulatory support.
4. B) In the presence of irreversible conditions known to be incompatible with life and futility.
5. D) Veno-venous ECLS in ARF due to diffuse bilateral pulmonary contusions in blunt chest trauma with no further co-injuries or coagulopathy.

56.

ECMO IN PATIENTS WITH BURN AND SMOKE INHALATION INJURY

Dirk M. Maybauer and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 38-year-old male patient had sustained a 50% total body surface area (TBSA) burn injury (approximately 25% total and partial thickness, respectively) to the face, left and right neck, both arms, and trunk, with additional smoke inhalation injury, during a house fire. He escaped to a second-floor balcony and jumped out of the burning building. The patient was in hypovolemic shock and was intubated and fluid resuscitated on scene.

Initially after admission he underwent escharotomies, left arm fasciotomy, wound debridement, and a bronchoscopy, which showed significant airway contamination with soot from inhalation injury. In addition, as a consequence of the fall, he had suffered concomitant injuries: a left femur fracture requiring osteosynthesis with femoral nailing and a left pubic rami fracture, which did not require surgical intervention.

Within 3 days, he developed hypoxemia and hypercapnia and deteriorated to a severe Acute Respiratory Distress Syndrome (ARDS) picture. The Extracorporeal Membrane Oxygenation (ECMO) team was involved, and, despite lung-protective ventilation, the situation worsened, and ECMO was initiated. Cannulation with a 23 French (23F) left femoral vein drainage cannula and a 23F right internal jugular vein return cannula was performed. An initially uneventful ECMO run was complicated 4 days later by oxygenator failure. The transmembrane pressure gradient had increased, and the postoxygenator PO_2 had dropped; therefore, the oxygenator was prophylactically changed to avoid oxygenation problems. The anticoagulation remained unchanged, activated clotting time (ACT) (normal range 70–120 seconds) was in the target range of 160 seconds, with an activated partial thromboplastin time (aPTT) of 40–50 seconds, and with an international normalized ratio (INR) of 2.1. The patient also developed acute kidney injury (AKI) and required continuous renal replacement therapy (CRRT) throughout the ECMO run. The CRRT device was connected to a separate temporary dialysis catheter and worked well without any technical complications during the ECMO run.

The patient developed neutropenic sepsis while on ECMO and received granulocyte colony-stimulating factor for his neutropenia. Another wound debridement was carried out while the patient was on ECMO. This procedure resulted in a significant amount of bleeding, requiring considerable volumes of blood products and fluid resuscitation, which contributed to weight gain during his ECMO course despite being on CRRT aimed for a daily negative balance of 3–5 L.

His burn wound grew a "coagulase-negative" *Staphylococcus* species, *Enterococcus* species, and *Candida albicans*. The blood culture was positive to *Staphylococcus aureus* and *Candida crusei*, and his urine sample was pneumococcal antigen positive. The patient's antimicrobial treatment course was extensive, requiring combinations of the following intravenous agents: piperacillin-tazobactam, gentamycin, clindamycin, meropenem, erythromycin, teicoplanin, and micafungin. He also received tobramycin nebulized into the airway.

Seventeen days after cannulation, the patient was weaned off ECMO, and a percutaneous dilational tracheostomy tube was inserted, followed by 10 days of respiratory weaning. After 6 more weeks of rehabilitation care, the patient was discharged home and attended follow -up clinics until his discharge from medical care.

HOW ARE BURN PATIENTS MANAGED AT THE SCENE OF INJURY?

At the scene of injury, a high-flow mask with 100% oxygen should be applied to reduce plasma carboxyhemoglobin levels. A full-body assessment should follow to estimate the burn injury and accompanying injuries (trauma evaluation). Cardiopulmonary monitoring, including electrocardiogram rhythm monitoring, noninvasive blood pressure assessment, and pulse oximetry must be established.[1]

Tracheal intubation should be considered if the injury is suggestive for inhalation injury. Symptoms usually include facial or neck burns; burned lips and vibrissae; soot-containing airway secretions; pathological respiratory patterns (stridor, coughing, hoarseness, dyspnea, and cyanosis); and neurological symptoms (unconsciousness, dizziness, nausea, and vomiting). Nebulization of epinephrine or salbutamol, as well as the application of corticosteroids, may be considered if stridor or airway obstruction is present; however, there is no evidence for the effectiveness of such treatment.[2]

Fluid resuscitation according to the Baxter-Parkland formula or to institutional fluid resuscitation regimens should start on scene and includes additional volume depending on

the extent of trauma, such as long-bone or pelvic fractures or severe smoke inhalation. It should be borne in mind that extensive resuscitation can increase the pulmonary microvascular pressure and might thereby cause increased edema formation. Fluid resuscitation should ideally be guided by urine output as soon as a urinary bladder catheter can be placed.[3]

Smoke inhalation usually represents a multifactorial intoxication of numerous agents burned. The most common intoxications result from carbon monoxide, cyanide, chloride, sulfide, phosgene, sulfur dioxide, ammonia, and aldehydes. Cyanide is commonly utilized in household materials such as appliances, plastics, carpets, upholstery, and furniture. Intoxication with cyanide may be assumed and prophylactically treated with hydroxocobalamin (Cyanokit).[4]

HOW ARE BURN PATIENTS MANAGED CLINICALLY BEFORE ECMO IS CONSIDERED?

After transport to the hospital, a reevaluation of the burn and smoke inhalation injuries is the first priority as this is a dynamic process, and airway swelling can occur with latency. If indicated (following tracheal intubation), bronchoscopy is the diagnostic gold standard for the airway examination, with the presence of mucosal hyperemia and soot being pathognomonic for inhalation injury.[5] The treatment is mainly focused on the maintenance and restoration of pulmonary gas exchange. Pulmonary toilet should be vigorously performed to clear the airway and to avoid airway occlusion since mucociliary function and cough reflexes are impaired and the patient is at risk of developing atelectasis.[6] The increased bronchial blood flow leads to increased mucous secretions with pulmonary and mucosal hyperemia.[7] Transudation of plasma into the airways and the lack of mucociliary escalator blocks airways and inactivates hypoxic pulmonary vasoconstriction. These insults collectively potentiate airway obstruction with casts formed from epithelial cell debris, fibrin clots, and mucus, resulting in impaired ventilation, pulmonary shunt formation, and edema.[8]

To directly administer therapeutic compounds via nebulization to the affected organ seems to be reasonable. Many compounds are under investigation or in preclinical trials, with a few clinical trials conducted and introduced to clinical practice. Continuous nebulized albuterol (10–40 mg/h) improved lung compliance and oxygenation without adverse events in children with smoke inhalation injury.[9] The combination of heparin (5000 U) and 3 mL of 20% N-acetylcysteine nebulized every 4 hours for 7 days significantly decreased reintubation rates, the incidence of atelectasis, and mortality.[10] Inhaled nitric oxide has not shown to improve outcome but might be considered as rescue treatment to temporarily improve oxygenation in life-threatening hypoxemia.[1]

Low tidal volume ventilation (4–6 mL/kg) with plateau pressures of less than 30 cm H_2O, permissive hypercapnia, and adjustment of positive end-expiratory pressure (PEEP), guided by either esophageal pressure monitoring or the National Institutes of Health PEEP-FiO_2 (fraction of inspired oxygen) table, currently represent the standard of ventilatory care in patients with ARDS.[11–13] Neuromuscular blockers have been shown to improve ventilatory synchrony and adjusted 90-day survival without increasing muscle weakness.[14] The early application of prolonged prone positioning has significantly reduced the 28- and 90-day mortality in patients with ARDS; however, the application of prone positioning depends on the feasibility and extent of injury and skin grafting on the frontal trunk of burn patients. Pressure from the patient's own body weight could reduce blood flow to the skin grafts. At the point of consideration of prone positioning, in our opinion, it is better to initiate ECMO in this patient population. Besides prone positioning, the Berlin criteria for ARDS[15] and the Murray score are useful tools in identifying potential candidates for ECMO. The score includes lung compliance, PaO_2/FiO_2 ratio, lung consolidation, and PEEP. Patients who score above 3 are recommended to be transferred to an ECMO-capable center for ECMO evaluation.[16]

HOW DID EXTRACORPOREAL LIFE SUPPORT DEVELOP IN BURN CARE?

Extracorporeal Membrane Oxygenation is a relatively new technology that emerged over the last five decades. Today, ECMO is routinely used in specialized centers for neonatal, pediatric, and adult respiratory and cardiac failure.[17] In 1994, the first ECMO run in a burn patient was performed.[18] Ever since, numerous case reports, though only a few studies, assessed Extracorporeal Life Support (ECLS) in the field of burn and/or acute smoke inhalation injury, followed in 2017 by an Extracorporeal Life Support Organization (ELSO) Registry analysis.[19]

WHAT IS THE EXPECTED OUTCOME FOR BURN PATIENTS REQUIRING ECLS?

While different studies reported a wide range of outcomes, from poor to good, of ECLS in burn patients, the ELSO Registry observed a 43% hospital survival rate in adult victims of burn-related injury. This is noteworthy as many patients would have been unlikely to survive without ECLS. It is unclear if all patients reported in previous publications were also added to the ELSO Registry. The number of patients reported by ELSO was inadequate to perform meaningful statistical comparisons between the extent of burn injury and survival; however, the observed mortality rates in severely injured patients suggested that burn injury greater than 45% TBSA may be a risk factor for death in adult patients.[19]

WHAT ARE COMMON FACTORS ASSOCIATED WITH MORTALITY?

Recent literature suggests that nonsurvivors have higher rates of AKI and higher rates of CRRT on ECLS. This finding is not unexpected since AKI is also a very well-known risk factor for death in patients with burn injury who do not receive ECLS.[20]

Survival differences were observed in patients managed with veno-arterial (V-A) versus veno-venous (V-V) ECLS, as clinical indicators of cardiac dysfunction and cardiopulmonary resuscitation during ECLS were associated with worse survival. Markers

of poor tissue perfusion and shock, including pre-ECLS acidosis and high inotropic and vasopressor support, were identified as independent predictors of increased mortality.[19]

In a recent case series of six ECMO patients, five suffered from more than 90% TBSA, resulting in death, while one patient had 50% TBSA and survived.[21] These findings correlate with the ELSO Registry publication, indicating that burn injury greater than 45% TBSA may be a risk factor for death in adult patients.[19] The greater the injury, the more likely are complications from infections, AKI, respiratory failure, cardiovascular failure with increased fluid and vasopressor requirements, and the risk for multiorgan failure. A recent meta-analysis showed that an ECMO duration of less than 200 hours correlated with survival, compared to treatment durations of 200 hours or more. Scald burns tended to have higher survival rates than flame burns. No statistical differences, however, were reported regarding early or late start of ECMO therapy. In cases that may be related to excessive fluid resuscitation, early ECMO might serve as an oxygenation bridge until excess fluids are removed.[22] It is our practice to start CRRT early in these patients, not necessarily for acute renal failure, but as a tool for early fluid removal in a range of 3–5 L/d and to avoid unwanted side effects of diuretics, such as electrolyte disturbances.

WHAT ROLE DOES CONCOMITANT TRAUMA HAVE ON MORBIDITY AND MORTALITY?

The ELSO Registry did not observe an association between hospital mortality and concomitant trauma; however, the ability to discern the impact of comorbid conditions on survival was likely limited by the size of the data set. Blunt and open trauma, especially pelvic or long-bone fractures, carry the risk of massive hemorrhage, which necessitates additional fluid requirements in the initial resuscitation phase and may contribute to the development of pulmonary edema and ARDS.

HOW IS THE RIGHT ECLS CONFIGURATION CHOSEN?

Veno-venous ECLS is typically employed for respiratory failure with minimal or no hemodynamic compromise that can be managed with vasopressor support. Burn patients usually display a stress-related hyperdynamic physiology. The use of echocardiography can be very effective in evaluating ventricular volume status and contractility.[23] In hemodynamically compromised patients who do not respond to fluid resuscitation and inotropes/vasopressors, V-A ECLS is typically employed. The lack of data on survival difference between modalities is due to limited patient numbers published as well as recorded in the ELSO Registry.[19]

WHAT CANNULAE CAN BE USED FOR ECLS IN BURN PATIENTS?

In a recent case series of V-V ECMO in burns, the following configurations were used: a 27F–31F Avalon Elite bicaval dual-lumen cannula via the right internal jugular vein, dual-site femoral-femoral (size 23F cannula, length 38 or 55 cm), or dual-site femoro-jugular (23F, 55-cm drainage cannula; 21F–23F, 20-cm return cannula).

For V-A cannulation, there is no difference for the choice of the venous drainage cannula and position; however, the drainage cannula should have a larger diameter compared to the arterial or return cannula, which usually come between 15F and 24F cannulae with a length of 24 cm.[24]

WHERE AND HOW SHOULD PATIENTS BE CANNULATED?

The ideal location to cannulate a burn patient depends on the hemodynamic stability of the patient and the local technical availabilities. Unstable patients may be cannulated at the bedside in the burn intensive care unit using transesophageal echocardiography (TEE) guidance. Hemodynamically stable patients can of course be cannulated in the same way; however, it is our practice to cannulate these patients using TEE and additional x-ray/fluoroscopy guidance since the blind insertion of wires may lead to dysrhythmic events or right ventricular or vascular perforation, especially when cannulating neck vessels. If the patient can be transported to a dedicated fluoroscopy suite (i.e., cardiac catheterization laboratory, interventional radiology, hybrid operating room, etc.), then this should be the location of choice for cannulation given the space and availability of technical resources. The type of cannula should be determined by the inserting consultant/attending physician depending on the individual and situation (e.g., patient size and expected flow requirements, as well as vascular access availability to avoid cannula placement through burned tissue). The cannulae should be stitched and tubing secured with adhesive dressings.

To date, there is no evidence on where to place cannulae in burned patients; however, we feel it is advantageous to avoid cannula placement through burned tissue for many reasons. One is the fixation of the cannulae; burned tissue is very soft and edematous and will also be removed during procedures for skin grafting. The risk to lose a cannula during transport or a procedure is high, and priority should be given to ECLS cannulae compared to resuscitation/fluid lines that can temporarily be placed in burned tissue and later replaced. Depending on the situation and the extent and TBSA burned, it may become necessary to insert an ECMO cannula through burned tissue (Figures 56.1–56.3).

WHAT CAUSED THE OXYGENATOR FAILURE IN THIS CASE?

We hypothesized that likely due to sepsis, inflammatory proteins adhered to the membrane, increasing the transmembrane pressure gradient and thereby reducing its capacity for gas exchange. In addition, coagulopathy and clot formation within the oxygenator may be considered.

HOW ARE BURN PATIENTS ANTICOAGULATED DURING ECLS?

Anticoagulation very much depends on local institutional protocols. Traditional and alternative anticoagulation



Figure 56.1 Facial burn with inhalation injury, burn injury to chest and arms.

strategies are discussed in more detail in further chapters of this book, as well as other publications.[25] In burn care, heparin is the most frequently used anticoagulant and is usually titrated to aim for an ACT in a range from 150 to 180 seconds or a partial thromboplastin time (PTT) of 40–50 seconds if there are no bleeding complications.[26] Tubing and oxygenators should be frequently checked for clots and cannula insertion sites or wounds for bleeding to adequately titrate heparin in order to provide an individually adapted anticoagulation regimen. For patients requiring debridements, grafting, or dressings, the anticoagulation may be stopped approximately 6 hours before and restarted approximately 12 hours after the procedure if there are no signs of bleeding. If bleeding from wounds occurs, it is reasonable to cease anticoagulation for as long as needed with no complications identified in a previous study.[24]

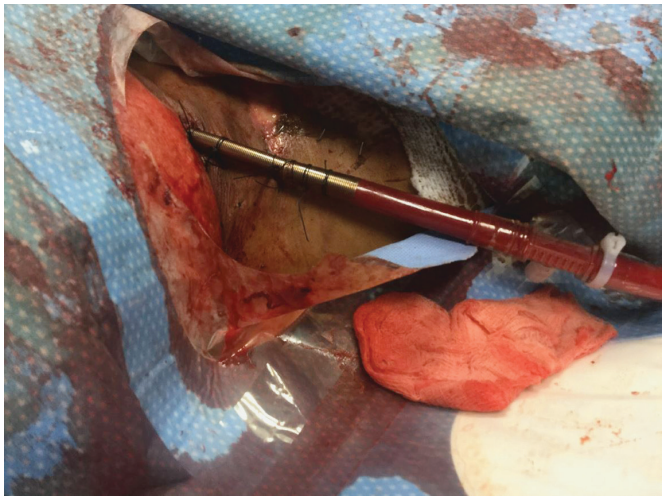


Figure 56.2 23 French ECMO return cannula inserted in the not burned skin area around the right internal jugular (IJ) vein.



Figure 56.3 ECMO cannula insertion is close to the burn injury but in the intact skin, just above the clavicle, to achieve adequate access in a patient with very short neck.

IS ESCHAROTOMY SAFE DURING ECLS?

In a report by Chou et al.,[27] two patients received debridement of eschar during ECMO support without bleeding- or coagulopathy-related complications. If debridement was needed to remove the unstable eschar, the ACT was reduced to 120–140 seconds, and platelets were transfused to 100,000/mm^3. Desmopressin (Ferring, Malmö, Sweden) 24 μg was infused during the debridement; however, there is no evidence for perioperative use of desmopressin for burn patients on ECMO.

IS THERE A REASON FOR B-BLOCKADE IN BURN PATIENTS?

Severe burn injury causes a catecholamine-mediated hypermetabolic response with increased energy expenditure and muscle-protein catabolism. Herndon et al.[28] showed that blockade of β-adrenergic stimulation with propranolol decreased resting energy expenditure and muscle catabolism in patients with severe burns. The authors achieved this significant improvement by titrating propranolol to a resting heart rate of 20% less from each patient's baseline value.

This hyperdynamic catecholamine-mediated response to the injury is a disadvantage for ECMO management. Patients have cardiac outputs in a range from 10 to 15 L/min, which, depending on the ECMO flow, adds considerable shunt. It is important to place cannulae with a large diameter to increase ECMO flow to a high range between 6 and 7 L/min without causing hemolysis (monitor plasma free hemoglobin). Burn patients in the acute phase usually present with heart rates between 100 and 150 beats/min. Our practice is to reduce the shunt fraction by titrating esmolol to achieve a heart

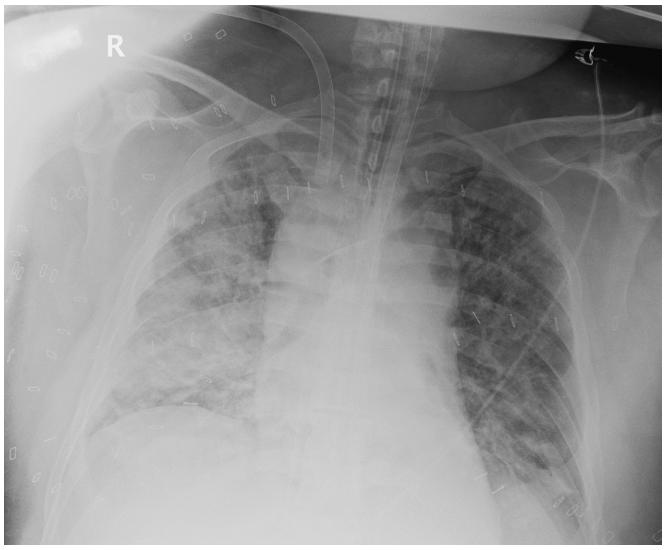


Figure 56.4 Chest radiograph with typical ARDS picture post burn injury with combined inhalation injury. Endotracheal tube, left subclavian central line, ECMO drainage and return cannulae.

rate between 90 and 99 beats/min. The reduction of heart rate reduces cardiac output and thereby the shunt fraction of deoxygenated blood. Esmolol is a very short-acting cardioselective β_1-receptor antagonist that can easily be titrated to effect without causing potential overdosing or risk for bradycardia in the acute phase. Injection of 500–(1000) μg/kg as a slow intravenous bolus over 30–60 seconds is followed by an infusion of 150 μg/kg/min, titrated to effective heart rate with a maximum dose of 300 μg/kg per minute.

After achieving stable flows and hemodynamic stability on ECMO, but latest after decannulation, esmolol may be replaced by propranolol. SpO_2 measurements in the 80% plus or minus 10% range are not uncommon in burn patients on ECMO and are routinely well tolerated.

HOW ARE BURN PATIENTS VENTILATED DURING ECLS?

Ventilation strategies for burn patients vary between institutions. Lung-protective ventilatory settings on ECMO or so-called rest settings are applied using pressure control mode (peak inspiratory pressure [PIP] 20–25 cm H_2O, PEEP 10 cm H_2O, respiratory rate 5–10 breaths/min, FiO_2 < 0.4) all along the ECMO runs except during the final ECMO trial-off phases. These ventilator settings were chosen to avoid the following:



Figure 56.5 25 French left femoral ECMO drainage cannula placed in non burned tissue.

1. "Atelectrauma" is the repetitive opening and closing of unstable lung units that can be avoided by the application of adequate levels of PEEP.
2. "Volutrauma" (high tidal volumes) may cause lung overdistension in patients with ARDS. Volume can elongate the collagen fibers and may cause "microfractures" of the extracellular matrix, inflammatory signaling, and vascular stress that leads to tissue inflammatory activation.
3. Barotrauma is the rupture of the alveoli with subsequent entry of air into the pleural space (pneumothorax) or to the mediastinum (pneumomediastinum). Large tidal volumes (>10 mL/kg) and elevated peak inspiratory and plateau pressures (Pplat > 30 cm H_2O) are the most important risk factors for barotrauma in patients with ARDS.

Depending on institutional practices, the airway pressure release ventilation (APRV) may be used with a pressure high (P_{high}) of 25 cm H_2O and a pressure low (P_{low}) of 0–10 cm H_2O depending on the time high (T_{high}) and time low (T_{low}) settings in order to prevent or use auto-PEEP. These settings are very similar to the rest settings; however, the initial ratio of P_{high} to P_{low} may range from 8:1 to 10:1 and may better recruit the lungs with the ability for spontaneous ventilation on ECMO, which has been suggested to improve diaphragmatic dysfunction for patients on ECMO.[29] The potential increase in PCO_2 may be managed by adjustments of sweep flow while on ECMO. The optimal ventilation strategy for ECMO patients remains controversial and the level of evidence in the burn population is minimal.

WHAT IS THE ROLE OF AN INTERDISCIPLINARY TEAM APPROACH IN THIS PATIENT'S POPULATION?

In our practice, cardiac anesthesiologists with additional training in critical care medicine lead the cardiac intensive care unit to where burn patients will be admitted if they require ECMO care. ECMO specialist nurses take care of the ECMO circuits and general ECMO management, while intensive care nurses provide the nursing care in the critical care unit. Perfusionists check the circuits and console functions at least once daily. Specialist burn medical and nursing staff from the burn intensive care unit provide the daily burn wound care. Pharmacists and microbiologists consult for the pharmaceutical and antimicrobial management. Daily physiotherapy sessions and dietician reviews support the multidisciplinary effort. All subspecialties participate in daily rounds.

DISCUSSION

Brown and colleagues[30] were the first group who suggested, in 1987, based on animal studies, that partial V-V ECMO could be a useful intervention in the management of severe inhalation injury. In 1994, Ombrellaro et al.[18] performed the first successful ECMO run in a pediatric thermally injured patient who had developed ARDS, and in 1998, Patton and colleagues[31] reported the first successful ECMO intervention in adults with burn injury. Ever since, numerous cases have been published; however, the efficacy of ECMO in this patient population remained unclear because of variable outcomes. The survival ranged in small adult cohorts between 17% and 66%,[21,27] but in small pediatric cohorts survival was very promising, ranging between 53% and 67%, which is comparable to the survival rates of nonburned pediatric patients with respiratory failure requiring ECMO.[32–35]

The first systematic review and meta-analysis to assess the level of evidence for ECMO in ARDS resulting from burn and smoke inhalation injury was conducted in 2013 by Asmussen and colleagues [22]. The authors presented seven clinical and eight experimental (animal) studies, as well as 14 case reports of 18 patients. Sixteen out of 18 cases in an age range of 5 weeks to 42 years survived. The authors rightfully pointed out that case reports represent low evidence based on missing control groups and the fact that cases with negative results are not likely to be published. The clinical trials were published between 1998 and 2010 and included 68 patients and did not suggest significantly improved survival for burn patients supported by ECMO. The authors, however, demonstrated that ECMO run times of less than 200 hours correlated with higher survival compared to 200 hours or more. In addition, scald burns were associated with higher survival rates than flame burns. About 20 years after the first ECMO intervention in a burn patient, and 5 years after the first meta-analysis, publications on ECMO for these patients have become frequent. Devices, circuitry, and oxygenators have significantly improved, and heparin anticoagulation has transitioned to much lower doses. In addition, broad experience has been gained in specialized centers; therefore, the comparison of today's data and historical data should be interpreted cautiously.

The CESAR (Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial,[16] published in 2009, pushed the use of ECMO in general as well as in burn care. In 2016, the French PRONOBURN group showed a 28% 90-day survival rate for ECMO in 11 burn patients with refractory ARDS.[36] The 28-day mortality of 56%, 90-day mortality of 72%, and in-hospital mortality of 91% were devastating results. In all cases, death resulted from multiple-organ failure or septic shock associated with the burn injury. Only two patients left the intensive care unit, with one dying 1 month later.

The detrimental outcomes of this study are in contradiction to the 80% survival rate in the study of Szentgyorgyi et al.[24] In a recent retrospective study, this group presented the best outcomes to date for ECMO in patients with burn and smoke inhalation injury when compared to all previous reports. The patients in this study were young (28–37 years) with normal body mass indexes (21–28). All patients had some degree of inhalation injury, which was confirmed by bronchoscopy. Their revised Baux scores ranged between 62 and 102. All their cases were graded by the Berlin definition as severe ARDS.[37] V-V ECMO was initiated as traditional ventilation strategies failed to adequately oxygenate the patients and to prevent neurologic injury from hypoxemia. All patients required vasopressors to support the cardiovascular function. The patients' demographics were similar in both studies, but Szentgyorgyi and colleagues successfully weaned all five patients (100%) off ECMO, with one patient dying from multiorgan failure due to sepsis later. ECMO alone may not determine the outcome; confounding factors may also be different sources of infection, fluid resuscitation, necrotic tissue, or surgical interventions before, during, or after ECMO.

The 80% survival rate of Szentgyorgyi et al. is underlined by the results of Eldredge and colleagues who identified eight patients with ARDS secondary to burn injury who were placed on ECMO during a 10-year period. All of the patients met criteria for severe ARDS with a Murray score of 3 or greater; seven out of eight patients (87%) survived.[38] Additionally, Ainsworth et al.[39] presented favorable outcomes with a survival rate of 57% (8/14 patients) following V-V ECMO support over a 5-year period (2012–2017).

Nosanov and colleagues[40] recently reported a national perspective on the utilization of ECMO in burn patients in the United States. ECMO patients were matched with patients not requiring ECMO, based on their age, gender, TBSA, and inhalation injury. The authors reported comparable outcome data to the ELSO Registry and concluded that ECMO is a viable option for this patient population. Unfortunately, this was a retrospective data analysis (from 2002 to 2011), and it was not taken into account that technology and management of ECMO have significantly improved over the last decade. The authors were also unable to discern whether V-V or V-A support was used and could not give insights into procedural specifics, such as the specialty and training background of the team members who performed the cannulation and management of ECMO or their experience with ECMO and the amount of cases per year and hospital. Unfortunately, the random collection of data in this study does not appear to contribute to a serious evaluation of today's ECMO in burn care.

In 2017, Hsu et al.[21] reported on six soldiers who suffered injuries from a stun grenade explosion in Taiwan. For all patients, ECMO was initiated as salvage therapy. The study was aimed to evaluate the efficacy of ECMO in major burn patients. All patients had suffered severe injuries and had additional trauma, such as pneumothorax, from the blast injury. Five patients had a TBSA range of greater than 94%, and all suffered from rhabdomyolysis with consecutive AKI. All patients were coagulopathic and required debridement surgery while on ECMO support. They also presented with respiratory compromise and underwent torso escharotomy. The sixth patient had presented with third-degree burns of 50% TBSA and was successfully weaned from ECMO and was the only survivor. The survival rate of 16.7% (1/6) in this study should be discussed from different perspectives. The only

survivor was 49 years old with a TBSA burn of 50%. He had a survivable Baux score of 99 and a reversible cause of his acute respiratory failure and therefore should rightfully be managed with ECMO support. The Baux score is used to predict mortality due to burns. The score is an index that takes into account the correlative and causal relationship between mortality and factors including advancing age, burn size, and the presence of inhalational injury. The other patients, however, suffered 94% to 99% TBSA and Baux scores representing very high mortality risk (123, 129, 139, 149, and 155, respectively) with additional significant trauma and should be evaluated with caution. The problems of creating blood flow in these severely burned patients using V-A ECMO is not surprising, considering the loss of systemic vascular resistance, the presence of vascular leakage, and the burn shock–related volume depletion. On the positive side, the result of this study is evidence of expected undesirable outcomes of V-A ECMO for circulatory support as a desperate final measure in burn shock.

The effectiveness of ECMO, as shown by Hsu et al.[21], when used for reversible respiratory support, is in line with the findings of Kennedy and colleagues,[41] who reported two burn patients, 39 and 53 years of age, with revised Baux scores of 79 and 78, respectively. Both required V-V ECMO support for isolated ARDS and maintained adequate hemodynamics, resulting in positive outcomes.

Burn patients requiring ECMO are a very small proportion of all burn patients. Reports on survival/mortality rates are very important to estimate the value of the ECMO intervention. These reports should be a comprehensive account, considering that prospective studies do not presently exist and are very difficult to perform due to the small number of patients per institution. The more detailed the reports are, the easier it may be in the future to find common ground and standardized treatment protocols for a potential future multicenter trial.

CONCLUSION

- Extracorporeal Life Support is an effective therapeutic option for life-threatening cardiopulmonary failure following burn injury.
- Roughly half of all burn patients managed with ECLS survive to hospital discharge.
- Complication rates are similar to those reported in adult patients who do not receive ECLS.
- ECMO can be a life-saving bridge to recovery for burn patients with pulmonary edema following excessive fluid resuscitation.

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REVIEW QUESTIONS

1. The fire department rescued a man from a burning house; he presents with burn injury to the neck and face. What is the first thing to do?

   A. Apply sterile gauze over the burn injury.
   B. Apply a high-flow oxygen mask.
   C. Give Cyanokit 5 g IV.
   D. Apply pulse oximetry and cardiovascular monitoring.

2. Which of the following statements is incorrect?

   A. Airway swelling can be a dynamic process and needs frequent reevaluation.
   B. Bronchoscopy is the gold standard for diagnosis of inhalation injury.
   C. Soot in the airway is pathognomonic for inhalation injury.
   D. An impaired cough reflex is pathognomonic for inhalation injury.

3. Which of the following statements is incorrect?

   A. Inhalation injury can lead to reduced bronchial blood flow.
   B. Loss of hypoxic pulmonary vasoconstriction is a common finding in severe inhalation injury.
   C. Epithelial cell debris and fibrin can form an airway obstructing cast.
   D. Pulmonary shunt formation can be increased in inhalation injury.

4. Which of the following statements is incorrect?

   A. Nebulized albuterol improves lung compliance in children.
   B. Nebulization of heparin and N-acetylcysteine reduces the formation of atelectasis.
   C. Inhaled nitric oxide can temporarily improve oxygenation.
   D. Inhaled corticosteroids have proven effectiveness in inhalation injury.

5. Which of the following statements is incorrect?

   A. ECMO was first used in a burn patient in 1994.
   B. The first prospective randomized trial of ECMO in burns was in 1999.
   C. Burn injury of greater than 45% TBSA may be a predictor of high mortality.
   D. The survival rate of burn patients on ECMO varies in the present literature between 15% and 85%.

6. Which of the following statements is incorrect?

   A. The recent literature suggests that ECLS nonsurvivors have higher rates of AKI.
   B. The recent literature suggests that nonsurvivors have higher rates of CRRT on ECLS.
   C. Acute kidney injury is a known risk factor for death in patients with burn injury who do not receive ECLS.
   D. Acute kidney injury does not impact the survival rates for burn patients on ECLS.

7. Which of the following statements for survival on ECMO is incorrect?

   A. Cardiopulmonary resuscitation during ECMO is associated with worse survival rates.
   B. Burns of 90% of TBSA are not associated with high mortality rates.

C. Metabolic acidosis is an independent predictor for increased mortality.
D. High vasopressor support increases the risk for mortality.

8. Which of the following statements is correct?

A. ECMO duration of longer than 200 hours is associated with better survival rates than duration less than 200 hours.
B. Patients with flame burns show better survival rates than scald burns on ECMO.
C. ECMO can serve as the oxygenation bridge in fluid-overloaded patients.
D. Increased fluid resuscitation for concomitant trauma does not bear the risk for pulmonary edema.

9. Which of the following statements is incorrect?

A. Echocardiography can be helpful in evaluating ventricular volume status and contractility.
B. Echocardiography can help verify the ECMO cannula position.
C. Echocardiography can exclude tamponade after ECMO cannula placement.
D. Echocardiography does not have a role in ECMO cannula placement.

10. Which of the following statements is incorrect?

A. The average size for an Avalon cannula is 27F–31F.
B. The arterial/return cannula in V-A ECMO usually is a 15F–19F cannula.
C. The arterial/return cannula in V-A ECMO should be larger in diameter than the drainage cannula.
D. The arterial/return cannula in V-A ECMO is usually shorter than the drainage cannula.

11. Which of the following statements is incorrect?

A. The ECMO cannulae should primarily be placed through burned tissue because it is a sterile area.
B. If the ECMO cannula must be placed in a burned area, it should be properly fixated.
C. ECMO cannula placement through burned tissue should be avoided.
D. The ECMO cannulae should have priority over resuscitation lines in terms of location and placement.

12. What does not usually cause oxygenator failure in burned patients?

A. Inflammatory proteins adhering to the oxygenator membrane
B. Low-flow ECMO of 1.5 L/min
C. Anticoagulation with heparin and a PTT goal of 60 seconds
D. Sepsis

13. Which of the following statements is incorrect?

A. Heparin should be stopped 24 hours before wound debridement.
B. Heparin can be safely restarted 12 hours postprocedure if there are no signs of bleeding.
C. If bleeding from wounds occurs, it is reasonable to keep anticoagulation stopped until there is no bleeding.
D. If patients bleed during escharotomy, the administration of platelets and desmopressin may be indicated.

14. Which statement on ventilation during ECLS is incorrect?

A. The so-called rest settings are PIP 20–25 cm H_2O, PEEP 10–15 cm H_2O, respiratory rate 5–10 breaths/min, FiO_2 less than 0.4.
B. Tidal volumes of 12 mL/kg avoid atelectrauma and are called an open lung approach.
C. Volutrauma causes "microfractures" of the extracellular matrix.
D. The plateau pressure should not exceed 30 cm H_2O.

15. Which statement on β-blockade in burn patients is incorrect?

A. Esmolol reduces the heart rate, which is increasing the shunt fraction in burn patients on ECMO.
B. Propranolol treatment for 12 months following thermal injury ameliorates the hyperdynamic, hypermetabolic, hypercatabolic, and osteopenic responses in burn patients.
C. Esmolol contributes to improved oxygenation by reducing shunt fraction.
D. Esmolol can easily be titrated to effect due to its short half-life.

ANSWERS

1B Applying a high-flow oxygen mask is the first thing to do for a patient with signs of inhalation injury, such as burns in the face and neck region.

2D An impaired cough reflex may be due to many reasons but is not pathognomonic for inhalation injury. Answers A, B, and C are correct.

3A Inhalation injury leads to increased bronchial blood flow. Answers B, C, and D are correct.

4D Inhaled corticosteroids may work in inhalation injury, but there is no proven effectiveness. Answers A, B, and C are correct.

5B To date there is no prospective randomized trial of ECMO in burns. Answers A, C, and D are correct.

6D Acute kidney injury is known as a risk factor for mortality. Answers A, B, and C are correct.

7B The mortality risk worsens with an increase in percentage of TBSA burned. Answers A, C, and D are correct.

8C C is the correct answer; fluid resuscitation of burn patients bears a high risk for volume overload and pulmonary edema.

9D Echocardiography can be helpful in evaluating ventricular volume status and contractility, verifying the ECMO cannula position, and excluding tamponade after ECMO cannula placement.

10C The venous drainage cannula should have the largest diameter in order to guarantee adequate flow. Answers A, B, and D are correct.

11A The ECMO cannulae should not be placed in burned areas if this can be avoided. Answers B, C, and D are correct.

12C Answers A, B, and D may be causative for oxygenator failure. High-level anticoagulation like PTT of 60 seconds is rather unlikely.

13A Heparin may be stopped about 6 hours before procedures. Answers B, C, and D are correct.

14B Positive end-expiratory pressure avoids atelectrauma; tidal volumes of 12 mL/kg are obsolete. Answers A, C, and D are correct.

15A Esmolol reduces the heart rate and thereby cardiac output, which is reducing the blood flow that is not going through the ECMO device, therefore reducing the shunt fraction. Answers B, C, and D are correct.

REHABILITATION, NEUROLOGICAL AND ETHICAL ASPECTS OF ECMO

57.

ECMO IN THE AWAKE PATIENT, EARLY EXTUBATION, AND PHYSICAL REHABILITATION

Michael Salna, Darryl Abrams, and Daniel Brodie

STEM CASE AND KEY QUESTIONS

A 36-year-old woman with cystic fibrosis, actively listed for lung transplantation, presented to the emergency room with respiratory distress. Her history was notable for multiple prior hospitalizations for multidrug-resistant pneumonias requiring prolonged intravenous antibiotics; she also had pancreatic insufficiency with recent unintentional weight loss. On presentation, her body mass index was 16.2 kg/m^2, she was febrile to 38.6°C, had a sinus tachycardia to 110 beats/min, and a blood pressure of 103/77 mm Hg. Her arterial oxygen saturation was 84% while breathing supplemental oxygen via a non-rebreather mask. Her arterial blood gas at that time was 7.28/63/42mmHg, and a chest radiograph demonstrated bilateral patchy opacities throughout her lung fields. Bedside echocardiography demonstrated hyperdynamic function with no regional wall motion abnormalities, effusions, or tamponade physiology.

She was admitted to the medical intensive care unit (ICU) for an exacerbation of her cystic fibrosis with pneumonia and acute respiratory insufficiency and, given her increased work of breathing to maintain her saturations on the non-rebreather mask, was endotracheally intubated later that night. Over the course of the next few hours, despite optimal mechanical ventilation, she remained severely hypoxemic and hypercapnic and was consequently cannulated for veno-venous (V-V) extracorporeal membrane oxygenation (ECMO) with right femoral venous drainage and right internal jugular venous reinfusion as a bridge to transplantation (BTT) of the lungs.

HOW MIGHT EARLY MOBILIZATION IMPROVE THIS PATIENT'S PRE- AND POSTOPERATIVE TRANSPLANT COURSE?

Discussions during multidisciplinary transplant rounds the next morning highlighted the importance of mobilizing patients supported with ECMO who are awaiting transplantation. Physical deconditioning is a relative contraindication to lung transplantation, and critically ill patients awaiting transplant who require invasive mechanical ventilation (IMV) along with ECMO for respiratory failure are at high risk of worsening physical conditioning, becoming unsuitable for transplantation typically in a matter of days. Pretransplantation participation in physical therapy during ECMO, used to maintain or even improve physical conditioning, is supported by evidence suggesting that posttransplantation survival is at least as good as in those who never reached that level of illness prior to transplantation.

In this setting, physical therapy was consulted on hospital day 1. On initial assessment, the patient was sedated with a Richmond Agitation-Sedation Scale of -4 and orally intubated. She had a right radial arterial line, right femoral venous ECMO drainage cannula, a right internal jugular ECMO reinfusion cannula, a left internal jugular triple-lumen central venous catheter, a nasogastric tube, a Foley catheter, and electrocardiographic leads for cardiac monitoring.

WHAT STEPS MAY BE TAKEN TO FACILITATE PHYSICAL REHABILITATION, INCLUDING AMBULATION?

There were multiple factors limiting the patient's ambulation. The principle barriers were her level of sedation and, to varying degrees, her lines, catheters, and the endotracheal tube.

One day after the initiation of V-V ECMO, her repeat arterial blood gas was 7.36/41/116mmHg. The use of ECMO has the potential to facilitate gas exchange and thereby improve hypercapnia and hypoxemia to the point of considering endotracheal extubation. If, however, extubation was not advisable, early percutaneous tracheostomy may improve patient comfort, permit sedation weaning, and facilitate respiratory secretion clearance—thereby creating a greater likelihood of success for mobilization than with an oral endotracheal tube.

Femoral cannulation is not a contraindication to mobilization, including ambulation. Some centers may opt for placement of a bicaval dual-lumen internal jugular cannula to avoid femoral cannulation in order to facilitate ambulation, although this is a technically more complicated cannulation approach that requires advanced imaging guidance.

WHAT IS THE PROGRESSION OF PHYSICAL REHABILITATION DURING ECMO?

While the patient was orally intubated and sedated, physical and occupational therapists worked on passive range of motion exercises to all upper and lower extremity joints to

reduce the risk of contracture development. Moreover, nurses continued to turn her in bed every hour to prevent the development of decubitus ulcers.

With ECMO-supported improvements in oxygenation and ventilation, the patient's ventilator settings were weaned and sedation subsequently discontinued. By ECMO day 2, she was awake and following commands; with the assistance of physical therapists, she began bed-level cycle ergometry. Over the subsequent days her activity levels were rapidly escalated, and the degree of assistance she required decreased. She transitioned from sitting on the edge of the bed to sitting in a chair, to standing with assistance, walking in place, and, finally, ambulation around the ICU.

WHAT ARE SOME REASONS TO DELAY OR DEFER PHYSICAL REHABILITATION?

Participation in physical therapy should be deferred if the risks of mobilization are felt to outweigh the benefits. Circumstances that may be considered contraindications to physical therapy include clinically significant hemorrhage, unstable arrhythmias, hemodynamic instability requiring moderate- to high-dose vasopressors, severe hypoxemia or acidemia, or other issues related to clinical instability that may be deemed inappropriate for rehabilitation. Similarly, physical therapy should be discontinued if clinical instability arises during the session.

WHAT ARE CONSIDERATIONS TO LOOK OUT FOR WHEN REHABILITATING PATIENTS WHO ARE RECEIVING ECMO, PARTICULARLY WHEN AMBULATING THESE PATIENTS?

An important aspect of physical rehabilitation during ECMO is ensuring that therapy does not compromise the positions of the cannulae or the degree of support provided by the ECMO circuit. Providers should confirm that cannulae are well secured to the patient, via either sutures or securement straps, to minimize the risk of cannula malpositioning or dislodgment during mobilization. Of note, arterial reinfusion cannulae used in veno-arterial (V-A) ECMO are typically shorter than venous drainage cannulae and may therefore be at greater risk for dislodgment. The team must also ensure that adequate slack in the ECMO tubing is available to permit movement and afford a sufficient range of motion.

During physical therapy itself, patients receiving ECMO are at risk of worsening gas exchange or hemodynamics, depending on the physiological demands of the therapy and the patient's underlying organ failures and indication for ECMO. Close monitoring of respiratory and hemodynamic status throughout therapy sessions is essential to ensure adequate support is being provided. Changes in ECMO settings (e.g. increases in sweep gas flow rates and blood flow rates) may be necessary prior to or during therapy to meet the accompanying increases in physiologic demand. For example, depending on the amount of ECMO support available, the addition of supplemental oxygen, inotropic agents, or vasopressors may be required. If mobilization is anticipated prior to cannulation, consideration should be made for cannula sizes that can accommodate increases in extracorporeal blood flow to meet patients' needs during therapy.[1]

HOW DOES THE ECMO CANNULATION CONFIGURATION AND EQUIPMENT IMPACT MOBILIZATION?

The location of the ECMO cannulae, which itself is dictated by the type of support a patient is receiving, influences the ease of physiotherapy participation. Traditionally, both V-V (Figure 57.1) and V-A (Figure 57.2) ECMO have relied on the use of femoral venous drainage. Recent literature has demonstrated that mobilization may be safely conducted in highly selected patients with femoral catheters, including studies involving femoral V-A ECMO.[2–4] Nevertheless, one must be mindful of the potential risks associated with mobilization in the presence of femoral cannulation, including cannula kinking or dislodgment, and pay particular attention to cannula integrity and securement during mobilization.

Single-site, bicaval, dual-lumen cannulae offer an alternative to femoral cannulation in V-V ECMO. The cannula is placed into the internal jugular vein and situated such that drainage occurs from both the superior and inferior venae cavae, and reinfusion is directed from a side port toward the tricuspid valve.[5] The advanced imaging techniques (e.g., transesophageal echocardiography and fluoroscopy) required to ensure optimal placement make this cannulation approach more technically challenging to perform and may limit its applicability in emergent cannulation settings.[6] However, this may be the preferred approach when the need for V-V ECMO is anticipated in less emergent situations (e.g., planned BTT).

In the case of V-A ECMO for cardiogenic shock, a variety of upper body configurations can obviate the need for femoral cannulation, including internal jugular venous drainage with ipsilateral subclavian or innominate arterial reinfusion.[7–9] Similarly, right atrium to aorta,[10,11] pulmonary artery to left atrium in severe pulmonary hypertension,[12] and various other central configurations may also provide secure cannulation modalities for physical rehabilitation and specifically for

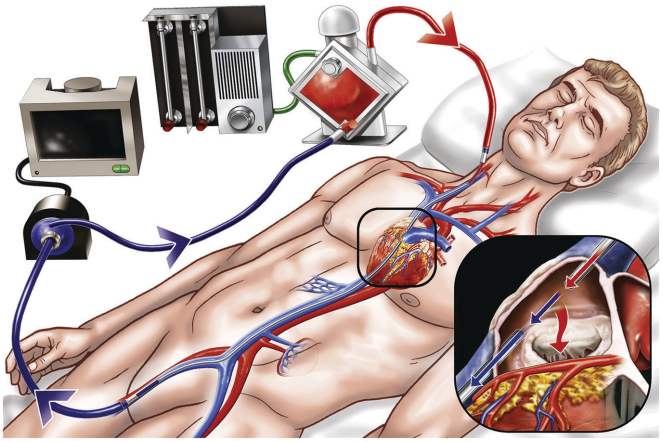


Figure 57.1 Veno-venous ECMO with femoral venous drainage and right internal jugular return.

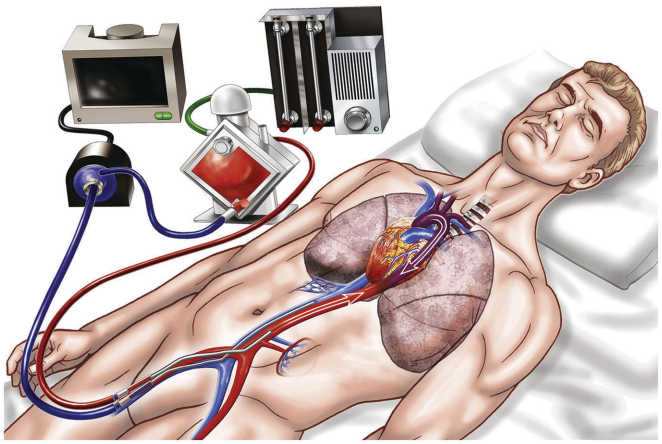


Figure 57.2 Veno-arterial ECMO with femoral venous drainage and ipsilateral common femoral artery return.

ambulation in patients with cardiogenic shock from right- or left-sided heart failure. A specific technique allowing V-V ECMO cannulation that can support patients with pulmonary hypertension and severe right ventricular failure is possible when there is a concomitant atrial septal defect. A bicaval, dual-lumen cannula can be inserted through the internal jugular vein with the reinfusion jet directed across the defect, effectively providing both right ventricular decompression and an oxygenated right-to-left shunt.[13–15] If no atrial septal defect is present, one can be created with an atrial septostomy in select patients.[16]

In addition to cannula location, mobilization during ECMO is also dependent on the transportability of the equipment itself. Advances in extracorporeal circuitry, with more compact circuits with integrated pumps, membranes, and consoles, have made it easier to mobilize equipment alongside patients, thereby facilitating out-of-bed activities, including ambulation.[17,18]

DISCUSSION

Weakness acquired in the ICU is common, particularly in those with prolonged mechanical ventilation,[19] and is associated with increased duration of mechanical ventilation and increased overall lengths of stay in the ICU and hospital.[20–22] In an effort to reduce the morbidity associated with critical illness, a rapidly growing body of literature is focusing on the benefits of minimizing sedation and engaging in early physical therapy in ICU patients. Indeed, a systematic review of studies involving interventions to mobilize ICU patients demonstrated an excellent safety profile with an adverse event rate of only 0.6%,[23] with some studies suggesting that early mobilization in the ICU may improve overall length of stay, rates of delirium, ventilator-free days, and ICU survival.[22,24,25]

Over the past decade, the population of critically ill patients considered eligible for mobilization has expanded to include those who traditionally would have been considered too critically ill to tolerate mobilization due to severe cardiac or respiratory failure. This includes patients receiving ECMO support, where concerns regarding cannula dislodgment and a perceived need for deep sedation previously precluded attempts at mobilization. However, because ECMO has the ability to provide sufficient gas exchange and circulatory support to substantially reduce the reliance on IMV, inotropes, or vasopressors, physiotherapy may be feasible even in the face of severe underlying respiratory or cardiac failure.[18] A study of 61 acute respiratory distress syndrome (ARDS) patients supported with V-V ECMO found that ICU physiotherapy consultation was associated with a significantly lower odds of death (odds ratio [OR] 0.19, 95% CI 0.04–0.98, $P = .048$) and a significantly lower sedation-agitation score, which also correlated with higher intensity physiotherapy.[26]

At this time, it is not known what level of physical therapy is necessary to achieve improved outcomes in critically ill patients, including those supported with ECMO. That said, although ambulation is often a goal of early mobilization within the ICU, those who are not yet capable of ambulation can still participate in bed-level physiotherapy, including active range-of-motion exercises, supine-to-sit transfers, cycle ergometry,[27] or playing physically active video games.[28] Determining which ECMO patients are appropriate candidates for early mobilization depends on the cannulation configuration, the etiology of the underlying illness, the goal of physical therapy, and associated risks, as well as the overall clinical status of the patient.

PHYSICAL THERAPY DURING ECMO FOR RESPIRATORY FAILURE

Historically, critically ill patients with severe respiratory failure who were supported with ECMO were simultaneously maintained on IMV, often with concomitant deep sedation and neuromuscular blockade to facilitate ventilator synchrony and the maintenance of adequate gas exchange—all factors that would have precluded participation in active physiotherapy. In some ECMO patients, the ability to take over gas exchange from the ventilator allows greater opportunity to not only liberate patients from neuromuscular blockers and sedatives, but also pursue endotracheal extubation and avoidance of IMV altogether.[18,19,30] Without the ventilator, there would be no risk of ventilator-associated complications, such as ventilator-associated pneumonia and ventilator-induced lung injury[31]; delivery of aerosolized medications would become more efficient, and out-of-bed activities may become easier with one less device to mobilize.[31,32] In those who require IMV despite ECMO, early tracheostomy may improve patient comfort, facilitate airway clearance, and further increase the likelihood of ambulation,[33] although it is not required in all patients. Of note, tracheostomy has been found to be safe to perform during ECMO, although the timing and indications for tracheostomy are not yet well established.[34] In cases where IMV is still needed despite ECMO support, efforts to attempt early mobilization should not necessarily be delayed, as evidenced by cohort studies demonstrating successful participation in physical therapy in pretransplant patients during ECMO support despite remaining on IMV.[18]

Much of the ECMO mobilization literature comes from the field of lung transplantation, with ECMO serving as a BTT in patients with advanced, irreversible respiratory failure. Physical deconditioning is considered a strong relative contraindication to transplant candidacy, as it is a marker of lower likelihood of survival and recovery posttransplantation.[35] Therefore, active participation in physical therapy is an essential component of maintaining transplant candidacy at centers where wait times for organs are prolonged. The International Society for Heart and Lung Transplantation recommends ECMO as BTT for lung transplant candidates who would otherwise be unable to participate in physical rehabilitation without ECMO support.[36] Early mobilization strategies have been associated with improved outcomes in BTT patients, with a recent study of 121 BTT patients (the largest cohort of these patients to date) demonstrating that ambulation was the only independent predictor of successful BTT in multivariable analysis (OR 7.6, 95% CI 2.2–26.6, $P = .002$).[37,38] Results from other cohorts have identified an association between immobilization of BTT patients in the pretransplant setting and greater risk for ICU-acquired weakness and being delisted for lung transplantation,[39] highlighting the importance of careful selection of those patients for whom ECMO support is most likely to facilitate active physical therapy.

Patients receiving ECMO as a bridge to recovery (BTR), such as those with severe, refractory ARDS, may also be candidates for being awake, endotracheally extubated, and performing physical rehabilitation[18,40] (Figure 57.3). While severe ARDS is often managed with a combination of IMV, deep sedation, neuromuscular blocking agents, and prone positioning prior to ECMO initiation, the subsequent gas exchange support provided by ECMO may be sufficient in select patients to wean or remove these adjunctive therapies altogether. However, this strategy is not without risks and should ensure that spontaneous respiratory efforts do not result in further lung injury.[41] Whether early mobilization in ARDS patients yields better outcomes than delayed or no active physical therapy is an area of ongoing investigation.[42] Other BTR patients with respiratory failure who may benefit from such a strategy include those with status asthmaticus and highly selected cases of chronic obstructive pulmonary disease.[43,44]

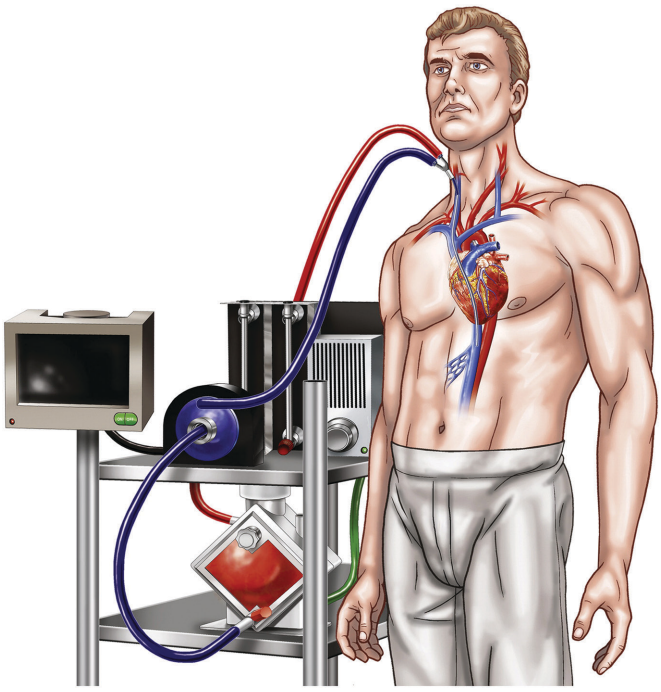


Figure 57.3 Veno-venous ECMO with a bicaval dual-lumen catheter. All figures reprinted from the Journal of the American College of Cardiology, 63(25), Darryl Abrams, Alain Combes, Daniel Brodie, Extracorporeal Membrane Oxygenation in Cardiopulmonary Disease in Adults, 2769–78, Copyright 2014 with permission from Elsevier.

PHYSICAL THERAPY IN ECMO PATIENTS WITH CARDIAC FAILURE

The feasibility of mobilizing patients in cardiogenic shock receiving V-A ECMO is mostly extrapolated from the respiratory failure literature, with supporting data comprising only small case series and reports.[1,45–47] When considering mobilization, there are several important differences between cardiac and respiratory failure patients worth noting.

First, there is a greater degree of variability in the need for IMV in patients with severe cardiac failure. In the cardiogenic shock population, impaired gas exchange may occur in the context of cardiogenic pulmonary edema or concomitant respiratory failure from noncardiogenic etiologies (e.g., ARDS or pneumonia), though not all of these patients will necessarily require IMV, which may, in turn, make mobilization easier. In cases where there is a substantial concomitant impairment in gas exchange, the addition of a venous reinfusion limb to an existing femoral-femoral V-A circuit (i.e., veno-arterial-venous [V-AV] ECMO) may improve oxygenation,[48] particularly to the upper body. The drawback of such reconfiguration is the added difficulty of mobilization with multiple ECMO cannulae, although this is still feasible. An alternative approach, which may maximize upper body oxygenation and further facilitate mobilization by avoiding femoral cannulation, is central cannulation (e.g. right atrial drainage and aortic reinfusion[11] or left ventricular drainage and axillary reinfusion[49]). Such a strategy, however, may invite a new set of complications due to the need for a sternotomy or thoracotomy.[50,51]

Another consideration in the cardiogenic shock population is the frequent concomitant use of intra-aortic balloon pumps or percutaneous ventricular assist devices (VADs) used to aid in decompression of the left ventricle.[52] These devices greatly complicate any attempt at physiotherapy given the risk of device displacement during activity. Axillary arterial approaches for percutaneous VADs[53] might theoretically help minimize this risk of mobilization, but this remains mostly speculative.

There is a need for more data on mobilization of patients receiving ECMO for cardiac failure, specifically with regard to safety and outcomes. Regardless, the principles governing physiotherapy in this population are similar to those with respiratory failure: ensure acceptable degrees of gas exchange and hemodynamic stability, sufficient alertness to participate

in therapy, and an impression that the benefits of physical therapy outweigh the risks.

THE IMPORTANCE OF MULTIDISCIPLINARY TEAMS

An important principle in successfully performing physical rehabilitation during ECMO, regardless of cannulation configuration or etiology, is ensuring a collaborative, multidisciplinary approach that may include nurses, physical and occupational therapists, respiratory therapists, perfusionists, surgeons, and intensive care clinicians.[18,26,40] Such a strategy has been associated with low complication rates at high-volume ECMO centers.[18–40] Well-delineated roles should be established for each team member prior to participation in physical therapy, and checklists should be strongly considered for all essential steps in the process in order to ensure patient safety and maximize success of the intervention.[18]

CONCLUSIONS

- Weakness acquired in the ICU is associated with suboptimal outcomes that may be mitigated by early mobilization.
- ECMO can reduce both the reliance on IMV for respiratory failure and inotrope and vasopressor dependence in cardiogenic shock.
- The minimization of dependence on IMV may facilitate weaning of sedation and endotracheal extubation during extracorporeal support. Early tracheostomy should be considered when there is an expected prolonged concomitant reliance on both ECMO and IMV.
- Femoral cannulation is not a contraindication to early mobilization. However, upper body cannulation configurations may increase the ease of ambulation in selected patients.
- Care should be taken during mobilization to ensure that ECMO cannulae are secure, there is sufficient slack in the circuit, and gas exchange and hemodynamic parameters are maintained within an acceptable range. ECMO support may need to be augmented prior to or during physical therapy to meet increased physiological demands.
- Multidisciplinary teams with well-defined roles are essential for a successful ambulatory ECMO program.

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REVIEW QUESTIONS

1. Which of the following may be suitable physiotherapy interventions for ECMO patients not yet ready for ambulation?

   A. Active range of motion exercises
   B. Playing interactive video games
   C. Assisted rolling in bed
   D. All of the above

2. Which of the following patients would NOT be a good candidate for ambulation while receiving ECMO?

   A. A 26-year-old woman with cystic fibrosis with a dual-lumen, right internal jugular V-V ECMO cannula, endotracheally extubated, and hemodynamically stable awaiting single-lung transplantation
   B. A 43-year-old man with viral myocarditis who was emergently cannulated with femoral-femoral V-A ECMO in the emergency room and recently had a percutaneous axial left VAD placed in the left femoral artery
   C. A 50-year-old woman with long-standing congestive heart failure who was admitted with a heart failure exacerbation and cannulated with femoral-femoral V-A ECMO with significant improvement in the dosages of her pressors and inotropes
   D. A 34-year-old man who was intubated in the field for severe respiratory distress in the setting of status asthmaticus, was cannulated with femoral-internal jugular V-V ECMO for severe hypercapnea, and has been weaned off sedation

3. All of the following interventions would facilitate mobilization EXCEPT

A. Conversion of femoral-femoral V-A ECMO to right internal jugular–to–axillary artery V-A ECMO
B. Surgical tracheostomy
C. Femoral-femoral V-A ECMO with an additional reinfusion cannula in the right internal jugular vein
D. Insertion of a dual-lumen internal jugular ECMO cannula

4. Which of the following would be a relative contraindication to ambulation during ECMO?

A. Platelet count 6000
B. Femoral-femoral V-A ECMO configuration
C. Bridge to heart transplantation
D. Frequent tracheostomy suctioning

5. Which of the following are known risks associated with physical therapy participation on ECMO?

A. Kinking or dislodgment of cannulae
B. Bleeding at cannulation sites
C. Need for greater blood flow or gas flow rates
D. All of the above

6. How soon after ECMO cannulation could a physical therapist be consulted?

A. As soon as possible after initiation of support
B. After the decision is made to list an ECMO patient for transplantation in BTT
C. When the patient has been weaned off all inotropes and vasopressors in patients with cardiogenic shock
D. Once the patient is endotracheally extubated

7. What differences must be taken into consideration for physical rehabilitation of a patient on V-V ECMO compared with a patient on V-A ECMO?

A. There are more data outlining ambulation strategies for V-A ECMO than for V-V ECMO.
B. Veno-arterial ECMO patients may have additional support devices rendering physical rehabilitation more difficult.
C. Veno-venous ECMO patients, on average, are more likely to be extubated than the average V-A ECMO patient.
D. The internal jugular reinfusion cannula of V-V ECMO is at higher risk of dislodgment than the femoral arterial cannula in peripheral V-A ECMO.

8. Ambulation may be made easier in patients on femoral-femoral V-A ECMO who develop upper body hypoxia by

A. Converting to central cannulation (right atrial to aortic)
B. Addition of a venous reinfusion limb into the internal jugular vein
C. Increasing mechanical ventilation support
D. Downsizing the arterial cannula

9. ECMO patients who may benefit from active physical therapy include all of the following except

A. Those with severe ARDS
B. Patients being bridged to lung transplantation
C. Patients with cardiogenic shock requiring a stable level of inotropes
D. None of the above

10. Early mobilization in the ICU may

A. Increase delirium
B. Decrease ventilator-free days
C. Reduce overall length of stay
D. Reduce ICU survival

11. What frequency of physical therapy is necessary to improve outcomes in ECMO patients?

A. Weekly
B. Not yet known
C. Daily
D. Every other day

12. What actions can be taken to facilitate ambulation?

A. Weaning neuromuscular blocking agents and sedatives
B. Tracheostomy in patients requiring persistent IMV
C. Conversion of femoral–internal jugular V-V ECMO to dual-lumen internal jugular cannula
D. All of the above

13. Which of the following statements regarding mobilization of ECMO patients is false?

A. Arterial reinfusion cannulae are shorter than venous drainage cannulae, putting them at greater risk for dislodgment during mobilization.
B. In rare circumstances, V-V ECMO may facilitate extubation, thereby facilitating mobilization.
C. Patients cannulated with femoral-femoral V-A ECMO must be converted to a central configuration prior to ambulation.
D. More compact ECMO circuits with integrated components have made ambulation easier.

14. Mobilization of ECMO patients

A. Is usually prohibitively risky to attempt
B. Can help prevent ICU-related myopathy
C. Only requires a single provider to accomplish safely and effectively
D. Has only been shown to benefit patients bridged to transplantation

15. Prior to mobilization, which of the following should be taken into account?

A. Cannula configuration
B. Amount of hemodynamic or ventilator support the patient is receiving
C. All of the necessary lines the patient requires
D. All of the above

ANSWERS

1. D. All of these activities are valuable physiotherapy techniques to prevent critical illness myopathy in patients receiving ECMO who are not yet ready for ambulation.

2. B. Oral endotracheal intubation and femoral cannulation do not preclude ambulation; however, the presence of a microaxial percutaneous left VAD (e.g., Impella) in the femoral artery prohibits ambulation given the very high risk of device malposition with ipsilateral leg movement.

3. C. While ambulation is still possible with femoral venous or arterial cannulation, V-AV ECMO makes mobilization considerably more difficult. Upper body cannulation strategies (answers A and D) and tracheostomy (to facilitate oral extubation) may make mobilization easier in selected patients.

4. A. Reasons to defer ambulation include significant hemorrhage, unstable arrhythmias, severe thrombocytopenia, hemodynamic instability requiring high-dose vasopressors, persistently severe hypoxemia, sedation, or the use of neuromuscular blockades.

5. D. All of these are potential risks associated with patient mobilization during ECMO support.

6. A. Provided patients are clinically stable, physical therapists or other ICU clinicians can work with them as soon as the patient is cannulated. Even if the patient is endotracheally intubated and unable to get out of bed, physical therapy can begin with bed rolls and range-of-motion exercises.

7. B. Patients on V-A ECMO are more likely to have additional mechanical circulatory support devices such as balloon pumps or percutaneous microaxial pumps for left ventricular unloading, which are at risk of dislodgment during physical rehabilitation.

8. A. Central cannulation, while necessitating a sternotomy or thoractotomy, can liberate patients of a femoral cannula while also providing adequate upper body oxygenation.

9. D. All ECMO patients may benefit from some form of physical rehabilitation unless there are relative contraindications to doing so at a given time.

10. C. Early mobilization of ICU patients has been shown to improve delirium, increase ventilator-free days, reduce overall length of stay, and improve ICU survival.

11. B. The frequency and amount of physical rehabilitation needed to improve outcomes in ECMO patients are still topics of ongoing investigation.

12. D. All of these interventions may improve patient comfort and facilitate ambulation.

13. C. Central cannulation is not mandatory for mobilization or ambulation with V-A ECMO. Femoral cannulation is not a contraindication to mobilization, and its safety has been described in the literature.

14. B. One of the most important benefits of physical rehabilitation in the ICU is the reduction in critical illness myopathy.

15. D. All of these aspects must be taken into consideration to ensure safe and effective patient participation in physical rehabilitation activities.

58.

NEURODEVELOPMENTAL OUTCOME AFTER PEDIATRIC CARDIAC ECMO SUPPORT

Aparna U. Hoskote, Suzan Kakat, and Katherine L. Brown

STEM CASE AND KEY QUESTIONS

A 13-month-old previously well child presented to the emergency room of a local district general hospital with a 2-day history of vomiting and poor oral intake. On clinical assessment, he was found to be in cardiogenic shock with tachycardia, unstable blood pressure, increased work of breathing, and hepatomegaly. Initial investigations revealed lactic acidosis and plethoric lung fields on the chest x-ray. On induction of anesthesia for intubation and mechanical ventilation, he suffered a 5-minute cardiac arrest with return of spontaneous circulation after cardiopulmonary resuscitation (CPR). With a presumptive diagnosis of myocarditis/dilated cardiomyopathy, he was transferred to a pediatric cardiac intensive care unit.

Following admission, he remained hemodynamically unstable and developed ventricular tachyarrhythmias. An echocardiogram confirmed severe global myocardial dysfunction with left atrial and left ventricular dilation with severe mitral regurgitation. The decision was made to urgently deploy veno-arterial (V-A) extracorporeal membrane oxygenation (ECMO) through cannulation of the right internal jugular vein (IJV) and right common carotid artery (CCA). A decompressive balloon atrial septostomy and endomyocardial biopsy were performed after initiation of V-A ECMO. The histology showed lymphocytic infiltrate, and the blood polymerase chain reaction was positive for parvovirus.

Over the following 7 days, he showed good myocardial recovery and was successfully decannulated from ECMO. However, 3 days later, he suffered further cardiac decompensation related to ventricular arrhythmias requiring recannulation for V-A ECMO. He developed focal seizures, which were controlled with phenobarbital. An electroencephalogram (EEG) confirmed some sharp spikes on the right side with poor background activity. He was commenced on antiepileptic medication (levetiracetam) and had no further seizures. A computerized tomogram (CT) brain scan urgently organized revealed no abnormalities. Given the anticipation of a prolonged requirement for mechanical circulatory support (MCS), the decision was made to convert V-A ECMO to Berlin Heart left ventricular assist device (LVAD) as a bridge to recovery or transplant.

The right IJV and CCA were surgically reconstructed during ECMO decannulation. His postoperative course was complicated by gram-negative sepsis, consumptive coagulopathy, and acute kidney injury. Despite broad-spectrum antibiotics, his sepsis proved difficult to clear, resulting in a persistent inflammatory state with pyrexia and ongoing bleeding from the ventricular assist device (VAD) cannula sites and chest drains. Serial echocardiograms on VAD showed gradual improvement of his left ventricular function, allowing successful VAD explantation after 20 days. Intraoperatively, he was found to have mediastinitis and required a 6-week course of antibiotics. He subsequently made good progress and was gradually weaned off cardiovascular and ventilatory support.

He was discharged to the cardiac ward 12 days later and to home on day 33 after LVAD explantation, where his myocardial function continued to improve slowly. Regular clinical evaluation at the cardiology outpatient clinic showed further improvement of his cardiac parameters. Neurologically, he demonstrated reasonable motor function and was gradually gaining his speech, and no further neurodevelopmental tests or neuroimaging were performed.

Eleven months following hospital discharge, at the age of 2 years, he presented to his local hospital with left-sided hemiplegia and left facial weakness. A subsequent urgent CT of the brain revealed extensive acute ischemic changes in the right middle cerebral artery (MCA) and right anterior cerebral artery (ACA) territories. He was admitted to the pediatric neurology ward for monitoring. Neurosurgical intervention was not required in the absence of signs of raised intracranial pressure. A follow-up CT brain angiogram showed evolution of the previous findings and also revealed occlusion of the proximal right CCA and the terminal branches of the right internal carotid artery. Antiplatelet therapy with acetylsalicylic acid was commenced. After hospital discharge, regular physiotherapy, occupational therapy, speech and language assessment, neurology, and cardiology follow-up appointments took place to evaluate his neurological and cardiac status.

At the age of 5 years, he developed a generalized tonic seizure 24 hours following a combined measles, mumps, and rubella (MMR) vaccine, which was terminated by rectal diazepam but required admission to the ICU for respiratory support. A follow-up CT of the brain showed chronic evolution of the areas of previous infarction in the right hemisphere, and the EEG did not show any epileptiform discharges. He was

successfully weaned from ICU support and returned to his baseline with no further events.

Since discharge from this admission, in his last follow-up at the age of 9 years, it was noted that he had made remarkable progress with a Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) score of 2—mild disability. The left hemiparesis was still evident, with the upper limb more affected than the lower limb at his last visit in the clinic; however, apart from an increased tone and brisk reflexes affecting the left upper and lower limb, the rest of the neurological examination was unremarkable. He however needed a hearing aid for sensorineural deafness in the right ear.

He remained under the community pediatric services and recently received a statement of special education to receive additional help at school. From the cardiology standpoint, his last echocardiogram demonstrated good biventricular systolic function with a fractional shortening of 34% and no dilation of the left ventricle, and his exercise tolerance was reasonable. His parents understood the importance of follow-up and remained engaged in his ongoing follow-up.

WHAT ARE THE RISK FACTORS THAT PREDISPOSED THIS CHILD TO NEUROLOGICAL COMPLICATIONS ON AND AFTER ECMO?

Children supported on ECMO for cardiopulmonary failure related to cardiac disease, whether due to structural causes such as congenital heart disease (CHD) or pump failure with normal heart, such as acquired heart disease (myocarditis or cardiomyopathy), represent a high-risk subgroup of patients for neurological morbidity. There are often multiple risk factors pre-, on-, and post-ECMO treatment (in isolation or in combination) that can contribute to an acute neurological event (ANE).[1–5] In the case of this child, the risk factors were hemodynamic instability and cardiogenic shock resulting in cardiac arrest, emergency ECMO cannulation, V-A ECMO, the cardiac catheter procedure on ECMO for decompression of the left ventricle, a second run of ECMO for ongoing decompensation, conversion from ECMO to VAD with reconstruction of the cervical vessels used for cannulation, postoperative systemic inflammatory state with superadded gram-negative sepsis with acute kidney injury, and the procedure of explantation.

All these factors can have an adverse impact on the cerebrovascular hemodynamics, contributing to the risk for neurological complications. Furthermore, maintaining a fine balance between clotting and hemorrhage with systemic heparinization is necessary to prevent the circuit from clotting without increasing the risk for bleeding. Any imbalance in this process, particularly in the context of infection, can lead to either hemorrhage or microemboli, and the cerebral circulation is particularly vulnerable.[6–8] The risk of bleeding can be especially high in cardiac ECMO support post–cardiac surgery.[8,9] Children supported on the Berlin Heart LVAD device have a further risk of neurological events as there is no longer an oxygenator to act as a filter for some of the clots.[2] Up to 30% of children supported on the Berlin Heart LVAD can have cerebrovascular events.[10,11] Furthermore, these children can continue to be at risk of neurovascular problems late removed from the support episode, as highlighted in this case. This is further discussed in this chapter.

WHAT ARE THE COMMON NEUROLOGICAL COMPLICATIONS SEEN ON ECMO?

The neurological complications commonly described on ECMO include seizures (clinical or encephalographic), diffuse ischemia, infarction, and hemorrhage.[2,8,12–14] The Extracorporeal Life Support Organization (ELSO; https://www.elso.org/Home.aspx) provides definitions for neurological complications (Table 58.1). It is important to remember that close vigilance has to be maintained to identify and intervene early to minimize any neurological morbidity. Bedside clinical examination and assessment by the ECMO nursing and medical staff is an important test to assess neurological status. However, most children on ECMO receive sedative medications and in some circumstances muscle relaxants, all of which may hinder neurological assessment. In these circumstances, neuromonitoring is crucial.

WHAT NEUROMONITORING AND NEURO ASSESSMENT DID THIS CHILD HAVE DURING MCS, WHAT WAS FEASIBLE, AND WHAT WERE THE CONSTRAINTS OR LIMITATIONS?

Many ECMO programs utilize standardized neuromonitoring protocols. The modalities for neuromonitoring on ECMO include near-infrared spectroscopy (NIRS), cranial ultrasound scan (CUS), cerebral function analysis monitor, EEG, transcranial Doppler, CT brain scan, and brain injury biomarkers.[12,15–21] This child received standard neuromonitoring, which involved regular bedside assessment and routine EEG. Neuroimaging in the form of CT brain scan was performed when a concern was identified. Clinical concern or any abnormality in the bedside monitoring such as EEG, CUS, or NIRS remain the main driver for a CT scan as this involves a potentially high-risk transfer to the radiology department. These ICU and logistic barriers mean that sometimes neuroimaging cannot be performed at the ideal time point, and this is an important inherent problem for children on MCS. Hence, close monitoring of the clinical status and bedside assessments are crucial. In addition, CT brain may not necessarily reveal all intracranial pathology.

Brain magnetic resonance imaging (MRI) scan is a superior imaging modality and provides better delineation but cannot be performed on patients while on ECMO. Hence, late neuroimaging with MRI, once the devices are removed, are of value. Abnormalities on MRI scans may also have prognostic implications on neurodevelopmental follow-up. Hence, most ECMO centers recommend imaging after decannulation or explantation. This child, however, did not receive any post-MCS CT or MRI neuroimaging.

Table 58.1 ELSO REGISTRY DEFINITIONS FOR NEUROLOGICAL COMPLICATIONS ON ECMO

NEUROLOGICAL	DEFINITION
Brain Death	***Brain Death*** *the irreversible loss of the capacity for consciousness combined with the irreversible loss of all brainstem functions, including the capacity to breathe. Brain death is equivalent to death of the individual, even though the heart continues to beat and spinal cord functions may persist.* ***Neurological determination of death (NDD)*** *is the process and procedure for determining brain death.* ***Ancillary Tests:*** *The demonstration of the absence of intracerebral blood flow is considered the standard as an ancillary test for brain death. Currently validated imaging techniques are cerebral angiography and radionuclide angiography.* ***Apnea Test on ECMO:*** *The patient should be placed on continuous positive airway pressure (CPAP) while the sweep gas flow rate is set to a maximum of 1.0 liter/minute. If the PaCO2 does not rise above 60 mmHg or change by 20 mmHg, the sweep flow can be incrementally lowered to as low as 0.1 liter/minute while still maintaining adequate oxygenation in most circumstances.*
Seizures Clinically Determined	*Clinically determined by assessment*
Seizures Confirmed by EEG	*Confirmed by Electroencephalograph*
CNS Diffuse Ischemia (CT/MRI)	*CT or MRI demonstrating diffuse ischemic changes*
CNS Infarction (US or CT or MRI)	*CT or US or MRI demonstrating localized ischemic change*
Intra/extra Parenchymal CNS Hemorrhage (US or CT or MRI)	*May be intraparenchymal, subdural or subarachnoid*
Intraventricular CNS Hemorrhage (US or CT or MRI)	*>= Grade 2 IVH on US, CT or MRI*
Neurosurgical intervention performed	*Neurosurgical procedure performed during ECLS run (***e.g.** *intracranial pressure monitor, external ventricular drain, craniotomy)*

Downloaded from the ELSO website. ECLS Registry Form Version 6.0–08/20/2019 pg 6/8 © 2019 Extracorporeal Life Support Organization.

WHAT IS THE LINK BETWEEN ANE ON ECMO AND SUBSEQUENT NEURODEVELOPMENTAL CONCERNS?

Multiple studies have shown that neurological complications on ECMO in the form of an ANE are closely linked to neurodevelopmental morbidity post-ECMO.[13,22–25] Furthermore, there may be subtle neurological concerns that may not be identified as an ANE but yet may have an impact on the neurodevelopmental profile.[23] Hence, all children supported on ECMO, including those supported for cardiac disease, need follow-up.[26,27] It is important that children who have had an ANE on ECMO be categorized as a high-risk group that requires targeted follow-up. Seizures on ECMO and impact on outcome have been well described in neonates with respiratory failure and in children with CHD who undergo cardiac surgery.[28] In the Boston Circulatory Arrest Study, postoperative seizure occurrence was the medical variable most consistently related to worse neuropsychologic outcomes at 16-year follow-up, including lower scores on reading and math composites, general memory index, executive function, and visuospatial testing.[28]

WHAT TYPES OF NEURODEVELOPMENTAL ISSUES DID THIS CHILD DISPLAY AT FOLLOW-UP?

The spectrum of neurodevelopmental outcome after cardiac ECMO is wide.[27,29–32] The outcome is dependent on various factors, including ANE on ECMO, any history of cardiac arrest, age when initiated on ECMO, and surgery preceding ECMO.[33–35] In this case study, the child developed ANE in the form of seizures (confirmed on EEG) but with normal CT report, putting him at high risk of developing later neurological impairment. Late into his discharge (11 months after hospital discharge), he developed a stroke and subsequent seizures. Neuroimaging then showed extensive acute ischemic changes in the right MCA and right ACA territories, and a further follow-up CT brain angiogram revealed occlusion of the proximal right CCA and the terminal branches of the right internal carotid artery. The right CCA had been reconstructed at the time of decannulation from ECMO—a process followed by many institutions and described in many studies in the 1990s.[36,37] However, the patency postreconstruction of the vessels remains of concern,[38,39] and the impact on long-term neurodevelopment is unclear.[38,40]

The patient subsequently developed a seizure related to immunization with MMR. He remained under the care of community pediatricians and has needed additional help at school. In addition, he was identified to have later significant hearing impairment and has needed to be fitted with a hearing aid. Sensorineural deafness can manifest late, despite having previous normal hearing tests.[41,42] Despite all of the above neurodevelopmental concerns, in his last follow-up at the age of 9 years, he had shown significant improvements with input from community developmental services and was scored with a PCPC/POPC score of 2—mild disability.

WHAT TYPE OF NEURODEVELOPMENTAL FOLLOW-UP DID THIS CHILD HAVE, AND WHAT COULD HAVE BEEN DONE TO IMPROVE HIS FOLLOW-UP?

Children supported on ECMO should have multidisciplinary follow-up targeted for general physical, medical, neurodevelopmental, and psychosocial care, in addition to the management of the underlying condition. Sequential follow-up that supports assessment at regular intervals is of paramount importance. From the case study, it is clear that neurodevelopmental problems can manifest late after the episode of MCS. These may be related to the primary MCS event, but in addition, they may also have new neurological events. Thus, regular surveillance is necessary to facilitate early assessment and intervention. This child had follow-up for the management of his heart condition. It is likely that he would have benefitted from having follow-up in services focusing on child development, particularly in light of his critically unwell state in the ICU and seizures on ECMO. Although he did have a normal CT brain scan while supported on ECMO, he did not have further after MCS neuroimaging.

A plan for structured follow-up needed to be established at the time of discharge from his first admission—including what type of neuroimaging and when and where and who will be the central point of contact to ensure that the child receives comprehensive follow-up. As there are wide variations in the way regional and subregional primary and secondary healthcare providers are set up, identifying this at the time of discharge is important.

Only after his second neurological event did this child receive detailed neurodevelopmental follow-up with input from a community pediatrician, physiotherapy and occupational therapy, and speech and language assessment. It is particularly noteworthy that some children have difficulties at school and need additional support.[43] Again, as described, this child needed special help at school. The reasons for this are speculated to be multifactorial and involve impairment in attention, memory, and executive functioning, which become particularly apparent as the child grows up; hence, longitudinal follow-up is of paramount importance.

DISCUSSION

The use of ECMO for refractory cardiac failure has been increasing over the years, with improved survival outcomes resulting in a growing population of survivors.[44–46] The primary etiology leading to cardiorespiratory failure necessitating ECMO varies from congenital to acquired conditions. The commonest scenario where ECMO may be needed is the child with complex CHD who develops cardiac failure in the postoperative period following a repair/palliative procedure.[47] The second common scenario is the child with new-onset heart failure in the context of myocarditis or cardiomyopathy who is rapidly deteriorating.[48] Finally, the third common indication for ECMO is in the context of extracorporeal cardiopulmonary resuscitation (ECPR) in children refractory to standard resuscitation.[49,50]

A common theme underlying all these clinical scenarios is severe hemodynamic instability with ischemia and hypoperfusion of the organs, including the brain, with or without hypoxemia, resulting in a state of severely compromised cerebral hemodynamics and oxygenation. On a background of this compromised state, the inherent risks posed by systemic anticoagulation, a systemic inflammatory state, and the dependence on the mechanical circuit until cardiac recovery occurs can increase the risk for neurological events on ECMO. Overt and subtle neurological events on ECMO can result in medium- to long-term neurological sequelae. While the ECMO rate within congenital heart surgery programs is on average 2%–3%, children with more severe forms of CHD undergoing complex cardiothoracic surgery such as stage 1 Norwood surgery for hypoplastic left heart syndrome or cardiothoracic transplants and those supported following cardiac arrest, are increasingly represented within this population.[47,49,51,52]

Outcomes of ECMO for children with cardiovascular disease are in general worse than for respiratory indications,[45] and many ECMO complications that are linked to poor outcome appear to be more frequently seen in children with cardiovascular diseases, including infections, bleeding and thrombosis, renal failure, and ANEs.[5] Hence, a clear understanding of

- Neurodevelopmental outcomes in this high-risk population and the caveats related to interpretation of outcomes published in the literature and
- The strategies to improve neurodevelopmental outcomes, which include
  1. Identifying risk factors,
  2. Minimizing neuro injury on ECMO, and
  3. Supporting a structured, longitudinal follow-up pathway and instituting interventions early once concerns are identified are increasingly important.

Figure 58.1 outlines the interplay of different strategies.

THE SPECTRUM OF NEURODEVELOPMENTAL OUTCOMES AFTER PEDIATRIC CARDIAC ECMO SUPPORT

As previously mentioned, the spectrum of neurodevelopmental outcomes is wide, and the extent of these neurodevelopmental deficits is dependent on

- The underlying cardiac condition
- Indication for ECMO
- Presence of risk factors such as cardiac arrest
- Any neurological morbidity experienced on ECMO
- Postdischarge neurodevelopmental surveillance and targeted interventions

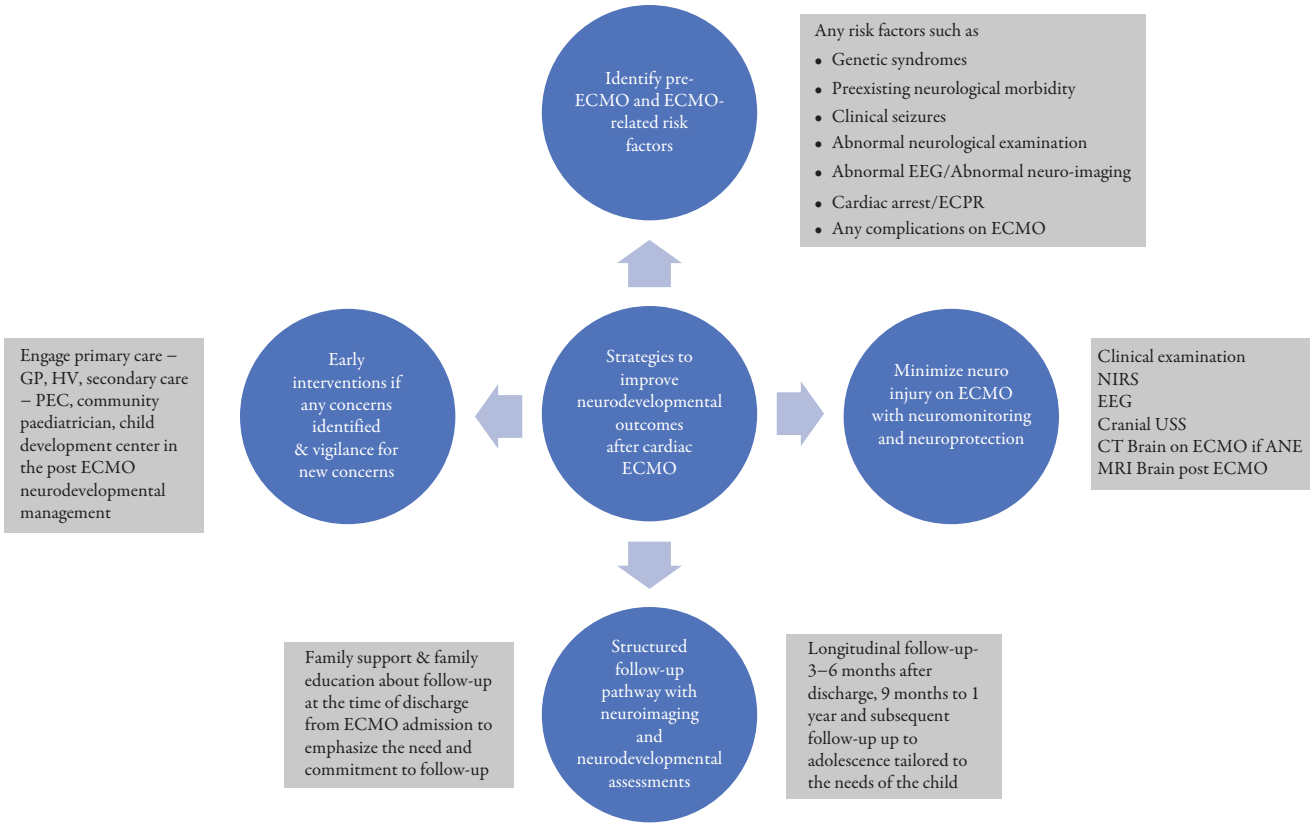


Figure 58.1 Strategies to improve neurodevelopmental outcomes after cardiac ECMO. The figure highlights the multiple factors that need to be taken into consideration and coordinated to optimize neurodevelopmental outcomes for children supported on ECMO for cardiac disease. ANE, acute neurological event; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalogram; ECPR, extracorporeal cardiopulmonary resuscitation; GP, general practitioner; HV, health visitor; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PEC, pediatrician with expertise in cardiology; USS, ultrasound scans

Long-term neurodevelopmental studies with longitudinal follow-up in this population are limited. The incidence of neurodevelopmental problems range from 20% to 73% depending on the study design, the type of test used, the outcome measure used, the inherent case mix, and local practice variations.[25,31,33,34,43,53–57] The range of difficulties described include

- Deficits in gross and fine motor
- Cognitive function
- Language
- Visual perception
- Processing speed
- Sustained attention
- Verbal, visuospatial, and working memory
- Executive functioning
- Academic achievement
- Behavior and psychosocial adjustment

Table 58.2 outlines some of the studies with long-term neurodevelopmental outcomes.

A 2018 systematic review[31] identified eight studies on cardiac (congenital or acquired heart disease) ECMO survivors, reporting a variable proportion of children with neurodevelopmental problems, dependent on the instrument used, that ranged from 25% to 50% at 1–5 years after discharge; these children were in the severely disabled range (defined as > 2 standard deviations [SD] below the population mean for the given test [Wechsler Preschool and Primary Scale of Intelligence – IV (WPPSI), Wechsler Intelligence Scale for Children (WISC), Bayley Scales of Infant Development (BSID)])[34,53,54] to 81%–91% reporting favorable outcomes (defined as PCPC/POPC < 3 or < 4 or no change from baseline)[22,58,59] at discharge or within 3 years of follow-up. Studies on quality of life (QoL) reported that 18% to 53% of cardiac ECMO survivors had significantly diminished QoL scores as compared to age-matched, healthy peers,[35,43,60] with one study demonstrating reduced scores compared to that of peers with cardiac disease but no history of ECMO.[60] We describe some of these outcomes in the discussion that follows.

NEUROPSYCHOLOGICAL OUTCOMES

Motor and Cognitive Outcomes

Neurodevelopmental problems may be identified as early as in the first year of life. A recent article looking at early outcomes

Table 58.2 STUDIES OF LONG-TERM NEURODEVELOPMENTAL OUTCOME IN CARDIAC ECMO PATIENTS

REFERENCE	POPULATION AND PROPORTION AVAILABLE AT FOLLOW-UP	TIME FRAME OF FOLLOW-UP	METHOD OF OUTCOME EVALUATION	OUTCOME DESCRIPTION	ANY IDENTIFIED RISK FACTORS FOR NEURODEVELOPMENTAL OUTCOME
Ibrahim 2000[33]	Children supported on ECMO n = 26 and VAD n = 11 25/67 (37%)	Median 43 (range 11 to 92) months	Telephone Questionnaire	80% good or excellent, 12% fair and 8% poor outcome	Small patient size, use of circulatory arrest during cardiac repair
Hamrick 2003[34]	Children with CHD supported on ECMO 14/53 (26%)	Assessment at 1, 1.5, 2.5 and 4.5 years	Age appropriate neuro-psychiatric tests	72% normal motor outcome, 50% normal cognitive outcome	Aortic cross clamp time of > 40 minutes
Chow 2004[107]	Children receiving ECLS for cardiac reasons 28/90 (31%)	Mean 4.5 years (range 4 months to 9 years)	Telephone Questionnaire	54% normal neurological outcome	No predictors identified
Wagner 2007[83]	Children receiving ECMO, 13 = cardiac, 9 = respiratory 22/49 (45%)	Mean 6.1 (+/−4.4) years	Age appropriate neuro-psychiatric test	73% moderate to severe impairment	Not studied
Taylor 2007[108]	Children receiving ECMO—mixed cohort 69/211 (33%)	Median 7.2 years (range 3.9 months to 12.6 years)	PCPC	61% good outcome, 22% mild disability, 13% moderate disability, 4% severe disability	Not studied
Lequier 2008[54]	Children receiving ECLS for cardiac reasons 16/39 (41%)	2 years post ECMO	Age appropriate neuro-psychiatric tests	Mental delay in 50%. Motor or sensory disability in 12.5%.	Time for lactate to normalize on ECLS, highest inotrope score during120 hours of ECLS, and chromosomal abnormality
Chrysostomou 2013[22]	Children receiving ECLS for cardiac reasons 63/95 (66%)	1.7 years post ECMO	PCPC	66% good outcome, 22% mild disability, 10% moderate disability, 2% severe disability	Not studied
Ryerson 2015[53]	Children receiving ECLS for cardiac reasons 50/98 (51%)	Mean age 52.9 months	Age appropriate neuro-psychiatric tests	Mean IQ in non-syndromic survivors 79.7, 25% had IQ > 2SD below mean	None identified
Sadhwani 2019[57]	Children with CHD supported on ECMO 21/75 (35%)	12–42 months of age	Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III)	ND scores at least one standard deviation below the normative mean in the gross motor (61%), language (43%), and cognitive (29%) domains of the Bayley-III.	Older age at first cannulation and more cardiac catheterization and cardiac surgical procedures prior to neurodevelopmental assessment
Bembea 2020[24]	Children receiving ECMO—mixed cohort 40/99 (40%)	Within 12 months of receiving ECMO	Age appropriate neuro-psychiatric tests–MSEL, VABS-II, PSOM, PCPC	Median scores for adaptive behavior, cognitive, neurologic and QoL were all below population norms.	New neuroimaging abnormalities during ECMO or within 6 weeks post-ECMO

CHD – congenital heart disease, ECLS – Extracorporeal life support, ECMO – Extracorporeal Membrane Oxygenation, MSEL, Mullen Scales of Early Learning; PCPC, Pediatric Cerebral Performance Category; PSOM, Pediatric Stroke Outcome Measure, QoL – quality of life, VABS-II – Vineland Adaptive Behaviour Scale, VAD – ventricular assist device.

in children younger than 36 months of age with cardiac disease and supported on ECMO reported that survivors had significant delays in multiple domains, with scores at least 1 SD below the normative mean in the gross motor (61%), language (43%), and cognitive (29%) domains of the Bayley-III in comparison to the matched non-ECMO group with CHD when tested at 12–42 months of age.[57] Gross motor function was most impaired, and differences between the groups in the motor

domain persisted even after controlling for the number of subsequent interventions—cardiac catheterizations and primary caregiver education. Motor abnormalities have been reported in other studies on cardiac ECMO survivors.[34,54,57] Hamrick et al. reported that 28% of children seen between 1 and 4.5 years had abnormal motor outcome.[34] In another study, Lequier et al. reported that 12.5% of children who were followed up 2 years after extracorporeal life support (ECLS) had abnormal motor performance.[54] However, studies of the long-term outcome of motor function beyond school age are currently lacking.

When considering cognitive outcomes, Ryerson et al. described below -average intelligence in 4-year-old children who needed ECLS for cardiovascular disease,[53] unlike in neonatal ECMO survivors, where intelligence is usually in the average range and remains stable over time.[61] However, it is becoming increasingly apparent that IQ alone (measured from formal neurodevelopmental tests) is insufficient to predict later neurodevelopmental outcomes and does not necessarily correlate with educational attainments. Nevertheless, many children who received ECMO in the neonatal period are reported to have problems with school performance later in life.[26,43,62] Rather than general intellectual functioning, these academic problems seem to be associated with specific impairments observed in the domains of sustained attention, verbal memory, and visuospatial memory at school age.[61–63] These deficits have been found to be specifically associated with small hippocampal volumes (memory) and impaired global white matter microstructure (attention) in school-aged children, irrespective of underlying disease or type of cannulation.[64,65]

Memory

Memory deficits—especially visual memory deficits associated with reduction in hippocampal size—are increasingly being reported in children who have survived critical illness, particularly in the neonatal period and in neonates who have undergone cardiac surgery.[31,63,66–73] This has been postulated to result from a shared vulnerability of the hippocampus in critically ill neonates (including ECLS survivors and those with CHD) to hypoxia, neuroinflammation, stress, and anesthetics.[71,72,74] Exposure to these factors during the course of the critical illness may lead to early hippocampal alterations and long-term memory impairments.[64,72]

It is also important to bear in mind that children with CHD have multiple reasons other than the ECLS run for impaired neurodevelopmental outcomes, like insults in fetal life such as cerebral blood flow patterns, cardiac surgery involving exposure to inhalational anesthetics, cardiopulmonary bypass, circulatory arrest, and associated noncardiac morbidities, including syndromes.[75–81]

Behavior

Clinically significant behavioral problems have been reported in the range of 16%–63% of mixed ECMO cohorts.[24,61,82] Lequier et al. reported that, out of the 16 survivors at 2 years of age, 63% had behavioral concerns. Information on long-term behavioral outcomes in survivors of cardiac ECMO are limited, but these may have a role to play in psychosocial maladjustment reported in older children and adolescents.

Hearing and Vision

Hearing loss and severe visual impairment (defined as blindness or abnormal vision after correction) is well reported, not only in neonatal ECMO survivors but also in cardiac ECMO survivors.[34,54,83]

Speech and Language

Delayed language and low scores (<1 SD of the population mean) on average expressive and receptive language scores or composite verbal scores have been described in ECMO survivors. Sadhwani et al. reported that the scores were low on BSID as well as the Receptive-Expressive Language Test in cardiac ECMO survivors when compared to matched non-ECMO survivors. In neonatal ECMO survivors, seizures pre- or on ECMO have been associated with speech and language disorder with low verbal scores at preschool and school ages.[84]

HIGHER LEVEL COGNITIVE SKILLS AND EDUCATIONAL ATTAINMENTS

Problems in higher level cognitive functions such as executive function are well described in older children with CHD as well as in neonatal ECMO survivors.[62,70,85]

Quality of Life

The evaluation of QoL has gained increased emphasis in recent years, with the development of new methods for assessment in children and growing interest in functional outcome of survivors.[86–88] The assessment of QoL remains challenging in young children under the age of 8 years, for whom measures are more limited. Available studies documenting QoL in children with cardiovascular disease post-ECMO are listed in Table 58.3. Studies indicated that QoL may be limited in some long-term survivors of ECMO for cardiovascular disease.

A recent article by Elias et al. reported that, among survivors of cardiac patients supported on ECMO, out of a cohort of 65/170 (38%) respondents, negative clinical outcomes (defined as having at least significant physical limitations or "fair" or "poor" health) were reported in 18%; 46% reported learning disability, and 29% received special education.[43] The Pediatric Quality of Life Inventory QoL scores were significantly lower in both self-reported and parent-reported surveys in children when compared with healthy individual normative data, but this was not seen in adolescents. The authors did not find any patient- or ECMO-related variables that were associated with negative outcomes in univariate analyses, but the study was limited by a small sample size and survivors who reported predominantly positive outcomes.[43] In a small cohort of single-ventricle patients supported on ECMO, Friedland-Little et al. reported no difference in the QoL scores in those supported with or without ECMO apart from perceived physical appearance; however, the scores were lower than population norms.[89]

Table 58.3 STUDIES OF QUALITY-OF-LIFE OUTCOME IN CARDIAC ECMO PATIENTS

REFERENCE	POPULATION AND PROPORTION AVAILABLE AT FOLLOW-UP[a]	TIME FRAME OF FOLLOW-UP	METHOD OF OUTCOME EVALUATION	OUTCOME DESCRIPTION	ANY IDENTIFIED RISK FACTORS FOR QUALITY-OF-LIFE OUTCOME
Mahle 2005[109]	Children with CHD supported on ECMO 14/32 (44%)	1-year postsupport	Health Utilities Index–2	Quality-of-life mean score 0.75 (±0.19) compared to full score 1.0	Not studied
Taylor 2007[108]	Children receiving ECMO—mixed cohort 69/211 (33%)	Median 7.2 years (range 3.9 months to 12.6 years)	Health State Utility Index	71% good, 23% moderate, and 6% poor quality of life	Not studied
Costello 2011[110]	Children with CHD supported on ECMO 41/397 (only 44% of eligible survivors)	Median 7 years (range 1.1 to 14 years)	Child Health Questionnaire	Physical summary lower—mean 42.4 (±-16.4), normal 53.0 (±8.8) Psychosocial summary mean similar to normal	Postcardiotomy ECMO, noncardiac medical conditions associated with low physical and psychosocial scores
Wray 2011[111]	Children with cardiomyopathy bridged to transplant 26/33 (79%)	Median 3.1 years (range 1.0 to 6.3 years)	Pediatric Quality of Life Inventory	Physical and psychosocial scores equivalent to nonbridged transplant (slightly lower than normal)	Age at transplant associated with lower emotional QoL
Garcia Guerra 2014[112]	Children receiving ECLS for cardiac reasons 47/98 (47%)	Median age 4 years	Pediatric Quality of Life Inventory	Mean summary scores 64.9, significantly lower than chronic health conditions and CHD not treated with ECMO	Higher inotrope score in the first 24 hours of ECLS and longer length of stay associated with lower Pediatric Quality of Life scores
Elias 2017[43]	Children receiving ECLS for cardiac disease 65/170 (38%) verbal 33/170 (19%) written	Median age 7.3 years	Pediatric Quality of Life Inventory	Negative clinical outcomes (defined as having at least significant physical limitations or "fair" or "poor" health) were reported in 18% of respondents	None identified
Fleck 2017[113]	Children receiving MCS—predominantly cardiac disease 22/58 (38%)	Median 4.5 (0.3–11.3) years; median age at follow-up 5 (0.6–29)	KINDL Questionnaires, SF-36 Health Survey	Health-related QoL as reported by parents lower than that of healthy children, self-assessment in > 12-year-olds comparable to healthy control population	Not studied

QoL, quality of life

[a]Unless stated, the patients not assessed were reported deceased.

Functional Outcomes

As morbidity following recovery from critical illness becomes evident, measures to assess functional outcome are increasingly needed, not only for objective assessment but also for outcome studies. The POPC and PCPC scales are subjective measures that have been used to assess overall functional morbidity and cognitive impairment, respectively.[90,91] The Functional Status Scale (FSS) is a recently developed tool that evaluates six functional domains—mental, sensory, communication, motor, feeding, and respiratory—using more objective definitions for all domain categories than the POPC and PCPC.[92,93]

Cashen et al. found that, in neonates, the development of renal failure and longer hospitalization and, in pediatric patients, chronic neurologic conditions, tracheostomy or home ventilator, ECPR, hepatic dysfunction, and longer ICU stay were independently associated with worse FSS at discharge from the hospital.[94] Both these scales provide a quick, quantitative, and reliable measure of short-term functional status, but do not replace the need for long-term neurocognitive follow-up, testing, and referral for services.

CAVEATS TO THE INTERPRETATION OF NEURODEVELOPMENTAL OUTCOME STUDIES

There are many compounding factors that do not permit generalization of neurodevelopmental outcomes published, as most studies are single-center studies, incorporate mixed age and mixed diagnosis cohorts, have a wide range of follow-up at differing intervals, and use a range of assessment tools. Furthermore, these study cohorts are small with significant attrition and biased, with less than a 50% follow-up response rate, making it difficult to generalize results.

Not all examine factors such as socioeconomic status; number of interventions—medical/surgical/catheter; the type of follow-up; early/late detection of neurodevelopmental issues; and the effect of appropriateness and timeliness of interventions to mitigate against unrecognized and untreated neurodevelopmental impairment. IQ alone is insufficient to judge later life academic performance, with the phenomenon of "growing into deficits" being increasingly evident as children experience more difficulties as they grow up.[26,69,95]

STRATEGIES TO IMPROVE NEURODEVELOPMENTAL OUTCOMES AFTER PEDIATRIC CARDIAC ECMO SUPPORT

Identifying Risk Factors Associated With Poor Neurodevelopmental Outcome

As previously alluded to, the risk factors for worse neurodevelopmental outcomes among cardiac ECMO patients are multiple and range from pre-, on-, and post-ECMO factors; however, there are few modifiable factors. The commonest risk factors include CPR, small patient size, circulatory arrest, surgery preceding ECMO, longer length of stay, and post-ECMO care. Sadhwani et al. identified older age at first cannulation and more cardiac catheterization and cardiac surgical procedures prior to neurodevelopmental assessment as risk factors for neurodevelopmental problems in more than one developmental domain.[57] Table 58.2 also outlines risk factors identified in the follow-up studies.

Minimizing Neuro Injury On and After ECMO

Protecting the brain and mitigating any injury are of paramount importance to any critically unwell child supported on ECMO. The Extracorporeal Life Support Organization (ELSO) Registry data show that over a 7-year period from 2009 to 2015, seizures identified by EEG were reported in 3%–4%, cerebral infarct in 3%–5%, and intracranial hemorrhage in 6%–11% of neonates and older children supported for cardiac indications, respectively.[45] A recent ELSO Registry report that focused specifically on neonatal cardiac patients on ECMO reported a rate of central nervous system (CNS) injury of 14%, with higher risk in low-weight babies, those with worse acidosis, and following ECPR.[5]

The journey to minimize neurological morbidity and improve neurological outcomes starts from the time when the referral for ECMO is first made. Any pre-ECMO risk factors for neurological injury (e.g., significant duration of hypotension/hypoxemia/acidosis, any history of cardiac arrest, significant hypoxic episode, or any history of seizures) can contribute toward neurological morbidity.[54] Close monitoring to prevent swings in the hemodynamics and oxygen saturations and ensuring a smooth transition to full mechanical support is critical, particularly in the context of ECPR. Once on ECMO, maintaining adequate flows to ensure good systemic perfusion and lactate clearance is of vital importance.[96]

Bedside neurological assessment and appropriate use of neuromonitoring, while being aware of the limitations, can facilitate early detection and early intervention. NIRS as a trend is important; however, there are no internationally accepted intervention algorithms.[97] EEG—particularly continuous EEG—has a higher yield[14]; and cranial ultrasound can identify abnormalities but cannot identify deep-seated lesions in the posterior fossa.[12,21] Although systemic hypothermia has been postulated and investigated as a neuroprotective modality in neonates with respiratory failure supported on ECMO[98] and in children after cardiac arrest[99,100] or ECPR,[25] it has not been shown to be effective in improving neurodevelopmental outcome. However, it is important to maintain normothermia and prevent the deleterious effects of hyperthermia on compromised cerebrovascular hemodynamics.

A recent systematic review of neuromonitoring on ECMO reported that there was large variability in the timing and definitions of the neurological event and the outcome measure.[101,102] Many studies are single-center studies and are underpowered due to small sample size. Furthermore, a recent review of the early and late neuromonitoring and neuroassessment modalities in adults and children has provided a comprehensive overview of the current literature.[21] No single modality can reliably, continuously, and safely predict neurological events; however, a combination of modalities may yield a higher chance of early detection of ANE on and after ECMO.[21,103]

Role of Neuroimaging Investigations On and After ECMO

Early neuroimaging (cranial ultrasounds, Doppler, CT, MRI) has been shown to help categorize the risk for development of neurodevelopmental sequelae, though not predict the neurodevelopmental outcome.

In a study looking at 5-year follow-up of 34 neonates with reconstructed RCA after ECMO, Desai et al. found no significant differences between reconstructed and ligated (historical cohort) groups in neonatal complications, EEG abnormalities, or ECMO courses or in developmental or IQ scores between the two groups. However, abnormalities on CT/MRI scans (4 of 31 vs. 11 of 29, $P = .025$) and cerebral palsy (0 of 34 vs. 5 of 35, $P = .054$) were more common in infants with RCA ligation, thus suggesting that RCA reconstruction after V-A ECMO may improve outcome.[40] A later study comparing the morphology and metabolism of the left and right basal ganglia in a small series of nine neonates after ECMO, using proton MRI and spectroscopy, showed no significant metabolic differences between either the left or right basal ganglia, despite a small right-sided thalamic infarct in one child, and all the infants showed symmetrical neurodevelopment.[104]

In light of these varying findings, follow-up of arterial patency with Doppler is not routinely advocated, although it may be performed by certain institutions. Post-ECMO MRI brain scans are recommended and may help risk stratify a subgroup of children who need more targeted follow-up. However, a single-center study on neonatal ECMO survivors reported that cranial ultrasound and MRI findings were not

predictive of delayed neurodevelopment on the BSID scale. Tube feeding at discharge was the only independent variable for moderate/severe neurodevelopment scores.[17] A recent two-center study by Bembea et al. showed that the presence of new neuroimaging abnormalities during ECMO, or within 6 weeks post-ECMO, was associated with abnormal neurodevelopment at 12-month assessment.[24]

SUPPORTING A STRUCTURED, LONGITUDINAL, MULTIDISCIPLINARY FOLLOW-UP PATHWAY FOR CARDIAC ECMO SURVIVORS

The Role of Structured Multidisciplinary Follow-up

Extracorporeal life support in children with heart disease constitutes yet another risk factor for developing neurodevelopmental disorders or disabilities, and close monitoring is warranted to facilitate early evaluation, diagnosis, and intervention. In general, all children supported on cardiac ECMO should have neurodevelopmental assessment in addition to disease-specific follow-up for the underlying cardiac disease. Specific follow-up recommendations depend on the indication for ECLS (e.g., ECPR), any presence of neurological comorbidity, and the nature and extent of the underlying disease. Patients with neurological comorbidity should be referred for follow-up by a neurologist and/or a community-based child development center. In case of any suspected neurological comorbidity that was not obvious at discharge, patients should be considered as having neurological comorbidity and referred for follow-up to a pediatric neurologist. The need for regular assessments and intervention is dependent on the extent of impairment. A multidisciplinary approach is essential as survivors can have impairment in many different aspects of neurodevelopmental functioning, ranging from motor, cognitive, speech, and language to behavioral outcomes.[21,26,43]

Recommendations for Follow-up and Neurodevelopmental Assessments

For children, irrespective of the presence of an underlying disease, a long-term follow-up program with regular assessments covering various medical and neurodevelopmental domains is recommended (Table 58.4). Such a follow-up program would preferably be offered within the ECMO center but could also be provided by a general pediatrician/community pediatrician and other healthcare providers closer to their home. A single-center 1-year ECMO follow-up program offered an opportunity for families to return to the ECMO center, so that any neurodevelopmental concerns could be identified, and children could be signposted to appropriate services.[23] In the United States, the American Heart Association has published a scientific statement endorsed by the American Academy of Pediatrics that outlines a program of surveillance for children with CHD.[27]

However, studies of sequential and longitudinal assessment of children with CHD supported on ECMO are limited.[34] An ideal pathway would consist of identifying risk factors at the time of the ECLS episode and planning a structured, longitudinal follow-up from the discharge and integrating this with regular cardiology follow-up.

Risk Stratification for Targeted Follow-up

Any child who has developed a neurological complication on ECLS will need an even more targeted follow-up. The ideal algorithm should incorporate follow-up, neuroimaging, and sequential age-appropriate neuropsychological testing up to school age and beyond, in a risk-stratified process depending on clinical neurological signs and neuroimaging findings. Furthermore, a standardized follow-up pathway tailored to the child's needs provides information and knowledge for pediatricians and community services to evaluate and support the infant/child's ongoing developmental needs. A structured framework and recommendations for longitudinal follow-up are outlined in Table 58.4.

Cardiac Arrest and ECPR Subgroup

The survivors of ECPR present an unique group that is likely to have a higher incidence of neurological complications and neurodevelopmental sequelae. An ELSO Registry–based assessment of acute CNS complications after ECPR, which predominantly reflects cardiac patients, reported a high incidence of ANE in 22%, including 11% brain death, 7% cerebral infarction, and 7% cerebral hemorrhage.[4] Given that CNS complications on ECMO are linked to the use of ECPR, LVAD, V-A support, bicarbonate, and inotropes, such complications are inherently more likely in children with cardiovascular disease. As a secondary analysis of a wider hypothermia after cardiac arrest study, Meert et al. reported the 1-year survival and neurobehavioral outcome at baseline and 1-year follow-up using the second edition of the Vineland Adaptive Behavior Scales (VABS) in survivors of E-CPR for in-hospital arrest. They found that 22.1% had VABS scores that decreased by 15 points or less, and 30.5% had VABS scores that increased by 70 points or more from baseline. They reported that open-chest cardiac massage and minimum postarrest lactate were associated with survival with good neurobehavioral outcome at 1 year.[25] Importantly, many cardiac ECMO outcome studies include a significant proportion of children supported as having ECPR, and this may have an impact on the overall neurodevelopmental outcome findings.[24,43,57,94]

Children Supported on Ventricular Assist Devices

Mechanical circulatory support using VADs is a life-saving strategy while waiting for a heart transplant for children in end-stage heart failure refractory to medical therapy. Use of VADs has increased over the last 5 years with the availability of devices such as the Berlin Heart Excor Device. However, the waiting time for the children on these devices is unpredictable, and they are exposed to the risks of anticoagulation while on device. The risks of a cerebrovascular event ranges from 18% to 50% depending on the age, size of pumping chambers, and the length of support on the VAD.[10,11,105] There is little information on the long-term neurodevelopmental outcome of these children, and they need targeted longitudinal neurodevelopmental follow-up.

Table 58.4 PROPOSED FRAMEWORK AND RECOMMENDATIONS FOR LONGITUDINAL FOLLOW-UP FOR NEONATES AND CHILDREN WITH CARDIOVASCULAR DISEASE

TIMING OF TESTS		DOMAIN	TEST	INTERVENTION
Predischarge at any age		Growth Neurodevelopment	Anthropometry Neuroimaging if any ANE Baseline age-appropriate neurodevelopmental screen	• Dietician referral and input • Focused care with input from specialist nurses • Structured follow-up
Infancy 1 month to 1 year	Assessments may be performed at 3–6 months, 9 months, or 1 year. American Heart Association recommendations	Growth	Anthropometry	• Dietician referral and input
		Neurodevelopment	Physical examination MRI brain if any new neurological deficit Age-appropriate neurodevelopmental screen	• Neurology/neonatologist/ pediatrician/community pediatrician referral and support (depending on local practice) • Physiotherapist
		Hearing	Hearing tests	• Audiology assessment and input
		Vision	Vision tests	• Ophthalmology/optometrist referral
Preschool	2 years	Growth	Anthropometry	• Dietician referral and input
If age at ECMO in the preschool range, then fit in with the American Heart Association recommended assessment times.		Mental and motor development, vision	• Formal assessment tool (BSID, etc.) as per local practice • Age-appropriate ASQ • Vision tests	• Pediatrician/community pediatrician (depending on local practice) • Physiotherapist
		Hearing	Hearing tests	• Audiology assessment and input
		Language	Speech and language assessment	• Speech and language input
	4–5 years	Growth, mental and motor development, speech and language, behavior	• Formal assessment tool as per local practice • Age-appropriate ASQ • Child Behaviour Checklist	• Pediatrician/community pediatrician (depending on local practice) • Physiotherapist • Speech and language therapist
Early school age If age at ECMO in the school range	5–12 years	Growth, mental and motor development, speech and language, behavior	• Formal assessment tool as per local practice • Age-appropriate ASQ • Child Behaviour Checklist	• Pediatrician/community pediatrician (depending on local practice) • Physiotherapist • Speech and language therapist
		Memory	Children's Memory Scale	
		Self-esteem	PEDSQoL	
Late school age (Adolescence) If age at ECMO in adolescence	>12 years	Growth, neuropsychological tests, intelligence, motor, behavior	• Formal assessment tool as per local practice • Age-appropriate ASQ • Child Behaviour Checklist	Pediatrician/community pediatrician (depending on local practice) Physiotherapist Speech and language therapist
		Memory	Children's memory scale	
		Quality of life/ self-esteem	Pediatric Quality of Life	

ASQ, Ages and Stages Questionnaire; BSID, Bayley Scale of Infant Development; PEDSQoL, Pediatric Quality of Life Inventory™.

Neuropsychological Tests

There is marked international variation in the use of instruments to assess neurodevelopmental outcome. Various measures are available and should be chosen based on the norm of the country of origin and primary language of the patient. It is preferable for centers to choose validated, culturally appropriate tests, with age-appropriate references, at standardized intervals to facilitate interpretation and any future collaboration. Any new focal neurological deficit or regression of neurodevelopmental milestones at any time will need neurology referral and assessment.

Instituting Interventions Early Once Concerns Are Identified

It is crucial to intervene early once concerns are identified. The types of intervention range from physical therapy, occupational

therapy, speech therapy, hearing aids, psychosocial support, behavioral therapy, and dietetics. More specialized input such as a special education needs coordinator and an educational psychologist become necessary if problems at school are identified.

Parental Engagement in Follow-up

Having a structured follow-up right from the beginning facilitates parental engagement early in the process and helps them understand the importance of continuing follow-up. In a recent study in the United Kingdom, parents highlighted the need for structured follow-up and support in the community and the importance of education and sharing of information about ECMO with general practitioners/family physicians, community professionals, and schools.[106]

CONCLUSIONS

- Overall, children supported on ECMO for cardiac reasons have significant neurodevelopmental difficulties and warrant close neurodevelopmental follow-up.
- Given the complex and high-risk nature of ECMO and underlying healthcare needs of children with heart disease, the evaluation of neurodevelopmental outcomes is an important aspect of patient care.
- A clear understanding of the mechanisms, timing, and consequences of the brain injuries is essential to the development of interventions aimed at preventing them or mitigating their effects with neuroprotective measures.
- All children who have received ECLS regardless of primary etiology should have neurodevelopmental follow-up. Referral for neurodevelopmental surveillance as well as tracking of long-term cardiorespiratory function should be routine aspects of long-term follow-up of cardiac ECMO patients.
- Evidence-based protocols for the evaluation and follow-up of children at risk of developmental disorders, informed by outcome data, are important for the purposes of quality improvement.
- The variability within neurodevelopmental surveillance and follow-up pathways for children surviving cardiac ECMO warrants review and standardization.
- Protocolized follow-up of children with cardiovascular disease undergoing ECMO should be prioritized and will enable children with neurodevelopmental needs to access early intervention and support services more readily.

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REVIEW QUESTIONS

1. The following are the risk factors for neurological complications on ECMO. Which of the following statements are true? Please choose all that apply.

A. History of cardiac arrest
B. Significant hemodynamic instability and severe hypoxemia pre-ECMO
C. Cannulation with ligation of right IJV and CCA
D. Infection and disseminated intravascular coagulation on ECMO
E. Extracorporeal CPR

2. The factors that mitigate against ANEs on ECMO include the following. Which of the following statements are true? Please choose all that apply.

A. Bedside daily neurological assessment
B. Awake ECMO with minimal sedation
C. Multimodal neuromonitoring
D. Careful attention to systemic anticoagulation, maintaining the balance between prevention of thrombosis and bleeding
E. Neuroprotection with systemic hypothermia

3. Neurodevelopmental issues are commonly seen in children with CHD due to the following. Which of the following statements are true? Please choose all that apply.

A. High incidence of syndromes
B. Abnormal cerebrovascular blood flow in fetal life
C. Exposure to inhalational anesthetics
D. Cardiac surgery involving cardiopulmonary bypass and circulatory arrest or low-flow bypass
E. Structural heart disease

4. Optimum neurosurveillance for neurodevelopmental deficits involves the following. Which of the following statements are true? Please choose all that apply.

A. Identification of high-risk subgroup
B. Structured longitudinal follow-up
C. Multidisciplinary follow-up
D. Parental education on importance of follow-up
E. Engagement of community pediatric services or child development center

5. Known risk factors for neurodevelopmental abnormalities in later life available from published literature include the following. Which of the following statements are true? Please choose all that apply.

A. Single-ventricle physiology
B. Extracorporeal CPR
C. Small patient size
D. Surgery preceding ECMO
E. Cardiac surgical procedures/catheterizations post-ECMO

6. Neuropsychological tests should involve assessment of the following to provide appropriate intervention. Which of the following statements are true? Please choose all that apply.

A. Motor outcomes
B. Cognitive outcomes
C. Speech and language and hearing
D. Quality of life
E. Behavior

7. John is a 14-year-old boy who developed fever, myalgia, and tummy upset. His local doctor treats him for flu. He however deteriorates rapidly and now develops a fast heart rate and presents cold and clammy in a state of cardiovascular collapse in his local emergency department. He is noted to have arrhythmia, which progresses to an arrest, with a total downtime of 6 minutes. He is resuscitated, intubated, and commenced on ECMO. The mobile ECMO team transfers him to the tertiary ECMO center. He is later diagnosed with parvovirus myocarditis. CT brain shows cerebral edema and a watershed infarct in MCA territory. He makes significant cardiac recovery to be able to come off ECMO. Which of the following statements are true? Please choose all that apply.

A. He needs only cardiology/heart failure follow-up.
B. He needs MRI of the brain before discharge home.
C. As he is a teenager, he does not need neuropsychological assessment.

D. Getting back to school may be a lengthy process, and he may need time to catch up to his preillness state.
E. He will need physiotherapy and neurorehabilitation and may have exercise intolerance, which will need to be monitored.

8. Anna is a 4-week-old neonate with CHD who undergoes complex cardiac surgery. She develops a severe low cardiac output state with hypotension, and a decision is made to put her on chest cannulation V-A ECMO. After a period of rest over 5 days, her heart recovers, and she comes off ECMO. Which of the following statements are true? Please choose all that apply.

A. In addition to her cardiologist, she needs a general pediatrician to follow her at her local hospital.
B. She does not need neuroimaging as her preoperative head ultrasound scan was normal.
C. The importance of regular neurodevelopmental assessment needs to be explained to her parents.
D. Hearing assessment is important.
E. Sequential, longitudinal neurodevelopmental assessment until adulthood should be part of her long-term care package.

9. Tom had cardiac surgery for transposition of the great arteries as a baby and unfortunately needed ECMO support in the postoperative period. He improved after a second surgical procedure and came off ECMO. He has since had cardiac catheterizations. He is now 3 years old and a bit behind on his speech and communication skills. Mum reports that he has frequent temper tantrums. Mum has been trying to engage community services, but it has been difficult. Which of the following statements are true? Please choose all that apply.

A. He needs a full neurodevelopmental assessment.
B. The primary healthcare doctor advises that repeat hearing is not needed as his neonatal hearing screen was normal.
C. Age-appropriate questionnaires such as Ages and Stages Questionnaires filled by parents are helpful and complement a full neuropsychological assessment.
D. He needs a referral to a psychologist if problems are identified on behavioral assessment.
E. He needs only a referral to speech and language therapy.

10. David is a newborn with antenatally diagnosed hypoplastic left heart syndrome who underwent Norwood stage 1 surgery. Unfortunately, he suffered a cardiac arrest for a blocked shunt and needed to be supported on V-A ECMO for 4 days. He had normal EEG/HUS on ECMO. He is now being prepared for discharge home. Advice needs to be given to his parents before his discharge. Which of the following statements are true? Please choose all that apply.

A. He needs close monitoring of physical growth and oxygen saturations.
B. He should have regular echocardiograms and be followed up by cardiology.
C. He needs to be under a general pediatrician or a pediatrician with expertise in cardiology.
D. He needs brain MRI predischarge or within 3 months of discharge.
E. He needs to have structured neurodevelopmental follow-up in light of his single-ventricle physiology.

11. Tara, a 4-year-old child with dilated cardiomyopathy, presents with worsening clinical condition. She suffers a cardiac arrest in the ICU and receives ECPR. She has an EEG, which shows a sedative effect and no seizures; neuroimaging is normal. She is then transitioned to VAD. She develops a left MCA territory infarct on VAD. She improves over time, is listed for heart transplant, and receives one in due course. She is left with residual weakness on the right side of the body and expressive language difficulties. Which of the following statements are true? Please choose all that apply.

A. She needs further MRI of the brain predischarge.
B. She needs to have a referral to a community pediatric service.
C. Her parents need to be aware of her ongoing need for longitudinal follow-up.
D. She needs to have ongoing physical therapy.
E. She needs only a referral to speech and language therapy.

ANSWERS

1. A T, B T, C F, D T, E T
2. A T, B T, C T, D T, E F
3. A T, B T, C T, D T, E F
4. A T, B T, C T, D T, E T
5. A T, B T, C T, D T, E T
6. A T, B T, C T, D F, E T
7. A F, B T, C F, D T, E T
8. A T, B F, C T, D T, E T
9. A T, B F, C T, D T, E F
10. A T, B T, C T, D T, E T
11. A T, B T, C T, D T, E F

59.

NEUROLOGIC COMPLICATIONS IN ADULT ECMO

Bernhard Holzgraefe and Håkan Kalzén

STEM CASE AND KEY QUESTIONS

A 45-years-old male patient was admitted to the intensive care unit (ICU) of a minor community hospital with fever, coughing, and ongoing respiratory failure. The symptoms started approximately 10 days earlier, but during the last few days the respiratory situation had deteriorated. On arrival, blood gas analysis showed severe arterial hypoxemia (PaO_2 45 mm Hg, SaO_2 [arterial hemoglobin oxygen saturation] 79%) and respiratory acidosis (PCO_2 65 mm Hg, pH 7.28). Blood pressure was 100/48 mm Hg, and the heart rate was 120 beats/min. Initially noninvasive pressure support ventilation was started with F_iO_2 (fraction of inspired oxygen) of 0.7. Chest x-ray revealed bilateral pulmonary opacities/infiltrates in all quadrants.

The respiratory situation did not improve, and the patient was orotracheally intubated and mechanically ventilated. After 2 hours of mechanical ventilation with varying F_IO_2 of 0.8–1.0 levels and hemodynamic instability, the regional extracorporeal membrane oxygenation (ECMO) facility was contacted. The pneumococcal urine antigen test was positive, the leucocyte count (WBCs, white blood cells) was below normal, and procalcitonin level was elevated. Because the patient fulfilled fast-entry ECMO criteria, a decision was made to send the mobile ECMO team to the referring hospital. Five hours after intubation, the patient was cannulated for veno-venous (V-V) ECMO with a 25 French (25F)/38-cm right jugular vein drainage cannula and a 23F/18-cm left femoral vein reinfusion cannula and transported by ambulance to the ECMO unit. The ECMO pump was running at 4 L/min with a preoxygenator venous blood saturation of 68% and a postoxygenator blood saturation of 100%. Sweep gas flow was 100% oxygen at a flow rate of 6 L to achieve a normal postoxygenator PCO_2 level.

On day 2 of V-V ECMO support, the WBCs had increased above a normal level, but clinical and echocardiographic findings indicated that the patient was developing right ventricular failure. The circuit was changed to veno-arterial (V-A) ECMO with a left-sided 21F/18-cm femoral artery cannula and a 8F distal perfusion cannula. During the V-A treatment, the patient developed significant hemolysis, and it was argued that this could have been caused by clot formation in the ECMO circuit. Therefore, the entire circuit was changed on ECMO day 5. Inspection of the changed circuit revealed clot formation in the impeller (Figure 59.1). Hemolysis completely resolved after the change of ECMO circuit.

After 10 days of ECMO, lung function had partially recovered, and right ventricular function improved markedly. The circuit was changed back to V-V ECMO, and after a further 4 days of ECMO treatment, the patient was decannulated. A tracheostomy had been performed on day 5 according to local treatment protocol, and the patient was slowly gaining consciousness when he was converted back to V-V ECMO. He was able to communicate and show some motoric response on day 11, but a difference in strength between right and left side was noticed. Post-ECMO magnetic resonance imaging revealed a left-sided cerebral infarction (Figure 59.2). The patient was discharged from hospital to neurological rehabilitation after 7 more weeks of in-hospital medical care. Follow-up examination 12 months after the start of the ECMO treatment showed moderate cognitive impairment, paresthesia in the right leg, and reduced health-related quality of life.

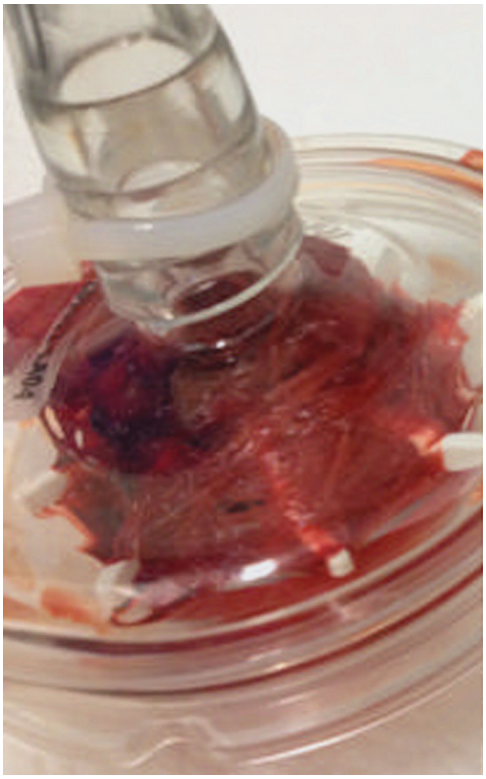


Figure 59.1 Clot formation in the impeller.

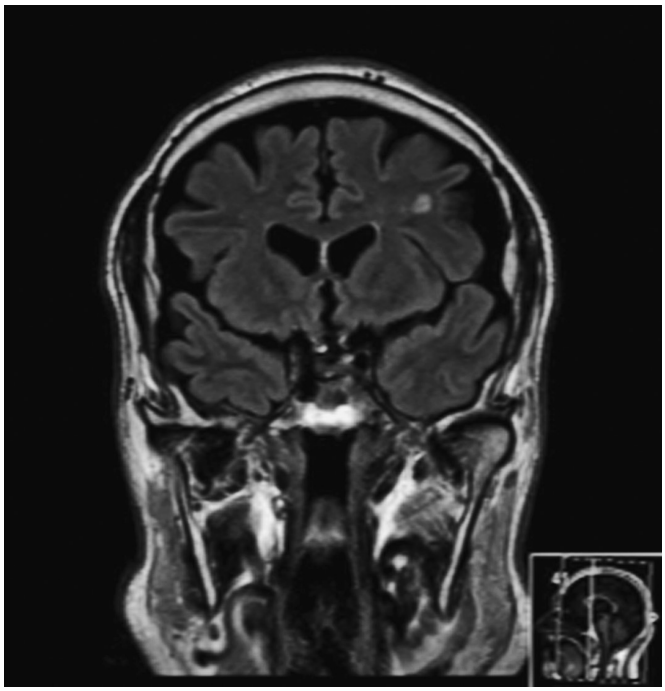


Figure 59.2 Left-sided intracranial lesion.

WHAT ARE CANNULATION STRATEGIES FOR V-V AND V-A ECMO?

V-V ECMO is a rescue treatment in patients with severe hypoxemic respiratory failure (e.g., severe acute respiratory distress syndrome [ARDS], not responding to conventional critical care treatment).[1–4] In V-V ECMO cardiac function is preserved. The aim of a cannulation strategy for V-V ECMO is to optimize oxygen delivery and minimize recirculation for the whole treatment course. Usually, a femoro-atrial cannula configuration is used (i.e., drainage from the lower part of the body and reinfusion into the upper part of the body). However, some centers prefer an atrio-femoral configuration where the blood is drained from the right superior caval vein and the right atrium and return of oxygenated blood is into the inferior caval vein.[5] This configuration is less prone to changes in intra-abdominal pressure and the volume state of the patient. A third possibility would be to insert both cannulae into the groin and to reinfuse proximal to the draining cannula.

V-A ECMO is indicated in patients with severe cardiorespiratory failure or cardiac failure alone when conventional medical treatment fails.[4] In the presented case, V-A ECMO was established because of right ventricular failure during the course of V-V ECMO treatment for severe hypoxemic respiratory failure. According to our experience, right ventricular function is determined by the degree of pulmonary disease, and after lung function had improved, the circuit could be changed back to V-V ECMO.

Principally, peripheral or central cannulations are possible techniques for V-A ECMO.

The femoral or subclavian artery can be used for blood return in peripheral V-A ECMO cannulation with a draining (venous) cannula in the femoral or internal jugular vein aiming to drain blood from the vena cava superior and the right atrium. Cannulation of the subclavian artery provides antegrade blood flow into the ascending aorta without increasing left ventricular afterload with higher arterial oxygen content if oxygenation is necessary as in the presented case. This should result in (1) sufficient cerebral oxygenation and (2) avoidance of competitive flows as in femoral artery cannulation, which may result in differential hypoxemia.[6] However, from our clinical experience there is an increased risk for cerebral stroke with this technique. Usually, the femoral artery is used for peripheral V-A ECMO.

WHY DID THE CIRCUIT HAVE TO BE CHANGED FROM V-V TO V-A ECMO?

The patient was suffering from severe hypoxemic ARDS. Common features of ARDS are intravascular coagulation, pulmonary edema, and epithelial cell damage with alveolar hypoxia.[7] This results in acute increased pulmonary artery pressure (i.e., increased right ventricular afterload), which is partially caused by hypoxic pulmonary vasoconstriction (HPV), with right ventricular failure in some patients.[8,9] The HPV response is impaired in inflammatory conditions (e.g., in severe ARDS), but may still be present and contribute to the aforementioned pathophysiology.[10,11] Right ventricular failure may occur before or during ECMO, and it has been suggested that increasing the oxygen tension in the pulmonary artery by V-V ECMO may decrease right ventricular afterload.[12,13] However, we recently observed in an experimental model of global alveolar hypoxia that the effect of V-V ECMO on HPV is dominated by the degree of alveolar hypoxia.[14] Therefore this will not work in every patient, and in these patients changing the circuit to V-A ECMO is the appropriate therapeutic approach until lung function has improved again.

WHAT ARE THE RISK FACTORS FOR NEUROLOGICAL COMPLICATIONS IN THIS VIRTUAL CASE?

Risk factors for the development of neurological complications are the underlying illness per se. The patient is severely hypoxemic, which might contribute to cognitive impairment and is discussed further in this chapter. Other factors influencing the cognitive outcome are, for example, inflammation, hyper- and hypoglycemia, brain hypoperfusion, and prolonged sedation.[15,16] There is also an increased risk for stroke during critical illness, which is further increased by ECMO treatment. Peripheral nerve lesions may occur as a result of neuropathy or direct nerve lesions due to compression of nerves by the ECMO cannulae.

WHAT ARE POSSIBLE NEUROLOGICAL COMPLICATIONS RELATED TO V-V ECMO?

In a recent analysis from the Extracorporeal Life Support Organization's (ELSO) database, 426 neurologic complications occurred in 356 (7.1%) of 4988 included adult patients treated with V-V ECMO for severe respiratory failure refractory to conventional critical care. Complications included

intracerebral hemorrhage (ICH) (42.5%), brain death (23.5%), stroke (19.9%), and seizure events (14.1%). Underlying causes were the need for prolonged anticoagulation for ECMO treatment, increased inflammatory response due to the contact of blood with the surface of the ECMO system, coagulation disorders, and the rapid normalization of respiratory acidosis during the start of ECMO treatment.[17] In a long-term follow-up study with 38 patients, 27 were treated with V-V ECMO. In 7 patients (26%), neurological complications were diagnosed (hemorrhagic 11%, nonhemorrhagic 15%).[18]

Minor neurological complications include peripheral nerve lesions such as paresthesia induced by compression of the lateral cutaneous nerve by the ECMO cannula.[19]

Moreover, it has been suggested that prolonged periods of hypoxemia in patients with severe ARDS may lead to cerebral hypoxia with short- and long-term neurological impairment (i.e., cognitive dysfunction) in survivors.[20–22] During V-V ECMO support, SaO_2 may be as low as 75%–80%.[4] But there is no evidence that these levels of SaO_2 are associated with cognitive impairment or other cerebral complications in long-term survivors.[23,24]

WHAT ARE POSSIBLE NEUROLOGICAL COMPLICATIONS RELATED TO V-A ECMO?

From a principal point of view, the same risks of complications apply for the patient whether you use V-V or V-A ECMO, but, obviously, arterial cannulation with a constant high-flow blood infusion coming from an extracorporeal circuit carries an extra set of risks.

Both the femoral and subclavian arterial cannulation approaches have advantages and disadvantages. Cannulation of the subclavian artery may result in ischemia distal to the cannulation site. Cerebral ischemic events might happen due to hazardous content (i.e., air bubbles or clots) entering the carotid bloodstream with the arterial ECMO flow and (theoretically) ischemia through ipsilateral hyperperfusion of the brain.

However, comparative studies investigating the incidence of stroke are lacking. Possible neurological complications with cannulation of the femoral artery technique are differential hypoxemia resulting in cerebral hypoxemia and possibly even hypoxia, paresthesia distal to the cannulation because of nerve compression by the cannula, cerebral stroke, and paraplegia. The risk of embolic events must be considered depending on how much the beating heart is filling the aortic arch with blood that was filtered through the lungs and the ECMO flow retrogradely filling the aorta. Nerve lesions of the cannulated leg can also occur when the nerve is damaged at the inguinal cannulation site or when the leg develops severe ischemia due to an ischemic compartment syndrome situation caused by hypoperfusion and swelling of the leg.[25] Small cohort studies or retrospective register studies have investigated the incidence of stroke and cerebral lesions in patients treated with V-A ECMO.[18,26,27] Studies consisting of reported findings showed low incidence of 1.8%–3.6%, whereas screening studies showed incidences of 64%–75%.[18,26,27] To judge when the lesion occurred (pre-, per-, or post-ECMO) is difficult unless brain imaging in these patients is performed according to a protocol.

WHY IS DIFFERENTIAL HYPOXEMIA A PROBLEM, AND CAN IT BE AVOIDED?

Differential hypoxemia may occur during V-A ECMO treatment when the extracorporeal flow meets the flow from the native heart in the descending aorta. It may even occur despite the fact that V-A ECMO was established because of circulatory failure (e.g., isolated right ventricular failure with preserved left ventricular function or during recovery of left ventricular function). As a consequence, the SaO_2 in the upper part of the body may be significantly lower compared to SaO_2 in the lower part when the tip of the draining cannula is placed into the inferior caval vein.[28–30] This may lead to decreased arterial oxygen content and oxygen delivery to the brain, possibly resulting in cerebral hypoxia. Optimizing cannula position (i.e., venous blood should be drained from the superior caval vein and the right atrium) may decrease the degree of differential hypoxemia.[28–30]

WHAT ARE THE POSSIBLE NEUROLOGICAL COMPLICATIONS DUE TO HYPOXEMIA?

Periods of prolonged hypoxemia are common in severe respiratory and cardiorespiratory failure, before and during treatment with ECMO. It has been suggested that hypoxemia is associated with cognitive impairment in survivors of severe ARDS without ECMO treatment, but the evidence for this is not strong.[20–22,24] The rationale is that hypoxemia would lead to cerebral hypoxia. However, cellular oxygen supply is dependent on oxygen delivery (DO_2), which is dependent on arterial oxygen content (CaO_2) and the cardiac output (CO).

$$DO_2 = CO \times CaO_2$$

$$CaO_2 = 1.31 \times Hb \times SaO_2 + (0.003 \times PaO_2)$$

where 1.31 is milliliters of O_2 bound by 1 g of hemoglobin (Hb); SaO_2 indicates arterial hemoglobin oxygen saturation (%); and PaO_2 is the arterial oxygen tension (mm Hg). It becomes clear that PaO_2 plays a minor role in cellular oxygen supply. Usually, there are physiological compensation mechanisms for low SaO_2 (i.e., increased CO), which should be able to keep CaO_2 in an acceptable range. If these compensation mechanisms are insufficient, it is possible to increase the hemoglobin (blood transfusions) or the CO (β-sympathomimetics) or both. Therefore, it should be possible to avoid organ hypoxia (i.e., cerebral hypoxia) as long as perfusion with acceptable CaO_2 is preserved despite hypoxemia because cerebral hypoxia is usually caused by an ischemic event.[31–33] In small retrospective studies, hypoxemia during V-V or V-A ECMO treatment for severe respiratory failure was not associated with long-term cognitive impairment in survivors.[18,23]

WHICH FACTORS ARE ASSOCIATED WITH COGNITIVE IMPAIRMENT AFTER ECMO?

Cognitive impairment is a common long-term complication with multifactorial causes in patients treated for severe critical

illness on medical or surgical ICUs.[15,16,20–22] Inflammation due to the illness or the duration of delirium is an important factor in the pathophysiology of neuropsychological sequelae.[15,16] Results from cognitive outcome studies after critical illness are difficult to interpret due to the lack of premorbid cognitive data for most of the patients and a loss of a substantial number of patients to follow-up.

As already mentioned, cognitive impairment may occur after ECMO treatment but is possibly not associated with periods of short or prolonged hypoxemia. Contributing factors (e.g., hypoxemia) that specifically may be related to V-V or V-A ECMO treatment are difficult to determine because of the lack of well-conducted prospective studies.[24] Smaller retrospective studies, which investigated neuropsychological functioning at different time points after discharge from a hospital, could not find any association between the mode of ECMO applied (i.e., V-V or V-A) or hypoxemic events before or during the treatment.[18,23,27,34] Few studies performed cognitive testing and brain imaging in the same study.[18,23,27] They found that cognitive impairment was associated with brain lesions but not with the mode of ECMO (i.e., V-V or V-A).[18,27] Cognitive impairment in these patients was only associated with findings of intracranial lesions, and these lesions occurred more often in patients treated with V-A ECMO.

WHAT DO WE KNOW ABOUT PERIPHERAL NEUROLOGICAL COMPLICATIONS DURING ECMO?

The incidence of peripheral neurological complications in patients after ECMO treatment is not well investigated. Data from studies including a larger number of patients or from the ELSO Registry are lacking. In one study of 21 patients treated with V-V ECMO, paresthesia was the most common finding (n = 10). However, not all symptoms could specifically be related to ECMO. A lesion of the lateral femoral cutaneous nerve occurred in four patients.[19]

WHY MAY SPINAL CORD INJURY OCCUR DURING ECMO TREATMENT?

Spinal cord injury during ECMO treatment is a rare but very serious complication.[35,36] The spinal cord receives its blood supply by intracranial and extracranial vessels. The thoracic segments are most sensitive to ischemic events, which can be provoked by

- Pharmacologically induced vasoconstriction because of circulatory shock
- Infarct
- Obstruction of vessels supplying the spinal cord (e.g., by intra-aortal balloon counterpulsation [IABP])

To our best knowledge, there are only two reports in the literature about spinal cord injuries in combination with ECMO treatment. All patients were treated with V-A ECMO because of cardiogenic shock (n = 4) and three of them were treated in combination with IABP because of loss of left ventricular ejection.[35]

DISCUSSION

The rate of brain lesions during critical illness is not very well studied, but they may contribute significantly to the bad long-term neurological outcome of survivors.[37,38]

Central neurological complications in patients treated with ECMO for respiratory or circulatory failure seem to be common, but it is not clear whether they are directly related to the ECMO treatment. It seems reasonable that intracranial hemorrhage (ICH), discussed elsewhere in this book, and cerebrovascular lesions (i.e., stroke), are associated with ECMO. However, a problem with most of the studies addressing this question is that not all patients are routinely screened for neurological complications before or during ECMO treatment. Furthermore, there is a lack of short- and long-term follow-up studies with large sample sizes, including brain imaging. In retrospective studies the rate for central neurological complications varies from 7.1% to 26% for V-V ECMO and 15.1% to 64% in V-A ECMO.[17,18,26,27,39] The rate of ICH was higher in patients treated with V-V ECMO (3.6% vs. 1.8% in V-A ECMO).[17,26] Cerebrovascular lesions (e.g., stroke) seem to occur more often during V-A ECMO compared to V-V ECMO and are associated with cognitive impairment.[18,27]

In the largest study of central nervous system complications in adults during V-V ECMO, using data from the ELSO database, 4988 patients were included.[17] The authors reported 426 neurological complications, which occurred in 356 patients. There were 181 registered events with ICH, 100 with brain death, 85 with stroke, and 60 with seizures. There was no information about in how many patients brain imaging was performed as a screening method or only when symptoms occurred. It seems therefore likely that many complications are not registered because they were never detected.

Lorusso and coauthors reported also results from the ELSO database in 4522 adult patients treated with V-A ECMO.[26] They found that complications occurred in 682 patients. The leading complication was brain death (n = 358), followed by cerebrovascular lesions (n = 161), seizures (n = 83), and hemorrhage (n = 80). The in-hospital mortality in patients with neurological complications was significantly higher (89%) compared to patients without neurological complications (57%). It is not reported whether the patients were routinely screened with brain imaging. However, as this is very unlikely, an unknown number of patients categorized as "without neurological complications" might suffer from nondetected brain lesions. Publications providing information that brain imaging was performed showed a much higher incidence of an intracerebral pathology, ranging from 17% to 26% in V-V ECMO and from 64% to 75% in V-A ECMO.[18,27] These studies were performed in single-center cohorts with small sample sizes, and therefore they may not be representative of the ECMO patient population. However, the results give us an indication that the prevalence of brain lesions in

ECMO survivors might be much higher than reported in studies without screening of all included patients.

Long-term cognitive impairment is common in survivors of critical illness, ranging from 9% to 56%.[40] Intensive care patients are exposed to many contributing risk factors (e.g., inflammation, low organ perfusion pressure, decreased CaO_2, multimodal sedation, or multiorgan failure). It is therefore difficult to point out a single causal factor. Small sample size studies reported that patients treated with ECMO might have normal cognitive functioning but as already mentioned, there are no data available concerning their cognitive function before illness; therefore it might be possible that some patients performed significantly better before they developed their critical illness.[18,27]

Prolonged episodes of hypoxemia are often already present in patients with respiratory failure before ECMO treatment; they may occur during V-V ECMO when there is no or very little gas exchange in the native lungs or in states of differential hypoxemia during V-A ECMO. In V-V ECMO, cannula positioning can be optimized to reduce recirculation and improve oxygenation. If this is not possible, increasing hemoglobin concentration and/or the cardiac output can increase arterial oxygen content. During differential hypoxemia, the tip of the draining multistage cannula should be positioned in the vena cava superior to drain blood from the upper body and the right atrium. Either the internal jugular vein can be used for cannulation with a short (e.g., 25F/38-cm) cannula or a long (e.g., 25F/50-cm) cannula can be inserted via the femoral vein. It is well documented that this measure improves oxygenation substantially.[28–30]

As already mentioned, it has been suggested that hypoxemia may be associated with impaired cognitive functioning after critical illness without ECMO treatment.[20–22] These findings could not be supported by data from ECMO patients.[18,23] However, all of the aforementioned studies come with substantial limitations:

1. There was a significant loss to follow-up in the studies from Von Bahr et al. and Holzgraefe at al., 38% and 36.4%, respectively. Patients who could not be included might have shown significant cognitive impairment, which would have changed the results.
2. The definition of hypoxemia is not clear, ranging from an oxygen hemoglobin saturation of 94% to desaturations below 80%.[21,22,41]
3. The SaO_2 in the study of Mikkelsen et al. was the same (i.e., 94%) in patient groups with and without cognitive impairment. The arterial carbon dioxide tension ($PaCO_2$) was not reported in this study, and it might be possible that patients with cognitive dysfunction were hypocapnic. Hypocapnia is known to reduce cerebral perfusion and thereby contribute to ischemic events and decreased oxygen delivery to the brain.
4. Patients with brain lesions have a worse cognitive long-term outcome. The cognitive outcome studies in critical care patients without ECMO, which found an association between hypoxemia and cognitive dysfunction, did not perform brain imaging. It is possible that the results are biased by undetected cerebrovascular lesions.

In contrast to the studies of Hopkins et al. and Mikkelsen et al., results from a review from the Cochrane collaboration and the first International Study of POstoperative Cognitive Dysfunction (ISPOCD1) did not show any association between cognitive impairment and hypoxemia.[42,43]

The prevalence of peripheral neurologic complications after ECMO treatment, such as peripheral nerve injury with paresthesia or paresis, is poorly investigated. There is only one publication in this field.[19] In this study, 28 of 107 ARDS patients were available for investigation. Seventeen patients were treated with V-V ECMO with a mean follow-up time at 21.85 months. Paresthesia was a common finding (n = 10). In five patients, paresthesia could be related to a lesion of the lateral cutanean femoral nerve, probably caused by compression of the nerve by the ECMO cannula.

Limb ischemia resulting in compartment syndrome and peripheral nerve damage may occur distal to cannulation of the femoral or subclavian artery in V-A ECMO. In subclavian artery cannulation, an end-to-side graft, which is sewn onto the artery, can reduce the risk. The ECMO cannula is then placed into the graft. Cannulating a femoral artery is the commonest approach for returning blood from the ECMO device into the patient. Ischemia may be caused by obstruction of the artery by the cannula. This may happen when the diameter of the chosen cannula is too large; during states of hypovolemia or severely decreased ejection fraction of the left ventricle; or when high doses of vasoconstrictors are needed to stabilize the circulation. Insertion of a distal perfusion cannula decreases the rate of ischemic events (-15.7% compared to no distal perfusion cannula).[25] We recommend establishing a distal perfusion access when treatment is started, regardless of the perfusion state.

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REVIEW QUESTIONS

1. Which of the following cannulation strategies for V-A ECMO has the highest risk for differential hypoxemia?

A. Draining venous blood with a multistage cannula from the vena cava superior and right atrium and returning it into the left or right arteria femoralis
B. Draining from the vena cava inferior and returning into the right arteria subclavia
C. Draining from the vena cava inferior and returning it into the left or right arteria femoralis

D. Draining from the vena cava superior and right atrium with a multistage cannula inserted via the right vena femoralis and returning into the left arteria femoralis

2. Which of the following statements is incorrect?

A. In hypoxemic respiratory failure (e.g., severe ARDS) hypoxic pulmonary vasoconstriction is blunted but may still be present.
B. Increasing the oxygen tension in the pulmonary artery (PvO_2) by V-V ECMO always attenuates increased pulmonary vascular resistance due to hypoxic pulmonary vasoconstriction and unloads the right ventricle.
C. Hypoxic pulmonary vasoconstriction is mediated by alveolar oxygen tension (P_AO_2) and PvO_2, with P_AO_2 being the strongest stimulus.
D. Correcting respiratory acidosis by ECMO may decrease pulmonary vascular resistance.

3. The patient in the presented case showed some cognitive impairment in a long-term follow-up examination, which was most likely caused by

A. Prolonged arterial hypoxemia.
B. Hyperinflammation.
C. Cerebral ischemia (i.e., stroke).
D. Right ventricular failure.

4. Which is the most common neurological complication during V-V ECMO treatment?

A. Intracerebral hemorrhage
B. Brain death
C. Peripheral nerve lesions due to nerve compression by the ECMO cannula
D. Seizure

5. Which measure reduces the risk for limb ischemia in adult V-A ECMO distal to the arterial cannulation site best?

A. Increasing the blood pressure by correcting hypovolemia
B Choosing the smallest possible arterial cannula
C Intra-aortic balloon pump
D An 8F distal perfusion cannula

6. Limb ischemia resulting in compartment syndrome and peripheral nerve damage may occur distal to cannulation of the femoral or subclavian artery in V-A ECMO. Which of the following statements is wrong?

A. In subclavian artery cannulation, an end-to-side graft is attached, which is sewn onto the artery. This procedure can reduce the risk of peripheral ischemia distal to the cannulation site.
B. Obstruction of the vessel by the arterial cannula increases the risk for ischemia.
C. You always position your distal arterial cannula in the correct position if you puncture the femoral artery with a microintroducer/guide wire distally to the returning arterial cannula.
D. Peripheral nerve damage can be caused by compression of the nervus cutaneous femoris lateralis through the cannula.

7. Which of the following statements is true regarding cognitive impairment after treatment for severe ARDS on ECMO?

A. Severity of cognitive dysfunction found after severe ARDS is always worse for patients treated on ECMO compared to patients treated with conventional mechanical ventilation.
B. Severity of cognitive dysfunction found after severe ARDS is always better for patients treated on ECMO compared to patients treated with conventional mechanical ventilation.
C. Cognitive dysfunction found after severe ARDS treated with ECMO is not reversiblel, and patients rarely get back to work after convalescence.
D. Results of studies investigating cognitive dysfunction after ECMO treatment may be difficult to interpret because of the lack of pre-illness cognitive data.

8. The oxygen supply of the brain is dependent on the arterial oxygen content of the blood (CaO_2). Which of the following statements is incorrect?

A. Increasing the hemoglobin concentration may compensate for low SaO_2.
B. Increasing the cardiac output increases oxygen delivery to the brain.
C. Increasing the PaO_2 results in a substantial increase in CaO_2.
D. Cerebral hypoxia is often caused by ischemic events (e.g., stroke).

9. Which of the following statements is true regarding radiological findings and ECMO?

A. Cognitive outcome is always correlated to hypoxemic events during ECMO treatment.
B. Cerebral lesions found after ECMO treatment are related to the modality of ECMO treatment.
C. Cerebral lesions seem to correlate with impaired cognitive function post-ARDS with ECMO support.
D. The ARDS patients supported with V-V ECMO never show any signs of cerebral lesions post-ECMO treatment.

ANSWERS

1. C. V-A ECMO with a femoro-femoral configuration predisposes for differential hypoxemia when venous blood is drained from the inferior caval vein and the left ventricular ejection is high enough to equalize or overcome ECMO blood flow coming from the femoral artery. In these situations, the majority of oxygenated blood will not reach the upper part of the body but circulate in the lower parts of the body. Oxygenation will depend on native lung function. If lung function is severely compromised (e.g. in severe hypoxemic ARDS), oxygen content in the upper body may reach levels that are too low for sufficient cerebral oxygenation. In

the opposite, the lower part of the body is hyperoxygenated. Oxygenation of the upper body can be improved by draining venous blood from the vena cava superior and the right atrium.

2. B. Hypoxic pulmonary vasoconstriction depends on the P_AO_2, the PvO_2 and the oxygen tension in the bronchial arteries. P_AO_2 is the strongest stimulus. The stimulus for HPV can be defined as $PsO_2 = P_AO_2^{0.62} \times PvO_2^{0.38}$.[44] In V-V ECMO it will not be possible to increase PvO_2 to an amount that would compensate for any P_AO_2 because of the recirculation of returned oxygenated blood into the extracorporeal device and admixture of deoxygenated venous blood with ECMO oxygenated blood.

3. C. Small observational studies of neurological outcome in patients after ECMO treatment have shown that impaired cognitive functioning is associated with intracerebral lesions, which more often occur in patients treated with V-A ECMO. There is no strong evidence that prolonged arterial hypoxemia results in cognitive long-term impairment in surviving ECMO patients. Inflammation contributes to cognitive dysfunction, but this has not systematically been investigated in ECMO patients.

4. A. According to Lorusso et al., 181 of 426 registered neurological complications were intracerebral hemorrhage, followed by brain death, stroke, and seizures. This ELSO data registry analysis included 4988 patients.[17]

5. D. In their systematic review, Juo and coworkers showed that the rate of limb ischemia was 15.7% less in patients with a distal perfusion cannula compared to patients with no distal perfusion cannula.[25]

6. C. When cannulating the femoral artery distally to the proximal arterial cannula, due to the compromised intravascular filling, the needle can easily end up inside the vein, resulting in a distal perfusion into the femoral vein that results in a compromised leg. Therefore, this method always needs close monitoring after distal cannulation. If possible, the distal puncture and introducing the guide wire are performed before the proximal arterial reinfusion cannula is inserted (expert opinion).

7. D. It is possible that patients presenting with normal cognitive functioning after ECMO treatment performed significantly better before they became ill. Therefore, they might suffer from cognitive impairment that was not detected by testing. Studies have shown that despite hypoxemia during ECMO treatment, up to half of the patients can return to work. In conventionally treated ARDS patients, cognitive function improved at least during the first year postdischarge.[18,22] Good studies comparing cognitive outcome after severe ARDS with or without ECMO treatment are lacking.

8. C. The influence of PaO_2 on CaO_2 is negligible: $CaO_2 = 1.31 \times Hb \times SaO_2 + (0.003 \times PaO_2)$.

9. C. Studies have shown that patients treated with V-V or V-A ECMO for severe ARDS are at risk for cerebral lesions.[17,26] Impaired cognitive function, however, seems to correlate with cerebral lesions possible to visualize post-ECMO and not hypoxemic events during ECMO treatment.[18,27]

60.

MANAGEMENT OF ECMO COMPLICATED BY INTRACRANIAL HEMORRHAGE

Alexander Fletcher-Sandersjöö and Lars Mikael Broman

STEM CASE AND KEY QUESTIONS

A 46-year-old woman with a history of hypertension, hyperlipidemia, and diabetes was admitted to her local hospital after 7 days of dyspnea, fever, and myalgia. She was administered intravenous antibiotics against a suspected bacterial upper respiratory tract infection and later intubated. Despite these efforts, her respiratory function continued to decline, and extracorporeal membrane oxygenation (ECMO) treatment was advocated. She was cannulated for jugulo-femoral veno-venous (V-V) ECMO and transported to an ECMO intensive care unit (ICU), where she was diagnosed and appropriately treated for viral pneumonia.

Precannulation biochemistry showed a platelet count of 98 × 10^9/L, fibrinogen 1.9 g/L, prothrombin time (PT) 17 seconds, 1.3 international normalized ratio, and an activated partial thromboplastin time (aPTT) within normal range. An intravenous infusion of unfractionated heparin was used for anticoagulation, and the dose target was carefully monitored hourly with activated clotting time (ACT), and the aPTT was checked three times daily, aiming for 1.5–2 times the upper normal range. Meropenem and vancomycin were administered empirically. No positive cultures were obtained, but superinfection of staphylococci was suspected. The patient was tracheotomized on day 3. On day 5 and day 6, cautery was needed to stop bleeding from the stoma. However, it was uncertain if this "minor bleeding" was a true transfusion problem. Echocardiography and plain chest x-rays showed nothing abnormal. The patient showed a slow recovery, but this was expected considering the circumstances. Due to respiratory distress, the patient could not be fully awakened but did respond to verbal commands. Neuromuscular blockade was not necessary. Continuous renal replacement therapy (CRRT) was used for fluid balance and to keep metabolic control.

One week into ECMO treatment, she became unresponsive and developed a unilaterally dilated pupil. A computed tomographic (CT) scan showed a subarachnoid and intraventricular hemorrhage with secondary hydrocephalus (Figures 60.l and 60.2). No bleeding source was detected on the cerebral angiography. The heparin infusion was stopped immediately. The neurosurgical team was consulted, and 5 hours later, following hemostatic resuscitation using platelets, fibrinogen, and tranexamic acid, she underwent an external ventricular drainage (EVD) placement. Preoperative biochemistry showed a platelet count of 42 × 10^9/L but fibrinogen, aPTT, PT, and ACT all were within normal range. The surgery was uneventful, and the postoperative CT did not show any new hemorrhage. Intracranial pressure was managed through hyperosmolar therapy, hyperventilation, and pentobarbital coma.

Due to the patient's poor respiratory status, weaning from ECMO was not possible following surgery. Instead, ECMO support was continued without any anticoagulation. On postoperative day (POD) 9, the EVD clotted,



Figure 60.1 Axial plane image from a CT scan showing a spontaneous intracerebral hemorrhage that occurred during ECMO support.



Figure 60.2 Coronal plane image of the same patient.

and a new device was placed without any complications. On POD 12, her pupils showed normal size. Sedation was reduced, and the patient began showing signs of arousal. A week later, the ECMO circuit was replaced due to visible clots, and heparin anticoagulation was restarted after careful consideration of the patient's pro- and anticoagulatory demands. Three weeks following surgery, a CT scan showed no remaining hemorrhage, hydrocephalus, or ischemia, and the EVD was removed.

WAS ICH EVIDENT IN THIS PATIENT PRIOR TO CANNULATION?

The patient's medical history did not provide any information concerning preadmission antithrombotic medication or any other circumstance that would indicate an increased risk for Intracranial hemorrhage (ICH). There was no cardiac arrest or circulatory failure that preceded the referral for ECMO. However, a low platelet count was observed, which is a known risk factor for ICH development during ECMO treatment.[1] No CT scan was performed prior to cannulation or directly after commencement, and it is therefore unknown if there was any minor ICH early on. A routine of early neuroimaging to detect intracranial pathologies is practiced at some centers and impacts anticoagulation management accordingly, which may favor outcome.[2,3] In the case of ICH diagnosis prior to ECMO cannulation, treatment may not have been offered at all in accordance with the guidelines for adult respiratory ECMO published by the Extracorporeal Life Support Organization (ELSO; Ann Arbor, MI) (https://www.elso.org/Resources/Guidelines.aspx).

HOW WAS THIS PATIENT MANAGED BEFORE ICH?

In this case, the patient "followed protocol" although slower than someone with average viral pneumonia with bacterial superinfection. In the rear mirror, we can identify severe infection (sepsis, septic shock) and dialysis and the extracranial bleeding as risk factors.[1] One could argue that she was not in septic shock, but of course, she experienced severe systemic inflammation and had a bleeding problem from her stoma. Concerning dialysis, in this patient, CRRT was started to reach a negative fluid balance without problems from hypochloremic alkalosis. By definition, the use of dialysis equals renal failure is a known contributor to mortality in the critically ill.[4,5] Paradoxically, CRRT/dialysis is the extracorporeal organ support we can offer to these patients, and excessive fluid overload is also a factor increasing the risk of death. In many cases, the uses of dialysis regimens may be a marker of how sick the patient really is. The degree of sickness is the risk factor, not the method of support.

HOW IS PATIENT MANAGEMENT ADDRESSED AFTER AN ICH DIAGNOSIS?

When the patient became unconscious, an emergency CT scan of the brain was performed that showed two forms of ICH. The heparin infusion was stopped immediately, and a neurosurgeon was contacted. Here are some items to discuss:

1. Should the heparin infusion have been stopped when the pupil dilated?
2. What would have happened if the patient had been treated at a hospital without neurosurgical resources?
3. Was the bleeding caused by primary thromboembolism that transformed into ICH?

To begin, a decision to stop anticoagulation based on decreased consciousness and a dilated pupil alone needs to be weighed against the most probable diagnosis (intracranial infarct or hemorrhage?) and the time it will take to perform a diagnostic CT scan. Under normal circumstances, the half-life of heparin would allow for pausing the infusion until a CT has been performed. Thus, pausing the heparin infusion prior to CT scanning may have been indicated in this case, although there is no literature to guide us.

Second, when advanced and complex technologies, such as ECMO, are spread out from university hospitals to smaller regional ones, those centers expose their patients to a major risk. Arguments are very strong to consolidate ECMO to high-volume centers for best-quality care to lower costs.[6] This requires experienced and effective mobile ECMO services.[7] In this case, the time to treatment would have been delayed if the patient was not treated at a hospital with a neurosurgical unit. However, it should also be noted that surgery was not performed immediately but instead after adequate hemostatic resuscitation.

The third item refers to the complex balance between pro- and anticoagulation. In the sedated patient, with multiple

bleeding sources and sepsis (e.g., from a *Staphylococcus aureus* infection), the cause may be septic embolization. After the first hit, masked by sedation (or nonsymptomatic), the ischemic/necrotic tissue distal to the embolus may start to bleed.[8] This may occur even if the management of anticoagulation is maintained low within range, and when the bleeding has started coagulation is slower.

WHAT AFFECTS THE DECISION FOR HAZARDOUS SURGICAL INTERVENTION?

To convince a neurosurgeon to perform surgery on an anticoagulated ECMO patient will require a decent amount of persuasion in any hospital. Most would consider such patient a "no-no," as reflected by fewer than 10 cases ever reported of neurosurgical treatment of ECMO patients,[9] of whom 2 survived.[10,11] In the current case, a young woman with greater than 85% chance of favorable outcome suffers an ICH during ECMO, with intraventricular blood with secondary development of hydrocephalus. Without an EVD, her chances would be very slim. To continue ECMO heparin free, support coagulation, optimize blood pressure, and so on to limit expansion of hematoma(s) would be the path to follow before and during surgery. In the present case, no intraparenchymal hematoma was to be evacuated, and hemostasis was maintained. The majority of ICH bleeds are intraparenchymal.[1] It should be noted that most cases (even at our center), surgery is not offered as most bleedings are classified as "not compatible with life," and extracorporeal life support thus is withdrawn.

HOW IS POSTOPERATIVE CARE MANAGED?

Neuro intensive care was applied with conventional means to control and maintain cerebral perfusion pressure within range and minimize cerebral edema. The patient was deeply sedated for almost 2 weeks. The option to restart anticoagulation in close proximity to surgical intervention cannot be recommended. To run heparin free best would be to change to a new ECMO circuit. However, this risks exposure of the patient to additional secondary insult in a very vulnerable phase of recovery. Running heparin free for days and sometimes for more than a week is possible in some patients, but biochemistry should be monitored, including fibrin degradation products. One coagulation variable to consider that may be disregarded is the natural anticoagulant antithrombin (AT). AT may be consumed together with platelets and fibrinogen. The goal of AT supplementation is to keep values within reference ranges. However, there are no studies on this, and some marketed AT products, on the contrary, may promote and increase coagulation due to a high content of a degraded form, latent AT, which in itself consumes native AT.[12]

When to restart the heparin infusion is a delicate decision where one must balance the risk of rebleeding against the risk for clotting in the circuit and subsequent risk of oxygenator failure, cannula clot, or embolization from the circuit to the patient. To reduce clotting in the circuit, ECMO flow is kept at a higher flow rate than otherwise needed. The backside of higher flow is increased shear forces exerted on blood components (e.g., platelets, red blood cells, von Willebrand factor, etc.). The results may increase coagulation and elicit hemolysis and bleeding issues.

WHAT CANNULATION STRATEGIES ARE AVAILABLE?

The patient was cannulated according to the department's standard configuration for V-V ECMO using two single-lumen cannulae in the jugulo-femoral flow direction.[13,14] Drainage from the right atrium/lower vena cava superior maintains properties for high flows when the vena cava inferior is too collapsed for efficient drainage. Most centers today use a dual-lumen cannula (DLC) for V-V ECMO. To provide the same flow as a single-lumen application, the outer diameter has to be increased due to the limitation in cross-sectional area harboring the two laminae. The DLC risks obstructing venous outflow from the central nervous system when placed via the jugular vein, and ELSO Registry data have shown cannula size–related increased risk for cerebral bleeding.[15]

An interesting option, although not illustrated by this case, is that in veno-arterial (V-A) ECMO for cardiorespiratory support, the central venous pressures may be kept lower than in V-V ECMO, which improves cerebral venous drainage.[16] On the other hand, depending on cannula design, cannulation configuration, and the patient's cardiac and residual lung function, there is a high risk for differential hypoxemia that, especially in these patients, might be lethal.[17] Jugulo-subclavian V-A ECMO or veno-veno-arterial (V-VA) hybrid mode configuration may be an option.[18]

DISCUSSION

INTRACRANIAL HEMORRHAGE—INCIDENCE, PRESENTATION, AND OUTCOME

A recent meta-analysis found that the reported incidence of ICH in adults during ECMO varied between 1.8% and 21%.[9] While data on neurological presentation are limited, most patients (>2/3) seem to present with neurological symptoms before a lesion may be confirmed by a CT of the brain. However, sedatives and muscle relaxants used during ECMO may mask symptoms of brain injury, resulting in the risk of many undetected lesions. Solely relying on neurological assessment before performing a CT scan may therefore not be sensitive enough. According to a review, centers performing regular screening CT scans had among the highest rate of ICH, suggesting a correlation between high frequency of asymptomatic CT scanning and diagnosis of ICH.[1–3,9]

The location/type of diagnosed ICH may differ, and combinations are common. Intracerebral and subarachnoid hemorrhages appear to be the most common.[10]

Survival in ECMO patients with ICH is generally poor. Reports on outcome suggest 0–70% chance of survival in adult ECMO patients who develop an ICH.[19–26] In survivors, long-term morbidity can be expected.[27–29]

MANAGEMENT OF INTRACRANIAL HEMORRHAGE

Treating an ICH during ECMO represents a difficult balance between pro- and anticoagulatory demands. A previous study from our center has identified three broad treatment groups[10]:

1. ECMO is discontinued due to futility, typically due to large intracerebral hemorrhages often in combination with limited signs of native cardiorespiratory improvement during ECMO treatment. These patients generally pass away following ECMO withdrawal.
2. No intervention necessary. Typically, this involves small and possibly asymptomatic bleedings in patients that show promising cardiorespiratory improvement during ECMO support, in which the consequence of treating the hemorrhage is believed to do more harm than good (e.g., interrupting anticoagulation would increase the risk of ECMO circuit failure or systemic thromboembolism). This is weighed against the risk of hemorrhage progression.
3. Treatment given. Specific treatment varies on a case-by-case basis. If feasible, ECMO treatment may be stopped, and the ECMO cannula explanted, which enables hemostatic management without increasing the risk for systemic thromboembolism. If this is not possible, intervention will be performed during continued ECMO support, which highlights the hemostatic treatment paradox described in the previous discussion. The hemostatic management includes cessation of the heparin anticoagulation and on occasion reversal of heparin by protamine and administration of platelets, platelet-stimulating agents, and antifibrinolytic drugs (e.g., tranexamic acid). Bedside management turns "neuroprotective," including a sedation regimen; monitoring body temperature; tight control of the sweep gas flow ($PaCO_2$); ECMO blood flow (Oxygen delivery by ECMO support [$DecmoO_2$], Oxygen delivery by native cardiac output [DaO_2], PaO_2); electrolytes; blood glucose; plasma albumin; hemoglobin concentration; systolic and mean arterial blood pressure; ventilator settings (low positive end-expiratory pressures); and AT. While surgical management may be indicated when an ICH occurs during ECMO, the associated anticoagulation presents considerable risk. In addition, time restraints allow limited opportunity for preoperative optimization of coagulation, other than immediate heparin reversal, to decrease intra- and postoperative blood loss and hematoma progression. However, successful cases of surgical treatment of ECMO-associated ICH exist.[10,11]

MECHANISMS AND CLINICAL CONSIDERATIONS

The ECMO patient's hemostasis is affected by comorbidities, preadmission medication, the acute disease itself, ECMO-induced coagulopathy, and, on top of that, the anticoagulation regime (often intravenous infusion of unfractionated heparin). ECMO coagulopathy induced by exposure to artificial surfaces and shear forces on the circulation blood in the circuit results in activation of coagulation; pump-induced platelet dysfunction; thrombocytopenia/consumptive coagulopathy; factor XIII deficiency; acquired von Willebrand syndrome; fibrinogen deficiency; and AT consumption.[20,25,30–39] Prophylactic correction of coagulation factor deficiency may reduce the risk of ICH.[40] On the other hand, activation of clotting factors increases thrombin production and may contribute to enhanced coagulation imbalance and factor consumption, which the clinician counteracts by the anticoagulation regimen.[39,40] Emboli may form in the membrane lung or return cannula that can lead to ischemic stroke in V-A ECMO[41] or in patients with a patent foramen ovale on V-V ECMO.[42] Ischemic lesions risk transforming into ICH in as many as half of the patients (personal communication).

Events before or during initiation of ECMO may also play an important role in ICH development. For example, factors related to cardiogenic shock (low cerebral blood flow, hypoxia, acidosis, and hemostatic disorders due to liver failure) and reperfusion injury at ECMO initiation precipitate brain injury in V-A ECMO patients.[40,43] Abrupt CO_2 or O_2 changes at ECMO cannulation and commencement of ECMO may disrupt cerebral perfusion in both V-V and V-A ECMO, which may be augmented by deep sedation.[44–48] Ambitious sedation management has been identified as an independent risk factor for ICH in adults during ECMO[22,26] and may impair cerebral autoregulation, contributing to ischemic stroke transforming into a secondary ICH.[26,49,50]

Better understanding of ICH pathophysiology and predictors will help facilitate early identification of patients at risk of developing an ICH during ECMO treatment. Possible management strategies include running anticoagulation-free ECMO, tight neurologic control and more rigorous device monitoring, serial sampling of biomarkers of brain injury,[51] aiming for earlier weaning from ECMO, and more; continuation would be based on patient-specific considerations and decisions.[52–58] The best and cheapest monitoring of neurologic function is to keep the patient awake. However, all patients cannot handle being awake during critical care or ECMO due to multiple reasons. Monitoring the central nervous system is difficult, and, for feasibility, methods for continuous assessment need to be noninvasive to be effective for guiding when to initiate more resource-demanding diagnostic investigations or treatment strategies at an early stage. Near-infrared spectroscopy (NIRS) may be used for continuous assessment of the cerebral oxygenation profile.[59] Decreased brain tissue oxygenation has been demonstrated in neonates that later developed cerebral insult on neuroimaging.[60] The one study on NIRS in adults showed that a cerebral oxygenation response following hemodynamic intervention decreased the likelihood for ischemic cerebral complication.[61]

CONCLUSION

- In adult ECMO patients, ICH is a common and often fatal complication.

- The incidence of ICH is higher than recognized by most—up to one in five patients.
- Mortality from ICH is high; only one in five patients survives.
- Recognition depends on CT scan frequency since a large proportion of ICHs may be "silent."
- The best neuromonitoring would be to aim for awake ECMO and assess the patient's clinical status.
- This may be complemented by
  - brain CT scan on admission or early in course of ECMO,
  - daily sampling of biomarkers for brain damages,
  - electroencephalography,
  - near infrared spectroscopy, and
  - cranial Doppler, and so on, depending on patient context.
- Clinical manifestations call for cessation of anticoagulation and a CT scan.
- Surgical intervention is very hazardous but may be considered in patients with very high risk of death from the lesion but otherwise good prognosis concerning the cause for ECMO.
- Although we are far from solving the complete puzzle, our understanding is slowly increasing with regard to its pathophysiology: association of comorbidity, pre-ECMO morbidity, and inflammatory responses with hemostasis and anticoagulation.
- Increased understanding of these factors improves management of ICH during ECMO, which is an intricate balance between pro- and anticoagulatory demands, conservative treatment, or active intervention, which may include surgery.

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REVIEW QUESTIONS

1. At commencement, name *one* important item to consider regarding risk factors for ICH in the processing of starting the ECMO flow?

A. When the saline prime enters the microcirculation, vasoconstriction will occur, which leads to increased risk for water-shedding infarcts in a hypotensive situation. Thus, rev up the pump fast to guarantee a mean arterial blood pressure of at least 75 mm Hg.
B. Adjust sweep gas flow in an incremental fashion to reduce PCO_2 (in hypercarbia) over several hours or even more than a day.
C. Reduce vasopressor support just before start of ECMO flow to minimize the risk for a blood pressure spike.
D. Immediate reduction of positive end-expiratory pressure to improve cerebral venous drainage (i.e., reduce intracranial pressure).

2. Which of the following statements is *in*correct?

A. Patients on antithrombotic medication before ECMO that suffer an ICH during ECMO treatment have a very high risk of mortality.
B. In femoral return V-A ECMO, independently of jugular or femoral drainage, the brain is not protected against emboli from the ECMO circuitry if the arterial oxygen saturation is lower on the right hand than on the left hand.
C. Confirming brain death in an ECMO patient can be performed in any ECMO ICU.
D. In V-V ECMO the central nervous system is protected against microemboli from the ECMO return.

3. Monitoring of the central nervous system in the ECMO patient is best performed using

A. Continuous electroencephalography, daily assessment of biomarkers for brain damage, and NIRS.
B. Computed tomographic scans on admission and every third day thereafter.
C. Awake ECMO.
D. The combination A and B.

4. In suspicion of an intracerebral event, what is the first measure that should be taken?

A. Inform the family and call the transplant coordinator to start the donation process.
B. Stop anticoagulation and go for an immediate CT scan.
C. Continue anticoagulation and go for an immediate CT scan.
D. Perform bedside ultrasound of the optic nerve sheath followed by transcranial Doppler of arteria cerebri media.

5. Which one is correct considering V-A ECMO

A. Femoro-femoral V-A ECMO is preferred since there is no cannula obstruction of the jugular veins.
B In configurations using a grafted subclavian return cannula, there is no risk for cerebral embolization.
C In isolated lung failure, V-V ECMO using two single-lumen cannulae is probably better than one dual-lumen cannula or jugulo-femoral V-A ECMO without the distal perfusion catheter.
D Femoro-femoral V-A ECMO is always equal to a jugulo-femoral V-A configuration considering brain oxygenation.

6. Which one is *in*correct considering ECMO configurations

A. The medical definition of Harlequin syndrome has nothing to do with oxygen saturation.
B. Comparing two properly placed 31F and 27F dual-lumen cannulae for V-V ECMO, the smaller cannula will still provide adequate oxygenation in most adult patients.
C. Using the hybrid configuration femoro-jugulo-femoral V-VA ECMO for cardiorespiratory support will not increase the risk of device embolization/secondary ICH compared to a femoro-femoral V-A configuration.
D. Venous drainage from the brain could be augmented using a cephalad drainage catheter in patients with the major drainage cannula placed via the jugular vein.

7. What is *not* true concerning neurologic ECMO complications?

A. Cerebral events are the major cause of death related to ECMO treatment.
B. Veno-arterial ECMO is assumed to carry more cerebral complications but this is still not proven.
C. Patients who are offered surgical intervention recover with favorable outcome.
D. Low platelet count and antithrombotic treatment before ECMO affect survival.

8. Which is the most correct management of anticoagulation after an ICH?

A. When to start heparin again is an evaluation in each patient based on risk of circuit thrombosis, rebleeding, and other factors.
B. After two consecutive CT scans 2 days apart and no signs of rebleeding, the heparin infusion can be started without bolus.
C. When D-dimer/fibrinogen degradation products start to increase and there are signs of platelet and fibrinogen consumption, the heparin infusion can be started without bolus.
D. During the use of ventricular drainage, heparin should never be started. The protocol instructs changing the ECMO circuit when ocular inspection and biochemistry fulfill certain criteria.

ANSWERS

1. B. Rapid recovery, or changes in PCO_2 or PO_2 when the extracorporeal flow is commenced risk affecting cerebral perfusion in both V-V and V-A ECMO, which may be augmented by deep sedation.[33–37]

2. D. In V-V ECMO the central nervous system is protected against microemboli from the ECMO return. It is estimated that up to 25% of adults have a known or unknown patent foramen ovale. Thus, in situations with inversed pressures between the right and left atrium an embolus may pass over to the systemic circulation.

3. C. Awake ECMO. In many cases an ICH is discovered accidentally on a CT scan performed without any obvious symptoms. In almost 70% of patients later diagnosed with a lesion clinical symptoms are presented well before any pathological findings emerge on a CT. The sedated patient cannot alarm the staff on the occasion of an event. Albeit sedation may reduce cerebral oxygen demand, autoregulation may be affected as well as the general perfusion pressure.

4. B. Eliminate the most likely risk factor for continued bleeding. If bleeding is confirmed, consider continued

cessation of anticoagulation. If no signs of a bleeding event or finding of ischemic lesion, reconsider to restart anticoagulation but evaluate the risk of secondary bleeding of ischemic area, change anticoagulation targets, etc. Any delay that can be avoided is beneficial for the patient.

5. C. Using two separated cannulae requires a smaller cannula placed in, for example, the jugular vein; thus, the degree of venous obstruction will be less compared to using a dual-lumen cannula (DLC) in a jugular approach. ECMO support may be more efficient considering lower recirculation fraction for a correctly placed DLC, which, however, also is a discussion on cannula design and detailed configuration options. A slightly offset DLC may recirculate more than 50%.

6. C. When composing a circuit for dual return (to the arterial and venous sides of a patient's circulation), Y-piece connectors are used. These promote turbulence and are thus risk areas for platelet activation and hemolysis. Second, diverging flow to vascular compartments with different blood pressure mandates for some kind of control of the respective V and A flows. Gate clamps to squeeze the tubing may be used. These also create turbulence. One may use a long, small-diameter cannula for higher flow resistance to the V side, but balanced flow will vary depending on the arterial blood pressure. Also, note that separating flows into two limbs reduces the driving pressure before the arterial return cannula, where the distal perfusion catheter may be connected. Thus, here is yet another region of differential pressure/flow, and the distal perfusion flow may cease, especially when the ECMO flow is reduced at weaning/trial off. It is wise to continuously monitor the flow in one of the major limbs (V or A) of the circuit and in the tubing for distal perfusion. Comment on A: Harlequin syndrome originates from a vascular autonomic phenomenon observed in neonates more than 100 years ago. In ECMO, it is a misnomer that came to use in the 1980s. The correct terminology is differential hypoxemia.

7. C. Discussion on only two survivors with good outcome after neurosurgery has been published thus far. One additional case is known to us. Thus, the chance of favorable outcome seems very slim. However, to date we do not really know.

8. A. When starting heparin again can never be protocolized and should be based on individual patient evaluation, where the balance between risk of bleeding is weighed against risk of circuit failure and thromboembolism from the circuit or thrombus formation in the patient.

61.

NEUROLOGICAL MONITORING AND DETERMINATION OF BRAIN DEATH IN ECMO PATIENTS

Michael D. Harper, Dirk M. Maybauer, and Marc O. Maybauer

STEM CASE AND KEY QUESTIONS

A 51-year-old Caucasian female presented to the emergency department (ED) via Emergency Medical Services (EMS) with a cardiac arrest (CA) onset 20 minutes prior to arrival in the ED. She had a witnessed seizure, fell, and struck her head on a wall and went into CA. EMS stated the patient was cyanotic for approximately 10 minutes prior to their arrival. The patient had approximately 10 minutes of cardiopulmonary resuscitation (CPR), 2 doses of epinephrine (1 mg each), and bicarbonate 100 mmol for asystolic CA. In the ED, she had return of spontaneous circulation (ROSC); however, it was with cardiogenic shock. The patient also had a history of seizure disorder.

The patient was intubated in the ED. Computed tomographic (CT) scans of the brain and cervical spine were negative for any acute pathology. A laceration repair was performed on the occipital scalp with a skin stapler. As the patient continued to be in shock post-ROSC and required an epinephrine drip at 0.3 μg/kg/min with a lactic acid level of 18 mmol/L, the extracorporeal membrane oxygenation (ECMO) team was called, and the patient was cannulated for veno-arterial (V-A) ECMO in the ED.

The patient exhibited intermittent seizure activity and was started on intravenous levetiracetam prior to being transported to the intensive care unit (ICU). The initial ED laboratory tests were significant for pH 6.83, PCO_2 greater than 105 mm Hg, glucose 331 mg/dL, sodium 146 mEq/L, potassium 4.6 mEq/L, carbon dioxide 13 mm Hg, anion gap 27 mEq/L, creatinine 1.58 mg/dL, troponin I less than 0.010 ng/mL, lactic acid 18.49 mmol/L, white blood cells $6.4 \times 10^3/\mu L$, hemoglobin 10.5 g/dL, and platelets $261 \times 10^3/\mu L$.

On arrival at the ICU, the epinephrine drip was weaned completely due to restoration of systemic perfusion with good ECMO flow with adequate circulatory support and maintenance of left ventricular (LV) ejection. A transthoracic echocardiogram was performed. This technically difficult study on V-A ECMO at a speed of 4200 revolutions/min (3.5 L/min) showed a LV ejection fraction of 20%–25%. The global right ventricular systolic function was mildly to moderately reduced. No significant valvular lesions were noted. The venous ECMO drainage cannula was seen in the inferior vena cava extending into the right atrium. There was no pericardial effusion and no prior study available for comparison.

The patient was sedated and paralyzed for targeted temperature management (TTM) at 33°C for 24 hours utilizing a heater-cooler device connected to the membrane lung of the ECMO circuit. After safe rewarming, a temperature of 36°C was achieved; sedation was subsequently discontinued. The next morning the patient was unresponsive, and a poor neurologic examination lacking both gag and cough reflexes was obtained.

She was transported for a CT scan of the brain, which showed effacement of the sulci and ventricles and loss of the gray-white matter junction. The findings were consistent with anoxic brain injury with moderate-to-severe cerebral edema (Figure 61.1). During the day, she lost all brainstem reflexes, and a modified apnea test (with CO_2 supplementation) confirmed brain death. The family decided to proceed with organ donation, for which kidneys, liver, lungs, and corneas were procured and successfully transplanted.

IS THERE A ROLE FOR CEREBRAL OXIMETRY IN THE SETTING OF CARDIAC ARREST?

In a recent systematic review and meta-analysis by Sanfilippo et al.,[1] the authors described the prediction of ROSC during resuscitation of patients suffering from CA as particularly challenging. Regional cerebral oxygen saturation (rSO_2) monitoring through near-infrared spectroscopy (NIRS) is feasible during CA and could provide guidance during and after resuscitation.

Nishiyama and colleagues published their experience with rSO_2 post-ROSC after out-of-hospital cardiac arrest (OHCA) as a predictor of neurologic outcomes and found that an initial rSO_2 greater than 40% was associated with favorable outcomes if the individuals also underwent TTM and/or left heart catheterization.[2] Higher initial and average regional cerebral oxygen saturation values are both associated with greater chances of achieving ROSC in patients suffering from CA, as well as increasing the likelihood of achieving favorable neurologic outcomes (Cerebral Performance Category [CPC] 1 or 2) with TTM.[1,3] These predictions may be particularly helpful to determine if extracorporeal CPR (ECPR) or V-A ECMO should be initiated once available.

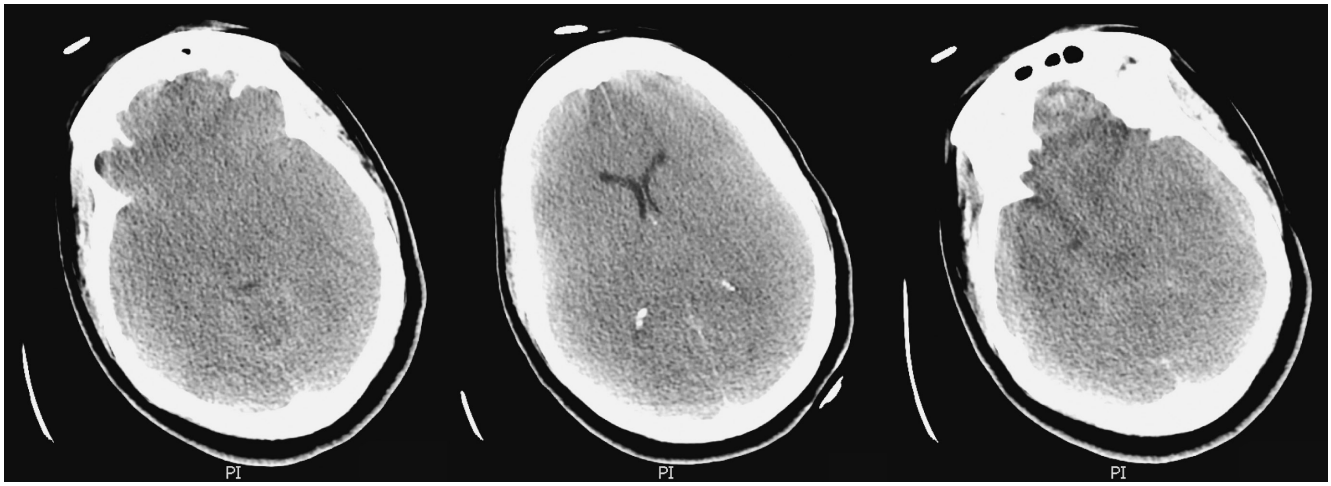


Figure 61.1 Computed tomography CT) scan. There is loss of gray-white differentiation in the bilateral hemispheres. Diffuse low attenuation is seen throughout the brain, consistent with global hypoxic ischemic injury. There is diffuse sulcal effacement with uncal herniation (middle) and polysinusitis (right).

IS BIS MONITORING USEFUL IN THE EARLY DETECTION OF BRAIN DEATH OR POOR NEUROLOGIC OUTCOME IN ECMO PATIENTS?

Bispectral Index (BIS) is a noninvasive device utilized in monitoring the depth of sedation during general anesthesia and in the ICU.[4–6] The use of BIS monitoring for neuroprognostication in the setting of CA has been studied in multiple settings, and there appears to be good evidence to support its use in that role. Jouffroy et al. examined its use in patients after OHCA requiring ECPR, finding that the average values during TTM and after rewarming were highly predictive of progression to brain death. A BIS value under 30 during TTM predicted brain death with a sensitivity and specificity of 96% and 82%, respectively.[7] In Burjek's observational study of 141 CA patients treated with TTM, there was a clear separation of BIS values at 7 hours that, when coupled with sedative dose requirements, predicted all poor neurologic outcomes (CPC 3–5) and did not incorrectly classify any good outcome patients as poor outcome. Median BIS scores were 31 points lower at hour 7 in patients with poor neurologic outcome.[8] BIS utilization in this patient population is an incredibly useful tool that can aid with early prognostication postCA.

IS NEURON-SPECIFIC ENOLASE A GOOD PREDICTOR FOR NEUROLOGIC OUTCOME?

Neuron-specific enolase (NSE) is an enolase isoenzyme produced by neurons and peripheral neuroendocrine cells. It is used as a tumor marker for neuroendocrine tumors[9] and is showing promise as a biomarker for hypoxic-ischemic encephalopathy (HIE).[10] In a substudy analysis of the TTM trial, Stammet and colleagues measured NSE in 686 patients after OHCA undergoing TTM at 24, 48, and 72 hours after ROSC. They demonstrated that NSE was a reliable predictor of neurologic outcome, and that TTM, at either 33°C or 36°C, did not alter serum NSE levels significantly.[11]

Streitberger et al. performed a multicenter study of OHCA and in-hospital CA patients, and NSE was measured 72 hours after ROSC. In this study, they were able to demonstrate that a serum NSE greater than 90 μg/L predicted poor neurologic outcome, with a positive predictive value of 99% and a sensitivity of 48%; additionally, a serum NSE less than 17 μg/L had a negative predictive value of 92% (if patients who died due to causes other than HIE are excluded, then this value is higher).[10] When considering patients post-CA on ECMO, there is a paucity of data currently published.

Schrage and colleagues evaluated CA patients who received V-A ECMO during resuscitation, examining NSE measurements at 24, 48, and 72 hours after ROSC. They determined that the NSE trend over the 3 days following ROSC was the strongest predictor of neurologic outcome. Increasing or decreasing serum NSE values predicted poor or good outcomes, respectively.[12] This study was important because NSE measurement in ECMO patients had not been evaluated previously, and hemolysis can lead to false elevation of NSE due to release of enolase isoenzymes from erythrocytes and thrombocytes.[13]

The hemolytic markers plasma free hemoglobin and lactate dehydrogenase should be measured when sampling NSE in patients on ECMO support to prevent erroneous neuroprognostication. While many studies have demonstrated that very elevated NSE levels can be predictive of poor neurologic outcome, there are outliers in every data set that has been published with good neurologic outcome, which would make an absolute value of NSE at which poor neurologic outcome occurs very difficult to ascertain.

Chung-Esaki and colleagues published their prospective cohort of post-CA patients with serum NSE assayed at 24, 48, and 72 hours postarrest. They found that the NSE ratio 48:24 hours was 100% specific for poor outcome, with values above 1.7.

An NSE ratio greater than 1.0 is indicative of rising NSE levels and could reflect ongoing neuronal injury. NSE can be a valuable tool to evaluate the chances for neurologic recovery

after CA, but it is only one of many tools and assessments that must be employed to accurately predict neurologic outcomes with a high degree of certainty.

WHAT IS THE ROLE OF EEG IN ECMO PATIENTS?

Electroencephalography (EEG) is a commonly utilized diagnostic tool to assess patients with seizure or undifferentiated encephalopathy while in the ICU. EEG is primarily a measure of cortical function, and as the cortex is sensitive to periods of hypoxia and/or low flow, it becomes a very useful tool to aid in the neuroprognostication for CA patients.[14] This has been recognized, and standardized terminology for EEG interpretation in the critically ill has been proposed.[15] Data on EEG in the setting of postarrest V-A ECMO remains minimal, and further research is significantly needed as the numbers of CA patients treated with ECPR increases.

Alterations in cerebral autoregulation after ECPR can occur due to continuous flow of blood with a high partial pressure of oxygen, and these effects may directly affect neurological outcomes.[16] Kim et al. published their experience utilizing EEG in all CA patients requiring ECPR with Glasgow Coma Score (GCS) less than 13 after ROSC with EEG performed within 4 days of ROSC. Over the study period, they evaluated 69 patients and found that malignant EEG patterns were associated with a poor neurologic outcome, and that all patients with highly malignant EEG patterns (suppressed background [amplitude < 10 μV, 100% of recording] without discharges, suppressed background with continuous periodic discharges, or burst-suppression background with or without discharges) had an unfavorable neurologic outcome (CPC 3–5). Abnormal EEG findings were even more successful at neuroprognostication when coupled with duration of CPR, with the receiver operating characteristic curve of malignant EEG plus CPR duration yielding an area under the curve of 0.908 (0.813–0.968).[17] Cho and colleagues studied the prognostic value of early EEG and somatosensory evoked potentials (SSEPs) in ECPR patients with GCS less than 8 and motor GCS less than 4, respectively. Out of 13 patients included, 12 had poor neurological outcomes. Those 12 patients had malignant findings on EEG, but all had preservation of the N20 response on SSEP testing.[18] This bolsters the statement that further prospective analysis is needed to give more granularity to the diagnostic and prognostic reliability of these tests (Figure 61.2).

IS TRANSCRANIAL DOPPLER SONOGRAPHY A USEFUL TOOL FOR NEUROLOGIC ASSESSMENT IN ECMO PATIENTS?

Transcranial Doppler (TCD) ultrasonography is a noninvasive imaging modality that measures velocity and direction of blood flow in the cerebral vasculature. Though cerebral angiography is the gold standard,[19] TCD is extremely useful due to lack of requirement for contrast media and the ability to



Figure 61.2 Electroencephalogram (EEG) of patient post–cardiac arrest. Severe cortical suppression and absence of cortical activity is consistent with severe diffuse encephalopathy.

perform it at bedside, serially if needed.[20] Neurologic sequelae associated with ECMO represent a significant source of morbidity and mortality. The use of TCD in V-A ECMO has not been extensively reported, but the effect of monophasic blood flow cannot be disregarded when trying to use this imaging modality in that patient population. Patients on V-A ECMO have altered pulsatility indices, mean flow velocities, and peak systolic/diastolic velocities—this effect can be altered depending on cannulation location (i.e., femoral artery, subclavian artery, or aorta); volume of flow; and native cardiac function.[21,22]

Despite these alterations in the characteristics of blood flow, TCD has the potential to be an extremely useful tool when assessing the comatose V-A ECMO patient. TCD can be utilized to assess for cerebral circulatory arrest (CCA) (defined as oscillatory flow with systolic spikes) as part of a brain death evaluation and is part of standard practice in Italy. Marinoni et al. presented their retrospective data on TCD in V-A ECMO patients for the determination of brain death via CCA assessment. Their findings showed that pulsatility must be maintained on the arterial line tracing with either native LV ejection or with intra-aortic balloon pump (IABP) support in order to safely make that diagnosis.[23] Proximally obstructive vascular lesions must be excluded, and systemic hypotension must not be present as these can lead to a false-positive assessment for CCA. If the patient has a ventricular drain or craniotomy, cerebral blood flow can be maintained in the setting of brain death, and thus other assessments must be utilized.[24] TCD has the potential to be a very useful tool in this patient population, but further study is required in order to obtain reliable data in each clinical scenario.

Melmed and colleagues published their study examining TCD characteristics in 86 mechanical circulatory support (MCS) patients, including V-A ECMO, LV assist device, total artificial heart, Impella, and IABP. They were able to elucidate characteristic waveforms for each device.[21] This represents a good first step in better arming physicians with the data needed to interpret this complex physiologic assessment in this patient population.

IS COMPUTED TOMOGRAPHY WITH ANGIOGRAPHY OF THE BRAIN A USEFUL TOOL FOR NEUROLOGIC ASSESSMENT IN ECMO PATIENTS? ARE THERE PITFALLS TO ITS PERFORMANCE?

Computed tomographic angiography of the brain is a commonly utilized tool in the diagnosis of intracranial pathology, a common sequelae of V-A ECMO support. Adequate diagnostic images require homogeneously opacified blood filling the cerebral circulation during the contrast bolus injection. Peripheral V-A ECMO poses the difficult scenario of draining all or most of the injected contrast from the venous circulation and returning it in retrograde fashion via the femorally placed arterial cannula with its tip within the proximal common iliac artery or distal abdominal aorta. When this occurs, there will be mixing of nonopacified/underopacified blood being ejected in antegrade fashion from the LV with well-opacified blood within the aortic arch. The antegrade flow without adequate contrast material present will preferentially fill the brachiocephalic and the right subclavian arteries; thus, the right-sided cerebral circulation will be underopacified compared to the left.[25] Centrally cannulated patients with a return cannula in the ascending aorta should not have this complication.

Concerns for poor-quality CT angiography are also present in patients with saddle pulmonary embolism on V-A ECMO, and techniques have been described to mitigate this. Lee et al. described a method in which V-A ECMO flows are reduced to 500 mL/min for 15–25 seconds during contrast bolus and image acquisition.[26] CT angiography of the brain is not as straightforward as this, however. With decreased ECMO flow, the mixing cloud of antegrade and retrograde flow will move more distally within the aorta. If able, the ECMO circuit could be clamped for the duration of the scan and resumed immediately on its completion (15- to 25-second duration as described previously). However, the patient may not be able to hemodynamically tolerate decreased ECMO flows, or the native cardiac function may be insufficient to adequately perfuse the brain with contrast media.[25]

Malinzak and Hurwitz described, in a case report, the administration of 1 mg epinephrine prior to clamping ECMO support for the performance of a CT angiogram of the pulmonary arteries. This resulted in a transient increase in cardiac output, which allowed both the adequate opacification of the vessels and the maintenance of hemodynamics for the study.[27] We cannot recommend this practice for routine imaging, but it represents a feasible methodology for obtaining necessary imaging that would directly impact the care of a potentially unstable ECMO patient.

In summary, adequate knowledge of the patient's underlying cardiac function should be present prior to attempting to obtain CT images. Simulation of the planned decrease or cessation of ECMO support should be done in advance to ensure that the changes will be tolerated. Consideration of cannulation methodology (central vs. peripheral) should be made prior to image acquisition.

WHAT TYPE OF MONITORING IS USEFUL OR PREDICTIVE IN PATIENTS WITH SUSPECTED BRAIN DAMAGE?

In a study by Casadio et al., reviewing 112 CA patients who received ECPR, 82 (73.2%) died in the hospital.[28] The authors showed that at the time of the first neurological evaluation after rewarming, variables related to the evolution to brain death were as follows:

- A lower GCS: 3 (3–3) versus 8 (3–11) ($P < .001$).
- A higher level of NSE: 269.3 ± 49.4 versus 55.2 ± 37.2 ng/mL ($P < .001$).
- A higher presence of EEG indices of poor outcome (84% vs. 15%, $P < .001$).
- Absence of brainstem reflexes ($P < .001$).

- Absence of bilateral negative 20 SSEPs (N20 SSEP) waves (66.7% vs. 3.7%, $P < .001$).
- None of the brain-dead patients presented with a normal CT scan (at 2.5 ± 2 days), with 85% prevalence of diffuse hypoxic injury and a mean gray/white matter ratio of 1.1 ± 0.1.

WHAT ARE PREREQUISITES FOR THE DIAGNOSIS OF BRAIN DEATH?

Clinical or neuroimaging evidence of an acute central nervous system (CNS) catastrophe that is compatible with the clinical diagnosis of brain death is very helpful in decision-making. The exclusion of complicating medical conditions that may confound the clinical assessment (no severe electrolyte, acid-base, or endocrine disturbance) is of utmost importance and must be documented. Drug intoxication, poisoning, or neuromuscular blocking agent effects must be ruled out. In addition, the core temperature should be at least 36°C (96.8°F).

WHICH DRUGS COULD INTERFERE WITH A BRAIN DEATH DIAGNOSIS?

Toxic or even therapeutic levels of the following could interfere with a brain death diagnosis:

- Sedatives
  - Barbiturate coma precludes the ability to make a clinical diagnosis of brain death.[29]
- Aminoglycosides
- Tricyclic antidepressants
- Anticholinergics
- Antiepileptic drugs
- Chemotherapeutic agents
- Neuromuscular blocking agents

WHAT COULD INTERFERE WITH THE CLINICAL DIAGNOSIS OF BRAIN DEATH?

The following conditions may interfere with the clinical diagnosis of brain death, with confirmatory tests recommended:

- Severe facial trauma
- Preexisting pupillary abnormalities
- Sleep apnea or severe pulmonary disease resulting in chronic retention of CO_2

HOW IS THE ABSENCE OF CEREBRAL FUNCTION ESTABLISHED?

To establish the absence of cerebral function, determine that the patient is comatose or unresponsive. There must be no cerebral motor response to pain in any extremity after the introduction of painful stimuli, such as supraorbital pressure and nail bed pressure stimulus. This must be assessed in the absence of spinal cord injury.

HOW IS THE ABSENCE OF BRAINSTEM REFLEXES ESTABLISHED?

The absence of brainstem reflexes is established by the following:

- The patient must exhibit no response to bright light in both eyes. Pupils may be in middle position (4 mm) or dilated (9 mm).
- The oculocephalic reflex is tested by vigorous turning of the head from middle position to 90° on both sides. (Testing is done only when there is no apparent fracture or instability of the cervical spine. Head-injured patients should be imaged to exclude potential fractures or instability.) The normal response to this test is eye deviation to the opposite side of the head-turning.
- Ocular movements are absent after head-turning and caloric testing. Caloric testing should be done by elevating the head to 30° during irrigation of each ear with 50 mL of cold water. Allow 1 minute after irrigation and at least 5 minutes between testing on each side.
- Facial sensation and the facial motor response are tested by response to painful stimuli and reflex assessment, including
  - Corneal reflex to touch with a throat swab.
    - Pathology indicated with absence of response.
  - Jaw reflex: An index finger is placed over the chin with a slightly open and relaxed jaw; the finger is then struck in a downward fashion with a reflex hammer.
    - Pathology indicated with hyperreflexia.
  - Deep pressure on the nail bed, supraorbital ridge, or temporomandibular joint.
    - Pathology indicated with absence of response.
- Pharyngeal and tracheal reflexes are tested by
  - Stimulation of the posterior pharynx with a tongue blade to elicit gag response, and
  - Bronchial suctioning to elicit cough or bradyarrhythmia.

HOW IS AN APNEA TEST DONE?

Prerequisites for Apnea Testing

- Core temperature greater than 36.5°C (97°F)
- Systolic blood pressure greater than 90 mm Hg (adults only)
- Euvolemia (or positive fluid balance in the previous 6 hours)
- Normal PCO_2 (or arterial PCO_2 > 40 mm Hg)

- Normal PO_2 (or preoxygenation to obtain arterial PO_2 > 200 mm Hg)

Apnea Testing in a Patient Not Supported by ECMO

For apnea testing in a patient not supported by ECMO, connect a pulse oximeter and preoxygenate with FiO_2 (fraction of inspired oxygen) of 1.0 for 10 minutes. Disconnect the patient from the ventilator and place on a T-tube and administer 100% O_2 at 8 L/min. Disconnect the ventilator and place a cannula at the level of the carina and administer 100% O_2 endotracheally at 8 L/min or place the patient on continuous positive airway pressure at an appropriate level of support.

Observe closely for respiratory movements or abdominal or chest excursions. Measure arterial PO_2, PCO_2, and pH after approximately 8 minutes (10 minutes for children) and afterward resume mechanical ventilation.

The absence of spontaneous respiratory effort with PCO_2 20 mm Hg greater than baseline (PCO_2 > 60 mm Hg) confirms apnea and supports the diagnosis of death. If respiratory efforts are present, the test is inconsistent with brain death and should be repeated.

Apnea Testing in a Patient Supported by ECMO

For patients on ECMO support, the apnea test is extremely difficult to interpret and basically not feasible without supplementation of CO_2 (either blended in the oxygenator or supplemented through the airways) as CO_2 levels and oxygenation are related to the ECMO circuit. CO_2 is constantly removed in the oxygenator, while O_2 is substituted into the blood. This is especially true since CO_2 is so much more soluble in blood than O_2 and it is more readily diffused across any membrane as compared to O_2.[30]

In the membrane lung, CO_2 clearance depends on the "sweep" gas flow (L/min), blood temperature, and pH, while oxygenation depends on blood flow, the concentration of hemoglobin, blood temperature, sweep gas fraction of O_2, and premembrane O_2 saturation. The high degree of CO_2 solubility compared to O_2 combined with the efficiency of CO_2 removal in oxygenators explains why decreasing sweep gas flow may affect oxygenation more than the CO_2.[31] Consequently, to perform the apnea test correctly, the sweep gas flow is reduced to approximately 1 L/min, while the FiO_2 to the membrane lung should be kept at 1.0.[30] To avoid derecruitment and hypoxia during or after the apnea test, the application of positive end-expiratory pressure (PEEP; via bag/mask with PEEP valve) is recommended. Afterward, a recruitment maneuver should be performed.[32]

A method to supplement CO_2 into the circuit was recently described by Beam and colleagues. The authors described a case in which they utilized a D-size CO_2 tank with a CGA 940 Insufflation Yoke attached to a Western Medica Regulator connected to a Cole Palmer Flowmeter with a 0–200 mL/min range which was then attached to the Sechrist Air–O_2 mixer (Model 3500). They maintained baseline ECMO sweep flow and FiO2 at prior settings. After removal from mechanical ventilation without oxygen supplementation, 100% CO_2 was added to the ECMO circuit with an 8% sweep volume ratio (160 mL/min). The patient was observed for five minutes before obtaining an ABG for comparison to a pre-test ABG. Increasing CO_2 partial pressure was noted, and over an additional 4 minutes no respiratory effort was observed. Hemodynamic stability was maintained throughout their assessment, and the patient was subsequently declared brain dead.[31]

WHICH CLINICAL OBSERVATIONS ARE COMPATIBLE WITH BRAIN DEATH?

The following clinical observations are consistent with the diagnosis of brain death and should not be interpreted as evidence of brainstem function:

- Spontaneous movements of the limbs not caused by pathologic flexion or extension response
- Respiratory-like movements characterized by shoulder elevation and adduction, back arching, and intercostal expansion without significant tidal volume
- Sweating, blushing, and tachycardia
- Normal blood pressure without pharmacological support or sudden increase in blood pressure
- Absence of diabetes insipidus
- The presence of deep tendon reflexes, triple flexion response, and superficial abdominal reflexes
- Babinski reflex

WHAT ARE CONFIRMATORY TESTS FOR BRAIN DEATH DIAGNOSIS?

The following tests are not required in most cases but may be used at the physician's discretion to supplement the clinical evaluation of death when the irreversibility of brain damage is uncertain. A confirmatory test is necessary when an element of the clinical criteria cannot be evaluated reliably. These tests are listed in the order of decreasing sensitivity:

- Conventional cerebral angiography
- Electroencephalography
- Transcranial Doppler ultrasonography
- Technetium 99m hexamethylpropyleneamineoxime (Tc-HMPAO) brain scan
- Somatosensory evoked potentials

IS THERE A STANDARD IN DETERMINING DEATH?

A person is dead when, according to ordinary standards of medical practice, there is irreversible cessation of the person's spontaneous respiratory and circulatory functions. (The patient is pulseless, apneic, and unresponsive to verbal stimuli for a period of at least 2–5 minutes.)

If artificial means of support preclude a determination that a person's spontaneous respiratory and circulatory functions have ceased, the person is dead when, in the announced opinion of a physician, according to ordinary standards of medical practice, there is irreversible cessation of all spontaneous brain function. Death occurs when the relevant functions cease.

In cases of brain death, death must be pronounced before artificial means of supporting a person's respiratory and circulatory functions are terminated.

DISCUSSION

Extracorporeal life support is increasingly used in patients with severe/acute hypoxemic and hypercapnic respiratory failure in form of veno-venous (V-V) ECMO or in multiple scenarios of acute cardiac and circulatory failure, as well as CA, in the form of V-A ECMO.[33,34] ECMO technology has developed to a new level, and this type of MCS has more and more become the standard of care in centers with experienced ECMO/MCS services.

However, new technologies and treatments also create new fields in medical ethics.[35] The in-hospital mortality of ECMO patients remains high and depends on the collective experience of the center. For specific indications for ECMO, such as ECPR, the prognosis of good neurologic recovery is often unclear and needs further assessment.[36] Logically, with increasing use of ECPR, the number of patients diagnosed with brain death under extracorporeal life support (ECLS) will rise, and the expectations of neurologic monitoring, early diagnosis, and outcome prediction of complications will increase.

The practical application of neurological monitoring of the V-A ECMO patient should be multimodal. No one device or diagnostic has demonstrated superiority to another, and in this scenario, more data are better. In postarrest patients, it has been clearly demonstrated that EEG assessment within the first 3–4 days of achieving ROSC provides reliable data for neuroprognostication in both ECMO and non-ECMO patients.[16,18] BIS monitoring, in the our opinion, should be a mainstay for comatose patients on ECMO support: With seizure, shivering, tremor, and so on, the data can become unreliable and neuromuscular blocking agents would be required if clinically appropriate. BIS data are useful for neuroprognostication based on initial values during, and after, ROSC, but also as a trend during the ICU course.[7]

Cerebral oximetry has been shown to be useful for neuroprognostication during resuscitation and as a trend following ROSC once the patient is on ECMO support.[2,3] Additionally, it can be used to monitor in real time for differential oxygenation, which can occur in the setting of worsening lung function, leading to adequate oxygen delivery to the left side of the brain (supplied from ECMO) and hypoxia of the right side of the brain (supplied via the native circulation)—this could lead to early intervention for thromboembolic stroke.

Transcranial Doppler ultrasonography, in our opinion, has great potential to aid in neurological assessment of comatose V-A ECMO patients for multiple reasons. It is a rapidly deployable diagnostic that is noninvasive and can be performed at the bedside for singular or serial assessments. The pitfalls of its use are related to the alterations in cerebral blood flow patterns as compared to patients not receiving MCS therapies. With the increasing prevalence of acute and chronic MCS therapies, there must be further research to define what is "normal" blood flow in these patients, as well as increasing understanding of what defines pathologic blood flow. These definitions must be present, but it will also require that the physicians interpreting the studies be familiar with MCS therapies and have a clear understanding of how each one alters cerebral blood flow characteristics. For the foreseeable future, this will likely only be truly available and reliable at select centers with high volumes of such patients.

The serial monitoring of NSE in post-CA patients on V-A ECMO presents a biomarker that can aid with neuroprognostication. The Schrage study demonstrating that NSE can be reliably measured in ECMO patients provided important groundwork for validation of this assay in that patient population. In the absence of hemolysis, NSE may be followed to aid with neuroprognostication.[12] Absolute values with which one could reliably prognosticate neurologic outcomes remain undefined in the literature in a manner that is useful for widespread usage.

Lorusso and colleagues retrospectively reviewed the Extracorporeal Life Support Organization database from 1992 to 2005.[37] The authors included 4988 adult patients supported with V-V ECMO for respiratory failure. They defined neurologic injury as brain death, seizures, stroke, and intracranial hemorrhage occurring during ECMO support. The median age of the study cohort was 46 (interquartile range 32–58). Four hundred twenty-six neurologic complications were reported in 356 patients (7.1%) and included 181 intracranial hemorrhages (42.5%), 100 brain deaths (23.5%), 85 strokes (19.9%), and 60 seizure events (14.1%). The in-hospital mortality was significantly higher for those patients with CNS complications (75.8% vs. 37.8%; $P < .001$) and varied by type of CNS injury. The mortality rates were 79.6% in patients with intracranial hemorrhage, 68.2% in patients with stroke, and 50% in patients with seizures. Pre-ECMO CA, continuous veno-venous hemofiltration, and hyperbilirubinemia during ECMO were associated with increased odds of neurologic injury. The authors concluded that approximately 7% of adults supported with V-V ECMO had neurologic injury, with intracranial hemorrhage as the most frequent type. Survival for patients with neurologic injury was poor.[37]

Bronchard et al. reported concerning 22,270 brain-dead patients who were registered with the French Biomedicine Agency between 2007 and 2013. Out of 22,270 donors after brain death, 161 were ECMO patients, and of these, 64 (39.8%) became organ donors. One hundred nine kidneys, 37 livers, 7 hearts, and 1 lung were successfully transplanted from donors on ECMO. There was no significant difference in graft survival or function between patients with or without ECMO support, and the authors concluded that ECMO patients are suitable transplant candidates.[38]

Similar results were found in an observational study by Casadio et al., who concluded that refractory CA patients

treated with ECPR have a high prevalence of brain death.[28] However, this population has a high potential for considering organ donation with good outcome and function. In their study, 112 CA patients received ECPR, with a mortality of 82 (73.2%) who died during the hospital stay. The rate of organ donation in brain-dead patients was 56%, with 39 donated organs (23 kidneys, 12 livers, and 4 lungs). Of the transplanted organs, 89.74% reached an early good functional recovery.

In a recent retrospective study by Fan et al., ECMO supported unstable brain-dead donors on high doses of vasopressors and resulted in a higher rate of good posttransplant liver function compared to unstable donors without ECMO.[39]

Increased use of ECMO can be expected and accurate knowledge about the pathophysiology and specific challenges of brain death diagnosis, especially under ECLS, is essential to support patient survival or potential organ donation.

CONCLUSION

- Regional cerebral oximetry with NIRS is a useful tool with neuroprognostic value post-CA.
- Bispectral Index monitoring, both discrete and trend data, should be used in comatose patients on V-A ECMO after CA to aid with neuroprognostication.
- Transcranial Doppler ultrasonography can give useful data to aid in determination of brain death or evaluation of the cerebral circulation, but there is a steep learning curve to make appropriate interpretations of the data collected.
- Computed tomographic angiography of the brain requires careful planning for the V-A ECMO patient but can be successfully performed with a brief period of low-flow versus clamping of the circuit. Individual assessment is a must to ensure the patient can hemodynamically tolerate the study.
- Neuron-specific enolase is a useful biomarker that can aid with neuroprognostication in the post-CA patient on ECMO. Hemolysis confounds elevated values and must be excluded. Absolute values for good versus poor neurologic outcome do not yet exist, and serial values with trends likely give the best information.
- Determination of brain death in patients supported by ECLS is expected to become an increasing event with increasing use of ECPR.
- Clear protocols are required to successfully and legally diagnose brain death.
- Apnea testing may be associated with cardiopulmonary alterations.
- ECMO sweep flow should be adjusted to give adequate respiratory drive during apnea testing.
- Knowledge of the pathophysiology and awareness of possible complications are helpful for organ conservation.
- After careful evaluation and professional management, organ donation should be considered for brain-dead ECMO patients.

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REVIEW QUESTIONS

1. Which of the following statements with regard to BIS values in post-CA patients is true?

   A. An initially low BIS value does not indicate poor neurologic outcome.
   B. Decreasing BIS value with decreasing sedative requirements is associated with good neurologic outcome.
   C. Bispectral Index value less than 50 is associated with poor neurologic outcome.
   D. Increasing BIS value with increasing sedative requirements is associated with good neurologic outcome.

2. Initial regional cerebral oximetry with NIRS values greater than 40% indicated a high likelihood of achieving a good neurologic outcome if which of the following additional interventions were performed as well?

   A. Targeted temperature management
   B. Left heart catheterization with intervention if necessary
   C. A and B
   D. Computed tomographic brain with and without contrast

3. Neuron-specific enolase is a biomarker indicative of neuronal cell death or damage. Which of the following can lead to elevation of this in the post-CA patient on V-A ECMO?

   A. Targeted temperature management to 33°C
   B. Presence of a neuroendocrine tumor
   C. Hemolysis
   D. B and C

4. Which of the following statements is true regarding the use of transcranial Doppler in the determination of CCA?

   A. Acute and chronic MCS therapies do not alter its diagnostic utility.
   B. Oscillatory blood flow with systolic peaks is indicative of CCA.
   C. The presence of shock does not alter or confound its findings.
   D. Transcranial Doppler is the gold standard imaging modality for the determination of CCA.

5. Which of the following statements is false with regard to EEG in the post-CA patient?

   A. Veno-arterial ECMO patients have no potential for alteration of EEG patterns as compared to non-ECMO patients.
   B. Early malignant EEG after CA portends poor neurologic outcome.

C. Malignant EEG can indicate poor neurologic outcome even with preservation of N20 response on SSEP.
D. Duration of CPR coupled with EEG is more sensitive to predict neurologic outcome than either one individually.

ANSWERS

1. D
2. C
3. D
4. B
5. A

62.

ETHICAL CONSIDERATIONS FOR ECMO INITIATION AND END-OF-LIFE CARE

Roxanne Kirsch and Ryan D. Coleman

STEM CASE AND KEY QUESTIONS

VB is a 1-week-old neonate with truncus arteriosus and moderate truncal insufficiency. She undergoes truncus arteriosus repair with right ventricular–to–pulmonary artery conduit, truncal valvuloplasty, and ventricular septal defect closure. She has some ventricular hypertrophy, mild neoaortic insufficiency, but no significant residual lesions. She separates from cardiopulmonary bypass and returns to the intensive care unit (ICU) uneventfully. Later that day, she has severe ventricular dysfunction and hemodynamic instability, prompting extracorporeal membrane oxygenation (ECMO) initiation for a low cardiac output state. Investigations after ECMO initiation reveal a left coronary artery occlusion. She returns to the operating room, and a thrombectomy is performed as well as patch augmentation of the left coronary artery. Echocardiography demonstrates good flow profiles in the coronary artery, but ventricular function remains poor, and VB returns to the ICU on ECMO.

The cardiac team is in agreement that time should be spent monitoring for cardiac recovery and maintaining end-organ perfusion. The family is counseled a 5–7 day timeline to await ventricular recovery. Across the next 4 days, the patient develops seizures with cessation after dual-antiepileptic therapy, and head computed tomography has revealed a small stroke that does not have hemorrhagic transformation despite anticoagulation for ECMO. There is evidence of acute kidney injury with stable creatinine and oliguria. At day 4 of ECMO (postoperative day 6 from original operation), the patient has adequate hemodynamics to separate from ECMO despite ongoing poor (but improved) left ventricular function. Renal replacement therapy is able to be discontinued, and the patient has elevated creatinine but adequate urine output.

Over the next 10 days the patient progresses acceptably in the ICU, is maintained on milrinone, and is on weaning ventilator settings. Unfortunately, a few days before projected extubation, her ventilator needs increase, and her lungs become more congested. There is progressive mitral regurgitation noted on an echocardiogram and a decrease in left ventricular function; flow can no longer be demonstrated in the left coronary artery. The patient is planned for urgent operative intervention the next morning for reintervention on the left coronary artery and mitral valve repair. Overnight, there is a cardiac arrest, and ECMO is initiated with compressions ongoing (extracorporeal cardiopulmonary resuscitation [ECPR]).

WHAT ARE THE ETHICAL CONSIDERATIONS FOR ECMO INITIATION?

Ethical considerations in ECMO therapy encompass core concepts including: informed consent, capacity, decisional authority, nonmaleficience, best interests, disclosure and resource allocation. When considering a patient for ECMO, there are similar considerations as for any therapy: Does the therapy in question have an appropriate risk-benefit ratio that justifies its implementation, and is it likely to achieve its intended a priori purpose? The more burdensome the proposed therapy, the higher the threshold should be for its implementation. When a therapy as invasive and resource intense as ECMO is being considered, having in mind the end point of the therapy and the path off ECMO is of utmost importance prior to its initiation. ECMO is often viewed as a "bridge" therapy as it in and of itself does not treat any given condition—it can be a bridge to recovery, bridge to transplant, bridge to optimization of medical therapy, bridge to decision, or bridge to a bridge. Unfortunately, it can also become a bridge to nowhere, merely prolonging death without serving a beneficial purpose. Where time allows, fulsome information regarding risks and benefits of the therapy, where known, should be shared as well as potential complications. It is important to explain at the time of initiation that not all courses of ECMO are successful and what that pathway may look like for discontinuing ECMO should its burdens become too great or its goal unachievable.[1] It may not be possible, in an emergency initiation, to achieve this standard of informed consent. However, in upholding a respect for persons, this information must be shared as early as possible so that the surrogate decision-makers can be aware of the risks and benefits in the intervention you have applied in a medical emergency and can help set limits that are consistent with their personal values.[1,2]

Capacity is an important consideration in informed consent. This assessment is done by the clinician, without requirement for additional consult. The patient who has capacity

needs to be able to demonstrate an understanding of the procedure or therapy, of the risks and benefits therein, and of alternate options or how the course of illness may progress without the intervention of therapy. They also need to demonstrate an appreciation of the consequences of their choice, either in accepting the recommended therapy or declining it. In this manner, agreement with their physician is not required, but rather a clear understanding and approach to why they agree or disagree must be demonstrated. This is deeply important, as it respects the person and allows the autonomy to determine what happens to one's own body. This has been furthermore engrained in law, and patients have the right to refuse therapies, even if life-saving or sustaining.[3] Note, however, that this is a negative right, meaning a right to refuse.[4,5] Patients do not have the right to demand therapies that are not recommended by their physicians. Across the course of the last decade, there has been ongoing case law evolving around the topic of refusals to discontinue therapies when recommended that is relevant beyond the scope of ECMO. Exploration of values, viewpoints, and beliefs underpinning disagreements should be explored and often provide the nidus for a path forward.[1,2]

When a patient is incapacitated by age, cognitive ability, or illness, decisions rest with a surrogate decision-maker in conjunction with the physician team. Surrogate decision-makers are meant first and foremost to make a substituted decision. This means they are to make the decision the patient themselves would have made were they granted capacity and full understanding and appreciation in that moment.[2,6] In our case, the patient is incapacitated due to both illness and age. This may not be the case in all patients, and certainly the previously spoken or written wishes of the patient should be considered in understanding the decision to make on their behalf regarding therapies. This upholds autonomy in allowing each person to determine what is done to their body. In the absence of the ability to make a substituted decision, the surrogate then needs to decide based on the patient's best interests.

Best interest is not a clearly definable concept and has a degree of subjectivity. Much has been written to expand on and better understand how to apply the best interest concept in clinical cases. As in many cases in medicine, there is not necessarily a singular "best" therapy or way to proceed. Additionally, it has been noted that there is a range of possible acceptable therapies that may be less than what is deemed the "medically best" but still upholds other important principles and values. The child, in particular, is seated within their family unit and is likely not only to decide in accordance with their parents' belief system, but also to leave the hospital in the care of that family unit and set of values.[7] Therefore, in a practical sense, we tend only to deny surrogate (or family) decisional authority in a setting where their decision is causing harm to the child.[8–10] This does not relieve the clinician from a duty to protect the vulnerable child and to question decisions felt to be made not in their best interests. It does, however, behoove them to examine their own value systems and judgments to ensure they are not substituting their own value systems over that of the patient and family. Healthcare teams will often hold certain values (e.g., the absolute need for full cognitive function) that may not be universally held by the populations they serve. Ongoing discussion to understand the moral basis for disagreements about best interests is helpful in mediating conflict.[10]

In the case of VB, it would be ethically permissible either to proceed with ECMO or to withhold it. If it was agreed on that a highly interventional course with low likelihood of intact survival can be accomplished, it would be acceptable not to offer that intervention as it is of no benefit to the patient in actually changing the course of their underlying illness. To rescue with ECMO and then have no possible way to recover the patient, or replace the failing organ, leaves the patient on a bridge to nowhere. This, therefore, has granted them no benefit beyond the immediate rescue and is merely prolonging death. However, as is often the case in an emergent situation, it may be unclear early on regarding the inability to recover adequately to separate from ECMO. Therefore, unless there was a clear understanding of the family's goals and values and the likelihood of ECMO accomplishing those goals, it is essentially impossible to expect a decision to withhold therapy be undertaken in the crisis moment of cardiac arrest in an ICU environment where ECMO rescue is frequently undertaken with well-established systems for rapid, high-quality provision.

Therefore, in this setting, ECMO for VB has been used as a bridge to a surgical intervention in the hopes of improving cardiac function and ability to progress back to a state of much less invasive intensive therapies. It is both medically and ethically appropriate to utilize the techniques, tools, and therapies commonly employed in a given institution to stabilize a patient in order to allow time for important decision-making. Note that in a large-volume cardiac ICU, such as the one VB is in, ECMO rescue would generally be standard practice of that unit. This does not imply, however, that in a different case, or in an institution where ECPR is not standard practice, that all patients should be given ECMO therapy. The ethical justification of best interests is not altered in this instance, but rather the risk-benefit, which will be greatly impacted by prolonged time to ECMO and inexperienced teams without processes already in place to address such a scenario. Should ECMO be initiated as it was in the case of VB, it is important to recognize that the initiation of ECMO does not predicate that the family must agree to proceed with surgical reintervention and, in fact, only provides a time for careful counseling before determining ongoing therapies.

In the case of VB, it was understood that there would be agreement from the parents to the recommendation to attempt a potentially beneficial surgical intervention, this being predicated on the necessary time required to understand if other comorbidities evolved following cardiac arrest or worsened to a degree that cardiac intervention would no longer be appropriate. The conversation after cannulation is likely to need to focus on potential postsurgical expectations (guarded) and considerations for discontinuation of ECMO or full withdrawal of life-sustaining therapy should additional burdens come into play.

WHY ARE PARENTS THE ASSUMED DECISION-MAKERS FOR THEIR CHILDREN?

The family as surrogate, even when it is not a child patient, allows knowledge and incorporation of patient values and previously expressed treatment preferences. This grants respect to the patient as a person, a core moral obligation of the medical profession. It also respects the "family" unit, which is highly valued in most societies. As argued by Malek, when assessing what is in the "best" interest of a child, out of 13 key areas, only 3 are related or closely related to health and healthcare; all other areas of importance are housed within the family and societal units, rendering parents the most capable of making these judgments.[7] Finally, in the most practical sense, most people would want their families involved.[8] Obviously, things become more complex in older patients, and a medical proxy may be designated as the person to best represent their wishes and values. Within pediatrics, the parents become the default decisional authority unless there is legal guardianship or alternate legally defined decisional authority in place.

HOW DOES THIS DECISION FIT WITHIN THE "FOUR PRINCIPLES"?

When considering the principlist system of bioethics, the predominant moral theory utilized in the Canadian and US context, one is meant to consider the principles of autonomy, beneficence, nonmaleficence, and justice. In considering, one is meant to balance all four principles at all times. In the absence of being able to uphold one principle, there should be considerations to mitigate the harm in suboptimally upholding any of the other principles. In this sense, there is no hierarchy to the system, and all too often in the clinical realm, providers are left picking and choosing a principle to "follow" rather than a fulsome consideration of all the principles together (Table 62.1). In addition, there may be many other duties, obligations, and considerations that should be borne thoughtfully in ethical consideration.[6] In any complex case, it may be helpful to engage in bioethics consultation to help determine how one might consider all values and judgments, to understand the ethical validity of multiple options, and to aid with navigating an appropriate course forward.[1,10]

In the case of VB, the beneficence and nonmaleficence balance might be considered with special attention to the context of family values and considerations for potential future quality of life using a best interest framework to uphold respect for the patient as a person. Furthermore, attention to ensuring the interventions are for her own benefit as best as this can be understood and agreed on ensures she is treated as a means in and of herself, which also upholds the autonomy principle. Finally, in the system in which she is being treated, there are no restrictions placed on the high cost, potentially beneficial therapy. Policy considerations for what therapies are offered or not and at what degree of demonstrated benefit they would be offered, need to consider the scope of all the patients within that hospital or health system to ensure she is fairly granted an equitable access to standard therapies.

Beneficence obligates physicians to only provide treatments that further a patient's well-being, including not only their health, but also how this intervention would allow them to function within the particular values of a given family unit, belief system, and society. In a patient who is unable to express their particular decision-making schema for whatever reason, beneficence becomes part of the overall "best interest" calculus.

Nonmaleficence dictates that no procedures or therapies be performed on or prescribed for a patient that would inflict any potential harms on a patient. The risk-benefit ratio should always favor benefit; if the balance at any point shifts to more burden than benefit, the therapy is no longer justified.

Table 62.1 **THE FOUR PRINCIPLES IN PRINCIPLIST BIOMEDICAL ETHICS**

Autonomy	**Respect for persons. Humans are a means unto themselves and not a means to an end. This encompasses the right to be free to make choices about your body.**
Beneficence	**Obligation to contribute to persons' welfare. Interventions and provisions should provide benefit directly to the patient. This focuses on doing things that are of benefit to another. It requires positive steps to help, and not merely avoiding doing harm.**
Nonmaleficence	**Obligation not to inflict harm on other persons. Harm is to be avoided or minimized. Underlying tenet of medical professional mission statements (Hippocratic oath).**
Justice	**For health care, this is the distribution of health (and health care) in a fair and equitable manner. This requires attention to prioritization and rationing. There is no one just way to allocate resources, and most systems utilize several prioritization schemes in concert to attempt to achieve a just distribution.**

The four principles are meant to be used in concert with each other and not in isolation. To use them one aims to uphold ALL of the principles for any issue. If one or more are violated, the violation needs to be minimal. Additionally, there is no hierarchy of principles—which principle is most important (or which two or three) is dependent on the context of the dilemma.

Principlist moral theory can be problematic in that there is no guidance for proceeding when the four principles cannot be balanced (or upheld). It also considers ONLY the four principles, although there are many other principles, considerations, and values to be considered and weighed into decision making in most ethical dilemmas.

In western nations, such as USA, autonomy tends to have a higher emphasis than it may in other places.

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Justice, as it relates to medical care, dictates that those in similar situations are treated similarly. The nuances in this relate to what is available for a given patient within a given system, meaning what a given population receives as standard of care therapy at one institution may be markedly different from that at a differently resourced institution. If the implementation of ECMO as a part of CPR is considered routine at a particular hospital, then all children who meet ECMO candidacy requirements and suffer an arrest should receive ECMO. To deny that patient ECMO would be in violation of the justice principle. However, if ECMO is not part of the routine at a hospital, physicians are not suddenly obligated to provide ECMO.

DISCUSSION

In cases of high complexity, such as the use of ECPR in congenital heart disease patients, there may not be particular outcomes-based measures that can clearly guide one through the potential options for any particular patient. Advanced reasoning on potential medical options should be embedded within a rigorous ethical framework to guide both what may be appropriate to offer and what might not be appropriate to offer. The dangers of the technological imperative, which is the tendency to apply technology to solve problems and to feel the need to utilize technology because it exists, may mislead obligations to provide ECMO simply because we have the ability to do so.[11,12] As with other devices, a rigorous ethical approach to each patient can alleviate the technological imperative by considering the therapy as it applies to a given patient while avoiding treating the application of the technology as the end in itself. This requires understanding key ethical concepts to facilitate application in the clinical sphere. Across any treatment course, a key component of truly upholding respect for the patient as a person onto themselves will require multiple conversations with their surrogate decision-maker and an ability to stay present as a care provider through the uncertainty that will come. This requires engagement and time, careful communication, and preparation for both the intended outcome and the potential of a failed treatment course and need to transition to end-of-life care.

SHOULD VB HAVE RECEIVED ECMO THE SECOND TIME?

There is often not a clear answer to the appropriateness of repeat ECMO interventions. Certainly, in cardiac disease with reversible lesions that can be intervened upon, the most common course of action is to initiate ECMO, address the residual lesions, and then determine if separation from ECMO can occur. In this particular patient, the risks and benefits of reintervention were weighed and an agreed-on plan was in place to attempt to change the trajectory of disease burden. The team placing the patient on ECMO would certainly need to consider in a practical sense the degree of organ burdens already present and anticipate worsening of end-organ injuries across the course of CPR and ECMO. However, without initiating ECMO, this patient is unlikely to stabilize with return of spontaneous circulation and will not survive to intervention. Under these conditions, the patient's best interests have been dictated by the medical assessment of a possible, although challenging, recovery should surgery be accomplished, with this intervention framed in knowledge of parental values and views on quality of life.

The best interests of the patient are an overarching key concept when considering therapies for incapacitated patients. It is important to understand that the patient's autonomy as a 1-week-old neonate cannot be upheld. The patient has not developed this capability, and the patient herself is obviously incapacitated from interjecting their values, thoughts, or opinions on the medical therapies undertaken for them. However, the autonomy principle can still be upheld by ensuring respect for persons and ensuring they are treated as a means in and of themselves.[6] The benefits and risks are weighed in a careful fashion, understanding that interventions should be done with careful attention to escalating harms.

SHOULD VB BE DEEMED NOT FOR ECMO AFTER THE SECOND COURSE OF ECMO?

It is unlikely in the current era that parental refusal of ECMO for this patient would be deemed inadmissible. They have experienced firsthand the burdens and perceived benefits their daughter has had with ECMO, and they have heard honest counseling about potential outcomes. The likelihood of successful intervention is very low with minimal ongoing consequences in a patient with an underlying disease that is still likely to require multiple medical and surgical admissions, have an impact on quality of life, and will remain life limiting in and of itself when combined with multiple acquired morbidities. Therefore, the team should very carefully consider if offering an additional ECMO course would be warranted. Again, considering the goals and values of the family will be important to the decision-making. The disease process now involves multiple organs, and the underlying problem—post–ischemic cardiac disease—will have an unclear trajectory of recovery or stabilization to chronic heart failure management. In this sense, it would not be strictly wrong to offer ECMO, particularly if a reasonable intervention could be offered to alter the trajectory or burdens of illness, but this needs to be considered at escalating cost and diminishing returns. There may be technical impediments to cannulation at this point, and the likelihood of further intervention being of benefit may be miniscule. The decision then may hinge on the longer term potential, such as transplant considerations, which would involve understanding if the patient was a candidate for a ventricular assist device as a bridge to transplant. In some centers, this would require a clear understanding of improvement in renal disease and a size and weight that could be maintained on a long-term mechanical device system.

Importantly, the team could consider not offering ECPR separately from offering ECMO. This would allow a differentiation of the additional harms another course of CPR may impose from an end-organ aspect and allow agreement

that the harms outweighed a very low likelihood of benefit at that point.

Once again, there is unlikely to be a single best course of action for this patient. Honest conversations with the family regarding expectations and uncertainty will be required, and clear timelines for the team to understand what the expectations are to be able to proceed with next steps are likely to be helpful. Debriefings may be required with the team to maintain a clear understanding of the purpose of this support time, as concerns may escalate quickly given the multiple care providers across an already complicated intensive care admission. Importantly, the intensive care team will need to initiate discussions of what might or might not constitute candidacy for additional ECMO at this time and really challenge themselves about why yet another course would be appropriate. Diminishing returns over multiple ECMO runs denote an anticipated poor outcome; however, team members may feel inclined to continue because of multiple influences, such as their level of investment in the patient's care thus far, unspoken promises they feel they have made to the patient or family, and a tendency toward a sunk costs phenomenon where further time and effort seems necessary only because of how much time and energy has already been utilized. This can feel compelling but may cloud an objective assessment of the true likelihood of success. Finally, the influence of guilt or feelings of failure by members of the care provider team can inhibit them from recognizing that additional courses may not be appropriate. Open, transparent conversation in a multidisciplinary and interprofessional forum is appropriate to ensure all viewpoints have been heard and potential options have been considered fully.[1] Ideally this would occur, at the very least with key stakeholders even now, prior to separation from ECMO after a second course of ECMO therapy.

ARE ALL CARDIAC PATIENTS ALWAYS CANDIDATES FOR ECMO?

It is not necessarily true that all cardiac patients are always candidates for ECMO, although in the current era of pediatric cardiac intensive care a majority of patients are often considered candidates for ECMO. With a high likelihood of potential surgical or interventional amenable lesion and multiple options for potential longer term mechanical circulatory support devices, the use of ECMO as a bridge to treatment (e.g., surgery) with potential for recovery or bridge to longer term device with transplantation candidacy has led to wide-ranging use. Often, it is more informative to the team to consider who is not an ECMO candidate and in what setting. Here, teams often have better agreement on the potential poor outcomes associated with ECMO initiation after CPR (ECPR), such as in pulmonary hypertension versus those who may benefit from novel uses of ECMO to support therapies that may modify disease (e.g. elective ECMO cannulation to stabilize in order to proceed with pulmonary vein dilation). Technical potential for cannulation, the intended purpose for ECMO specific to that patient, and agreed-on end-point goal can often be clarified in these discussions. This team consensus on the purpose of ECMO allows for better decision-making by the clinical team at the time of crisis or deterioration and leaves teams to assume ECMO will be utilized for most patients, including those who could potentially benefit from a trial of ECMO to determine therapeutic options or recovery or for the purposes of procedure support. Note that the ethical underpinnings for use continue to rest on a best interests framework with careful attention to potential benefit and the utilization of ECMO with purpose toward a medically reasonable and beneficial goal (clear bridge strategy), given ECMO's highly invasive nature, known potential for complications, and lack of curative purpose in and of itself.

WHAT IF THIS PATIENT DOES NOT HAVE ENOUGH RECOVERY OF VENTRICULAR FUNCTION TO SEPARATE FROM ECMO? CAN ECMO BE DISCONTINUED?

Even if VB has recovery of some end-organ functions, if the cardiac function does not recover adequately to separate from ECMO, her options are limited. In some centers, transplantation may be considered, and ECMO then is used as a bridge to transplant. In other centers, however, after reviewing the poor outcomes in the patients transplanted from ECMO, they do not offer transplant unless an alternate longer term mechanical support device is available. There may be limitations due to size for mechanical supports, and this would need to be discussed and understood in advance. Certainly, VB has already impaired neurologic and renal function, so she may have other reasons that she is unlikely to be a candidate for transplantation. If VB is not a candidate for transplantation (because she cannot separate from ECMO and cannot be supported by alternate mechanical circulatory devices or because she has multiple organ injuries and a degree of critical illness that precludes transplantation), then it is both medically and ethically appropriate to discontinue ECMO and undergo a withdrawal of life-sustaining therapy. Additionally, if the family would not wish for transplantation, ECMO would not be used for a bridge to transplant, and this should be understood prior to ECMO initiation ideally. In the absence of a definable strategy to mitigate her ventricular failure (e.g., transplant), ECMO provides no ongoing benefit and only prolongs death, and withdrawal of this life-sustaining therapy is appropriate.

Withdrawal and withholding of life-sustaining therapies are considered morally and legally equivalent in many countries, including Canada, the United States, the United Kingdom, and Australia, for example. The ethical justifications include that intended benefits cannot be achieved by life-sustaining therapy (imminent death, irreversible organ failure); the disease or treatment burdens outweigh the benefits so that continuing is no longer in the patient's best interest; or a patient with capacity makes an informed voluntary choice. Application of multiple moral theories supports these reasons, and all moral theories justify a discontinuation of life-sustaining therapy, as even within deontology the sanctity of life is highly important but not absolute.[10,13]

In the instance of ECMO, or any mechanical circulatory support, these justifications are still upheld. The ethical permissibility does not lie in the machine itself or in the speed at

which death follows a withdrawal of therapy, but rather in the justification for the withdrawal of therapy in the first place.[1,14–16]

It is important at this point to again counsel the family about the possibility of an unsuccessful ECMO course. Stating broad expectations of what pathways—stopping or continuing may "look like" can help them to recognize how the team will reach a decision to recommend stopping and better prepare them for the necessary conversations that will need to occur at that time. It may also help to prepare the family to contemplate what degree of burden is acceptable for the degree of uncertainty in the outcome, especially considering there will be known additional comorbidities even if VB survives.

WHAT IF VB HAS REGAINED WAKEFULNESS?

It is important to recognize that while teams and families often struggle to face the realities of a failed course of ECMO, in general this is often felt to be more difficult if the patient is not severely neurologically impaired. However, neurologic functioning does not dictate the ethical permissibility for discontinuation of life-sustaining therapy if that therapy is not obtaining its stated goal. While this fact may make her more suitable for alternate options such as alternate mechanical support or transplantation, it is not in and of itself the key ethical determination. If VB has no options for alternate therapies to sustain her life or reverse her course of illness, there is no purpose to the course of ECMO therapy, and it should be stopped. The navigation of this in the practical sense may depend on each case uniquely, but it is important to recognize that "waiting" for a catastrophe of the ECMO circuit or a significant patient complication (i.e., large cerebral intraparenchymal hemorrhage) are often avoidances of the difficult but ethically appropriate decision to stop and may be only prolonging time to death with a highly burdensome therapy.

WHAT ARE THE RESOURCE CONSIDERATIONS FOR A SINGLE PATIENT WITH MULTIPLE ECMO CIRCUITS AND PROLONGED BUT LIMITED ABILITY FOR RECOVERY, INCLUDING SEVERE NEUROLOGIC INJURY?

It is difficult to balance the justice considerations, particularly within an individual case. Policy is meant to attend to the appropriate considerations for access to therapies and limitations in what would be offered so that there is appropriate attention to fairness and equality of access to therapies or denial of therapies.[2]

To deny more than one ECMO course in all patients does not bear appropriate consideration to the disease process prompting consideration for ECMO. Some diseases may not be amenable to ECMO at all and should not have any ECMO offered, while the next might have three ECMO courses with an acceptable outcome. This then leaves one subject to anticipating the cost-benefit considerations. While one ECMO course is of higher cost than 5 days in the ICU without ECMO, it may be of high benefit in some and low benefit in others; furthermore, it might be unclear who will receive the benefit. To decide to withhold the entire group of patients from ECMO, one has to accept that the 5/50 who would have survived will not survive by virtue of ECMO being withheld from all in that group. It is unclear at what ratio we are comfortable accepting poor outcome when "better" outcome might be achieved as both a healthcare provider group and as a societal value, particularly in resource-rich and technology-focused healthcare systems.

This individual patient should not be deemed unsuitable for ECMO due to the cost alone unless the entire regional medical system is allocating resources at a similar cost point to other patients with similar prognosis or outcomes.[1,2] Whether judged by cost benefit or by total cost or by quality-adjusted life-years, it is unclear that this patient is any more "costly" than multiple others outside the ICU with life-limiting illnesses and high-cost medical therapies. Currently, there are few systems with policies in place to weigh the cost-effectiveness of therapies with an eye to determining what is and is not allowable, and physicians are left to make the best decision for the patient in front of them at the time with few instances where limitation of therapy is explored based on cost alone in high-income, resource-replete contexts.

CASE CONCLUSION

The infant VB has a successful surgical intervention and recovers some ventricular function, adequate to decannulate. She has the evolution of severe hypoxic-ischemic encephalopathy and is able to be extubated but only to a noninvasive ventilator for a prolonged wean. The family is in agreement not to proceed with tracheostomy, but wishes to continue medical therapies for heart failure. They are clear that they would not want additional invasive therapies added, although would consider percutaneous jejunostomy tube for nutritional support to maximize her comfort. Their goal is to maximize quality of life where possible, and they wish to consider overnight noninvasive ventilation support as a suitable home therapy with the hopes of eventually weaning it to discontinuation.

CONCLUSIONS

- Informed consent has many elements for consideration in ECMO therapy, including those considered with all therapies: capacity, surrogate decision-making, decisional authority, and best-interest standard.
- Decisional authority is assumed to belong to the parent(s) unless they are making decisions that are felt NOT to be in the best interests of the child, at which point medical care teams are obligated to seek appropriate interventions as dictated by local legal/policy mandates. However, it is important to remember this does not require parents to agree with all medical recommendations as there may be more than one lens to best

interests of the patient. Remember, the "optimal" medical treatment in terms of treatment results may carry a risk or side-effect profile the family feels overall does not justify the burdens it carries.

- ECMO, when applied as an emergent life-saving therapy in the context of ongoing CPR, may impede the informed consent process but behooves one to undertake fulsome information sharing to mitigate the impacts from inadequate time for consideration and decision-making prior to initiation of therapy.
- ECMO is not a curative procedure, but it is a bridge to something else (recovery, transplant, further bridge, medication optimization, decision). Therefore, prior to initiation of ECMO, there must be a clear plan for its purpose, along with agreed-on measures of success or failure.
- Repeat courses of ECMO require careful attention to anticipated interventions to reverse the underlying pathology driving the need for ECMO as well as considerations of the current burdens of the patient and family values and views on those burdens and potential future quality of life. Just because a family was willing to consent for ECMO once does not mean they are willing to do it twice.
- Withdrawal and withholding of therapies in the face of life-limiting illness is accepted widely in many countries and can be justified by all moral theories.
- Discontinuation of ECMO, once initiated, is no different from discontinuing any other form of life-sustaining medical technology, such as a ventilator. If the technology is no longer serving a purpose or is felt to have burdens that far outweigh its benefits, it is ethically permissible to discontinue.
- When deciding if ECMO is appropriate to offer, it can be helpful to consider the difference between the burdens associated with ECPR separate from elective ECMO. The occurrence of CPR will add additional morbidities that may limit the ability to accomplish recovery, improvement, or benefits from ECMO. It can be appropriate in some instances to offer ECMO without offering ECPR.
- Unclear outcomes will increase distress and uncertainty; this also allows a wider range of acceptable decisions and increases parental burden of decision regarding therapies.
- Broader considerations of resource allocation across programs and hospital systems beyond the individual case are required for just allocation. These need to be systematic policy considerations if at all possible and are better done preemptively than at a particular patient's bedside.

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REVIEW QUESTIONS

1. You are the critical care physician taking care of a 4-year-old male with status asthmaticus with worsening respiratory and metabolic acidosis despite aggressive vasoactive support and institution of volatile anesthetic. His most recent blood gas is notable for a lactate of 7, $PaCO_2$ of 70, and pH of 6.95. The patient is on infusions of epinephrine, norepinephrine, and vasopressin, but remains hypotensive. You approach the mother to obtain consent to proceed with veno-venous (V-V)

extracorporeal membrane oxygenation (ECMO), where survival is greater than 90% for the indication of status asthmaticus. The mother of the patient refuses to provide consent, stating that she is Jehovah's Witness and will not consent to ECMO because of the need for blood products. You

A. Withhold V-V ECMO and continue current support to honor the mother's decision-making rights on behalf of her child.
B. Declare the mother lacks capacity because she seemingly wants her child to die, and you proceed with cannulation.
C. Obtain an emergency court order to proceed with cannulation as the mother is violating the best interests standard.

2. You have been providing care for a patient who has now been on V-V ECMO for 72 days. The now 9-month-old was initially placed on V-V ECMO at your institution after being transferred for progressive difficulty ventilating and oxygenating at an outside institution as a bridge to recovery. Cultures following cannulation were positive for *Pseudomonas aeruginosa*. A tracheostomy was completed to facilitate weaning from sedation. However, as more testing was completed, it was revealed that the patient has a rare and poorly characterized immune deficiency detected via whole-exome sequencing and confirmed via subsequent immunologic assays. His lung function remains poor, with no significant recovery of gas exchange capabilities to date. After much discussion, his parents have chosen to withdraw life-sustaining technology. The bedside nurses and fellows express concern about this strategy, as the infant is awake and interactive with those around them despite being on ECMO. Which of the following provide the ethical justification for this withdrawal of life-sustaining technologies?

A. Continuing support in the setting of an immune deficiency and no recovery of innate lung function represents prolongation of suffering with no reasonably expected chance of recovery or benefit.
B. Parents, as arbiters of the child's best interest, have the right and obligation to prevent undue harm and accrual of burdens.
C. Stopping of mechanical circulatory support contains no unique ethical or moral distinctions from stopping any other life-sustaining technologies.
D. ECMO cannot be stopped if the infant is otherwise neurologically intact, as stopping ECMO would violate the best interest standard as it would end the child's life.
E. A–C.

3. Which of the following concepts apply to withdrawal of ECMO support?

I. Nonmaleficence dictates that any therapy that no longer provides reasonable expectation of its initial intent can be stopped.
II. Just resource allocation would suggest that providing the substantial physical, financial, personnel, and emotional resources necessary to provide care to a patient in whom ECMO no longer serves a purpose is inappropriate.
III. Maintaining ECMO support in a patient who has no reasonable hope of benefit from the therapy in order to provide a low-volume center with experience in providing care to ECMO patients to benefit the next potential ECMO patient cannot be justified.
IV. Because of the proximity between discontinuation of ECMO and a patient's death, discontinuation of ECMO holds a different degree of moral authority than discontinuation of other life-sustaining therapies such as inotropic or vasopressor support, where stopping such therapies may not result in immediate death (or death at all).

A. I
B. I and II
C. I, II, and III
D. I, II, and IV
E. All of the above

4. A 4-year-old child with severe chemotherapy-induced cardiomyopathy presents to the emergency room in profound shock. She carries the diagnosis of Acute Myelogenous Leukemia and has failed to achieve remission; the most recent care plan from oncology indicates they are now working toward potential salvage bone marrow transplant as the next potential step in her care. She has been followed by the heart failure and cardiomyopathy service for progressive worsening of her function over the past 9 months, with the most recent ejection fractions trending below 30%. Bedside echocardiogram in the trauma room shows severe biventricular dysfunction with near-ventricular standstill, and during the echocardiogram, the patient suffers a cardiac arrest. The emergency room physician wishes to activate ECPR as the patient had an in-hospital witnessed cardiac arrest. The cardiology fellow at the bedside objects, stating this child is not an appropriate candidate for ECPR. The family "wants everything done." Which of the following arguments would most strongly support the *fellow*'s reasoning?

A. ECPR is a highly resource-intensive therapy that carries high burdens for the patient. Proportionality would dictate that the ratio of benefit to burden in this patient, who has a likely terminal underlying illness with no clear next therapy, would render ECPR inappropriate.
B. Nonmaleficence would mandate that the child be protected from harm; ECPR is invasive and painful and, in this particular setting, would be unlikely to provide the patient with the expected benefit of long-term survival.
C. Any therapy initiated should have an a priori reasonable expectation of success; in the setting of ECPR, that expectation would be resumption of circulation so that a reversible cause of its sudden stopping could be adequately treated. In this case, because of the etiology of her cardiac dysfunction coupled with her underlying malignancy, ECPR would likely become a bridge to

nowhere, as recovery, transplantation, or bridge to a second bridge are not reasonable expectations.

D. A–C.

E. None of the above. The emergency room physician is correct, and parental wishes for everything mandate that ECPR be activated and the child placed on mechanical circulatory support.

ANSWERS

1. C
2. E
3. C
4. D

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