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Extracorporeal Membrane Oxygenation

Advances in Therapy

Edited by Michael S. Firstenberg

EXTRACORPOREAL MEMBRANE OXYGENATION - ADVANCES IN THERAPY

Edited by **Michael S. Firstenberg**

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Notice

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Preface

Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support (ECLS), is rapidly evolving from a salvage therapy to a routinely available therapeutic option. Historically, ECMO was associated with poor outcomes and use was restricted to neonatal and cardiac ICU in patients in which all other interventions have failed. Now, ECMO has become a mainstream, successful, therapy, across many patient populations. It is becoming recognized that therapy needs to be pursued as early as indicated to achieve optimal outcomes. ECMO therapy is typically divided into veno-veno (VV) when needed for pulmonary support and venoarterial (VA) for cardiac support. Obviously, there is an overlap between the two-patient populations. The goal of this book is to provide, thanks to the thorough contributions by known experts in the field, a framework for successful program development.

This text is divided into several overlapping themes. To appropriately use and understand ECMO, it is critical to understand the specifics of the different types of support, pump technology, and—most importantly—patient selection and management. Several chapters focus on education and pump technology. Furthermore, there are key differences between veno-veno and venoarterial, and several chapters include discussions that focus on these differences as applied to cannulation strategies and patient selection. In addition, chapters focusing on specific patient populations, such as cardiogenic shock, thoracic organ transplantation, trauma, and neonates, provide insight into the particular challenges in dealing with the unusual problems of these very diverse groups. Most importantly, once the decision is made to support a patient with ECMO, management of the patient then remains the most important step in achieving a good outcome.

Patients requiring ECMO can be very difficult to manage. Providers at all levels need to be able to react and respond, often immediately, to the problems that arise. Teamwork is paramount. Management is often based upon not only the daily care of the critically ill patient but also the specific care issues that ECMO patients require. "Resting" to allow recovery of acutely injured hearts and lungs must be a priority. Several chapters that address these topics provide valuable insight into these concepts. Finally, as importantly, several chapters focus specifically on the diagnosis and management of complications that continue to challenge these therapies. Additional organ failure (ongoing cardiac, renal, and neurologic) is, unfortunately, not uncommon, and navigating through these issues can often be the critical step in separating success from failure. Weaning to recovery or advanced therapies are also discussed.

ECMO is a rapidly evolving and extremely complex technology. With a better understanding of the technology, the indications for support, patient selection, and the nuances of man-

aging patients who both are acutely ill and require extracorporeal support, outcomes will continue to improve. By no means is this text all inclusive or the final word on these topics but hopefully a starting point for those who want to develop, grow, and improve their programs. Hopefully this text will also inspire others to further advance this field.

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Introduction

Chapter 1

Introductory Chapter: Evolution of ECMO from Salvage to Mainstream Supportive and Resuscitative Therapy

Michael S. Firstenberg

Additional information is available at the end of the chapter

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1. Introduction

Extracorporeal membrane oxygenation (ECMO), also known as extracorporeal life support (ECLS), has evolved from a salvage form of life support, used only in cases in which all other therapies have failed, to a mainstream therapy for patients experiencing acute cardiac and/or respiratory failure. Initial experiences were associated with poor outcomes and few survivors [1]. Challenges to success included difficulties in optimal patient selection, crudely designed and implemented technologies, an unclear understanding of the relationship between the patient and the extracorporeal circuit, lack of management guidelines, and difficulties in managing complications and guiding patients. However, over the past 20–30 years, there has been a growing recognition of the potential life-saving benefits of the role of extracorporeal support in allowing the failing heart/lungs to heal, possibly allowing for recovery, or serving as a bridge to more definitive end-organ replacement therapy, such as ventricular assist devices or transplantation [2]. This evolution has reflected a long journey—a journey that continues to evolve in part due to the hard work, dedication, and overall commitment by those who recognize that tremendous potential for ECMO to bring hope and restore life to those who would otherwise die [3].

This text reflects the collective efforts of those, worldwide, who have dedicated countless energy to achieving a better understanding of those details that will ultimately yield better outcomes. The key to clinical success—and not just in a single patient but also for a program and an Institution—is Teamwork.

The first step in success is understanding the theory, technology, and the development of a team. ECMO requires a comprehensive Team—and one that must be prepared to implement the therapy anytime and anywhere. The specifics of the Team may vary from program to program—but they must be organized and developed in advance. Effective Teams must work

and communicate together—they must trust and value the expertise and dedication that each member must bring to the patient. Most importantly, effective Teamwork must rise above traditional professional hierarchies and embrace in the principles of Crew Resource Management in which everyone has a voice and that voice is valued and respected. The Team must comprise of experts in all related disciplines—perfusionists, pharmacists, physicians (of all specialties—surgeons, critical care, pulmonary, infectious disease, etc.), nursing (bedside and advance practices), respiratory therapists—and most importantly, a champion to lead them all. The tremendous need for dedicated resources—often working long hours and under stressful conditions—also mandates the support and encouragement of hospital leadership and administration at all levels (**Figure 1**) [4].

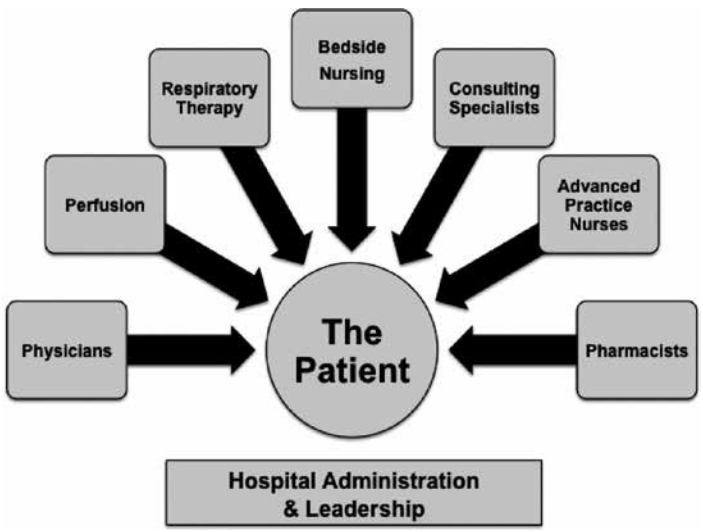

Figure 1. ECMO "Team".

Before the first patient is supported in ECMO, the Team must be prepared. The pump and circuit must be available, bedside nursing must be prepared and educated, protocols and guidelines need to be developed, and goals must be set [5]. The chapter by Yiu and colleagues on simulation training helps to outline those steps necessary to build and educate a Team. Clearly, a foundation in education is critical to success.

One of the most important aspects of ECMO is patient selection and choice of therapy. As the chapters in this text illustrated, there are significant differences in the support for failing lungs, failing heart, or both. Understanding the difference between veno-veno (VV) and veno-arterial is an important step even before consideration is given to patient selection. Indications for each type of therapy are critical to understanding the goals, and patient selection is an important first step. Much like understanding the differences between veno-veno (VV) and veno-arterial is important, so are the indications and timely implementation of the therapy. Various chapters in this text provide insight into some of the technical options for cannulation strategies, including some of the key differences between veno-veno and veno-arterial support and

circuit. The chapter describing the techniques and benefits of unusual cannulation algorithms —specifically triple cannulation—by Dr Christian helps to build on the chapter by Dr Ramaiah on the basics of ECMO cannulation.

As described above, the first step to a successful program is optimal patient selection. Recognizing that even successful programs have outcomes that range from 60 to 70% survival for ideally selected patients for veno-veno support to sometimes less than 20–30% for veno-arterial- and ECMO/ECLS-supported emergent cardiopulmonary resuscitation (E-CPR) [6, 7]. While it would not be unusual for starting programs to initially have lower success rates, over time, with experience, improvements in Institutional protocols, and better (and more timely) patient selection, the hope that outcomes would improve. Ironically, as programs become more successful and outcomes improve, there are also—as seen in other areas of innovative and novel clinical therapies—attempts at pursuing high-risk cases that might be slightly out of the boundaries of the traditional indications for therapy. Such dynamic attempts to support lower than higher risk patients on ECMO are not uncommon and typically based upon Institutional (and sometimes, personal) outcomes. A series of successful low-risk patients then help justify attempting the salvage a higher-risk patient and, conversely, potentially less than ideal outcomes in higher-risk patients might then limit selection back to lower risk patients. Nevertheless, there must always be Institutional processes established for reviewing outcomes (clinical and financial), and continuous quality improvement with refinements in local guidelines and protocols. Team engagement, including both bedside clinical support staff and hospital administration and leadership, is critical and cannot be emphasized enough. Active membership and participation in ELSO (the Extra-Corporeal Life Support Organization: https://www.elso.org) can provide important international outcome data to benchmark institutional success. In addition, membership is such organizations provide a community to exchange ideas, partner with colleagues, and serve as a resource for important and timely communications and developments in the field.

It is also important to understand that there are significant differences in patient populations that might require either VV or VA support. Inherent with these different populations comes different patient selection criteria, management guidelines, expectations, and goals of therapy. Specific chapters in this text help outline the nuances of selecting patients who are providing support—and hopefully weaning from support—to these very clinically diverse populations.

1. Neonatal applications (Dr Rais-Bahrami).
2. Support for lung transplant patients (Dr Young-Jae).
3. Support for heart transplant patients (Dr Loforte).
4. Applications for high-risk catheterization lab procedures—often in the setting of cardiogenic shock (Dr Ganyukov).
5. Applications in cardiac arrest (Dr Brunner).

One of the most rapidly expanding indications for the ECMO therapy is in unusual patient populations. As it is becoming more recognized that ECMO can be extremely useful in patients experiencing acute cardiopulmonary end-organ dysfunction, there is becoming a greater role

for the ECMO support (even if temporary) for high-risk procedures [8]. Typically, such applications are limited to high-risk procedures in the catheterization laboratory as defined by complex anatomy, baseline impaired cardiopulmonary function, or to reduce the inherent procedural-associated risk of complex interventions such as percutaneous aortic valve procedures, coronary or cardiac structural interventions, or electrophysiologic-guided ablative procedures for malignant or complex arrhythmias. The primary goal of providing support during these procedures is to minimize the inherent risks of end-organ dysfunction or failure during the anticipated cardiopulmonary impairments during the procedures or to mitigate the risk of a physiologic catastrophe in the event of a procedural-associated cardiopulmonary collapse and the inherent time delay (even if anticipated) in resuscitative interventions and reestablishing hemodynamic stability [9]. The chapter by Dr Ganyukov illustrates clearly the growing successes and applications in these areas.

The growing use of ECMO in patients experiencing "trauma" or out-of-hospital accidents, such as a blunt force or penetrating injuries, is also becoming more common [10]. Trauma patients also reflect a unique management challenge because often their injuries are extensive, involve multiple organ systems, are at high risk for bleeding (even if they are not already coagulopathic from the growing use of anticoagulation or antiplatelet agents), and are often susceptible to secondary nosocomial problems. Such nosocomial issues can often be catastrophic, difficult to manage, and be of greater physiologic impairment than the initial injury. Problems, including septic shock from acquired infections, cardiogenic shock from acute coronary syndromes (and potentially superimposed acute or chronic heart failure), pulmonary emboli from poor or limited mobility, and adult respiratory distress syndromes with pulmonary failure (either as a primary or secondary process), all lend themselves to support with ECMO. Furthermore, despite the inherently high risk for bleeding after an injury, there is also a growing experience with using ECMO for support the acutely injured lung or heart (i.e., pulmonary or cardiac contusions or destructive structural injuries that might require intervention) in these patients who often have multiple other injuries. A rapidly expanding area is also the use of ECMO to support higher risk trauma-associated procedures in which the need for early definitive repair, such as orthopedic stabilization, must be balanced against the risk of surgery in a patient with already difficult to manage cardiopulmonary status [11]. Ronson and colleagues, in their chapter on the use of ECMO in Trauma, discuss this evolving area in detail.

Once the decision to put a patient on support is made and the therapy is initiated, it must be made clear that the real work in patient management begins. Patient management on ECMO can be divided into several key areas—with each focusing on standard of care based upon evidence-based practice management of topics independent of the need for ECMO as a cornerstone to clinical success. However, any and all management decisions must be made in the context of the complex and often practical limitations of caring for patients on ECMO. For example, the management of acute neurologic problems (as discussed by Dr Bowling in her chapter) might be grounded in the extensive experiences and guidelines for dealing with non-ECMO patients who sustain an acute neurologic injury. Decisions must be made in the context of the challenges in anticoagulation/antiplatelet therapies. Even the ability to transport to or obtain routine imaging studies can be difficult in patients on ECMO [12]. While there are many

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concepts in how to manage patients on ECMO, as mentioned, there are some key concepts that are outlined in various chapters of this text:

1. Routine care of the critically ill patient—including ECMO-specific guidelines for the management of sedation, analgesia, and delirium (Dr Satypriya's and Dr Maldonado's chapters). Ventilator management and lung-protective strategies that allow for lung healing while on support is an extremely important topic as discussed in Dr Stahl's chapter.

2. Also of importance is understanding the complex biologic (human) to machine (ECMO circuit) interactions—both from a theoretical standpoint in the context of understanding the nuances of pump design, flow characteristics, and blood contact with nonbiologic surfaces (pumps, tubing, and oxygenators). Understanding these interactions and the role of anticoagulation testing and management is necessary to help maintain the delicate balance, as Dr Maul discusses in his chapter, between the inherent risks of bleeding and clotting while on ECMO.

3. While the need for ECMO support is often obvious and therapies once on support must be focused on "fixing" those problems, it must be remembered that often these patients have difficult problems that require a focused and integrated multidisciplinary Team. Involvement of expert consultants, such as infectious disease specialists, should be obvious in the setting on infectious problems. However, when patients are supported for primarily cardiovascular problems, the diagnosis and management of these problems often require aggressive testing and interventions in a catheterization laboratory. As illustrated by Dr Duke, even the transport of these patients can be difficult and risky and the ability to evaluate and treat problems often requires a Team approached with consideration for staged interventions.

4. It is well established that complications while on ECMO are, unfortunately, common. Such complications can have a significant impact on patient management and outcomes. An awareness of preventive strategies, role for early intervention, when they occur, and ECMO-specific treatment options are vital. Two of the most important complications—both in terms of frequency of occurrence while on support and in terms of impact on morbidity and/or mortality—are renal failure and neurologic complications. While prevention is key—and it is known that early implementation of ECMO can reduce the risk (and impact) of both of these complications, they nevertheless occur quite frequently. The chapters by Dr Bowling (neurologic) and Dr Thajudeen (renal) discuss the ECMO-specific issues that help in the diagnosis and management of noncardiopulmonary organ system dysfunction.

5. As the chapters that focus on specific patient populations discuss, once a patient is placed on support for whatever reason, the longer they are on support, the less likely they are for coming off and ultimately surviving. Therefore, a primary focus needs to be a continuous evaluation of those factors that either limit or need to be "fixed" or recovered before a patient can be weaned from support. Often recovery is based upon treating the primary problem and allowing the injured organ to recover. In addition to conventional

medical therapies, such as appropriate antibiotics for overwhelming pneumonias and sepsis, some patients might require invasive procedures, including catheter-based or surgical solutions. Regardless, the concept of weaning, as discussed by Dr Aissaoui and others in their chapters, must always be considered.

As with any intervention on a sick or high-risk patient, open, transparent, and honest on-going communications with families are paramount to help manage expectations. The emphasis of all communications should be on the reality that even in the best of circumstances and with the best of Teams, morbidity and mortality rates in patients supported on ECMO remain high. Even those who do survive will often have prolonged hospital stays, potentially prolonged and difficult recoveries, but many who do survive are able to return to productive lives [6].

2. Conclusions

As this book will hopefully illustrate, ECMO is very quickly becoming a mainstream therapy for patients experiencing acute, severe, and often medically refractory cardiopulmonary failure. Over the years, the technology has improved, the guidelines, protocols, and indications for therapy have been refined, and as experiences grow, the knowledge that comes from those experiences, hopefully, contributes to better outcomes [13]. Clearly, there is still much to be learned. Similar to other "resource intensive" technologies in which success or failure is often seen and experienced in the setting of a brief hospitalization, there is often much excitement, interest, and often intrigue when a patient is supported on ECMO. Success requires a Team effort and a tremendous amount of hard work and effective communication. Considering how many people, despite such enormous efforts and dedication, die on ECMO—even in the best of circumstances—it becomes so important that the victories are cherished and shared by all. Such victories can inspire and give hope even in times of when clinical success appears to be futile. Futility—a word that can often rally a Team or help accept the reality that life does not go on forever. Even though this text might not be the final word on this topic, as clearly there is still much to learn; the hope is that this will serve as a cornerstone for program growth and development—and as an inspiration for those intrigued by the potential benefits of ECMO [14].

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Technology discussed might not be approved by the CE/FDA, but is included due to its relevance to the research being presented.

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Chapter 2

Simulation Training on Extracorporeal Membrane Oxygenation

George Wing Yiu Ng, Eric Hang Kwong So and Lap Yin Ho

Additional information is available at the end of the chapter

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Abstract

Conventional extracorporeal membrane oxygenation (ECMO) training usually only consists of didactic lectures and water drill of ECMO circuit. However, learners cannot "experience" changes of clinical condition of patients. Simulation-based learning is a perfect answer to this by providing participantsauthentic, interactive, team-based training without risk to real patients. Hospital Authority (HA) of Hong Kong has implemented a corporatewide ECMO simulation-based training program since 2014. It aims to provide a structural and standardized training opportunity for clinical staff members to gain hands-on experience in ECMO circuit management and troubleshooting technique. In the program, participants will go through three categories of scenarios: (1) replicate common real patient clinical experience; (2) replicate incident that only happens infrequently; and (3) imitate clinical situation that is rarely happened but life threatening, and where prompt and correct actions are necessary. Every scenario has its own debriefing session that covers technical and human factor issues.Since 2014, 32 identical full-day courses were conducted and 285 doctors and nurses were trained. All participants were satisfied with the training and expressed that the simulation was an effective model for ECMO training. The training met their need and they could apply what they learned in real-life practice.

Keywords: crisis management, debriefing, extracorporeal membrane oxygenation, non-technical skill, simulation

1. Introduction

In this chapter, we will use extracorporeal membrane oxygenation (ECMO) simulation training organized by Hong Kong Hospital Authority (HA) as an example to illustrate how to develop and set up an ECMO simulation training. We will discuss overview of an ECMO training program in Hong Kong, goal and advantages of starting the ECMO simulation training, budgetary considerations, modification of old manikin and design of new manikin to facilitate ECMO training, set-up of high-fidelity-simulated environment, explanation on scenario design and flow, and what to debrief after every scenario.

2. Overview of the Hong Kong ECMO training program

Hong Kong experienced two large-scale infectious disease outbreaks, i.e., 2003 SARS outbreak and 2009 Swine H1N1 influenza outbreak. In 2003, SARS patients with severe respiratory failure were only supported by conventional mechanical ventilation [1]. In 2009, patients suffered from Swine H1N1 influenza were managed with ECMO when they were unlikely to survive by conventional mechanical ventilation [2, 3]. The use of ECMO in adult patients remained controversial until publication of the CESAR trial in 2009, which showed promising results with ECMO in terms of survival for patients with severe respiratory failure and ARDS after H1N1 pandemic [4].

HA is a statutory body established under the Hospital Authority Ordinance of Hong Kong in 1990. It is responsible to manage all Hong Kong's public hospitals services. Under the governance of HA, there are five ECMO centres in five different public hospitals. ECMO may be offered to the selected patients that have potentially reversible causes of cardiac and/or respiratory failure when the predicted mortality is high. As ECMO is a newly introduced, but complicated and high-risk procedure, it was suggested by head management that clinical staff of the ECMO centres should receive structural and comprehensive training to deal with routine management and emergency situations. In 2013, HA decided to develop a centralized simulation training program on ECMO for staff working in the five ECMO centres. The simulation training is free-of-charge. It composes a variety of learning objectives including ECMO knowledge, technical skills and crew resource management. It also allows the development of a standardized experience for all staff members. Instructors of the ECMO simulation training are intensive care specialists and senior nurses from the five ECMO centres. Most of the instructors are qualified by HA for using simulation to teach. Some of them received Train-the-trainer Courses of ECMO Simulation run by Extracorporeal Life Support Organization (ELSO).

3. Goaland advantages of starting the ECMO simulation training

ECMO is a complex technology that involves cannulation of big central vessels, operation of the ECMO console, circuit management and use of anticoagulation. Medical errors are not

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infrequent as ECMO patient is extremely critical and technology is complex. On the other hand, patients and their relatives become increasingly concerned that doctors are "practicing" on them, and clinical medicine is now more focusing on patient consent, safety and quality than on teaching and education. To solve this dilemma, clinical staff that take care of ECMO patients should receive proper and specialized training before they manage real patients.

ECMO is a extracorporeal life support system that has a pump to circulate blood through an oxygenator. VV ECMO has the return cannula placed in the venous system for lung support. VA ECMO has the return cannula placed in the arterial system for cardiac support. Different ECMO centres have different casemix due to geographic reason and specialization. Therefore, some ECMO centres have more VV ECMO cases, whereas other centres have more VA ECMO cases. And even within the same centre, the number of ECMO cases may vary from month to month. In Hong Kong, winter and summer are the peak seasons of influenza so we have higher number of VV ECMO cases in these seasons [5]. After the peak season, training is needed to keep our staff competent on managing this complex technology when there is no VV ECMO case in the unit.

Close collaboration among clinical staff members is mandatory for both daily ECMO care and crisis management. Appropriate team behaviour and clear communication are of utmost importance in caring for ECMO patient. Therefore, staff members that take care of ECMO patient should receive training on non-technical skills, namely, communication, situational awareness, assertiveness, leadership and teamwork.

In addition, medical crisis on ECMO occurs very rarely in real situation. Clinical staff members normally do not have the chance to experience or deal with this kind of situation. However, making correct decision depends upon understanding the situation under short time pressure. Therefore, simulation training can provide a standardized opportunity for staff members to experience and gain confidence in managing ECMO emergency.

4. Budgetary considerations

After the H1N1 pandemic in Hong Kong in 2009 and publication of CESAR trail in 2009, ECMO has been recognized as an option to patients that failed conventional mechanical ventilator support. However, there was insufficient formal and structural ECMO training locally. There were just didactic lectures supplemented with ECMO circuit priming hands-on training. Clinical staff members had to go overseas for receiving hands-on practice such as crisis management and troubleshooting. As there has been an increasing demand of ECMO service, a corporate wide ECMO simulation training was first proposed in 2013 by clinical expertise working group and local simulation training unit development group to the simulation training committee of HA. The goal of the training is to let clinical staff members acquire clinical competencies of handling ECMO patients. The funding consideration of the proposal was screened and prioritized by the Service and Budget Planning Committee and approved by the HA board for resource allocation. Every year the training has to undergo a service and budget

planning review process at the corporate level. It serves to secure consensus of the policy direction and program's service model.

4.1. Equipment

Only circuit and cannulae that are for training purpose were purchased. We usually changed a new set of ECMO circuit and console in every six sessions. The simulation centres provide manikin and help to modify the manikin so the ECMO circuit can be incorporated inside. Other essential items that the simulation centres will provide include mechanical ventilator, infusion devices, resuscitation cart and monitoring devices (**Table 1**). There was a list of consumables that need to purchase and replace after use. **Table 2** shows the number of items that we used in the past two years.

Items that are provided by the simulation centre	Items that needed to be purchased by the training program
Manikin	HLS Set (non-sterile)
Mechanical ventilator	PLS Set (non-sterile)
Portable ventilator	HG0291 Straight Connector 3/8 × 1/4 LL
Physiological monitor	HY0263 Y Connectors 3/8 × 3/8 × 3/8 LL (non-coating)
Infusion pump and tubing	BE-S 2085 Back Flow Tubing Line
Resuscitation cart	Tubing Line 3/8 × 3/32 × 150cm
Defibrillator	Tubing Line 1/4 × 1/16 × 50cm
Syringes	Arterial HLS Cannulae Fr 19 (non-sterile)
Clamp	Venous HLS Cannulae Fr 23 (non-sterile)
Intravenous access	BE-S 2086 High Flow Tubing Line (with Bioline Coating)
Wall oxygen	PIK 100 Percutaneous Insertion Kit
Portable oxygen cylinder	PIK 150 Percutaneous Insertion Kit
Wall suction	HG0285 Straight Connector 3/8 ×3/8
Endotracheal tube	Ultrasound Contact Cream
Computer	SU2855 Tubing Clamp Forceps w/guard
	PIK Guidewire 100cm
	PIK Guidewire 150cm
	Cordis 504608 (Vascular sheath)
	Bladder reservoir

Table 1. Essential items and consumables required for the ECMO training course.

4.2. Personnel

Instructors are all qualified ECMO specialists that are properly credentialed by the training units. We have two doctor instructors and two nurse instructors in each class. They come to conduct the training either by applying official release from their departments or being financially compensated for their time if they take leave for the teaching. Instructors are paid by the hours according to the class duration and their HA payroll. Participants are arranged to attend the training on the day of their compensation off or during their duty shift while their

clinical duties are covered by other clinical staff members. We also employ an executive assistant to provide administrative work that involves instructor and participant recruitment process and communication.

Items that purchased and replaced	Item used from 2014 to 2016	
1	HLS Set (non-sterile)	13
2	PLS Set (non-sterile)	13
3	HG0291 Straight Connector 3/8 × 1/4 LL (Box of 20s)	1
4	HY0263 Y Connectors 3/8 × 3/8 × 3/8 LL (non-coating) (20s)	1
5	BE-S 2085 Back Flow Tubing Line (with Bioline Coating)	12
6	Tubing Line 3/8 × 3/32 × 150cm	2
7	Tubing Line 1/4 × 1/16 × 50cm	2
8	Arterial HLS Cannulae Fr 19 (non-sterile)	23
9	Venous HLS Cannulae Fr 23 (non-sterile)	23
10	BE-S 2086 High Flow Tubing Line (with Bioline Coating)	6
11	PIK 100 Percutaneous Insertion Kit (sterile)	8
12	PIK 150 Percutaneous Insertion Kit (sterile)	9
13	HG0285 Straight Connector 3/8 ×3/8 (non-coating) (20s)	1
14	Ultrasound Contact Cream	11
15	SU2855 Tubing Clamp Forceps w/guard	10
16	PIK Guidewire 100cm (Box of 5s)	2
17	PIK Guidewire 150cm (Box of 5s)	2
18	Cordis 504608 (Vascular sheath) Box of 5 pc	2
19	Bladder	2

Table 2. Items that are consumed and replaced from 2014 to 2016.

5. Modification of old manikin to facilitate the ECMO training

An ideal manikin for the ECMO simulation training should possess realistic anatomical features for clinical assessment and intervention yet inexpensive and durable. However, there is no such manikin in the commercial market. Therefore, modification of an old manikin was done for facilitating hydrodynamic simulation. We drilled holes in our old manikin "Nursing Kelly" so that tubing can be incorporated into the manikin. Inside the manikin, a closed-loop system was made by connecting tubing with a plastic reservoir (bladder). There are two openings on the "bladder." Each of these is connected to a syringe with a long tubing. In

scenario of hypovolaemia, we would draw "blood" from the circuit with the syringe. In scenario of air embolism, we would inject "air" from the syringe into the circuit (**Figures 1–3**).

Figure 1. Modification of old manikin—forming a closed loop with a "bladder" reservoir and using a latex tube to pretend central vein.

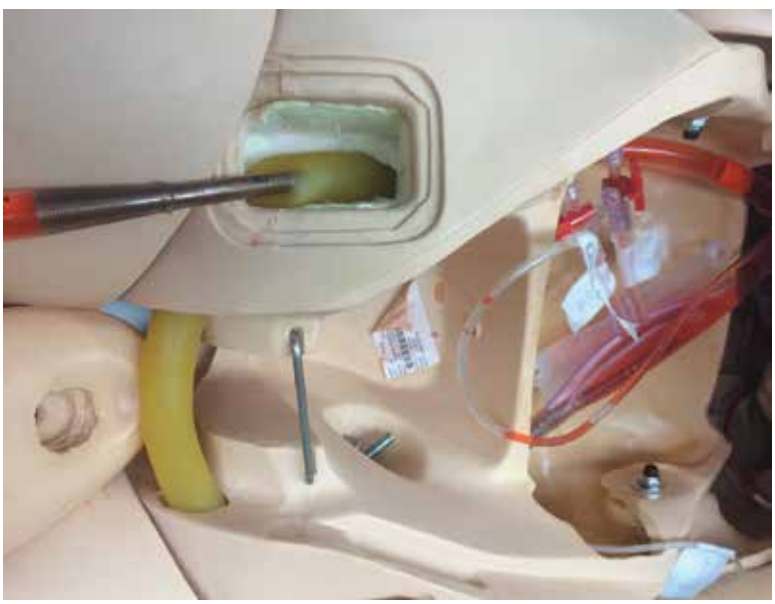

Figure 2. Modification of old manikin—inserting an ECMO cannula into the pretended vessel.

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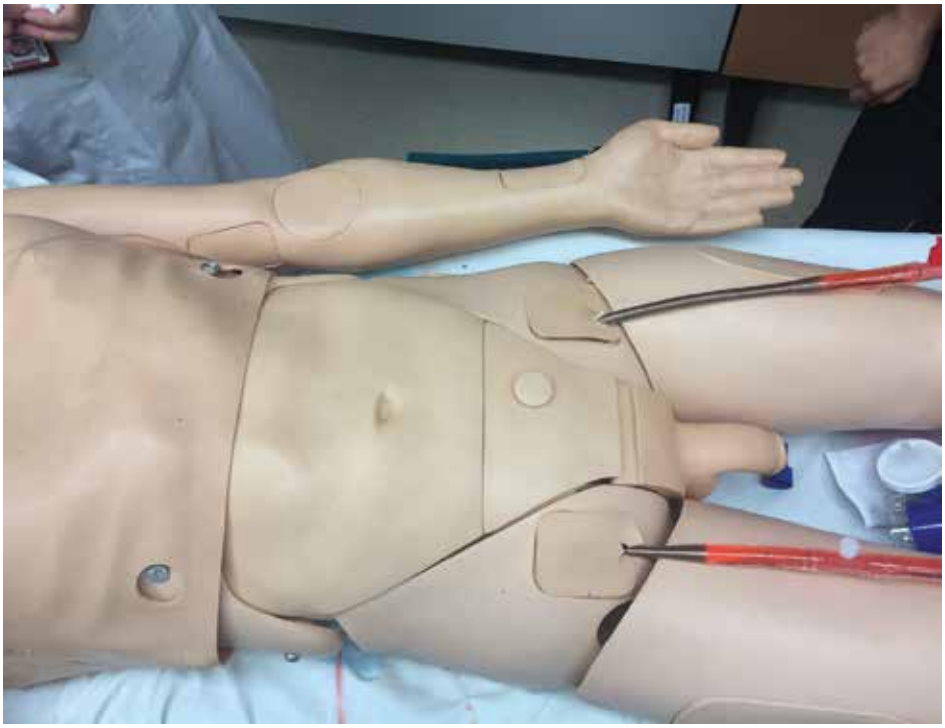

Figure 3. Modification of old manikin—finished model with cannulae placed.

6. Set-up of high-fidelity-simulated environment

Simulation refers to the artificial imitation of a real-life scenario or process with sufficient fidelity to achieve a particular goal, such as training or assessment [6]. A well-designed simulation program, complemented with high-fidelity simulator, allows learners to engage in the scenarios and immerse in the teamwork dynamic in the scenario play. It would provide learners with an environment to learn not only technical skills (theoretical knowledgeand procedures skills), but also non-technical aspects (teamwork, leadershipand communication).

Our training is conducted in two simulation training centres under HA. The simulation rooms are configured to mimic the intensive care environment. The manikins are intubated and put on mechanical ventilation. They have intravenous access that is connected to inotrope and sedative infusing agent. Participants can read the vital signs (i.e., arterial blood pressure, pulse rate, ECG, $O_2$and saturation) of the "patient" on a physiological monitor that is at the head of the patient bed. The parameters are controlled remotely by a simulation technician that is sitting behind a one-way mirror. The simulation technician can change the parameters at any time according to the scenario flow or instructor's instruction. Participants can get the relevant laboratory results, ECG, CXR, or echocardiography findings of the patient on request (**Figure 4**).

Figure 4. High-fidelity simulation environment for the ECMO simulation training.

7. Explanation on scenario design and flow

"See one, do one and teach one" has been the classical method in learning, when the trainees are exposed to patients in the clinical environment. However, this mode of education may expose patients to harm because participants may have inadequate initial experience, knowledge and technical skills necessary to manage the patient in a safe manner. Medical simulation provides a solution by providing a safe environment for both the learners and patients, especially for high-risk procedure like ECMO. Moreover, the use of simulation in our training can let us provide three categories of scenarios: (1) replicate common real patient clinical experience; (2) replicate incident that only happens infrequentlyand (3) imitate clinical situation that is rarely happened but life threatening, and where prompt and correct actions are necessary.

In the first category of scenario, scenarios are designed such that participants can acquaint basic ECMO concepts, circuit components, relevant parameters and alarms. The second category contains scenarios that are rarely happened. This kind of scenario serves to develop and maintain competency of skills and decision making for troubleshooting emergencies. The third category consists of life-threatening emergencies. These provide participants immersive and experiential opportunity to manage as in real life. Participants need to troubleshoot the crisis in a team-based approach with the use of both technical and non-technical skills (**Table 3**).

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Category	Training scenarios
Replicate common real patient clinical experience	• Pinched return tubing
	• Recirculation due to femoral drainage cannula is shifted in accidentally
	• Transportation to CT suite
	• Differential hypoxia
	• Retrieval transportation to another hospital
Replicate incident that only happens infrequently	• Hypovolaemia due to blood leak from a broken pigtail
	• Forget to switch on water heater leading to hypothermia
	• Progressive oxygenator failure with increasing delta pressure, minor clot in oxygenator
	• O_2 supply failure due to disconnection of O_2 tubing
	• Limb ischaemia due to kinked reperfusion cannula of a peripheral VA ECMO
Imitate clinical situation that is rarely happened but life threatening, and where prompt and correct actions are necessary	• Air bubbles were inside theaccess side of the ECMO circuit (pre-oxygenator)
	• Console failure due to short circuit
	• Accidental decannulation of the femoral access catheter
	• VT/VF arrest in a patient on VV ECMO

Table 3. Categories of training scenario.

The rundown of this whole day training is listed in **Table 4**. Participants are welcomed and registered before the starting of the training. They will be introduced to one another and briefed about the simulation environment. They will be informed that the training is only for learning purpose and will not be used for assessment or punitive purposes. The training will be videotaped for debriefing and future education use.

08:45–09:00	**Registration**	
	HLS circuit and Cardiohelp	PLS circuit and Rotaflow pump
09:00–09:30	Pinched return tubing	O_2 supply failure due to disconnection of O_2 tubing
09:30–10:00	Hypovolaemia due to blood leak from a broken pigtail	Console failure due to short circuit
10:00–10:30	Forget to switch on water heater leading to hypothermia	Accidental decannulation of the femoral access catheter
10:30–10:45	Recirculation due to femoral drainage cannula is shifted in accidentally	VT/VF arrest in a patient on VV ECMO
10:45–11:15	Air bubbles were inside the access side of the ECMO circuit (pre-oxygenator)	Differential hypoxia
11:15–11:45	Progressive oxygenator failure with increasing delta pressure, minor clot in oxygenator	Limb ischaemia due to kinked reperfusion cannula of a peripheral VA ECMO
11:45–12:15	Transportation to CT suite	Retrieval transportation to another hospital
12:15–13:15	**Lunch break**	
	PLS circuit and Rotaflow pump	HLS circuit and Cardiohelp
13:15–13:45	O_2 supply failure due to disconnection of O_2 tubing	Pinched return tubing
13:45–14:15	Console failure due to short circuit	Hypovolaemia due to blood leak from a broken pigtail
14:15–14:45	Accidental decannulation of the femoral access catheter	Forget to switch on water heater leading to hypothermia
14:45–15:00	**Tea break**	
15:00–15:30	VT/VF arrest in a patient on VV ECMO	Recirculation due to femoral drainage cannula is shifted in accidentally
15:30–16:00	Differential hypoxia	Air bubbles were inside the access side of the ECMO circuit (pre-oxygenator)
16:00–16:30	Limb ischaemia due to kinked reperfusion cannula of a peripheral VA ECMO	Progressive oxygenator failure with increasing delta pressure, minor clot in oxygenator

16:30–17:30	Retrieval transportation to another hospital	Transportation to CT suite
17:30–18:00	Q&A Closure of training Evaluation	

Table 4. Rundown of the simulation training.

Participants are split into two groups such that one group has 5–6 participants. In the morning session, group A will undergo seven scenarios that use MAQUET PLS circuit system and Rotaflow pump, whereas group B will undergo seven scenarios that use HLS circuit and Cardiohelp as the ECMO system. In the afternoon, group A will swap with group B and go through the scenarios that group B had in the morning.

The participants are brought into the simulation rooms. The group instructors orientate the participants the simulation environment inside the simulation room. Instructors explain what can the simulator do, and what are the limitations of the simulator, what equipment is available, where is the physiological monitor and what parameters will be shown. Participants are told that they can manage the ECMO circuit and adjust the parameter freely according to their clinical judgement and decision. One of the instructors will serve as a confederate in the scenario to facilitate scenario flow.

Figure 5. Instructor is briefing participants the simulation environment.

When the scenario starts, the instructor will introduce the patient's case history, present clinical status and issues, IV access, medications and laboratory results (e.g., arterial blood gas, plasma-free haemoglobinleveland post-oxygenator PO_2 level). On request, relevant imaging studies result will be provided (e.g., X-ray, CT scan and echocardiography). In each scenario, participants in the group haveto appoint one leader to lead the team. After the scenario training is

complete, participants move to a separate cubicle for debriefing. Instructors have to debrief according to the manual with preset teaching objectives and debriefing notes. All learners are expected to actively participate in the discussion, and the facilitator serves as a guide for the discussion rather than a "lecturer." If there is any technical issues that participants want to go back and practice again, instructors will arrange the practice at the end of the debriefing session. At the end of the training course, there is a question and answer session that allows participants to further reinforce the learning. Participants are invited to fill in the feedback survey that helps to evaluate the course and guide future direction (**Figure 5**).

8. What to debrief after every scenario

There is a debriefing session after each scenario. Each debriefing session lasts about 15 min. Debriefing is the most important part in simulation training. To ensure a fruitful debriefing process and learning experience, instructors should create a supportive environment so that participants feel valued and respected, and are willing to share their experiences in an open and honest manner. Participants are encouraged to recall and reflect the experience in the scenarios they have just participated and observe the gap between desire and actual. Instructors will help participants to clarify thinking, clear misunderstanding and reinforce specific defined teaching objectives.

8.1. Technical aspect

Tables 5 and **6** illustrate technical issues for discussion in debriefing session.

Scenario	Technical issues to debrief
Pinched return tubing	Always check systematically on three areas: ECMO circuit and console, O2 source and patient. Understand the concept of PVen, PArt, PDelta, Pint. Identification of flow drop and trigger of the flow and pressure alarms. Reasons of flow drop.
Hypovolaemia due to blood leak from a broken pigtail	Identification of very negative venous pressure and possible reasons behind. Blood leak from a broken pigtail if after-pump, air embolism will happen if the broken pigtail is pre-pump. Reinforce to check systematically on three areas: ECMO circuit (the three-way Stop-cocks) and console, O_2 source, and patient (any physical signs of bleeding) Increase RPM will further impede the blood flow. Treatment to correct very negative venous pressure.
Forget to switch on water heater leading to hypothermia	Recognition of hypothermia. Importance of systematic circuit check, including the water tank and heater. How to recognize the water heater is working. Find out other possible causes of bradycardia. Pharmacological causes (e.g., beta-blocker, dexmedetomidine, propofol, high dose alpha agonist). Endocrine causes (e.g., hypothyroidism). Cardiac causes (e.g., heart block after contusion). CNS causes (e.g., Cushing reflex after bleeding).
Recirculation due to femoral drainage	Clinical features of recirculation (e.g., low SpO_2 with high SvO_2 readings) Return Red + Access Blue → Normal. Return Red + Access Red → Recirculation. Return Blue + Access Blue → Oxygenation failure. Optimal distance between the return and access ECMO cannula tips,

Scenario	Technical issues to debrief
cannula is shifted accidentally	and how to appreciate the distance with X-ray and/or USG. Recognize recirculation is not a major problem as long as enough blood flow for oxygen delivery. Recirculation only happens in VV ECMO.
Air bubbles were inside the access side of the ECMO circuit (pre-oxygenator)	Identification of venous bubbles in the circuit and trigger of the gas bubble alarm. Air embolism is a major crisis and need to speak out immediately. When, where and how to clamp the circuit. Methods to de-air micro-bubbles. Systematic circuit check to look for leak site. Risk of air embolism is higher at pre-pump. Cracked three-way is always a possible source. Management of air embolism pre-oxygenator and post-oxygenator is different.
Progressive oxygenator failure with increasing delta pressure, minor clot in oxygenator	Hints that suggest a failing oxygenator:Elevating delta pressure; presence of clots on oxygenator membrane; post-oxygenator PO_2<200 mmHg; elevated plasma-free Hb. Oxygenators of HLS (Cardiohelp) and BLS (Rotaflow) have different lifespan. How to examine the circuit and oxygenator to find clot. In Cardiohelp only the post-oxygenator membrane can be seen. Can go through the technical aspect of changing oxygenator if time allows.

Table 5. Technical issues for discussion in debriefing session—when using HLS and Cardiohelp system.

Scenario	Technical issues to debrief
O_2 supply failure due to disconnection of O_2 tubing	Always check systematically on three areas: ECMO circuit and console, O_2 source and patient. Recognize disconnected O_2 supply has no alarm.
Console failure due to short circuit	Recognize pump failure is an emergency condition and need immediate reaction. Technique of switching to hand crank. Logistic of getting a new ECMO machine. Procedure of resuming the ECMO flow with the new ECMO machine.
Accidental decannulation of the femoral access catheter	Recognition of accidental decannulation can lead to massive bleeding. Immediate management of the massive bleeding. Recognition of accidental decannulation can lead to massive air embolism. Immediate management of the massive air embolism. Crisis management when ECMO is off accidentally (e.g., ventilator setting, inotropic support)
VT/VF arrest in a patient on VV ECMO	Perform CPR as usual as VV ECMO does not provide circulatory support. Adjustment of ECMO flow during CPR. When to decide switching VV ECMO to VA ECMO.
Differential hypoxia	Possible causes of O2 desaturation and check the three areas of ECMO circuit i.e. console and tubing, O2 source, and patient systematically. Pathophysiology of differential hypoxia (e.g., bad lungs and a recovering heart). Only happened in peripheral VA ECMO with femoral artery as return cannula. Features of differential hypoxia (e.g., right hand finger has a lower SpO2 reading than the left hand finger). Decision to switch VA ECMO to V-AV ECMO
Limb ischaemia due to kinked reperfusion cannula of a peripheral VA ECMO	Features of limb ischaemia (6 "P"). Method to check flow/patency/position of reperfusion cannula. When checking the cannula avoid flushing the cannula. Technique of line secure and dressing is important to avoid kinking of cannula.

Scenario	Technical issues to debrief
Transportation	Know what equipment and experienced personnel to assemble for ECMO transportation. Know the logistic of the whole transportation process. To recognize common potential problems in ECMO transportation. To troubleshoot during transportation if problems arise

Table 6. Technical issues for discussion in debriefing session—when using PLS and Rotaflow system.

8.2. Non-technical aspect

Appropriate team behaviours and clear communication are of utmost importance in caring for ECMO patients. Therefore, staff members that take care of ECMO patient should possess both technical (medical knowledge and technical skills) andnon-technical skills. Non-technical skills include situation awareness, communication, teamwork, leadership and decisionmaking. The importance of non-technical skills is to increase the work safety and ensure effective working environment, with a minimum of technical errors.

No.	Description	2014	2015
		Score of the item	
1	This program has achieved its stated objective(s).	4.43	4.47
2	This program meets my training needs.	4.47	4.25
3	The program content that I learned can be applied to my real practice.	4.51	4.49
4	The program is organized.	4.48	4.56
5	Length of the course is appropriate.	4.23	4.28
6	Scenarios are able to facilitate participation and learning.	4.51	4.49
7	Debriefing session is useful.	4.55	4.53
8	Trainer is effective in facilitating my learning.	4.55	4.57
9	Trainer helped me understand my performance.	4.42	4.54
10	I am overall satisfied with this training program.	4.5	4.49
11	For the learning objective of this course, I find that simulation is an effective mode of education.	4.55	4.49
12	Would you recommend this program to other colleagues?	Yes 86.2% No 0% Not answer 13.8%	Yes 94.1% No 0.05% Not answer 0.54%

*Strongly disagree: 1; disagree: 2; neutral: 3; agree: 4; strongly agree: 5.

Table 7. Questions of the course evaluation form and summary of the participants' comments.

In each scenario, troubleshoot the ECMO-related problem and stabilize the patient is the common goal. Participants are requested to select a leader and demonstrate teamwork. During the scenario, a team member is expected to maintain dynamic awareness of the situation based on assembling data from the environment, understanding what they mean and thinking ahead what might happen next [7]. Every team member should speak out when they have identified abnormality (situation awareness) so that other team members have the same shared picture of the situation (communication) and can react accordingly. The team leader after collecting the information will make decision (leadership) and act accordingly (decision making).

Besides discussing technical skills knowledge, instructors would also encourage group discussion on their non-technical skill performance. They would be encouraged to express their views on issues such as any performance gaps, the reasons behind such gaps, what could have improved and the relevance to their real-life experience. During the process, the instructors, apart from encouraging the participants to speak out, have to assist the participants to clarify issues, correct misunderstanding and reinforce certain pre-defined teaching objectives.

Table 7 shows the post-course evaluation form and the summary of the participants' comments. Participants expressed that the course is very organized and meets the training objectives. They agreed that scenario-based teaching can facilitate participation and learning and the debriefing session is very useful. However, we do not have data to show how our simulation training can improve patient outcomes. Further research is needed to study the effect of simulation training on outcomes of the ECMO patients.

9. Conclusion

ECMO is a complex and high-risk procedure that requires a high level of training to acquire and maintain proficiency. Non-technical factors such asteamwork, communication, situation awareness and decision making are equally important factors for keeping ECMO patients safe. Since the development of the ECMO simulation training in 2014, 32 identical full-day courses were conducted and 285 doctors and nurses from fiveECMO centres of Hong Kong were trained. All participants were satisfied with the training and expressed that the simulation was an effective model for ECMO training. The training met their need and they could apply what they learned in real-life practice.

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Chapter 3

ECMO Biocompatibility: Surface Coatings, Anticoagulation, and Coagulation Monitoring

Timothy M. Maul, M Patricia Massicotte and Peter D. Wearden

Additional information is available at the end of the chapter

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Abstract

The interaction between the patient and the ECMO (extracorporeal membrane oxygenation) circuit initiates a significant coagulation and inflammatory response due to the large surface area of foreign material contained within the circuit. This response can be blunted with the appropriate mix of biocompatible materials and anticoagulation therapy. The use of anticoagulants, in turn, requires appropriate laboratory testing to determine whether the patient is appropriately anticoagulated. Physicians must balance the risks of bleeding with the risks of thrombosis; the proper interpretation of these tests is often shrouded in mystery. It is the purpose of this chapter to help demystify the coagulation system, anticoagulants, biocompatible surfaces, and coagulation testing so that ECMO practitioners can make informed decisions about their patients and to spur coordinated efforts for future research to improve our understanding of these complex processes.

Keywords: anticoagulation, coagulation testing, surface coatings, ACT, aPTT, TEG, heparin, direct thrombin inhibitors

1. Introduction

The ECMO circuit, as a whole, represents one of the largest surface areas and volumes for blood contact in any medical device. The oxygenator surface area ranges from 0.8–2.5m^2 with a volume of 75–250 mL depending on the manufacturer and size (pediatric to adult). In addition, there typically is an associated 250–500 cm of polyvinyl chloride (PVC) tubing to connect the pumps, oxygenators, and equipment to the patient, which creates an additional

0.05–0.15 m^2 surface area and 70–250 mL volume depending on length and diameter of the tubing. When blood comes into contact with any foreign surface, a series of reactions begin to occur within milliseconds that impact the coagulation and inflammatory systems, and essentially lead to the rejection of the material by the host organism. Therefore, in order to utilize ECMO in a clinical setting, these processes are required to be modulated through systemic anticoagulation or the utilization of materials and coatings designed to disguise the materials from the body. This currently represents one of the greatest challenges to the utilization of ECMO in patients, particularly in the long-term application for lung recovery and/or lung transplantation. According to the Extracorporeal Life Support (ELSO) registry, which is a self-reported database of ECMO patients and their associated diagnoses, equipment utilized, outcomes and complications, there are approximately 0.5 thrombotic events and 0.5 bleeding events per patient run [1]. Although survival statistics for ECMO patients are population-specific, the occurrence of these two adverse events often results in a 20–30% reduction in overall survival. Therefore, it is of utmost importance that ECMO practitioners create a better understanding of the complex processes involved in an effort to better utilize current technology. Further, it is of even greater importance that device manufacturers and researchers continue to work on new drugs, materials, and surfaces in an effort to modulate activation of coagulation and inflammation. The purpose of this chapter will be to provide an overview of the processes and principles of coagulation and anticoagulation in the setting of ECMO as a necessary foundation for understanding this problem.

2. Cell-based model of coagulation

Since 2001, the way that coagulation has been understood has undergone some fundamental changes. The traditional coagulation cascade has been replaced with the cell-based model of coagulation [2]. In this model, there are essentially three phases to the clotting cascade: initiation, propagation, and amplification. In each of the three phases, the impact of tissue factor (TF) bearing cells and platelets has been placed at the forefront and these are the platforms upon which much of the conversion of coagulation factors from their inactive to active forms occurs. The cell-based model provides a more accurate picture of the way that an enzymatic cascade works and allows for a clearer picture of the cross-talk between the inflammatory and coagulation systems which must be appreciated by clinicians for a true understanding of the hemostatic picture in ECMO patients. While the details of the cell-based model are beyond the scope of this chapter, an overview of the model along with the drugs that interact with the coagulation proteins is provided for visual reference (**Figure 1**)

3. Surface activation

The primary concern for most clinicians in ECMO is the prevention of thrombus formation on the surface of the ECMO circuit. Thrombi are composed of platelets, red cells, and fibrin meshes that are adherent to the surface. It is important to understand that cells cannot adhere directly

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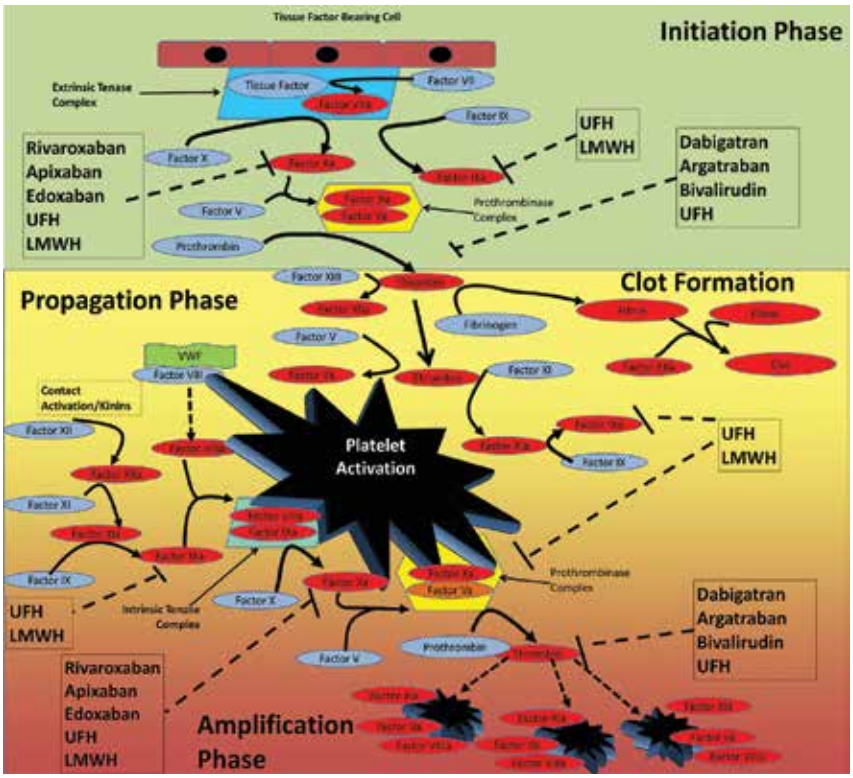

Figure 1. In the cell-based model of coagulation, three phases of coagulation take place on the surface of cellular elements of the blood. While platelets take center stage, the impact of TF-bearing cells cannot be overlooked because multiple cell types can express TF, including endothelial cells, monocytes, and macrophages. Inactive forms of the coagulation factors are presented in blue ovals while activated versions are presented in red ovals. Coagulation complexes are enclosed in parallelograms or hexagons. Drugs that interact with the coagulation cascade are identified and point to the specific factors they inhibit. Image adapted from Ahrens et al. [3].

to polymers, but rather require a receptor binding to a protein coating on the surface. Therefore, the first step in the coagulation and inflammatory response to the ECMO circuit is the adsorption (covalent or ionic reactions) of plasma proteins. This adsorption is based on stochastic processes driven by the thermodynamic reaction kinetics between the surface chemistry of the foreign material and the concentration of proteins available in the plasma [4]. For the ECMO circuit, these surfaces typically include PVC, silicone, polycarbonate, polymethylpentene, and/or polypropylene. Each of these materials is hydrophobic, with some being more hydrophobic than others depending on the side chain composition of the main polymer. The adsorptive process is also dynamic where proteins continually compete, adsorb, and desorb from the surface depending on both time and the changing concentrations of plasma [5]. Another important feature of this adsorptive process is that it often leads to a conformational change in the natural 3-D protein structure (**Figure 2**). In simple terms, the proteins may alter their shape to place their hydrophobic components near the hydrophobic polymer surface so as to exclude the water along a favourable thermodynamic gradient. This change in 3-D

structure can subsequently expose other hidden areas of the proteins to the aqueous environment and lead to hydrolysis (the breaking of bonds due to reaction with water) or provide ligands for receptors on the cellular elements (platelets and leukocytes) that will enable adhesions and subsequent cellular activation. The primary proteins of interest to prevent adsorption include fibrinogen and complement protein C3. Adsorption of fibrinogen is associated with platelet consumption [6]. C3 adsorption and subsequent autohydrolysis initiates the alternative complement system leads to the production of C5, which has been shown to significantly influence the homing of leukocytes to the intestine and lung tissues and promote the systemic inflammatory response syndrome and its deleterious effects [7].

Coagulation and inflammatory systems are interrelated such that activation of one will often result in cross-over activation of the other. Thus, it should be evident that the first step in mitigation of the deleterious effects of ECMO should be on the creation of biologically inert surfaces or masking of the surfaces from the coagulation and inflammatory proteins within the plasma. However, despite over 50 years of research, a perfectly biocompatible surface has not yet been created.

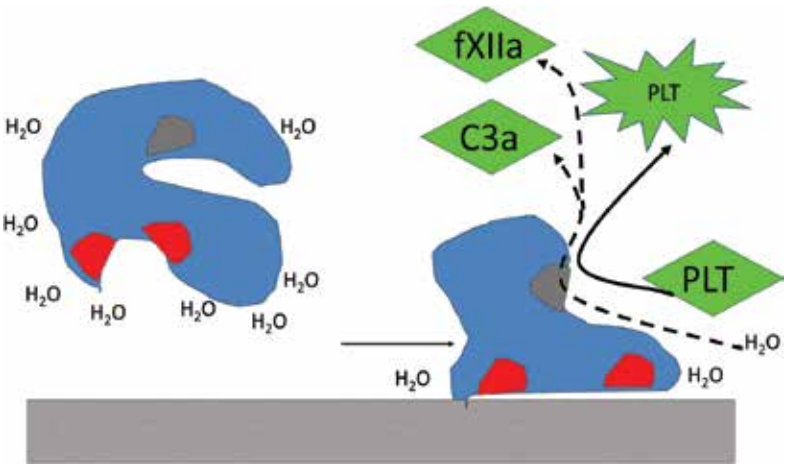

Figure 2. Representative image of the conformational change made by a protein in contact with a hydrophobic surface. The red zones are hydrophobic and are hidden from the surrounding aqueous solution until the protein comes near the hydrophobic surface. Upon approach, the thermodynamics favors a conformational change to exclude the water molecules and allow the hydrophobic patches to contact the hydrophobic surface, thereby inducing a conformation change that uncovers an active area of the protein (cross-hatched area). This area can react with the aqueous medium to initiate autohydrolysis and create the active forms of compliment or coagulation proteins (through intermediate steps such as bradykinins) or can provide the signal to activate platelets.

4. Surface coatings

In an effort to control the adsorption of plasma proteins to the ECMO circuit, the concept of pre-coating or surface modification has been in existence since nearly the beginning of

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extracorporeal circuit utilization. This section will examine the various coating technologies and their application to extracorporeal Technology. A table outlining the key points of each of the coatings discussed is provided (**Table 1**). One overarching theme from the research studies involving these and other novel coatings is that the strongest evidence for their implementation comes from in vitro short-term blood studies, and nearly all clinical studies have been performed in cardiopulmonary bypass settings. The clinical evidence for efficacy or changes in patient outcomes is often conflicting and most clinical studies have Class IIb recommendations to support them, and blinded, randomized trials are almost impossible to perform [8]. However, there is no evidence that coated circuits do any harm and their utility may be in those unusual clinical cases where protocol deviation is necessary or other factors that are not controlled may be influenced. These clinical scenarios are rare, thus creating challenges for adequate sample size in studies including only these unusual patients.

Manufacturer	Coating name	Coating technology
Medtronic	Carmeda	Covalently bonded heparin (anticoagulant)
	Trilium	Covalently bonded heparin (anticoagulant), sulfate and sulfonate groups (negative charge), polyethylene oxide (hydrophillic)
Maquet	Bioline	Covalently bonded recombinant human albumin (passivation) and heparin (anticoagulant)
	Safeline	Covalently bonded synthetic albumin (passivation)
	Softline	Amphyphilic polymer coating (reduced surface tension)
Terumo	X-Coating	Poly 2-methoxylacrylate (reduced cellular and protein adhesion)
Sorin	Smart-X	Tribloc Copolymer (Polycaprolactone-Polydimethylsiloxane-Polycaprolactone) integrated into plastic (reduced cellular and protein adhesion)
	P.h.i.s.i.o.	Phosphorylcholine (reduced cellular and protein adhesion)

Table 1. Listing of manufacturers and their coating products.

4.1. Albumin

One of the first proteins to be used for pre-coating blood-contacting surfaces was albumin [9]. Prior to the introduction of ionic or covalently bound surfaces, albumin was added to the circuit prime of adult circuits to increase the oncotic pressure of the priming solutions. In pediatrics, it was often used as a precursor to the addition of packed red cells. The purpose of the albumin pre-coat was to provide a base layer of protein that would delay or mitigate the biological response to the heavily hydrophobic surfaces [9, 10]. Adsorbed albumin both increases the hydrophilicity of the surface and provides a competitive protein that the fibrinogen must displace. Albumin covalently linked to surfaces (e.g., Safeline® by Maquet) ensures its retention and prevents displacement. Research on this coating technique has demonstrated short-term reductions in the concentration of fibrinogen and platelets on the surface and some evidence that it reduces complement activation [11].

4.2. Heparin

The most widely used anticoagulant in cardiopulmonary bypass and ECMO has been unfractionated heparin (UFH). The use of UFH has contributed significantly to the advancement of cardiac surgery and improved outcomes in these patients and will be discussed in detail in subsequent sections. Because UFH was such a successful systemic anticoagulant, a natural extension would be to immobilize it to a blood-contacting surface to provide local anticoagulant effects and potentially decrease some of the side effects of systemic anticoagulation, particularly in post-operative cardiac surgery patients where surgeons desire blood coagulation at the site of the incision but not in the extracorporeal circuit. Immobilization can be accomplished through covalent linkage to the surface, polymerization on the surface, or ionic interactions with the surface.

End-point covalent linkage of heparin to polymer surfaces was first made commercially available as Carmeda Bioactive Surface™ (Carmeda, Switzerland), available on Medtronic tubing and oxygenators. The process for linkage is relatively straightforward and applicable to a variety of biological compounds. The process begins adding a layer of an amide (NH_3) containing material to the surface. This amide surface is then easily reacted with the end of the polysaccharide chain of heparin. The covalent linkage of heparin has been demonstrated to be reproducible and stable, with the heparin reactivity present several hours after the initial exposure to the blood [12]. Other manufacturers have made similar heparin coatings (e.g., Rheoparin (Medos) and Bioline (Maquet)) using composite covalent and/or cross-linking techniques. The largest challenge with these methods is that the active site of heparin may be involved in the binding area and thus not available for interaction with antithrombin. In addition to covalent linkage, ionic linkage has also been demonstrated, most notably in the Duraflo (Baxter) products. However, the difference between ionic and covalent linkage is the retention of the heparin molecule after blood contact in the covalent bonding versus leaching of the heparin in the ionic linkage [13, 14].

Overall, the use of a heparin coating has been seen as a success in the medical community, and nearly 300 papers on heparin-coated circuits have been published. Most in vitro or animal models demonstrate benefits of heparin coating including reduced soluble thrombin production, platelet binding, and D-dimer production [12, 15–19, 20]. With respect to inflammation, most studies demonstrate reduced inflammatory response, particularly in the interleukins, alternative complement pathway and polymorphonuclear cells, compared to controls and other coating systems [12, 20–25, 26]. Meta-analyses of the benefits of heparin coating have consistently found improvements in transfusion requirements, arrhythmias, ventilator times, and lengths of stay in the hospital or ICUs when using heparin-coated circuits for cardiopulmonary bypass [17, 27, 28, 29]. One important aspect of many of these studies has been that many have focused on short-term impacts of heparin coatings. These studies also indicate that it does no harm to the patient, and therefore it may be worthwhile to utilize this technology in the absence of large studies containing a heterogeneous patient cohort. However, some studies have been published that demonstrate no appreciable systemic benefits to heparin coating during cardiopulmonary bypass [30] or for ECMO beyond 6 hours, for reasons that have never truly been elucidated [19]. Practitioners are cautioned to interpret these studies

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carefully because of their short-term nature and the significant effects of the air-blood interface found during cardiopulmonary bypass (CPB). In a statement which is reflected in the anticoagulation guidelines from the Extracorporeal Life Support Organization, "ECMO patients are highly complex and the additional time on support cannot be ignored as a key factor in their outcomes" [31].

4.3. Polymer surfaces

In addition to the biologic molecules of heparin and albumin, there are several other surfaces that have been developed with the aim of increasing hydrophilicity or surface charge similar to that of the endothelial cells lining mammalian blood vessels. These are typically polymers including phosphorylcholine, poly 2-methoxyethylacrylate, polyethylene oxide, and triblock surface-modifying additives. Each will be discussed in terms of relative chemistry, and studies examining their effectiveness at blunting the coagulation and/or inflammatory response.

4.3.1. Phosphorylcholine (PC)

Phospholipids make up the bulk of the cell membrane in mammalian cells and provide the ability to separate the plasma and cytosolic solutions, both of which are aqueous environments. Phosphorylcholine (PC) is a zwitterionic phospholipid compound with no overall charge that is found on the plasma leaflet of the red cell membrane. This compound has been previously demonstrated to be non-thrombogenic, as opposed to its cytoplasmic counterpart, phosphatidylserine, which has been shown to be pro-thrombogenic [32]. It has been successfully used in stent coating technology, and has also been used to coat PVC and polypropylene and polymethylpentene oxygenators for cardiopulmonary bypass and ECMO uses under the brand name P.h.i.s.i.o. from Sorin. The effects of PC on PVC have been shown to reduce fibrinogen binding and subsequent platelet binding through GPIIb receptors [32]. PC-coated circuits perform similar to heparin-coated circuits [33] in clinical studies with evidence of improved platelet retention and reduced postoperative transfusion requirements, but no effects on overall outcomes [34]. Further, PC coating may increase immune cell (T-Cell) response through an IL-8 mechanism [35].

4.3.2. Polyethylene oxide (PEO)

Polyethylene oxide (PEO) is a water-soluble, non-toxic, and non-immunogenic polymer that has been shown to reduce protein and bacterial adhesion in a variety of surfaces [36]. Its utility in blood-contacting materials was originally designed for increasing the hydrophilicity of the silicone polymers that made up the early membrane oxygenators. Silicone, while relatively biocompatible and an ideal biomaterial for many applications, is very hydrophobic, and increased hydrophobicity leads to increased protein adhesion, particularly fibrinogen adsorption [37]. A challenge with silicone coating is that production of functional groups for attachment is not as easy as with other polymers. However, it is possible with the use of mercury lamps to create radicals and oxidation by O_2 plasmas to create alcohol groups. Alternative preparations begin with incorporating hydromethylsilicone in the polymerization process and the subsequent use of platinum catalysts can create the functional groups for coating attach-

ment. Coating of PEO to the surface of silicone rubber has been demonstrated to increase water contact angles (increased hydrophilicity) and reduce both fibrinogen and albumin adhesion by 90% [36]. These reductions are dependent on a number of factors, including the molecular weight of the PEO and the functional structure of the PEO (single, monofunctional chains or bi-functional, loop structured PEO). Like most coating technologies, this coating is not a pure monolayer and gaps do exist. The use of PEO is commercially available as part of the Trillium package on Medtronic tubing. Studies using the Trillium surface have shown reductions in inflammatory markers and reduced bleeding events [38–40], but also increased stroke rates [38] from cardiopulmonary bypass. Like most CPB studies, these are small, single-center studies with variable sample collection, and no long-term studies have been performed.

4.3.3. Poly 2-methoxyethylacrylate

Poly 2-methoxyethylacrylate (PMEA) is a polymer coating generated on polypropylene and PVC surfaces through plasma charge preparation of a surface. Allowing 2-methoxyacrylate to react with the surface provides a weakly hydrophilic surface that has improved biocompatibility characteristics. PMEA was originally developed for plasma separation devices to permit non-hemolytic dry priming of the devices [41]. However, it was soon realized that this coating provided significant reduction in platelet and leukocyte activation and adhesion, and coagulation and complement activation [42]. Numerous laboratory studies have been undertaken to understand why this particular polymer has such effects, including variations of the polymer to include hydroxyl, phenyl, ethyl, and other groups. In all cases, the PMEA adsorbed fewer proteins and the protein conformation changes differed very little from the native surface [42, 43]. This coating is currently marketed under the SMARTx brand from Sorin. Clinical and in vitro studies using cardiopulmonary bypass circuits with this coating technology (available as the X Coating from Terumo) have had mixed results. Like other coatings, PMEA-coated systems have improved markers of inflammation and some clinical outcomes over non-coated systems [44, 45]. However, several studies have demonstrated increases in ventilator times, chest tube output, and inflammatory markers of PMEA compared to other coatings [39, 46, 47], while others studies found little or no difference between PMEA and heparin-coated surfaces [44, 48].

4.3.4. Surface-modifying additives

Another technique for producing more biocompatible surfaces is the use of surface-modifying additives (SMAs) that can either be blended with the base polymer resins during manufacturing and subsequently rise to the surface, or they can be coated onto a device's blood-contacting surfaces. One such SMA, a polycaprolactone-polysiloxane-polycaprolactone triblock copolymer, has been incorporated into the polyvinylchloride base resin and coated onto a polypropylene membrane [49]. The incorporation into the bulk resin yields significant surface modification and in initial in vitro tests demonstrated large reductions in thrombin and complement generation on SMA surfaces compared to uncoated surfaces. Clinical studies of the SMA coating have provided some evidence for a change in physiologic response, typically increased blood pressure and anti-inflammatory IL-10, reduced platelet and blood

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loss [50–52], and reduced use of inotropes [50, 51, 52]. Interestingly, terminal complement complex and complement protein C3 have been found to be no different in the SMA and control (uncoated) circuits in several studies [50, 53], and there is no difference in the generation of high-intensity transient signals in transcranial Doppler between SMA and non-coated circuits [52].

5. Anticoagulants

The need for systemic anticoagulation has been understood since the earliest extracorporeal circuits were developed in the laboratories in the 1800s. It wasn't until the discovery of the heparin molecule in the early 1900s that safe anticoagulation could be achieved for the purposes of moving and storage of blood outside of the body. As a result, heparin is the most widely used anticoagulant for ECLS owing to its long history, cheap production costs and reversibility with the fish-based enzyme, protamine. In addition to heparin, there are other classes of anticoagulants, including direct thrombin inhibitors. These have been utilized in extracorporeal circuits, particularly when heparin is not recommended to be used, such as patients with a heparin allergy (i.e., heparin-induced thrombocytopenia) or protamine allergy. Each of the anticoagulants will be discussed in terms of their mechanisms of action, cofactors required, dosing for ECMO, and case studies or clinical trials related to their use in ECMO. **Table 2** at the end of this section provides relevant dosing for pediatric and adult patients along with responses to bleeding for each drug.

5.1. Heparins

Heparin is a natural anticoagulant produced by the basal and mast cells in the body. Its discovery in 1916 was instrumental in the progress of blood-contacting devices because it could effectively halt the coagulation process which was a consistent problem for blood-contacting materials at the time. Heparin is a variable length carbohydrate in the glycosaminoglycan family, with molecular weights ranging from 3 to 30kDa. The primary mechanism of action of heparin is its ability to interact with another naturally occurring anticoagulant, antithrombin (AT, discussed below) and increase its ability to bind and inhibit the enzymatic activity of thrombin (Factor IIa) and Factor Xa by over 2,000-fold [54]. Only heparins containing 15 or more saccharide chains are capable of binding and inhibiting thrombin and FXa; heparins with 5–15 saccharide chains can only bind and inhibit FXa. Of note, the heparin/AT complex can only bind to soluble thrombin or FXa due to the large size of the AT molecule. Thrombin or FXa already complexed within an adherent clot cannot be affected by the presence of heparin and will continue their enzymatic processes unimpeded.

Pharmaceutical preparation of heparin is derived from the mucosal tissues of farm animals including pigs and cows, although most current preparations are derived from pigs due an increased incidence of heparin-induced thrombocytopenia (HIT) with bovine-derived heparin [55]. As such, the derivation of heparin from these tissues is unfractionated, containing all the molecular weights. Low molecular weight heparin can be derived through a size fractionation

or chemo-enzymatic process. Heparin can be given intravenously or subcutaneously, and has a relatively short half-life of 60–90 minutes (unfractionated) to 4–5 hours (low molecular weight) [56]. As such, unfractionated heparin (UFH) is typically administered continuously intravenously while low molecular weight heparin (LMWH) is administered once or twice daily subcutaneously.

Drug	Clearance	Dose (mg/kg/hr)		Monitoring		Bleeding
		Child	Adult	Child	Adult	Child & Adult
UFH	Renal	15–28 IU/kg/hr	10–18 IU/kg/hr	aPTT 1.5–2X (<100 sec) ACT 180–220 sec Anti-Xa 0.3-0.6 IU/mL	PTT 40–60 ACT 180–220 sec	Protamine 1.5 mg/100 IU UFH (reversal)
LMWH	Renal	1.2 subcutaneous q 12hrs	1mg/kg subcutaneous q 12hrs	Anti-Xa 0.5–1 IU/mL		Protamine 1.5 mg/100 IU LMWH (partial reversal)
Argatroban	Hepatic	Infusion: 0.045 Adjust 0.06–0.015 Hepatic compromise 0.012 In HIT: 0.006-0.6;	Infusion: 0.12 In HIT: 0.012	PTT 1.5–3X (<100 sec) ACT 160–200	PTT 40–120 ACT 170–200	FVIIa** 30–90 μg/kg
Bivalirudin	Proteolysis: 75% Renal: 25%	Bolus 0.125–0.25 Infusion Primary: 0.125–0.2 Tx UFH: 0.1–0.8	Infusion:0.08–0.2 Adjust 0.03	PTT 50-70 ACT160–200	PTT 40–120 ACT 200–220	
Aspirin	Liver	1–5 mg/kg/d Max 91 mg		TEG MA and α depression TEG AA Inhibition 70%		Platelet Transfusion
Clopidogrel	Liver	0.2 mg/kg/d	1 mg/kg/d	TEG MA and α depression		Platelet Transfusion
Dypyridamole	Liver	1.5 mg/kg/d		TEG MA and α depression TEG ADP net G 4–8		Platelet Transfusion

Note: **Based on <10 case reports.

Table 2. Dosing guides for anticoagulants for mechanical circulatory support.

Heparin is cleared through two mechanisms. Low doses of heparin are rapidly cleared through a reticuloendothelial process, whereas higher doses which saturate these processes are cleared

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through the kidneys in a much slower fashion [57]. Additionally, heparin effects can be rapidly reversed through administration of a reversal agent, protamine sulfate, which is negatively charged and binds with UFH or LMWH to form a stable ionic pair preventing binding to AT3. The ionic complex goes on to be broken down through the reticuloendothelial system.

The ease of production, rapid onset, relatively linear dosing and ease of reversal has made heparin the standard anticoagulant for cardiopulmonary bypass and subsequently ECMO for the past 50+ years. For cardiopulmonary bypass, a loading dose of 300–350 units/kg is administered, which results in an activated clotting time >400 seconds (see ACT below), and the standard perfusion target of ACT>400 sec for the duration of surgery is easily met with additional bolus dosing as necessary. For ECMO, loading doses of 30–100 units/kg have been used for initiation and then a continuous infusion between 10 and 30units/kg/hr is administered according to a specified coagulation test target protocol [58].

5.1.1. Heparin-induced thrombocytopenia

In addition to binding to AT to mediate its anticoagulant effect, heparin can also interact with platelet factor 4 (PF4) to form very large (>670kDa), stable complexes. These complexes are more common with UFH than LMWH and can trigger pre-existing PF4/heparin-intolerant B cells [59]. The chances of a B cell reaction leading to proliferation and antibody production may increase in some patients with repeated exposure to exogenous UFH, leading to a condition called heparin-induced thrombocytopenia (HIT). HIT is characterized by a sudden and severe drop in platelet count, diffuse thromboses resulting in petechiae, and subsequent increases in risk for stroke, pulmonary embolism, or myocardial infarction. HIT occurs in approximately 2.5% of the general population, with higher incidences in patients with repeated heparin exposure. HIT is formally diagnosed through either an immunoassay to identify antibodies against the heparin-platelet factor 4 complex or the gold standard functional assays that measure the platelet activating capacity of this complex [55]. Patients who are found to be HIT positive can no longer receive heparin without serious risk for stroke or sudden death. Alternative anticoagulants are typically used (see direct thrombin inhibitors below). High dose IV gamma globulins or plasmapheresis can also be employed to reduce the presence of the heparin antibodies and mitigate the effects of HIT [60, 61].

5.1.2. Antithrombin

Antithrombin (AT) is a 58 kDa serine protease inhibitor produced by the liver. Because a majority of the coagulation cascade proteins are themselves serine proteases, AT can target many of them; including kallikrein, plasmin, FXIIa, FXIa, FXa, FIXa, FVIIa, and FIIa. In the presence of heparin, AT activity against FIIa, FIXa, and Fxa is increased. AT inhibition of FIIa is accelerated 2,000–4,000, and only 500–1,000-fold against FXa [62]. With sufficient calcium and heparin, AT inhibition of FIXa can increase over 1 million fold [63].

In patients on heparin therapy with no known genetic deficiency in AT production, the apparent heparin resistance (i.e., increasing heparin dosing with no effect) can often be attributed to low AT levels in the plasma. AT levels also change developmentally, with

approximately half as much AT at birth that rises towards adult levels around 6 months of age [64]. The drop in AT levels can occur for a variety of reasons in the setting of ECMO. First and foremost, for pediatric patients, there is a high likelihood of factor dilution when connecting to the ECMO circuit (average ECMO circuits range from 270 −700 mL and are primed with packed red cells and/or crystalloid). Second, the activation of the coagulation cascade as a result of the additional foreign surface, inflammatory response to the hypoxic state, and the surgical procedure can cause significant amounts of AT to complex with the activated blood elements in equimolar and extremely stable complexes [65] as well as to complex with any immobilized heparin on the surface of the ECMO circuit [66].

Administration of AT on ECMO is routinely performed, and there are reports of patients who have received only AT as their sole anticoagulant [58]. There are relatively few studies that have examined the effects of AT administration on ECMO patients. Most are severely underpowered, lacking sufficient events for efficacy analysis. However, those that are published do indicate that AT increases heparin levels in the blood and reduces the heparin dose in ECMO patients, and that AT can be safely administered to patients on ECMO without increased risk of bleeding [67–69, 70]. There have been reports of increased failure rates of ECMO circuits in patients receiving AT, but this may be due primarily to sub-therapeutic heparin effect (for which AT is being given) [68]. However, it is the lack of true efficacy (reduced bleeding or thrombosis events) in these studies that continues to raise questions about the utility of this costly therapy in ECMO patients.

5.2. Direct thrombin inhibitors

In the setting of conditions that limit the use of heparin, such as HIT, direct thrombin inhibitors (DTIs) can be used. These drugs specifically target FIIa and have the advantage that they do not require cofactors like AT to function; nor are they neutralized by PF4 like heparin [71]. Furthermore, they are small molecules and can bind to FIIa that is currently enmeshed in a clot as well as FIIa in the plasma (i.e., soluble and insoluble thrombin). The primary disadvantage to their use in ECMO is the relative lack of experience using these drugs along with the differing clearance mechanisms that may make one DTI preferable to another in the setting of multiple organ failure. There is also no antidote, unlike heparin which can be specifically reversed with protamine. Each of the various DTIs that have been used with ECMO will be discussed, along with specific mechanisms of action and dosing that have been documented in ECMO patients.

5.2.1. Argatroban

Argatroban is a small site-directed DTI first discovered in 1981 and became the first oral DTI available in the market for patients with HIT. The primary interaction is a reversible binding between a hydrophobic portion of the argatroban molecule and the hydrophobic pockets near the active site of the thrombin molecule [72]. Although primarily given intravenously, the main advantage that argatroban has over other DTIs like Bivalirudin is that it is a very small molecule (~500 Da). The half-life of argatroban is ~50 minutes, and it is cleared solely through hepatic mechanisms, making it suitable for use in patients with acute renal failure. Anticoagulation

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monitoring is typically performed through the activated thromboplastin time (aPTT) test because argatroban can lead to false increases in the international normalised ratio (INR) level [71].

Of all the DTIs, argatroban has seen the greatest clinical use in the settings of cardiopulmonary bypass and ECMO for patients with confirmed or suspected HIT [71, 73, 74]. Dosing for argatroban in these therapies ranges from 0.1–250 μg/kg loading dose depending on the setting (CPB vs PCI), patient age (neonates may require a smaller bolus because their thrombin generation is lower than adults [75]), and physician experience, or 10–30 μg in an extracorporeal circuit. The loading dose is followed by 0.1–24 μg/kg/min continuous infusion [71, 74]. Target aPTTs are typically 1.5–2 times baseline or 45–65 seconds [71] or activated clotting times (ACTs) of 250–300 seconds [74]. Patients receiving argatroban during ECMO have experienced similar thrombotic complications as those on traditional heparin therapy (including circuit thrombosis, disseminated intravascular coagulation, and diffuse thrombotic disease) [71]. Although the case series are small, rates of complications hover around 25%, which is lower than the combined bleeding and thrombotic complications reported by ELSO for their registry (~40–50%). Larger, randomized control studies should be performed to determine whether the use of argatroban is associated with significantly reduced complications in the extracorporeal setting or if these small case series are simply a result of higher anticoagulation vigilance in the setting of a higher risk patient.

5.2.2. Bivalirudin

Bivalirudin is a synthetic version of the leech-derived anticoagulant hirudin. It is a slightly larger molecule than argatroban (~2,000 Da) requiring that it be delivered intravenously. Bivalirudin has two thrombin binding sites, one in the catalytic pocket of thrombin and the other on fibrin-binding exosite. After binding to thrombin, a portion is cleaved off that will restore some thrombin activity. The remainder of the drug is cleared through renal mechanisms, making it suitable for use in patients with acute liver dysfunction where argatroban may be unsuitable [72]. Because of the partial enzymatic cleavage, the half-life of bivalirudin is shorter (~30 min), which makes it attractive for short-term procedures like percutaneous coronary intervention and cardiopulmonary bypass [71]. However, the challenge with using bivalirudin is that the drug is degraded with stasis of blood flow and therefore may cause unexpected clotting in the reservoir of the cardiopulmonary bypass machine or in any area of stasis in the ECMO circuit. Recommendations have been made by experts that left heart volume should be reduced as much as possible to prevent the occurrence of a "cardiac reservoir" and possible thrombosis [76]. For other extracorporeal therapies where there is no reservoir (ECMO or VADs), bivalirudin may be preferable over argatroban for patients who are in liver failure. Dosing for bivalirudin has been reported at 0.15–0.5 mg/kg bolus followed by 0.12–0.25 mg/kg/hr. The target ACTs and aPTTs are similar to that of argatroban at >200 seconds and 1.5–2 times baseline, respectively [71].

In the setting of ECMO, small case reports and single-center retrospective reviews have been generated describing the use of bivalirudin over heparin [77–79, 80]. One such report from Ranucci et al. [80] described the reduced use of platelet and plasma donor products in patients

receiving bivalirudin for postcardiotomy ECMO compared to patients receiving UFH. Another small case-controlled study from Pieri et al. [81] demonstrated less variation in aPTT but no difference in bleeding and thrombotic complications versus UFH. The consensus from these reports has primarily been that bivalirudin use in the extracorporeal setting is feasible provided the patients are closely monitored.

5.3. Factor Xa inhibitors

Another alternative to heparins is to use Factor Xa Inhibitors, which can either bind directly to FXa to prevent interaction or can catalyze inhibitory reactions via AT3 (similar to the action of UFH). The primary advantage to these drugs is that they can inhibit free and platelet-bound FXa and can be dosed infrequently due to long half-lives, and can be administered with intermittent subcutaneous injections. Several oral FXa inhibitors have been approved by the FDA for treatment of venous thromboembolism (VTE) and atrial fibrillation (AF). These

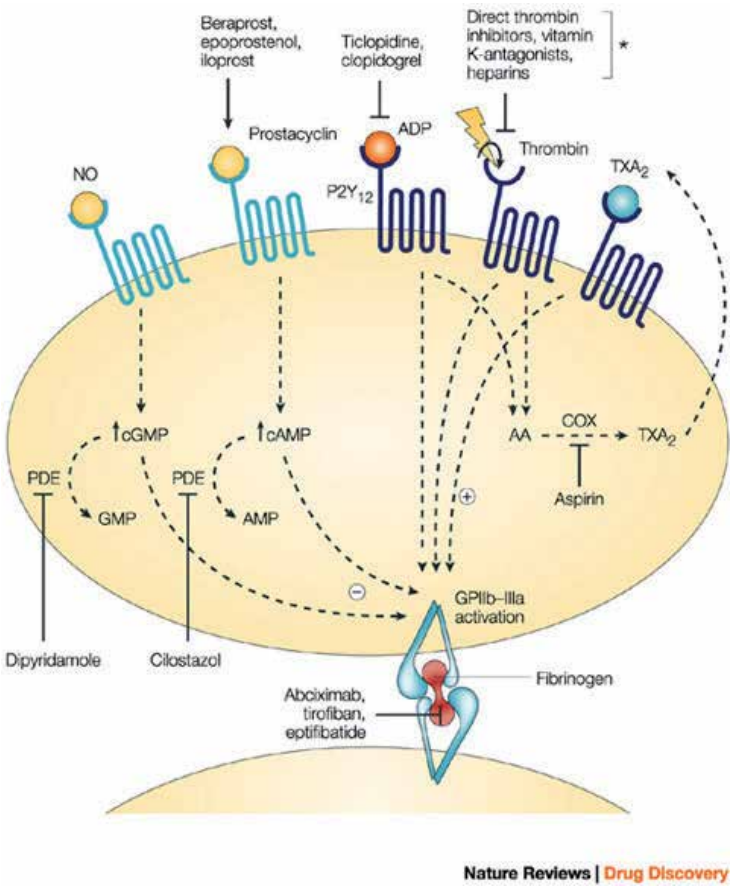

Figure 3. Regulatory pathways of platelets including their stimuli and pharmacologic inhibitors. Reprinted with permission from Macmillian Publishers Lt: Nature Reviews Drug Discovery, Copyright 2003 [85].

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include rivaroxaban, dabigatran, edoxiban, and apixaban. Dosing is typically once per day, and monitoring is performed performed through an anti-FXa assay or through aPTT [82]. There are no data currently on the use of these agents in the acute care setting, but it may become a possible choice for patients on long-term ECMO who are extubated and awaiting lung transplantation. A major caveat for this drug is that it has no antidote and in the case of worsening renal function, the drug will not be cleared efficiently and dialysis does not appear to alter plasma levels [83]. However, a recent study on a double-blind placebo trial of a general FXa-antidote (andexanet) is promising [84].

5.4. Anti-platelet agents

Platelet activation and deposition occur rapidly in the setting of extracorporeal circulation and have been a primary focus of coating technologies developed for extracorporeal therapies (see above). The deposition of fibrinogen to the artificial surfaces provides ample binding and activation signals to the platelet through their GIIb/IIIa receptors [85, 86]. Further, the altered shear stress environments are also known to activate platelets [87, 88] to form aggregates with other cells, including monocytes and other platelets via von Willebrand factor (vWF) and p-selectin mechanisms under inflammatory conditions related to mechanical circulatory support devices [89, 90]. Pharmacologic intervention into platelet activation and adhesion has only been recently explored in the laboratory and a few small case studies, but most studies show a potentially beneficial effect. Anti-platelet agents (**Figure 3**) have a long history in other forms of mechanical circulatory support such as the implantable ventricular assist devices [91–93], stents [94], and mechanical heart valves [95]. Anti-platelet therapy incorporation into ECMO anti-coagulation treatment has been successfully applied in La Pitie Hospital and reported previously [96, 97].

5.4.1. Nitric oxide

Nitric oxide (NO) is a natural inhibitor of platelet activity through cGMP mechanisms similar to those of dipyridamole [85]. Recently, efforts have begun to be explored in the laboratory to incorporate NO-releasing polymers in the ECMO circuit [98] and to provide NO in the sweep gas [99, 100, 101]. The reasoning for its use in the setting of extracorporeal life support is that the half-life is so short (2–6 sec) that only a local effect occurs [102]. This is the goal of the coated circuits where the anticoagulation activity is sequestered to the artificial surfaces and does not act systemically. In vitro and animal studies of the use of NO on ECMO circuits have demonstrated a significant improvement in platelet functionality and retention of platelets with minimal generation of the undesirable side effects of nitric oxide infusion, specifically methemoglobin [100, 101, 102]. The primary downsides to this type of therapy are the lack of current devices, which can accurately dose nitric oxide through the membrane, and the high cost of nitric oxide therapy. Materials that release nitric oxide have a finite lifespan (several hours up to 1 week) and regeneration of the NO production has yet to be realized. Future developments as companies and other research enter this space may provide unique solutions to these problems, making NO a viable adjunct to the anticoagulation regimen.

5.4.2. Clopidogrel

Clopidogrel is a specific inhibitor of ADP receptors on platelets that is often used as part of dual antiplatelet therapies in patients undergoing percutaneous coronary intervention (PCI) for stent placement or balloon angioplasty. It has been used in ventricular assist device patients in an effort to reduce pump thrombosis [103, 104]. Small subsets of patients receiving clopidogrel in addition to other anticoagulants while on ECMO have also been reported [105, 106]. Outcomes from patients receiving clopidogrel on mechanical circulatory support devices are similar to those receiving traditional anticoagulants alone. Transfusion requirements tend to be increased, with slightly more units of red cells and/or FFP required, but no ultimate effect on outcome has been noted.

5.4.3. Aspirin

Aspirin (acetylsalicylic acid) is an irreversible cyclooxygenase (COX) inhibitor in platelets that affects the COX-1 variant in a greater fashion than the COX-2 variant [107]. This effectively blocks the production of thromboxane from the platelet, which is a potent stimulator of surrounding platelets. Aspirin therapy has been recommended alone or as an adjunctive therapy in a variety of cardiovascular diseases, such as the prevention of primary or secondary myocardial infarctions and strokes [108–110], management of stents and mechanical valves [111–113], and the prevention of embolic phenomenon on ventricular assist devices [91, 93, 103, 114, 115]. The use of aspirin on ECMO technology has been reported in some small case series [116] and as part of the regular treatment of ECMO at La Pitie [96]. Because it is an irreversible inhibitor, there has always been concern for bleeding events post-ECMO until new platelets are produced by the body in the absence of aspirin. Interestingly, in contrast to the other anti-platelet agents mentioned here, the use of aspirin has been shown to reduce the need for transfusions [116]. In the same study, the use of aspirin was shown to dramatically reduce platelet binding to the surfaces of oxygenators through scanning electron microscopy imaging. Given the limited impairment of aspirin on the platelet systems (decreased thromboxane production to limit activation) and the apparent lack of adverse events in these small studies, and its routine use in ventricular assist devices, a multi-center trial of aspirin as adjunctive therapy in the ECMO setting may be warranted.

5.4.4. Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor that prevents the breakdown of cAMP, which is a key component in the prevention of signal transduction in platelet activation [117]. Like aspirin therapy, it has been extensively used in the realms of synthetic vascular graft, stent and valve therapies [111, 118] as well as ventricular assist devices, particularly in the development of the Berlin Heart protocols [91, 104, 114, 119]. The use of dipyridamole in the setting of ECMO has been reported in single-center studies aimed at demonstrating safety [96]. Interestingly, there have also been attempts at producing dipyridamole conjugated surfaces for applications in synthetic grafts [120]. The chemistry is quite similar to what would be required for use in ECMO devices and could be readily translated.

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5.4.5. GPIIb/IIIa inhibitors

GPIIb/IIIa inhibitors are drugs specifically targeted to the GPIIb/IIIa receptor on the surface of platelets permitting their adhesion to fibrinogen. These types of drugs are commonly used in the settings of percutaneous coronary interventions (PCI), but almost never used in the setting of extracorporeal mechanical circulatory assist, particularly ECMO. There is one small case report (N=18) on the rescue of PCI patients in cardiogenic shock using VA-ECMO [105]. The authors reported successful outcomes for most of the patients (65%) with a small subset (5 patients) who received GPIIb/IIIa inhibitors. Compared to the other antiplatelet agents used, those with the GPIIb/IIIa treatment had much higher transfusion requirements than those receiving only heparin. The authors attributed this to a consumptive coagulopathy that was set up by the use of the additional agents; although no increase in mortality was seen.

5.5. Antifibrinolytics

Cannula and surgical site bleeding are common complications in ECMO patients, particularly in cardiac ECMO where the patient may have an open chest or undergone significant vascular repair. According to the ELSO registry 7–21% of patients will experience one of these complications during their ECMO run [1]. The numbers vary based on patient age and reason for ECMO. Often this bleeding can occur in the face of reasonable anticoagulation parameters or even when anticoagulants are withheld. The reasons for this can be attributed to one or a combination of issues including low platelet counts, deranged hemostasis associated with consumptive coagulopathy where the circuit may be consuming most of the patient's coagulation factors and increasing the risk for bleeding, and fibrinolysis. Patients who are at risk for increased bleeding (e.g., planned surgical procedures) while on ECMO have often been treated with an antifibrinolytic drugs (e.g., aminocaproic acid or tranexemic acid) in an effort to reduce the chances for existing clots to break down and keep surgical sites intact. Evidence from the literature in these patients suggests that the use of antifibrinolytics decreases surgical site bleeding, but does not impact intracranial hemorrhage [121, 122]. There is some concern that using antifibrinolytics may decrease circuit lifespan because as thrombus is deposited on the interior surfaces, it cannot be remodelled in a normal fashion and continues to build to the point of requiring a component change. Some studies have found the use of antifibrinolytic drugs increases the change-out rates of ECMO circuits by approximately three-fold, while others have found no relationship [123]. Administration is typically done as a loading dose (e.g., 100 mg/kg aminocaproic acid) followed by 72 hours of continuous infusion at a lower dose (e.g., 25–30 mg/kg aminocaproic acid) [121, 122]. Additional vigilance should be provided to the patient and ECMO circuit during a period of treatment to be aware of additional thrombosis and address it appropriately.

6. Coagulation testing

As a consequence of the use of systemic anticoagulants, there exists a need for laboratory testing of the blood to determine whether acceptable levels of anticoagulation have been

reached. There have been two tests specifically developed to address the needs of coagulation testing as a result of heparin, the Heparin Activity Assay and the Activated Clotting Time, while others that have been in existence for the monitoring of hereditary bleeding disorders, pro-thrombin time and activated partial thromboplastin time, have been accepted for use in these instances. Another, relatively recent class of testing, thromboelastography or thromboelastometry, has been developed to provide a more global view of hemostasis with the purpose of identifying specific points where deficiencies might exist and interventions could be possible. Each of the tests will be discussed in terms of technical advantages and disadvantages as well as application to ECMO coagulation monitoring. **Table 3** at the end of this section provides an overview of the tests discussed.

6.1. Activated clotting time (ACT)

The ACT is a point-of-care whole blood test that was developed during the early adoption of cardiopulmonary bypass because perfusionists needed a way to rapidly determine in the OR setting whether a sufficient dose of heparin had been given to ensure that bypass could be conducted safely. The stimulating agents of the ACT (Celite or kaolin, silica, calcium and phospholipid) are in high concentration and designed to elicit a strong coagulation response and induce clot formation within 800 seconds even at high heparin concentration. Thus, the ACT was developed as essentially a binary coagulation test in the face of heparin and its linearity is primarily associated with higher concentrations of heparin that are seen during cardiopulmonary bypass (350–400 IU/kg). From the mid-1970s to the mid-2000s, most ECMO centers have used the traditional ACT as their gold standard test for determining heparin administration. However, after 2000, another form of the ACT became available. The low-range ACT (ACT-LR), which was designed for use in PCI settings where lower heparin dosing was the norm (150–200 IU/kg) and where the traditional ACT was not reproducibly linear, has become frequently used by ECMO practitioners. In fact, over 90% of hospitals use the ACT (traditional or ACT-LR) as part of their routine coagulation testing on ECMO [58]. Furthermore, a number of manufacturers began to alter their test procedures to reduce the size of the machine and the amount of blood required to run the test. Some ACT machines are based on mechanical methods of larger volumes (2mL) of blood to detect clot formation in real-time, while others use very small volumes (100 μL) in an optical-mechanical system in accelerated time, and still others use electrochemical resistance changes in even smaller volumes (10 μL) in real-time to determine clot formation. Despite these differences, clinicians have traditionally clung to relatively narrow ranges (180–220 seconds) to determine heparin doses [58]; with different machines having ACTs which may not correlate with each other. This has created significant confusion in the ECMO community and spurred several practitioners to look for alternatives to this long-standing tradition of ACT-based heparin management on ECMO.

6.2. Activated partial thromboplastin time (aPTT)

The aPTT is a well-established, validated laboratory test for the monitoring of a patient's coagulation status that is used for all patients where bleeding is a concern, not just those on ECMO. It is a laboratory-based test of plasma, thus eliminating the effects of platelets and other

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cellular elements from the test process, and is performed on citrated blood which removes the cofactor calcium from the coagulation cascade during collection. This effectively arrests the clotting cascade at the levels of factor IX and X and below, preventing further progression through the common pathway until exogenous calcium is added. Similar to the ACT, the initiating agent is silica, which represents blood activation by a foreign substance, or the intrinsic pathway. However, the amounts of silica and phospholipids and the lack of other exogenous factors make the aPTT reagents a milder pro-coagulant and particularly useful for low-dose heparin monitoring. Recently, the aPTT has begun to find favor amongst clinicians for monitoring heparin therapy on ECMO because it has a better correlation to the heparin doses in adults [124–127], and is now typically measured on the modern ECMO patient [31]. The trend in lower heparin dosing and use of the aPTT have been shown to reduce patient bleeding events, and thereby decrease mortality [126]. aPTT goals for most patients are 1.5–2.5 times age-normal values., which is important for the neonatal patient who will have prolonged aPTT times due to the nature of the development of their coagulation system [64, 75].

6.3. Thromboelastography

Thromboelastography (or thrombelastometry) is a real-time image of the coagulation of whole blood in the presence of a stimulating agent (typically kaolin and calcium). Two main manufacturers have abbreviated their tests as TEG and ROTEM, respectively. The advantages of this test are that it provides several pieces of information related to different aspects of the coagulation cascade (**Figure 4**), instead of just a single endpoint of "thrombus formed" that is found in the PT/INR, ACT, and aPTT tests. Addition of the enzyme heparinase to the test

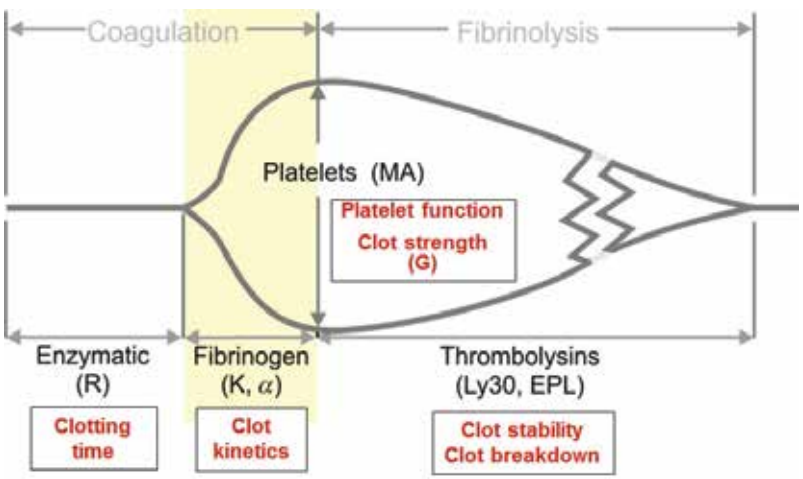

Figure 4. Overview of the TEG tracing. The initial phase of the curve (R time) represents the time from initiation to the beginning of clot formation via the enzymatic activation of coagulation factors through thrombin. The parameters K and α represent the clot kinetics as fibrinogen cross-links begin to form. The MA is the ultimate clot strength and is composed of 80% platelet concentration and function plus 20% fibrinogen concentration and function. The fibrinolysis cascade is represented by the Ly30 and EPL parameters. TEG® Hemostasis Analyzer tracing images are used by permission of Haemonetics Corporation. TEG® and Thromboelastograph® are registered trademarks of Haemonetics Corporation in the US, other countries, or both.

sample can also give a clinician a glimpse of the patients' underlying hemostasis independent of the presence of heparin anticoagulation, and reveal a coagulopathy that may be masked by the presence of being on an anticoagulant. The use of heparinase may also highlight that there is some underlying liver dysfunction in the presence of little or no heparin through the release of so-called heparanoids, which are small heparin-like molecules like chondroitin sulfate that may affect the TEG test and show an altered curve in the presence of heparinase [128–131] Thromboelastography has been used by several authors to manage anticoagulation in ECMO patients [58, 132–138]. The primary finding from these studies is that thromboelastography detects platelet dysfunction and can help guide specific factor therapy. Only one study showed that the thromboelastography results could actually predict bleeding [133]. The ultimate utility of the test is to provide additional insight into the underlying coagulation cascade, and pinpoint areas of concern when used in conjunction with the other coagulation tests [139, 140].

6.4. Prothrombin time (PT)

The prothrombin time is a laboratory test to assay the formation of a clot from the addition of tissue factor, phospholipids, and calcium to patient plasma. The key difference between the PT and the aPTT is the activating agent being tissue factor, which is believed to activate the clotting cascade through the extrinsic pathway associated with cellular or tissue injury. Although the traditional description of the clotting cascade being a waterfall cascade divided into the separate intrinsic and extrinsic pathways that converge at the common pathway is no longer technically valid, it is conceptually useful for teaching and some interpretation of coagulation tests [141]. The PT test is very sensitive to particular reagents used because the source of tissue factor and phospholipids was extraction from brain and other organs. As such, it is necessary to normalize patient results in the face of changing lot numbers or manufacturers by creating comparative assays on normal patients with no known liver dysfunction or oral anticoagulant use (e.g., warfarin). The World Health Organization (WHO) provides an international reference preparation of thromboplastin for calibration to create the international sensitivity index (ISI) for a given preparation, and this is what is currently used in most facilities [142]. For patients receiving heparin, the PT/INR is useful for determining the effects of disease on the liver-independent of lower doses of heparin. Patients who are septic typically exhibit an elevated INR due to derangement of the clotting cascade from multiple areas associated with sepsis and/or liver dysfunction [143]. Thus, the goal INR for a patient on ECMO receiving heparin therapy should be less than 1.5. For other anticoagulants, such the vitamin K antagonists (e.g., warfarin), DTIs, or the newer oral Factor Xa inhibitors, the PT/INR would be expected to be in the range of 2–3 or higher [144].

6.5. Anti-Xa assay

The anti-Xa assay is a chromogenic laboratory assay for determining the effective heparin concentration in patient plasma. It is typically conducted by combining patient plasma (containing UFH or LMWH) with an exogenous amount of factor Xa followed by a chromogenic reaction for unbound factor Xa. Thus, more the color change, the less the heparin/AT complex interacted with factor Xa, and therefore the lower the drug level. The test is highly

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sensitive to the relationship between heparin and AT; meaning that even with high levels of UFH or LMWH, an AT deficiency will have more unbound factor Xa and read as a low heparin level. Most importantly, this test does not measure thrombosis generation or the impact of heparin (UFH or LMWH) or oral Xa inhibitors on the ultimate generation of thrombin [145]. While the test is valuable in helping clinicians achieve stable heparin drug levels and eliminate inconsistency in the aPTT testing [146], patients on ECMO may have a complex underlying derangement in the balance of their clotting factors. It is important to keep in mind that the coagulation system is a series of enzymatic reactions, and having more substrate should naturally require more inhibitor to control the balance. For example, an increased presence of fibrinogen (i.e., hyperfibrinogenemia >500 mg/dL) or thrombin may tip the coagulation cascade towards pro-thrombotic requiring additional anti-Xa levels (i.e., more heparin) to modulate hemostasis. The expected range of anti-Xa levels on UFH therapy (0.3–0.8 IU/mL), however, should be accompanied by further coagulation testing to determine the actual effect. Xa levels of 0.3–0.8 IU/mL *normally* correlate with an aPTT of 90–110 seconds [147]. Because the aPTT is dependent upon the reagents used, individual ranges must be established at each institution in accordance with the College of American Pathologists' recommendations [148]. Even within the same institution, individual patients on ECMO may have variations in their underlying coagulation system or treatment that impacts the correlations between heparin levels and their coagulation tests [126].

6.6. Anti-thrombin (AT)

The AT assay can be performed in a quantitative (immunologic) or qualitative (functional) methodology, with the latter being preferred in most clinical labs because it can be done in a simple chromogenic assay similar to the methodology for anti-Xa testing. In the qualitative chromogenic assay, plasma is incubated with an excess amount of heparin in the presence of FIIa (thrombin) followed by a chromogen for unbound FIIa. The values are reported as a percentage of standard normal adult plasma (100%). Standard cut-off values for AT replacement while on heparin therapy are typically ≥ 60%. Replacement can be accomplished through the use of fresh frozen plasma, which can raise AT levels approximately 20% for every 20ml/kg given. Alternatively, there are pharmacologic interventions using either pooled human donor AT or a recombinant AT. Routine testing to drive the administration of AT on ECMO has been performed at a number of centers and is gaining popularity despite a paucity of safety and efficacy data [58].

6.7. D-dimer

The D-dimer protein is the cleaved product of the fibrinolysis process. The D-dimer test is commercially available as an immunologic test for the specific D domain on cross-linked fibrin, although available kits may not test for the exact same epitope. As such, the presence of D-dimers in the blood indicates the formation of thrombin and subsequent conversion of fibrinogen to fibrin and its polymerization to form a clot has previously occurred and is in the process of resolving. D-dimer levels are typically elevated in patients who are experiencing DIC because of sepsis, DVTs, pulmonary embolism, or other thrombotic disorders [149]. In the

setting of ECMO, D-dimer may be a useful surrogate for the presence of thrombus in the interior of the oxygenator and signal the need for circuit change due to consumptive coagulopathy [150, 151].

	ACT++	**ACT-LR**	**aPTT**	**PT**	**TEG**	**Anti-Xa**	**AT**	**D-dimer**
Anticoagulant to be monitored	Moderate-high heparin dose (1-6 IU/mL)	Low-moderate heparin dose (0-2.5 IU/mL)	Low heparin dose (0–1.5 IU/mL), DTIs	Vitamin K inhibitors DTIs Anti-Xa agents	Low heparin dose (0–1.5 IU/mL) DTIs Anti-platelet agents	UFH, LMWH., oral anti-Xa drugs	Substrate availability for UFH and LMWH	Fibrinolysis end products
Used in	CPB	ECMO	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD	ECMO & VAD
Test kit	silica, kaolin, phospholipid	Lower conc. silica, kaolin, phospholipid	Glass, kaolin, phospholipid	Tissue factor, calcium	Kaolin and Calcium; Optional heparinase and platelet agonists for platelet mapping	Excess FXa Colorimetric Assay	Chromo-genic substrate	Latex Agglutination
Blood components Tested	Whole blood	Whole Blood	Citrated plasma	Citrated Plasma	Citrated whole blood	Citrated plasma	Citrated Plasma	Citrated Plasma
End point	Clot detection	Clot Detection	Thrombus detection	Thrombus detection	Clot Detection and breakdown	Bound FXa	Available AT	Available Fibrin split products

The tests range in sensitivity to hemostatic factors from left (least sensitive) to right (most sensitive) Note that only the ACT+, ACT-LR, aPTT, PT, and TEG measure coagulation as an endpoint.

Table 3. Table of the laboratory tests used for monitoring anticoagulation, their intended targets, test details, and endpoints.

7. Conclusion

The history of anticoagulation and biocompatibility is a relatively short, but important part of the development of mechanical circulatory assist devices. The use of surface coatings and

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systemic anticoagulation is at this point in clinical care considered a necessity for the successful application of ECMO in the clinical setting. Although heparin continues to be the primary anticoagulant of choice for patients on mechanical circulatory support, particularly ECMO, the continued use of direct thrombin inhibitors may signal an end to the heparin era. The philosophy adopted by the authors here is that it is important to start with a normal underlying coagulation and inflammatory system prior to the introduction of systemic drugs designed to alter the normal set point of this complex biological system. Furthermore, patients with altered hemostatic systems may require "reset" or adjusted laboratory parameters in order to achieve hemostasis. Many clinicians have often utilized plasmapheresis or plasma exchange to accomplish this, although the use of these techniques expressly for the purpose of resetting the hemostatic system in the ECMO setting is controversial and has not been adequately studied or validated in a multi-center clinical trial. At best, it is considered to be a reasonably safe adjuvant therapy to ECMO. Furthermore, the lack of a sufficient single coagulation test to accurately assess the hemostatic status of an ECMO patient has resulted in the utilization of a host of tests with the hopes that they agree and that we have achieved a safe, stable anticoagulation profile. However, future efforts may obviate the need for a systemic anticoagulant by providing a surface or material that is truly biologically inert.

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Cannulation Options

Chapter 4

ECMO Cannulation Techniques

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Additional information is available at the end of the chapter

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Abstract

An extracorporeal membrane oxygenation (ECMO) circuit consists of a pump and a membrane oxygenator. This circuit can interface with the human body in a variety of cannulation strategies to provide different forms and levels of support. These various support techniques can be divided into two broad categories: those designed to support the body's respiratory functions (lungs) and those designed to support the body's blood circulation (heart). In this chapter we discuss various cannulation techniques used.

Keywords: ECMO, VV ECMO, VA ECMO, arterial, venous

1. Introduction

We will briefly describe the types of extracorporeal membrane oxygenation (ECMO) support and cannulation options in two sections. In Section 3, we describe the techniques.

2. ECMO for respiratory support

Patients with preserved cardiac function but isolated lung dysfunction can be supported using venovenous (VV) ECMO. Classically VV ECMO support is provided using two separate cannulation sites. More recently a single-site venovenous ECMO cannula has become available for sizes suitable for adults and children which allows mobilization of the patient due to lack of a femoral cannula. Choice of cannula size is critical to enable good support of the patient. One would like to provide diversion of 80% of the cardiac output on VV ECMO. Due to sepsis physiology at play in some of these patients, cannulas that afford maximal flow for the patient's

body size are preferable. Regardless of cannula configuration, the basic principle is that venous blood is drained from the body, gas is exchanged, and the blood is returned into the right atrium. This will allow oxygenation and CO_2 removal prior to the blood entering the heart. The weakness of VV ECMO setup is that it is dependent on diverting a large portion of the cardiac output to allow support of arterial oxygen saturations. Also it is subject to recirculation from the return cannula into the drainage cannula, which will effectively limit its support. Proper cannulation technique can maximize circuit flow and limit recirculation.

2.1. Dual cannula VV ECMO support technique

This can be done with bilateral femoral cannulas or with a single femoral cannula and an upper body return cannula.

2.2. Femoral-internal jugular (IJ) VV ECMO

Guidance can be with transesophageal echo (TEE), but fluoroscopy is preferred. Stiff guidewires are advanced into the right atrium from the right internal jugular (R IJ) as well as from one of the common femoral veins. A 25 French venous drainage cannula is inserted from the femoral vein to the abdominal Inferior vena cava (IVC) with the tip at least 2 cm below the diaphragm. This will act as the drainage cannula to the circuit. The return cannula is a 19 French "arterial" style cannula that is inserted from the right internal jugular vein into the right atrium. This acts as the return cannula. The separation distance between the tips of these two cannulas is important to minimize recirculation of the oxygenated blood.

2.3. Fem-fem VV ECMO

Guidance can be with transesophageal echo (TEE), but fluoroscopy is preferred. Stiff guidewires are advanced into the right atrium from right and left common femoral veins. A standard 25 French percutaneous venous drainage cannula is inserted from one of the femoral veins into the IVC, leaving its tip at least 2 cm below the diaphragm. This will act as the drainage cannula to the circuit. The return cannula must be a long cannula with a limited length of outflow ports. Standard percutaneous venous cannulas will not work for this application. Medtronic Bio-Medicus "venous" cannulas have a very short outflow segment but long total lengths and enable the use of a femoral return cannula. Insertion of a 19 French Bio-Medicus venous cannula from the other groin with all of its outflow ports in the superior right atrium will minimize recirculation and allow maximal flows.

2.4. Avalon single-site venovenous ECMO

This cannula is best placed with fluoroscopic guidance, though it can be accomplished with transesophageal echo as well. Ultrasound-guided micropuncture access is gained to the right internal jugular vein. The wire provided with the Avalon introducer kit is advanced into the abdominal IVC. Serial dilation is performed, and the Avalon cannula is inserted over the wire. Initially the tip should be laced well into the IVC. The outflow port of the cannula should be aligned rotationally with the tricuspid valve orifice. This can be accomplished easily as the

outflow port external to the body is aligned with the internal outflow port. Thus, this part of the cannula is pointed medially on the patient's neck. Additionally, one should attempt to align the outflow port vertically with the tricuspid valve. This can be done by visualizing the outflow port by fluoroscopy as it is shown by a defect in the wire reinforcement. It can also be done by visualizing the outflow color jet on TEE after the ECMO circuit is started. The alignment of this is probably not critical, and one should balance this against deep insertion of the cannula into the IVC which may impair drainage from that segment of the cannula.

3. ECMO for cardiogenic shock

Venoarterial (VA) ECMO can be used to support patients in cardiogenic shock from the following etiologies: acute exacerbation of chronic heart failure, acute Myocardial Infarction (MI), myocarditis, drug-induced or stress-induced cardiomyopathy, refractory cardiac arrest, and refractory arrhythmia. VA ECMO provides biventricular support and allows full restitution of cardiac output [1]. It also allows full respiratory support depending on the condition of the native heart. The critical weakness of VA ECMO is the lack of left ventricular (LV) unloading that we will discuss further.

3.1. Peripheral femoral VA ECMO

The most common cannulation technique for VA ECMO is via the femoral artery and vein. This can be done expeditiously under most conditions, including emergency cannulation during Cardiopulmonary resuscitation (CPR). Please see details of cannulation technique and cannula choice in the next section. The femoral venous cannula is inserted into the right atrium to provide excellent drainage of venous blood to the circuit. The femoral arterial cannula is left with its tip in the external iliac artery and provides retrograde flow in the aorta. It is preferable to place the venous and arterial cannulas on opposite limbs. The reason for this is the cut down to repair the artery during decannulation is made easier by not having a venous cannula in the way. Additionally the venous cannula can be decannulated without cut down if it is in a separate groin. A critical consideration with femoral cannulation is that of limb ischemia in the limb that has an arterial cannula. Many times the arterial cannula is large enough that it will obstruct flow in the common femoral artery and create a cold limb. Routine use of an antegrade distal limb perfusion cannula is recommended. This is done by accessing the superficial femoral artery (SFA) by antegrade needle access with a 5 French sheath. This technique is described in Section 3. The cannula is connected to the arterial circuit to allow limb perfusion. Adequate limb perfusion should be confirmed later by physical examination of the foot. Capillary refill and temperature are useful physical signs. However in the setting of high-dose vasopressors, they may not be accurate. Additionally, Doppler examination can be performed, and one may expect a true continuous signal as often there will be no pulse in the cannulated extremity. Most importantly, one can confirm the adequacy of the limb perfusion cannula with a dye injection in the cannula under fluoroscopy if there is any question of limb perfusion.

3.2. Central VA ECMO

There are times when one cannot place cannulas peripherally due to vascular disease or other concerns. Central cannulation should always be considered in these settings. However, bleeding risk is significantly greater once the chest cavity is opened and should only be done when required. This can be done via sternotomy or thoracotomy technique. If undertaking central cannulation, strong consideration must be given to left ventricular venting at the time of cannulation, simply because one has access at this time, and the need for venting is likely to arise. Additionally, if the etiology of cardiogenic shock is likely to be prolonged, one should give strong consideration to placement of temporary biventricular assist device (BiVAD) as this will be a more durable support strategy. If oxygenation support is required, an oxygenator can be placed in line to the Right ventricular assist device (RVAD) or Left ventricular assist device (LVAD). This can later be removed when the lungs have recovered.

Central ECMO is the easiest to deploy via sternotomy. Difficulty in peripheral cannulation is typically encountered with the artery, and the indication for central conversion is related to arterial outflow. We recommended attachment of a sidearm graft to the ascending aorta for outflow as this is much less prone to subsequent bleeding complications that direct cannulation. The minimal size graft used should be a 10 mm Dacron graft. A large cannula can be tunneled in the subxiphoid position and tied into place within the graft. Some groups will use a 3/8" by 3/8" connector in this setting, but this may require leaving some of the graft external to the skin which may be less preferable. If one is expecting to convert the patient to a durable LVAD, one should consider using the graft diameter of the planned durable LVAD. If one is planning to use a Thoratec device, a 14 mm Dacron graft should be utilized so as to ease the next operation. Venous drainage can still come from a percutaneous venous cannula (preferably the internal jugular vein for mobility). However, if those sites are not available, a venous cannula can be placed via the right atrial appendage. A lighthouse tip cannula of 32 French size or greater is used. This can be a right angle type cannula or a malleable cannula that can be formed to the desired shape. Not only is a purse string used to secure this with a tourniquet but an additional heavy silk tie or umbilical tape tied around the base of the appendage will allow additional hemostasis.

Left ventricular venting should be performed as described in the section on LV venting. If done via sternotomy, venting via the LV apex is the best choice. The patient must already be on ECMO support to allow lifting of the LV apex. We recommend usage of the Thoratec® CentriMag® 34 French Drainage Cannula Kit for this purpose. The sewing ring is attached to the epicardium using a running suture. The 34 French cannula provided is tunneled under the costal margin at the patient's anterior axillary line and advanced through this sewing ring. Great care must be taken to ensure all side holes are within the LV cavity, but the cannula is not inserted too far to contact a wall or the mitral valve and cause inadequate drainage. This cannula is connected in a "Y" configuration to the venous limb of the ECMO circuit. The cannula is secured to the sewing ring using multiple silk ties as well as the umbilical tapes provided by the manufacturer. Great care is required to ensure good placement of this cannula within the ventricular cavity. The proper entry location of the cannula is important for future

durable LVAD placement. Additionally, it should lie parallel to the septum. Proper tunneling angle is important for this as well.

Right anterior thoracotomy is also a viable approach for central ECMO cannulation if one wants to avoid sternotomy. The right atrium and ascending aorta are available here for direct cannulation. However, aortic sidearm graft attachment may be difficult from this location due to exposure. In this setting, direct cannulation through purse string may be required. Additionally, venting of the left side of the heart can be performed via placement of a cannula into the left atrium through the left atrial wall or the right superior pulmonary vein. This is done through a purse string, and a 20 French malleable vent can be used[2]. This can also be used to cross the mitral valve to place a true left ventricular vent. One downside to this approach is the potential for clot formation on this cannula that has significant length present in the intracardiac space.

3.3. Ambulatory peripheral VA ECMO

Ambulatory ECMO can easily be accomplished by central cannulation as described above. However, central cannulation should be avoided unless absolutely necessary. Alternatively, one can perform venous drainage from the right internal jugular vein as described in "Techniques" section. Axillary artery outflow can be performed as described below. This will allow full-flow VA ECMO support without any femoral cannulas and can allow significant ambulation.

3.4. LV venting on ECMO

Left ventricular distention and the lack of LV unloading are some of the primary problems related to VA ECMO in the patient with LV failure. Though ECMO provides right atrial drainage, it cannot drain the left side of the heart directly. The blood, which bypasses the circuit in addition to the bronchial artery circulation, continues to fill the left atrium. The failing LV is unable to eject due to the high afterload created by the ECMO circuit. These factors combined lead to a full left ventricle and elevation of the left atrial pressure. Patients will in turn develop pulmonary edema and ongoing pulmonary hypertension which is deleterious to the right ventricle as well. LV distention is a common problem on ECMO and is often under-recognized. Venting of the left side can be performed in a variety of ways as detailed below. Two main categories of LV venting include percutaneous and surgical vents.

Percutaneous venting techniques are ideal when the need for venting is thought to be short in duration, and surgery may be less desirable due to antiplatelet therapy, liver dysfunction, and severe organ failure [2]. Classically balloon atrial septostomy has been performed, but this may not be universally efficacious. The use of the TandemHeart (CardiacAssist Inc., Pittsburgh, PA) transseptal cannula as a left atrial drainage to the ECMO circuit is another percutaneous technique. The transseptal cannula is inserted via the femoral vein and thus has the lowest bleeding risk of all techniques. Additionally there should not be any risk of limb ischemia. This cannula does create an atrial septal defect large enough to require closure at the time of LVAD implant. Operator expertise in transseptal puncture and hospital availability of the device are

two issues related to access to this technique. The Abiomed (Danvers, MA) Impella device is offered in a range of sizes and can be a very effective LV vent as well. LV venting does not require a large amount of flow, and typically the Impella CP device may provide adequate decompression of the LV cavity [3]. This is a micro-axial flow pump that traverses the aortic valve and pumps blood from the LV into the ascending aorta. It can be deployed from the femoral artery or the axillary artery. Again this can be a percutaneous technique, and thus bleeding risk may be lower than open surgery. However there is some risk of limb ischemia. Additionally there is an incidence of hemolysis and device migration/malposition that can occur.

Surgical vents can be placed via the LV apex or into the left atrium. Second or third interspace right anterior thoracotomy can be utilized not only for central ECMO cannulation and can also provide access to the interatrial groove for direct left atrial cannulation. A 20 French malleable vent can be placed into the left atrium through a purse string. This can even be advanced across the mitral valve. One must pay close attention to anticoagulation as this catheter may be at risk for developing thrombus due to its long intravascular length. An alternative method to provide direct LV cannulation is via a left anterolateral thoracotomy, similar to that performed for transapical Transcatheter aortic valve replacement (TAVR). A sewing cuff from Thoratec (Pleasanton, CA) (CentriMag® LV drainage cannula) is attached to the true apex of the heart with a running suture. The provided 34 French cannula is inserted via this sewing ring with its tip in the LV apex, and this is connected to the venous limb of the ECMO circuit. This cannula can support as much as 7 LPM of drainage, and it can be the basis of a temporary LVAD once ECMO support is no longer necessary (**Figure 1**) [4].

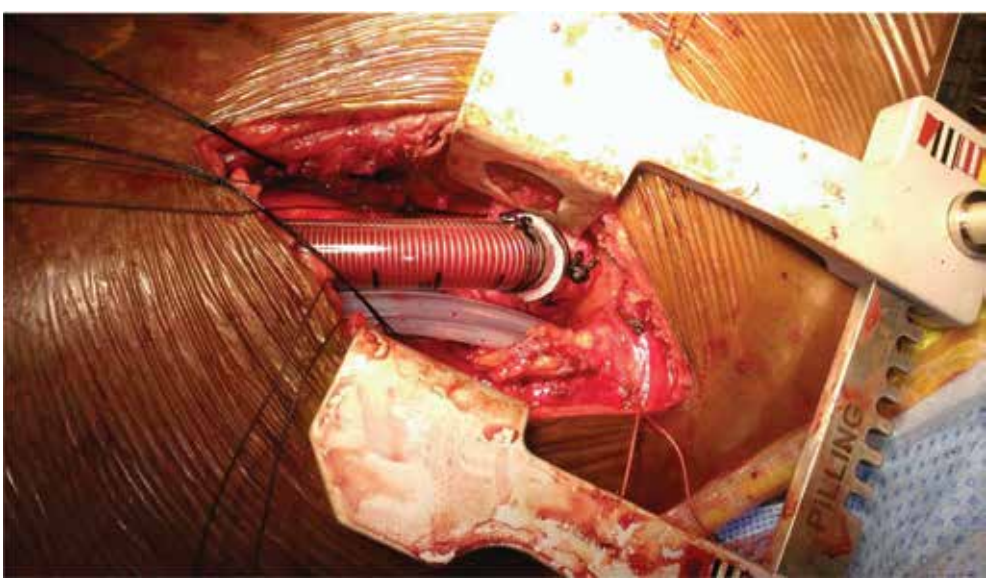

Figure 1. Apical LV vent/cannula via left anterior thoracotomy.

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4. Technical aspects

4.1. Choice of cannulas

For venoarterial ECMO, one should choose cannulas that can provide a cardiac index of >2.4 LPM/m^2. In most adult patients, this will require 5 LPM or more. A 25 French venous cannula is adequate for most adults and will easily fit in most adults. A 19 French arterial cannula will support most adults. However, there are some patients, specifically smaller females, that cannot accommodate a cannula of this size and also do not require that degree of flow. In these cases lesser cannulas should be chosen based on ultrasound measurements of the common femoral artery and the desired flow rate for patient body size. For the antegrade superficial femoral artery cannula, a 5 French or 6 French sheath is adequate in every patient.

For venovenous ECMO one should typically choose the largest size cannulas that will fit into the planned cannulation sites. One desires about 80 % flow diversion on VV ECMO, and in septic patients, it can be difficult to predict the degree of flow required. As such, having larger cannulas can help to augment support as needed. In the case of single-site VV ECMO, we prefer to use the 31 French Avalon cannula in every patient, if the IJ vein will accommodate this. The only exception is when the VV ECMO is being used for CO_2 removal and not for oxygenation. In these cases smaller cannulas can be used. However VV ECMO most commonly is being used primarily for oxygenation support, where high flows are required. For dual-site VV ECMO, a 25 French drainage cannula is preferred, and a 19 French return cannula is preferred.

4.2. Peripheral cannulation: open vs percutaneous technique

Peripheral cannulation is the mainstay for most ECMO patients, regardless of disease process or support technique. Classically this was done by open technique, but now many centers have moved toward percutaneous technique as it may afford some advantages [5]. The authors feel that percutaneous technique should be applied whenever safe and feasible, though this may still be controversial. If placed with appropriate technique, cannulas placed percutaneously are likely more resistant to infectious issues. They are also less likely to have bleeding complications. Securing the cannulas so they cannot be dislodged is also easier with cannulas placed percutaneously. Even in the setting of ongoing CPR, if one is able to gain good visualization by ultrasound imaging, percutaneous cannulation can be a superior technique. Proper percutaneous cannulation requires an operator that is very familiar with ultrasound imaging of the femoral artery, femoral vein, and internal jugular vein. Open technique may be required when sidearm grafting is required due to vessel size or if percutaneous access to the vessels fails.

4.3. Percutaneous cannulation of the right internal jugular (R IJ) vein

A 5 French micropuncture kit is used to access the R IJ vein under ultrasound guidance. A stiff wire similar to an Amplatz Extra Stiff 180 cm is passed through the micropuncture catheter under fluoroscopic guidance. R IJ cannulation is best done with fluoroscopy to ensure that the wire traverses into the abdominal IVC. If the wire does not go to the IVC, a pigtail or angled

catheter over the wire may be needed to direct the wire into the IVC. Again, fluoroscopy facilitates this much better than transesophageal echo. Once wire access is established into the IVC, the tract is dilated and the venous cannula is advanced. If the chosen venous cannula has a long segment of side holes as most do, the tip must be placed into the IVC so that all the side holes are inside the body. If the cannula has a limited section of side holes as with the Medtronic Bio-Medicus venous cannulas, then it can be left in the right atrium. This technique should not be used in the emergency setting and during CPR as it requires access to the neck and fluoroscopy to ensure safety.

4.4. Percutaneous cannulation: femoral vein

Under ultrasound guidance, a 5 French micropuncture kit is used to gain access to the common femoral vein on either side. A stiff wire such as Amplatz Extra Stiff 180 cm is advanced into the right atrium. Some type of guidance with transesophageal echo or fluoroscopy is preferred. However in the emergent setting, this can be done without guidance, accepting a lower level of safety. Serial dilation over the wire is performed, and the selected venous cannula is placed with its tip in the right atrium near the SVC junction (**Figure 2**).

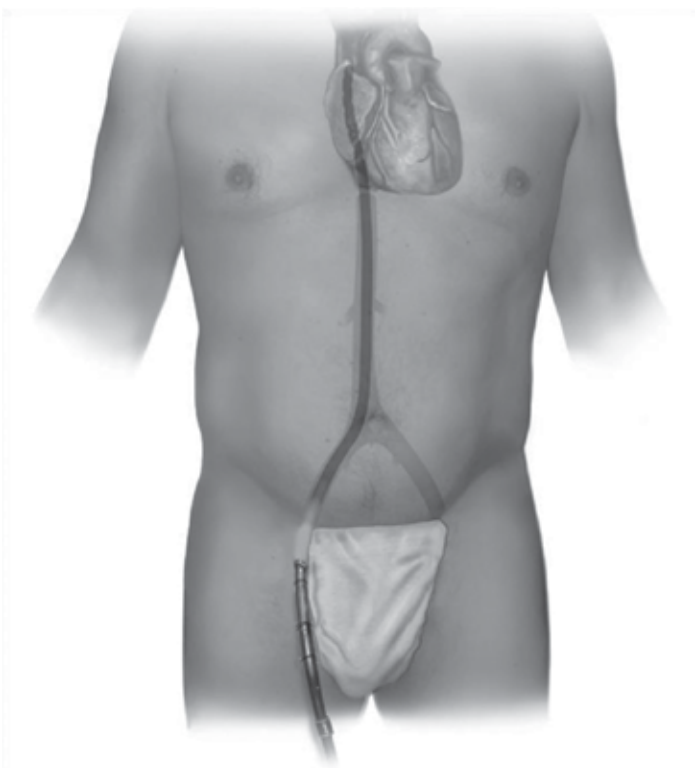

Figure 2. Femoral venous cannulation for VA ECMO [4].

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4.5. Percutaneous cannulation for antegrade limb perfusion cannula

Under ultrasound guidance and PRIOR to access of the common femoral artery for cannulation, the antegrade limb perfusion cannula should be placed. Ultrasound is used to locate the bifurcation of the common femoral artery. The superficial femoral artery (SFA) is accessed in an antegrade fashion just past the bifurcation. The wire should pass freely down the leg. Fluoroscopy can be used to help guide this but not usually required. After the micropuncture catheter is placed, a guidewire is inserted and a 5 French sheath placed into the SFA. A segment of high-pressure tubing will later be used to connect this sheath to the Luer Lock port on the arterial cannula to allow circuit blood to perfuse the lower limb (**Figure 3**).

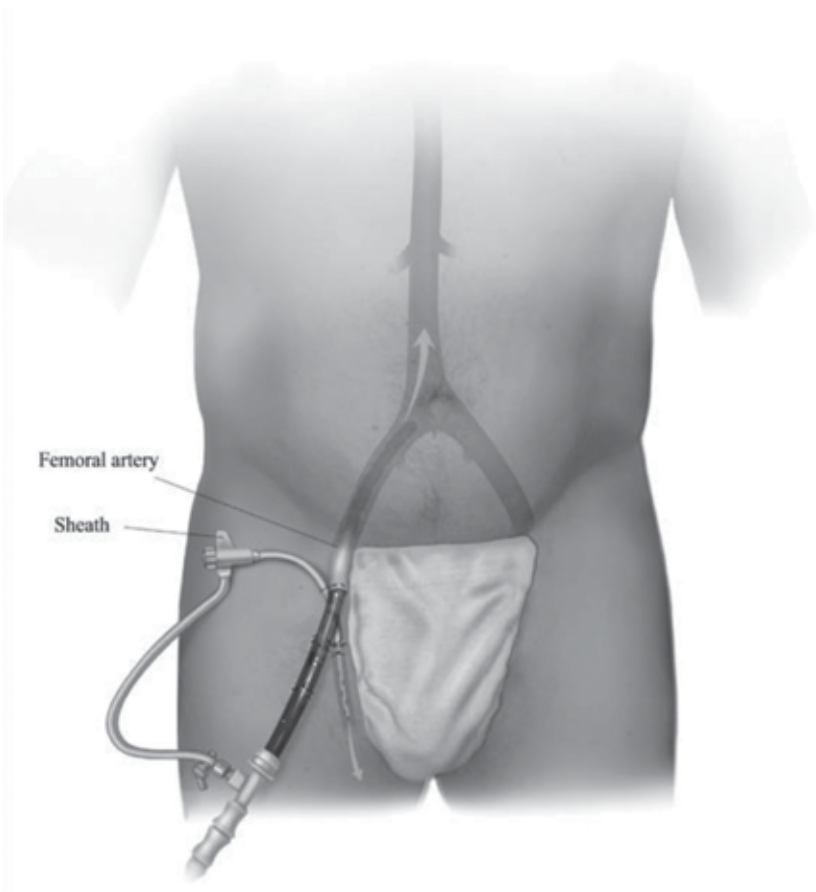

Figure 3. Femoral arterial cannulation with antegrade perfusion cannula [4].

4.6. Percutaneous cannulation for common femoral artery

Ultrasound is used to measure the size of the common femoral artery. A cannula size is selected based on this dimension as well as the required flow rate. Ultrasound-guided access with a

5 French micropuncture is critical. A single stick to the artery with the micropuncture needle is preferred. Using large bore needles with failed punctures can lead to hematoma formation. A 0.035″ stiff wire such as an Amplatz Extra Stiff 180 cm is advanced to the descending thoracic aorta under TEE or fluoroscopic guidance. Under emergent conditions this may have to be done without guidance. Serial dilation is performed, and the cannula is inserted deep enough that there is no risk that the side holes of the cannula can come outside the femoral artery (**Figure 3**).

4.7. Open femoral cannulation and sidearm grafting

During CPR or in conditions where ultrasound guidance is not possible, cannulation via open approach may be required. An oblique incision is preferred, and the common femoral artery, common femoral vein, and superficial femoral artery are exposed. Purse strings are placed in each vessel and cannulas placed through skin tunnels for added security. This also allows for wound closure. Sidearm grafting of the femoral artery is also a good technique that can be used when the artery is small and may not accommodate an appropriate-sized cannula. The common femoral artery is controlled proximally and distally. An arteriotomy is made. A 10 mm Dacron graft is sewn to the artery in an end-to-side fashion using a small needle. This graft is de-aired and then can be cannulated with a 3/8″ by 3/8″ connector. This technique allows bidirectional flow in the femoral artery, and thus no distal perfusion cannula is required.

4.8. Axillary artery direct cannulation

Although axillary artery can be cannulated directly for short-term access during cardiopulmonary bypass, it is not advisable in this situation. It can lead to arm ischemia and more bleeding problems.

4.9. Axillary artery sidearm cannulation

Expose the axillary artery in standard technique paying extra attention toward hemostasis. Distal and proximal control can be obtained with clamps and/or vessel loops. Alternatively

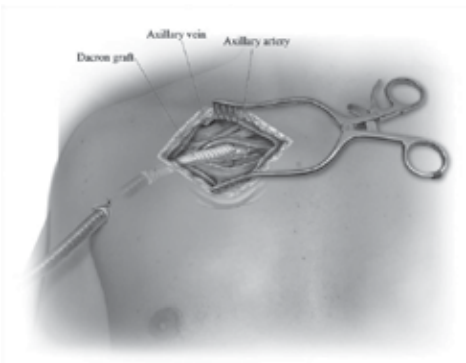

Figure 4. Axillary artery graft cannulation [4].

one can use a partial occlusion clamp without needing too much dissection, which is our preferred technique. A 10 mm Dacron graft is sewn to the artery using a small needle 6-0 or 5-0 polypropylene suture to minimize bleeding. Meticulous attention should be given toward hemostasis. A 32 French malleable venous cannula is tunneled from a small incision below the nipple in the anterior or midaxillary line into the axillary incision. Covering this with a glove tip or placing it inside a 36 French chest tube will prevent damage or debris from entering the lumen. The tip is cut off and inserted into the Dacron graft after de-airing. It is secured with multiple ties and positioned so that there is no kinking. A 32 French cannula will be connected to the arterial outflow of the ECMO circuit with a 3/8″ by 3/8″ connector (**Figure 4**).

4.10. Aortic cannulation with sidearm graft

Best exposure is using a full sternotomy but does lead to more bleeding problems early on. Upper hemi-sternotomy and right anterior thoracotomy can be used in some patients. After exposing the aorta, heparin is administered, and a partial clamp is placed after making sure there is no plaque by pre-op imaging by CT and ECHO or direct imaging using epiaortic ultrasound and digital palpation. Sew a 10 mm or larger graft in a beveled fashion using 4-0 or 5-0 polypropylene suture with small needles. A 32 French malleable venous cannula is tunneled up from the subxiphoid space (in the case of sternotomy) or anterior chest wall, one or two interspaces below the thoracotomy incision. Connection is made after de-airing between the graft and cannula with tip cut off. It is secured with multiple heavy ties. Secure it in such a way that there is no kinking of the graft and only the cannula is exiting the skin and not the graft.

4.11. Central venous cannulation

When using aortic approach for arterial cannulation, venous cannulation can also be done without having to resort to peripheral placement. Through the same incision, a 36 French malleable venous cannula or a 32 French angled metal-tipped cannula can be placed into the right atrium with purse-string sutures on the appendage. Care should be taken to place more than one suture, and leave all the side holes of the plastic cannula well inside the atrial cavity to avoid sucking air. The purse-string suture "keepers" are tied to the cannula with several heavy sutures. Cannula must be tunneled from the exit site prior to inserting into the atrium. Cannula is then de-aired and connected to the venous side of the ECMO circuit with a 3/8″ by 3/8″ connector (**Figure 3**).

5. Securing the cannula

Cannulas are secured to the skin using #1 braided suture. Four sutures should be used to secure each cannula to avoid inadvertent dislodgement, which is universally catastrophic. Inspect the sutures every few days, and place additional sutures if necessary, especially after patient starts ambulation in cases of central ECMO.

6. Management of cannulation site bleeding

Percutaneous peripheral cannulation sites seldom bleed. Most of the bleeding is seen with manipulation and can be controlled with securing the cannula better. Sometimes a "U" stitch around the insertion site is required to stop the bleeding. Some bleeding is universally seen in all open incisions. Reversing the heparin with protamine and surgical hemostasis can control most bleeding. Topical hemostatic agents can be used on the anastomotic suture lines. If there is ongoing oozing, we prefer to place a negative therapy wound vacuum system. Bleeding usually stops within 24–48 h, and we return to the operating suite to close the incisions.

7. Conclusions

This chapter provides simple instructions for various types of cannulation options for VA and VV ECMO as well as LV venting. Types of cannulas used are not necessarily endorsement of the products but just what we use. Any other manufacturers' cannula can be used with some modifications.

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Chapter 5

Triple Cannulation ECMO

L. Christian Napp and Johann Bauersachs

Additional information is available at the end of the chapter

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Abstract

Extracorporeal membrane oxygenation (ECMO) has emerged as an invaluable tool for bridging severe isolated or combined failure of lung and heart. Due to massive technical improvements, the application of ECMO is growing fast. While historically ECMO was initiated and maintained by cardiac surgeons, in recent times interventional cardiologists and intensive care specialists increasingly run ECMO systems independently with great success. Percutaneous ECMO circuits are usually set up in a dual cannulation mode, either as veno-venous or as veno-arterial configuration. A novel advanced strategy is the cannulation of three large vessels (triple cannulation), resulting in veno-veno-arterial or veno-arterio-venous cannulation. Both veno-venous and veno-arterio-venous cannulation may further be upgraded to veno-pulmonary-arterial or veno-arterial-pulmonary arterial cannulation, respectively. Triple cannulation expands the field of ECMO application but substantially increases the complexity of ECMO circuits. In this chapter, we review percutaneous dual and triple cannulation strategies, featuring a recently proposed unifying nomenclature. This unequivocal code universally applies to both dual and triple cannulation strategies (VV, VPa, VA, VVA, VAV, VAPa). The technical evolution of ECMO is growing fast, but it has to be noted that current knowledge of ECMO support is mainly based on observation. Thus controlled trials are urgently needed to prospectively evaluate different ECMO modes.

Keywords: cardiogenic shock, heart failure, ECMO, extracorporeal circulation, mechanical circulatory support, triple cannulation

1. Introduction

In 1972, the first report of successful extracorporeal membrane oxygenation (ECMO) was published [1]. Since then extracorporeal membrane oxygenation (ECMO) has emerged as a central method for supporting acute severe heart and lung failure. The current broad use of

ECMO was made possible by many technical improvements of tubings, surfaces, oxygenators, and other parts of the circuit. Recently, randomized and observational studies have demonstrated that the so far widely used intra-aortic balloon pumps are not as beneficial as expected in patients with shock [2, 3]. Thus, the frequency of use of ECMO will likely further increase in the future.

Strategy	Indication (example)	Principle	Exit	Reference
Bridge to recovery	Myocarditis	Replacement of organ function until recovery allows weaning of ECMO	ECMO removal	Asaumi et al. [29], Lorusso et al. [30]
	ARDS	Preoxygenation of venous blood to allow for lung-protective ventilator settings and pulmonary recovery	ECMO removal	Hoeper et al. [18]
Bridge to transplantation	Respiratory failure from lung disease without prospect of recovery	Replacement of organ function until transplantation of the failing organ	Transplantation	Fuehner et al. [15] Schmidt et al. [17]
Bridge to destination	Terminal heart failure	Replacement of organ function until implantation of a permanent assist device	LVAD surgery	Haneya et al. [38]
Bridge to decision	Resuscitation	Replacement of organ function with the intention to gain time until decision on the final strategy can be made	Improve end organ function, assess neurological outcome on ECMO support, to evaluate the patient for a reasonable exit strategy (e.g., potential LVAD implantation)	Rousse et al. [39]
	Interhospital transfer of patients with ARDS or cardiogenic shock, refractory to medical therapy	ECMO implantation in the peripheral hospital, transfer of stabilized patient to tertiary cardiovascular center	Improve end organ function and complete diagnostics to determine exit strategy (recovery vs. permanent assist device)	Javidfar et al. [35]

ARDS, acute respiratory distress syndrome; LVAD, left ventricular assist device.

Table 1. Strategies of ECMO support for heart and/or lung failure.

The most common ECMO configuration is "dual-cannulation," i.e., veno-venous (VV) or veno-arterial (VA) cannulation with two large-bore cannulae. VV-ECMO drains desaturated blood from the right atrium and returns it after oxygenation and decarboxylation again to the right atrium. By this, it works like an extracorporeal lung and is classically used in patients with severe acute respiratory distress syndrome (ARDS). In contrast, VA-ECMO drains blood from the right atrium and returns it after passing the ECMO device to the patient's arterial system,

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usually via the femoral artery toward the aorta. By this, VA-ECMO generates a large extracorporeal right-to-left shunt and primarily provides hemodynamic support, whereas the effect on oxygenation depends on several factors such as cannulation sites, the patient's cardiac output, and respiratory function. Thus, considering the profound effects on hemodynamics and gas exchange, VA-ECMO is essentially different from VV-ECMO, and each has its own indications.

Regardless of the cannulation mode, ECMO can be used with different strategies (**Table 1**): *bridge-to-recovery*, *bridge-to-transplantation*, *bridge-to-destination*, or *bridge-to-decision*.

However, notwithstanding today's very quick setup of the system due to major technical improvements, ECMO is an invasive life support system potentially leading to vascular complications, bleeding, thromboembolic events, and infection [4]. ECMO support can be easily initiated, but its termination in a *bridge-to-recovery* strategy requires careful weaning. Therefore, an experienced team of cardiologists, cardiac surgeons and intensive care specialists (and pulmonologists on the case of lung failure) should evaluate every patient before ECMO initiation, in order to reach consensus on the individualized therapeutic concept. Guidelines on indications, use, and weaning from ECMO support in children and adults are available from the Extracorporeal Life Support Organization (ELSO) [5]. In general and compared to other invasive therapies, the level of evidence is limited for ECMO. Large prospective trials are sparse, even if several smaller studies, case series, and registries are available. This is in part due to the acute lifesaving nature of the device, where the clinical need has passed the chance to conduct prospective studies.

Drainage	Return	Abbreviation	Figure	Draining cannula*	Supplying cannula*	Indication
V	V	VV	1	Inferior Vena cava	Superior Vena cava	ARDS
V	Pa	VPa	2	Right atrium	Pulmonary artery	Rightsided heart failure
V	A	VA	3	Right atrium	Common iliac artery	Post-cardiotomy cardiogenic shock Acute decompensated heart failure Cardiogenic shock during AMI or fulminant myocarditis Massive pulmonary embolism with shock High-Risk PCI support Extracorporeal resuscitation
V V	A	VVA	4	Inferior Vena cava Superior Vena cava (or RV)	Common iliac artery	Insufficient unloading during VA-ECMO Left ventricular distension during VA-ECMO
V	A V	VAV	5	Inferior Vena cava	Common iliac artery Superior Vena cava	Respiratory failure during VA-ECMO Cardiogenic shock during VV-ECMO
V	A Pa	VAPa	6	Right atrium	Common iliac artery Pulmonary artery	Severe rightsided heart failure during VAV-ECMO Severe lung and rightsided heart failure during VA-ECMO

ARDS denotes acute respiratory distress syndrome

Table 2. ECMO cannulation modes.

The clinical need has also led to innovative applications for ECMO under special circumstances, beyond classical dual cannulation. The novel concept of triple cannulation addresses inadequate draining during veno-arterial ECMO and combined cardiopulmonary failure on

either veno-arterial or veno-venous ECMO. As triple cannulation resulted in a confusing use of multiple abbreviations during clinical routine, we have recently proposed a unifying terminology of ECMO cannulation modes [6].

In this chapter, we very briefly review the features of dual cannulation ECMO and then summarize current indications, pathophysiology, and strategies for percutaneous triple cannulation ECMO support. An overview on cannulation modes is given in **Table 2**. It should not remain unmentioned that other extracorporeal systems beyond ECMO are available, but these are off the focus of this chapter and are described elsewhere [7, 8].

2. Dual cannulation ECMO

Dual cannulation ECMO may be instituted as veno-venous or veno-arterial ECMO. Both are essentially different in terms of setup, support, and monitoring.

2.1. Veno-venous cannulation (VV)

During VV-ECMO, deoxygenated blood is drained from the right atrium and returned after extracorporeal reoxygenation and decarboxylation again to the right atrium (**Figure 1**). ECMO-derived preoxygenated blood enters the pulmonary circuit and provides systemic oxygenation, thus allowing for establishing lung-protective respirator settings. The most common indication for VV-ECMO is ARDS [9–14]. In ARDS, ECMO is considered with a Horovitz index below 100 to 150 or uncompensated acidosis (pH <7.2) and has already been applied in awake patients [15–17] or even to fully avoid invasive ventilation [18]. Notwithstanding the need of prospective controlled trials, VV-ECMO has already entered center stage in severe ARDS in tertiary centers, which was further promoted by the recent H1N1 wave [19–22]. VV-ECMO should not be initiated in patients with terminal respiratory failure, when there is no perspective of organ recovery or lung transplantation.

VV-ECMO cannulae are usually introduced via the femoral and jugular veins (**Figure 1**), with upper-body cannulation by using a bicaval dual lumen cannula [6, 23] only through the right-sided jugular vein as an elegant alternative. With femoral-jugular cannulation, it is essential to position the tips of both cannulae at the border between the right atrium and the caval veins (**Figure 1**) to minimize recirculation. On VV-ECMO, oxygen saturation in the central aorta results from a mixture of reoxygenation in the ECMO and remaining gas exchange in the lungs. Improvement of end organ supply often results in a reduction of vasopressors, but VV-ECMO does not influence hemodynamics *per se*, as equal blood volumes are drained from and supplied to the right atrium (**Table 1**). Right or left heart failure in patients on VV-ECMO is a potential indication for triple cannulation (see below), thus echocardiographic monitoring is very important during support.

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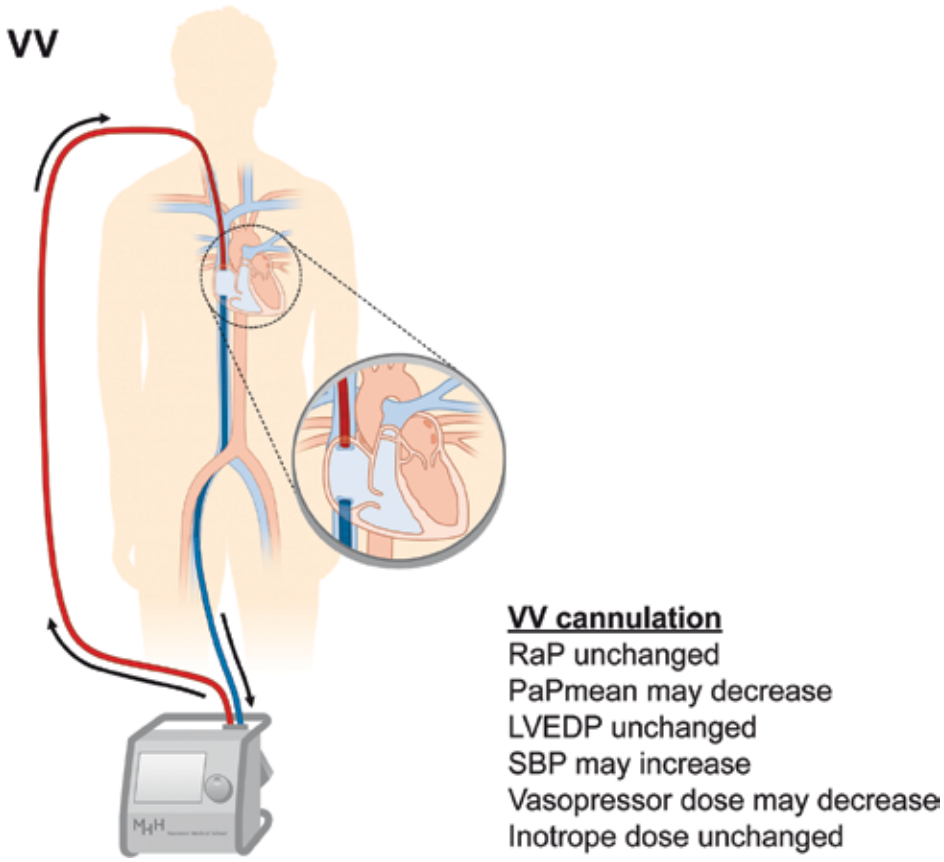

Figure 1. Veno-venous ECMO (VV). VV-ECMO drains venous blood (blue) from the right atrium and the inferior vena cava and returns an equal volume after reoxygenation and decarboxylation (red) again to the right atrium. PaPmean denotes the mean pulmonary arterial pressure, LVEDP left-end diastolic pressure, RaP mean right atrial pressure, and SBP systemic blood pressure. Pressure and medication changes given in the figures are mainly derived from clinical experience and remain to be validated by dedicated studies. LVEDP denotes left ventricular end diastolic pressure, PaP pulmonary arterial pressure, RaP right atrial pressure, and SBP systolic blood pressure.

2.2. Veno-pulmonary-arterial cannulation (VPa)

This is a very recent modification of VV-ECMO, which has not been validated in studies und is just described here for the purpose of completeness. VPa cannulation intends to provide similar support as VV-ECMO, i.e., to drain venous blood from the right atrium and to supply reoxygenated and decarboxylated blood back toward the pulmonary circulation. The difference to VV-ECMO is that the supplying cannula does not end at the right atrium but is forwarded through the tricuspid valve, the right ventricle, and the pulmonary valve to the pulmonary artery (**Figure 2**). This has to be performed under angiographic (or transesophageal echocardiographic) guidance, and for this purpose a flexible 17-French cannula is necessary. Furthermore, the draining cannula tip should be positioned in the mid right atrium to facilitate homogenous drainage of the upper and lower body.

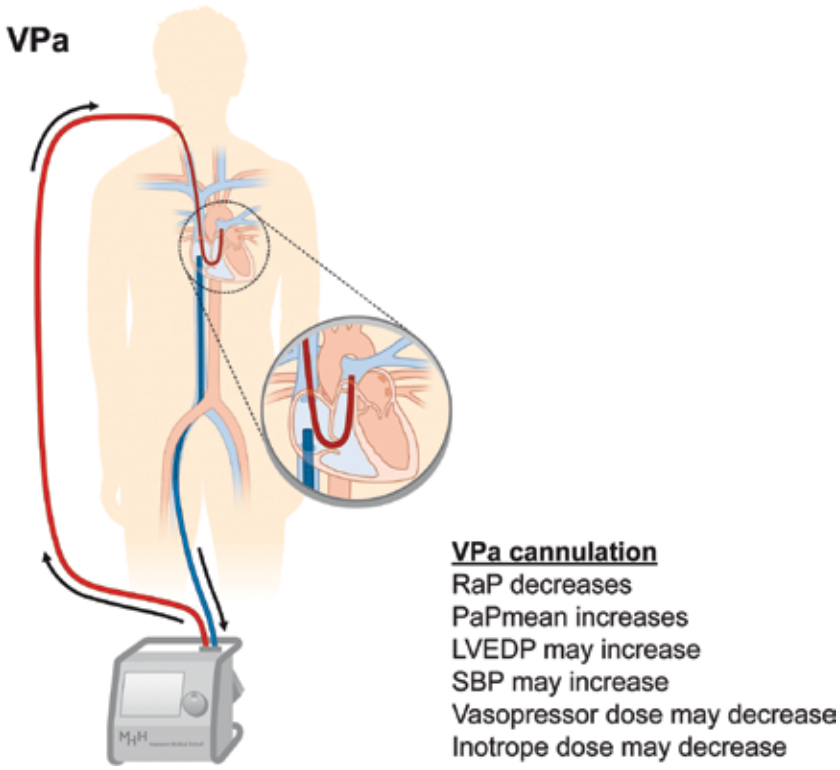

Figure 2. Veno-pulmonary-arterial ECMO (VPa). VPa-ECMO drains venous blood (blue) from the right atrium and returns an equal volume after reoxygenation and decarboxylation (red) to the pulmonary artery. Note the modified position of the draining venous cannula tip compared to VV-ECMO.

The main advantage of VPa cannulation is the bypass of the right ventricle, which in turn requires a competent pulmonary valve. As such, this type of cannulation may be used in patients with isolated right heart failure or with right heart failure while on VV-ECMO support. Again, it has to be noted that this type of ECMO is novel and has not been validated in clinical trials. It further requires sufficient left ventricular function, and left heart failure on VPa-ECMO may be an indication for triple cannulation (see below). In general, isolated right heart failure may also be bridged by a novel dedicated microaxial right heart assist device (Impella RP®, Abiomed) [24]. However, in contrast to VPa-ECMO, this approach provides mere hemodynamic assistance but no respiratory support by reoxygenation and decarboxylation of venous blood.

2.3. Veno-arterial cannulation (VA)

The second major indication for ECMO is hemodynamic support in severe heart failure, which has already been introduced to current guidelines [25]. For hemodynamic support, VA-cannulation is performed. Here blood is drained from the right atrium similar to VV-ECMO but returned to a large artery toward the aorta (**Figure 3**). This institutes an extracorporeal

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right-to-left-shunt in order to reduce preload and to increase aortic blood flow for end organ perfusion (**Figure 3**). That leads to the stabilization of blood pressure in most cases, but this secondary effect depends on vascular resistance and filling. As such, vasopressor dosing and volume supplementation have to be carefully adjusted during VA-ECMO.

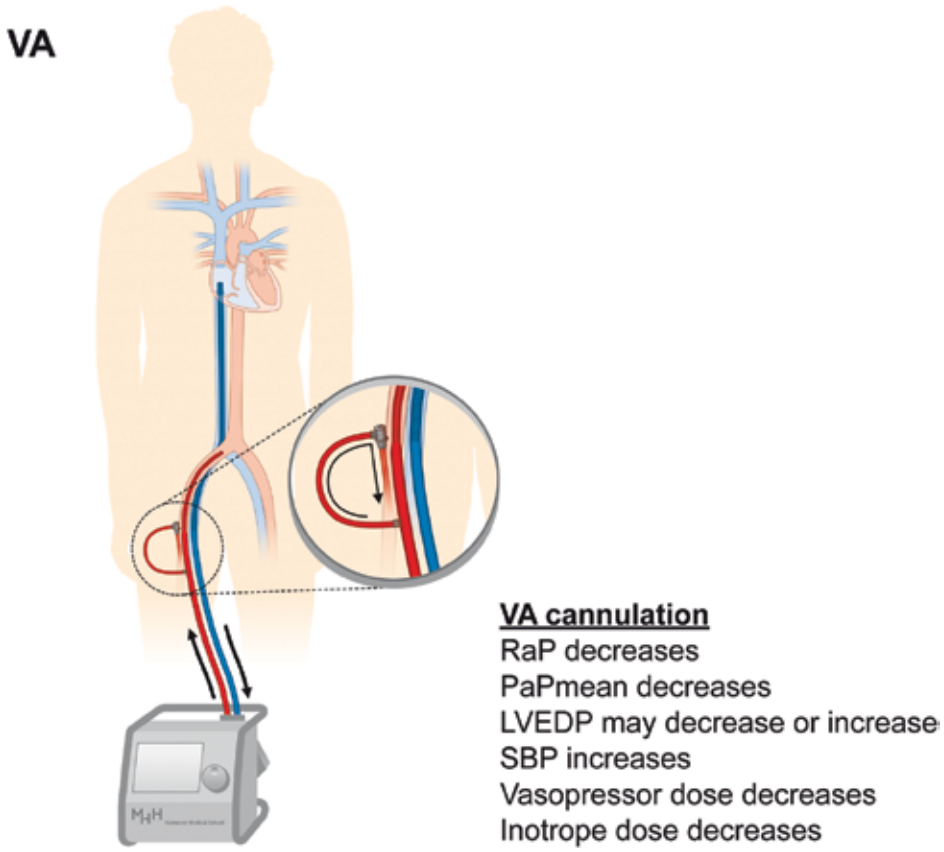

Figure 3. Veno-arterial ECMO (VA). VA-ECMO drains venous blood (blue) from the right atrium and returns an equal volume after reoxygenation and decarboxylation (red) to the iliac artery toward the aorta. Note the modified position of the draining venous cannula tip compared to VV-ECMO. Femoral arterial cannulation requires an extra sheath for antegrade perfusion of the leg (inset).

VA-ECMO has successfully been used in various conditions such as post-cardiotomy cardiogenic shock [26], shock caused by myocardial infarction [27], decompensated non-ischemic heart failure [28], fulminant myocarditis [29, 30], or pulmonary embolism prior to embolectomy [31, 32] in all of the aforementioned cases in a *bridge-to-recovery* strategy. As with VV-ECMO, VA-ECMO has successfully been used in awake patients avoiding mechanical ventilation [33]. VA-ECMO is further used in a *bridge-to-transplantation* strategy for right ventricular failure during decompensated pulmonary arterial hypertension before lung transplantation [34]. Transportable ECMO systems are available for the stabilization of

patients with cardiogenic shock in order to transfer them to a tertiary cardiovascular center [35]. While elective high-risk percutaneous coronary intervention has been successfully performed under VA-ECMO support [36], a percutaneous microaxial pump (Impella®) appears to be equally effective with lower procedural risk [37]. VA-ECMO can further be useful for preconditioning prior to implantation of a permanent left ventricular assist device (LVAD) in a *bridge-to-destination* strategy [38]. Regarding donor organ shortage, this approach will be increasingly important in the future compared to a *bridge-to-transplantation* strategy. A *bridge-to-decision* strategy [39] is followed in patients after resuscitation, with the intention to gain time, while end organ perfusion is improved until neurological outcome after resuscitation can be evaluated. The use of VA-ECMO is further beneficial during the early postoperative phase after lung transplantation, while the heart is not ready to manage reconstituted left ventricular preload [40]. As in recent years, efforts are made to improve the outcome after out-of-hospital resuscitation, and VA-ECMO will also play an important role here [41], since available outcome data suggest a benefit in this context [42, 43]. Notwithstanding the broad use of VA-ECMO, and promising results from smaller studies, large prospective studies are missing.

VA-ECMO cannulae are usually introduced via the femoral vein and artery (**Figure 3**), but the venous cannula may also drain blood via a jugular vein, especially when VV-ECMO with existing jugular access is switched to VA-ECMO. In contrast to VV-ECMO, the venous cannula tip should be placed in the mid right atrium (**Figure 3**) to enable homogenous drainage of the upper and lower body. Upper-body cannulation via the jugular vein and subclavian artery is also possible [6].

Arterial cannulation introduces several important differences to VV-ECMO, which have to be considered in both VA- and triple cannulation ECMO. One of the most important issues is the so-called watershed phenomenon, i.e., an artificial competition zone between antegrade blood flow from the heart and retrograde blood flow from the ECMO [6, 31, 44]. It is located at a region somewhere between the ascending aorta and the thoracic aorta at the diaphragm level in most cases, and varies over time [44] and between individual patients. As a result, the upper body including the brain is perfused with “heart blood” and the lower body with “ECMO blood.” Accordingly, lung failure during VA-ECMO may result in hypoxic damage to the heart and brain despite good perfusion pressure, because blood derived from the heart is incompletely saturated. This condition is a potential indication for triple cannulation ECMO (see below). Second, femoral arterial cannulation requires an additional sheath to ensure distal arterial perfusion (**Figure 3**, inset) [45], and arterial access may lead to substantial vascular complications [45]. Lastly, left ventricular distension and pulmonary congestion may emerge after the onset of VA-ECMO support, especially in cases of extremely low left ventricular output or aortic regurgitation. In such cases, triple cannulation for enhanced venous unloading can be helpful (see below) [5]. A novel promising solution to compensate for insufficient or missing antegrade flow across the aortic valve on VA-ECMO support is additional percutaneous left ventricular unloading by a microaxial pump (Impella®, Abiomed), which is described elsewhere [46–48].

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The aspects described above (watershed, antegrade perfusion sheath, LV distension/pulmonary edema) have to be considered in all patients on femoral-arterial cannulation, however, do not apply to central and only in part to subclavian arterial cannulation.

3. Triple cannulation

Triple cannulation ECMO is a novel and complex form of mechanical support. In most cases, it is instituted by adding a third cannula to an existing VV- or VA-ECMO circuit. The term "triple cannulation" primarily means the use of three cannulae; however, these may be used in a veno-veno-arterial (VVA) or veno-arterio-venous (VAV) mode. As VVA and VAV modes have strongly different effects on circulatory and respiratory support as well as associated ventilator and medical management, we here describe both configurations separately. In general, triple cannulation is a promising approach for selected patients, but evidence from the available literature is limited, and it should be used by experienced centers only.

3.1. Veno-veno-arterial cannulation (VVA)

VVA-ECMO is a special variant of VA-ECMO, in order to improve drainage with a second venous cannula. In general, VA-ECMO intends to provide hemodynamic support and cardiac unloading during severe left-sided, right-sided, or biventricular heart failure. In this context, filling pressures, i.e., pulmonary arterial and capillary wedge pressures, serve as robust markers of VA-ECMO efficacy. However, in some patients, venous drainage is not sufficient, resulting in either reduced ECMO flow or upper body hypoxemia (also termed differential hypoxia or two-circulation syndrome) [49, 50]. This may occur by using insufficient cannula diameters or in very large patients. Then, the addition of a second draining cannula aims to improve venous drainage, resulting in triple cannulation (two for drainage and one for supply, **Figure 4**).

Unloading by standard VA-ECMO may further be insufficient in special situations, e.g., congenital heart defects or coexisting intracardiac shunts and pulmonary arterial hypertension. Then intracardiac right-to-left shunt may result in myocardial and cerebral hypoxia. A third cannula which drains blood from the right atrium or the right ventricle (**Figure 4**) is often sufficient to optimize unloading, increase upper body drainage, and reduce intracardiac shunts. Left ventricular distension during VA-ECMO represents another indication for enhanced drainage by VVA triple cannulation. Furthermore, in patients with insufficient flow through the draining cannula or hemolysis due to high flows, VVA may be helpful to enable high flows and reduce hemolysis [51, 52].

While standard VA-cannulation is often performed on the ward with post-hoc imaging to verify cannula position, the second venous draining cannula should always be placed under live imaging, such as fluoroscopy or transesophageal echocardiography. Flows from both venous cannulae are then merged with a Y-connector outside of the body to return to the ECMO unit via a single tubing (**Figure 4**). As VVA ECMO is a special form of VA-ECMO with enhanced drainage, hemodynamic consequences are comparable to VA cannulation (**Figure 4**).

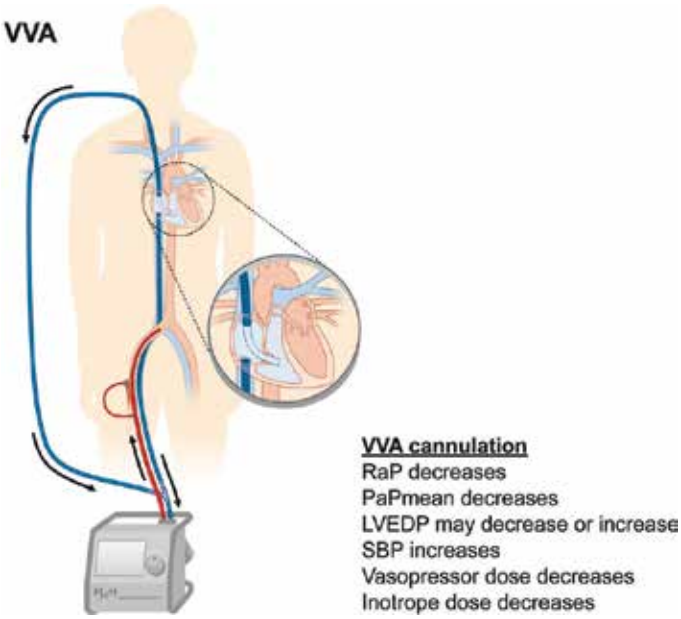

Figure 4. Veno-veno-arterial ECMO (VVA). VVA-ECMO drains venous blood (blue) via the jugular and femoral vein from the right atrium and returns all drained blood after reoxygenation and decarboxylation (red) to the iliac artery toward the aorta. The draining flows from the two venous cannulae are merged by a Y-connector.

VVA-ECMO	*N*	Description	Outcomes
Ford and Atkinson 1992 [52]	1	Respiratory failure from congenital diaphragmal hernia in a 3000-g newborn. After 24 h, VA-ECMO support was insufficient due to limited drainage. After upgrade to VVA cannulation, central venous oxygen saturation improved, indicating improvement of drainage and subsequent supply	Surgery for repair of hernia was performed, ECMO could be removed after weaning. The child was discharged home after 31 days.
Hou et al. 2015 [50]	Sheep model	Animal study investigating the role of different locations of drainage during ECMO support. Acute respiratory failure was induced while VA-ECMO with inferior vena cava drainage was running. Severe upper body hypoxemia developed, with no significant effect on blood pressure. The venous drainage cannula was repositioned to the superior vena cava, and aortic oxygen saturation increased from 35 to 75%, by this reverting upper body hypoxemia. This proof-of-principle study demonstrates that bicaval drainage is sufficient to disrupt "two-circulation syndrome."	
ELSO [5]	Guideline	The ELSO guideline for ECMO support in adults describes the option to change VA-cannulation to VVA-cannulation for improving venous drainage	

Table 3. Publications on VVA ECMO support.

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At present, VVA-ECMO has been used in selected cases only (**Table 3**), and robust study data do not exist.

3.2. Veno-arterio-venous cannulation (VAV)

This type of triple cannulation is probably one of the most promising steps forward in complex clinical situations. VAV-ECMO is used in patients with coexisting severe lung and heart failure. While the drainage cannula draws blood from the right atrium, the ECMO outflow is divided into two parts: One toward the aorta and one toward the right atrium (**Figure 5**). As such, VAV-ECMO represents a mixture of both VV- and VA-ECMO and provides hemodynamic and respiratory support at the same time. This approach is sufficient to rescue combined heart and lung failure in selected cases, such as severe left ventricular failure with secondary ARDS or right heart decompensation during ARDS.

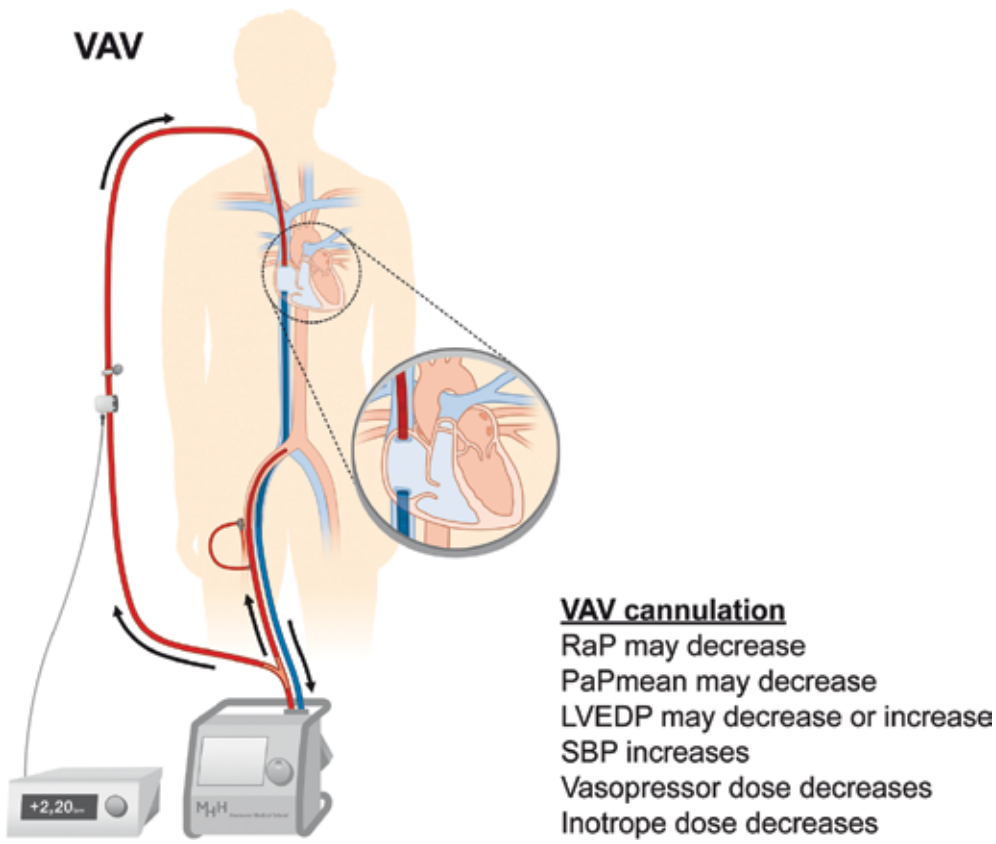

Figure 5. Veno-arterio-venous ECMO (VAV). VAV-ECMO drains venous blood (blue) from the right atrium and returns balanced volumes blood after reoxygenation and decarboxylation (red) to the iliac artery toward the aorta and to the right atrium toward the pulmonary circulation. For this purpose, the ECMO outflow is divided by a Y-connector. Flow through the returning cannulae is balanced with an adjustable clamp and monitored with a separate flow sensor on the upper return cannula.

VAV-ECMO	*N*	Description	Outcomes
Madershahian et al. 2007 [58]	1	3 pts. with VA-ECMO for ARDS and polytrauma. In 1 pt., persistent upper body hypoxemia on VA-ECMO, conversion to VAV	Recovery, weaning from ECMO, discharge
Stöhr et al. 2011 [60]	11	30 pts. with ARDS. Of these 18 with VV, 9 with VA and 3 with primary VAV cannulation. 8 were upgraded from VV or VA to VAV, and 2 were switched from VV to VA. 11 pts. had subclavian arterial cannulation	Bleeding in 8 pts., hyperperfusion/leg ischemia/wound healing complications in 1 pt. each. 15 pts. died on ECMO, 1 pt. died after ECMO removal. Mortality was higher in the VV (63%) and the VA cohort (75%) than in the VAV cohort (27%). Overall, 30-day mortality was 53%. 1 pt. was bridged to lung transplantation. During a mean follow-up of 21 months, 3 pts. died
Kustermann et al. 2013 [53]	1	30-year-old pt. with pneumonia, ARDS, and severe septic cardiomyopathy. VA-ECMO was expanded to VAV cannulation due to persistently low Horovitz index on VA-ECMO	Recovery, weaning from ECMO and invasive ventilation
Moravec et al. 2014 [55]	3	74-year-old pt. with pulmonary hypertension and pulmonary fibrosis, pneumonia, sepsis, and shock. VA-ECMO was expanded to VAV-ECMO via a jugular Shaldon catheter for ARDS. 59-year-old obese pt. with cardiogenic shock, resuscitation during cardiac catheterization and IABP. VA-ECMO was expanded to VAV-ECMO via a jugular Shaldon catheter for ARDS. A third pt. received VAV-ECMO with standard ECMO cannulae.	Successful ECMO weaning in all patients. Pt. 1 died from lung fibrosis, pts. 2 and 3 survived with good clinical result
Chung et al. 2014 [51]	Review	Excellent review on monitoring during ECMO support includes a description of the principle of VAV-ECMO	
Choi et al. 2014 [49]	1	39-year old pt. with acute myocardial infarction. VA-ECMO during resuscitation, after 5 days secondary respiratory failure and upper-body hypoxemia. Upgrade to VAV-ECMO	Successful ECMO and ventilator weaning, rehabilitation, uneventful recovery at 13 month follow-up
Kim et al. 2014 [57]	1	9 pts. with ECMO after resuscitation for near-drowning. 7 pts. with VA-ECMO, 1 was converted to VV. 1 pt. patient initially received VAV-ECMO	All pts. were successfully weaned from ECMO, 7 pts. survived with a favorable neurological outcome, 2 pts. had irreversible hypoxic brain damage and died. Outcome for the pt. with

VAV-ECMO	*N*	Description	Outcomes
			VAV-ECMO is not specifically provided.
Biscotti et al. 2014 [59]	21	21 pts. with VAV-ECMO. 11 with primary VAV, 8 with switching from VV to VAV, 1 had lung transplantation on VA-ECMO and received VAV-ECMO as a bridge to VV-ECMO. 1 had ARDS and upper body hypoxemia on VA-ECMO, which was subsequently expanded to VAV	8 pts. died on ECMO, 4 were weaned from ECMO but died before discharge, 9 survived to discharge. 4 of 11 on primary VAV-ECMO survived, 4 of 8 converted from VV to VAV survived, 1 of 2 converted from VA to VAV survived
Ius et al. 2015 [54]	10	9 pts. with VV- and 1 with VA-ECMO, for ARDS or other forms of lung failure. All were switched to VAV cannulation for new onset heart failure (right heart failure, pericardial tamponade or mitral regurgitation).	3 pts. were successfully bridged to lung transplantation, 2 of which survived to hospital discharge. 4 were successfully weaned off ECMO, 3 of which survived to discharge. 3 pts. died on ECMO
Lee et al. 2016 [61]	1	27-year-old pt. with ARDS from concurrent pneumonia and acute myocarditis. Primary VAV-ECMO for ARDS and cardiogenic shock	Successful ECMO and ventilator weaning, discharge
Jeon et al 2016 [62]	1	45-year old pt. with exacerbated asthma. VV-ECMO for hypoxia despite mechanical ventilation. Development of cardiogenic shock from Takotsubo syndrome, switch to VAV-ECMO, followed by reversion to VV-ECMO 3 days later	Successful ECMO and ventilator weaning, rehabilitation, discharge
ELSO [5]	Guideline	The ELSO guideline for ECMO support in adults describes to convert VA to VAV cannulation when severe respiratory failure occurs	

pt, patient, pts, patients.

Table 4. Publications on VAV-ECMO support.

VAV cannulation is in most cases initiated as an "upgrade" from VV or VA-ECMO, either when lung failure develops during heart failure on VA-ECMO or when heart failure develops during lung failure on VV-ECMO. In the former situation, e.g., when pulmonary edema, severe pneumonia, or ventilator-associated lung injury occur on VA-ECMO, myocardial and cerebral oxygenation may be severely compromised. This is a result from the watershed phenomenon, with cyanosis in the upper body and sufficient oxygenation in the lower body distal to the watershed. This has also been termed differential hypoxia or "two-circulation syndrome" [49, 50]. Then a third cannula can be introduced for supplying preoxygenated blood to the lungs, as such adding a VV-ECMO component to a running VA-ECMO.

In the latter situation, preoxygenated blood enters the pulmonary circuit, since the patient is already on VV-ECMO. However, when left-sided heart failure develops, e.g., by septic cardiomyopathy or myocarditis, insufficient cardiac output will emerge as a major problem irrespective of good oxygenation of venous blood [53, 54]. In this case, a third cannula can be introduced to supply blood toward the aorta, with the intention to add a VA-ECMO component to the running VV-ECMO. Until now, some case series and small observational studies have demonstrated that VAV-ECMO may be used with well acceptable safety and convincing efficacy [49, 53–62] (**Table 4**); however, prospective or controlled data are still missing.

For VAV cannulation, usually the right jugular vein and the femoral vein and artery are used as vascular access. The venous cannula tips should be positioned at the border between the caval veins and the right atrium, comparable to VV-ECMO (**Figures 5** and **1**). VV-ECMO running with a bicaval dual-lumen cannula may also be upgraded to VAV cannulation, with the drainage lumen being connected to ECMO input and the return lumen to ECMO output. In principle, ECMO outflow is divided using a Y-connector, for one cannula returning blood toward the central aorta and one returning blood toward the right atrium (**Figure 5**). The flow in both cannulae, which of course also depends on cannula diameters, is balanced by using an adjustable clamp and monitored by a flow sensor (**Figure 5**). This is necessary, since the demand of arterialized blood flow on each return cannula varies from patient to patient and over time. Every change in flow balance will have an influence on preload, afterload, the watershed position, and oxygen saturations at the same time. Modifications of oxygenator and sweep gas settings will also influence oxygen saturation and carbon dioxide content in both reinfusion cannulae at the same time. Therefore, during VAV-ECMO support, repetitive echocardiography and continuous upper- and lower-body oxygenation surveillance are mandatory to assess right and left ventricular filling and function, respectively as well as tissue oxygenation. Respiratory support by VAV-cannulation is sufficient in most cases as it allows for lung protective ventilation, but hemodynamic support is lower compared to VA or VVA cannulation [54].

3.3. Veno-arterio-pulmonary-arterial cannulation (VAPa)

This is a special variant of VAV cannulation. It has not been validated in studies and is just described here for the purpose of completeness. While VAV-ECMO combines the features of VV and VA ECMO, VAPa ECMO intends to further support right heart failure during VAV-ECMO. For this purpose, the returning venous cannula is forwarded through the tricuspid valve, the right ventricle, and the pulmonary valve to the pulmonary artery (**Figure 6**). This has to be performed under angiographic (or transesophageal echocardiographic) guidance, and for this purpose a flexible 17 French cannula has to be used, as for VPa cannulation. The smaller inner diameter of that cannula intrinsically influences the flow balance of both return cannulae, which is further adjusted by a clamp and monitored by a flow sensor as with VAV-ECMO. Similar to VA and VPa cannulation, the draining cannula tip should be positioned in the mid right atrium to facilitate homogenous drainage of the upper and lower body.

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By VAPa-ECMO, the right heart is bypassed, and as such right-sided heart failure on VAV-ECMO or left-sided heart failure on VPa-ECMO can be bridged but requires a competent pulmonary valve. Again, it has to be noted that this type of ECMO is novel, as such experimental and has not been validated in clinical trials. An existing transfemoral venous ECMO cannulation does not allow for additional implantation of a microaxial right heart-assist device (Impella RP®, Abiomed). Thus, the combination of VA-ECMO and Impella RP® is not an option, and in contrast to VPa-ECMO, this approach would not offer oxygenation and decarboxylation of pulmonary blood.

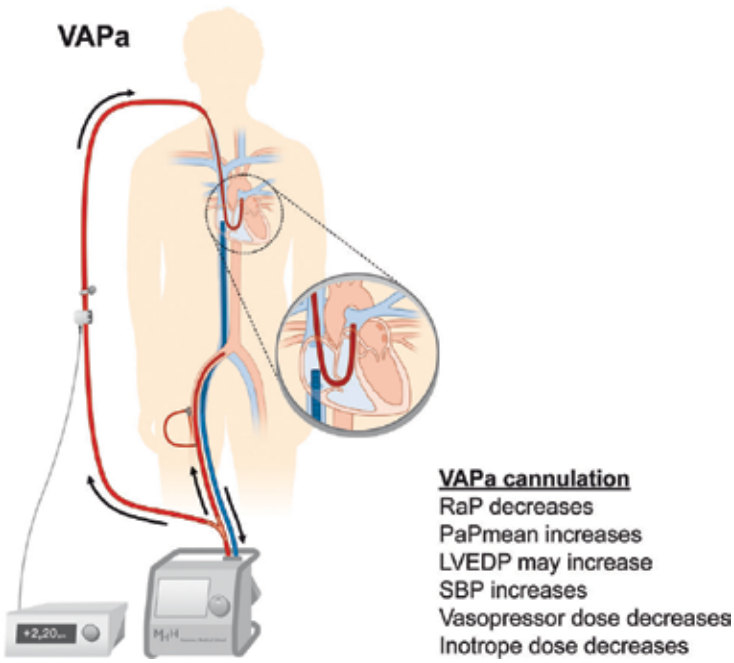

Figure 6. Veno-arterio-pulmonary arterial ECMO (VAPa). VAPa-ECMO drains venous blood (blue) from the right atrium and returns balanced volumes blood after reoxygenation and decarboxylation (red) to the iliac artery toward the aorta and to the pulmonary artery. For this purpose, the ECMO outflow is divided by a Y-connector. Flow through the returning cannulae is balanced with an adjustable clamp and monitored with a separate flow sensor on the upper return cannula.

4. Summary

VV and VA cannulation are the most common configurations of percutaneous ECMO support, serving to bridge severe respiratory and cardiac failure, respectively. VPa cannulation is a novel modification of VV ECMO to support respiratory failure complicated by right heart failure. Recently, triple cannulation ECMO has been introduced, either VVA cannulation for improved drainage or VAV cannulation for combined lung and heart failure. VAV may further

be modified to VAPa cannulation, mainly for severe right heart failure during VAV-ECMO. Novel and triple cannulations expand the spectrum of ECMO in special clinical situations; however, such configurations are even more complex than standard ECMO and require most intense monitoring and awareness. Notwithstanding these promising developments, we need prospective controlled trials of standard and advanced ECMO configurations to unequivocally assess safety and efficacy and to identify predictors of initiation and weaning of mechanical support.

Conflict of interest LCN and JB report no conflicts of interest related to this work.

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Section 3

Specific Patient Populations

Chapter 6

Venoarterial Extracorporeal Membrane Oxygenation in Refractory Cardiogenic Shock and Cardiac Arrest

Marie-Eve Brunner , Carlo Banfi and Raphaël Giraud

Additional information is available at the end of the chapter

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Abstract

The aim of this chapter is to discuss the indication and the role of a venoarterial extracorporeal membrane oxygenation (VA-ECMO) in the refractory cardiogenic shock and cardiac arrest.

Cardiogenic shock occurs in 5–10% of patients following acute myocardial infarction, and mortality remains high at 50–80% when using only medical treatment, while cardiac arrest has a poor prognosis, and despite conventional cardiopulmonary resuscitation maneuvers, only a few patients can fully return to a normal lifestyle.

VA-ECMO is a rapidly deployable temporary system for supporting the circulatory and respiratory systems. It allows time for reversible cardiac failure to recover and can prevent end-organ damage from hypoperfusion. Emergency VA-ECMO has been described for the treatment of refractory cardiogenic shock following acute myocardial infarction, electrical storm, myocarditis, and pulmonary embolism as well as in refractory cardiac arrest. VA-ECMO is used as bridge to decision to sustain life until a full clinical evaluation can be completed, as bridge to recovery until intrinsic cardiac function recovers, as bridge to candidacy to make an ineligible patient eligible for transplantation/LVAD, and sometimes as direct bridge to transplantation.

However, morbidity on VA-ECMO is rather high and has an impact on the outcome. Bleeding, lower limb ischemia, infections, and irreversible central nervous system damage still remain as serious complications.

After a few days of mechanical assistance, patients implanted with VA-ECMO for cardiogenic shock or cardiac arrest can sometimes be successfully weaned from the device, when they have partially or fully recovered from the condition that indicated ECMO use. Weaning parameters are discussed.

Finally, prognosis and survival of patients on VA-ECMO are discussed as well as the ethical aspects.

Keywords: venoarterial extracorporeal membrane oxygenation, VA-ECMO, refractory cardiogenic shock, refractory cardiac arrest, ECLS - Extracorporeal Life Support

1. Introduction

Venoarterial extracorporeal membrane oxygenation (VA-ECMO) is a temporary technique for supporting the cardiac and the pulmonary system in patients suffering from refractory cardiogenic shock [1]. It allows time for reversible forms of cardiac failure to recover and can prevent end-organ damage from under perfusion.

Cardiogenic shock (CS) is defined as critical end-organ hypoperfusion due to low cardiac output and myocardial contractile dysfunction without hypovolemia [2]. CS has a broad spectrum from mild hypoperfusion to refractory CS. Experts' recommendations for the management of adult patients with cardiogenic shock from the French-Language Society of Intensive Care (Société de Réanimation de Langue Française), with the participation of the French Society of Anesthesia and Intensive Care, the French Cardiology Society, the French Emergency Medicine Society, and the French Society of Thoracic and Cardiovascular Surgery recommend the use of peripheral VA-ECMO if temporary circulatory support is needed with a strong agreement [3]. Five percent of patients with acute myocardial infarction (AMI) develop a CS, with high mortality rates [4]. Despite optimal maximal therapy such as inotropes, Vasoconstrictors, intra-aortic balloon pump (IAPB), revascularization techniques, and mechanical circulatory support, CS remains the most frequent source of hospital death ranging between 60 and 70% compared to patients with AMI without advanced CS which is about 10% [5]. Cardiac arrest (CA) is the main cause of sudden death and occurs in almost 22% of patients with AMI [6]. CA has obviously a poor prognosis, and only a small percentage of the patients can return to a normal lifestyle. The principal causes for very poor outcome and prognosis in CA are an absence of return of spontaneous circulation (ROSC), long CPR, hypoxic encephalopathy, and out-of-hospital CA. In both refractory CS and CA following AMI, which are very critical circumstances, VA-ECMO has been proposed and utilized during the last decades to obtain rapid resuscitation, stabilization, and subsequent triage to bridge treatment. ECMO has remarkably progressed over the recent years; it became an invaluable tool in the care of adults with severe CS refractory to conventional management [7, 8].

The aim of this chapter is to describe VA-ECMO techniques, the more recent indications, and results in the use of the VA-ECMO in patients with refractory CS and CA.

2. ECMO techniques in CS and CA

VA-ECMO drains blood from the vascular system, which circulates outside the body by a mechanical pump, and is then re-infused into the circulation. In the circuit, hemoglobin

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becomes fully saturated with O_2, and CO_2 is removed. Oxygenation is determined by flow rate, and CO_2 elimination can be controlled by adjusting the rate of countercurrent gas flow through the oxygenator.

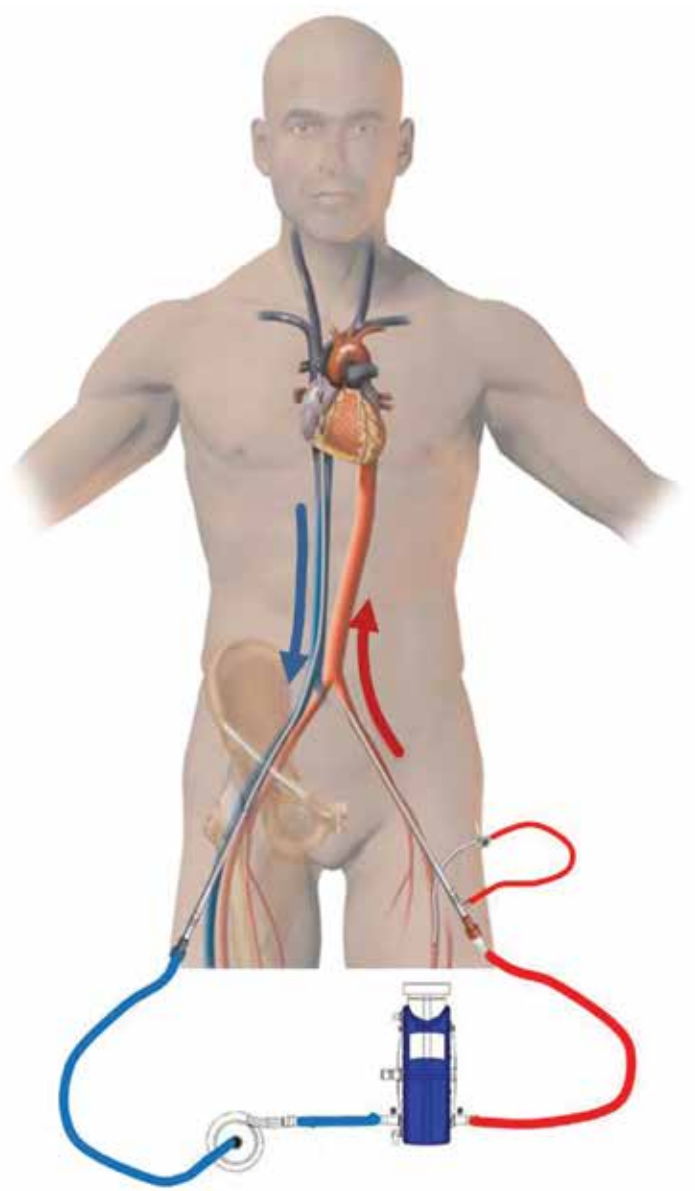

Figure 1. Percutaneous femoro-femoral VA-ECMO cannulation.

In CS and CA, where the cardiac circulation needs to be supported, a venoarterial configuration is required. This system includes a membrane oxygenator and a centrifugal pump to supply

up to 5 L/min of support. VA-ECMO can be performed either peripherally or centrally. In peripheral VA-ECMO, a venous cannula is inserted via the femoral vein to the right atrium for drainage and an arterial cannula is inserted via the femoral artery into the ascending aorta for perfusion [9] (**Figure 1**).

Peripheral VA-ECMO cannulation can be performed both surgically by semi-Seldinger cut down and percutaneously. Intensive care physicians, interventional cardiologists, and obviously cardiac surgeons can perform the percutaneous technique whereas only cardio-thoracic surgeons can perform central VA-ECMO [10].

3. Indications

There are a number of emergency indications. CS can occur in previously healthy patients or patients with chronic cardiac failure and with acute decompensation.

Refractory CS can take place after a myocardial infarction [11], any cardiomyopathy [12], a fulminant myocarditis [13, 14], intoxication with cardiotoxic drugs, electrical storm [15, 16], valvular insufficiency, massive pulmonary embolism [17], or CA with certain conditions.

Post cardiotomy CS (PCCS) can also occur after a cardiac surgery (heart transplantation for example) when it is not possible to wean from bypass [18].

Four types of situations can be described and are resumed in **Table 1**: bridge to decision, bridge to recovery, bridge to candidacy , and bridge to transplantation.

Bridge to decision (BTD)	Use of VA-ECMO in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to recovery (BTR)	Use of VA-ECMO to keep patient alive until intrinsic cardiac function recovers sufficiently to remove VA-ECMO.
Bridge to candidacy (BTC)	Use of VA-ECMO to improve end-organ function in order to make an ineligible patient eligible for transplantation/LVAD.
Bridge to transplantation (BTT)	Use of VA-ECMO to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.

Table 1. VA-ECMO: Types of situations.

Before VA-ECMO implantation, we should have several considerations. First of all, the likelihood of organ recovery has to be weighted. Initiation of VA-ECMO is appropriate only if the organ failure is thought to be reversible. When recovery is not expected, others options as transplantation or long term assist device as bridge to transplant versus destination therapy may be considered. The place of VA-ECMO in CS is shown in **Figure 2**.

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Figure 2. Place of VA-ECMO in CS.

Cardiogenic shock / Severe cardiac failure due to almost any cause	Myocardialinfarction
	Cardiacarrhythmicstorm refractory to other measures
	Fulminant myocarditis
	Massive pulmonary embolisms
	Drug overdose/toxicity with profound cardiac depression
	Septic cardiomyopathy
Post-cardiotomy	Inability to wean from cardiopulmonary bypass after cardiac surgery
Post heart transplant	Primary graft failure after heart or heart-lung transplantation
Refractory cardiac arrest (No ROSC despite 30 min of optimal CPR)	Indications: • Age < 65 years • First rhythm: "shockable" rhythm • No flow ≤ 5 min • Witnessed cardiac arrest • $EtCO_2$ per CPR > 10 mmHg • Time to ECMO < 60–90 min

Table 2. Main VA-ECMO indications for cardiogenic shock and cardiac arrest.

Advanced age, severe brain injury, long time cardiac arrest, disseminated malignancy are considered as contraindications to the institution of VA-ECMO. Finally, aortic insufficiency or aortic dissection are both major contraindications.

Indications for VA-ECMO are resumed in **Table 2**.

Clinical and biological signs as well as therapeutic measures leading to VA-ECMO implantations in cardiogenic shock are resumed in **Table 3**.

Clinical and biological signs	Therapeutic measures
SBP < 90 mmHg OR MAP < 60 mmHg	Fluid for optimal preload Vasoactive drugs (first choice: norepinephrine)
CI <2.2 l/min/m^2 S(c)vO_2 < 50% LVEF < 20% VTI < 10 cm	Inotropes (first choice: dobutamine) IABP
SaO_2 < 92%	Mechanical ventilation + sedation
Urine output < 30 ml/h	
Malignant arrhythmia	IV Loading of amiodarone and/or lidocaïne External electric shock
If despite these measures lactate levels significantly still increase within 2 hours	
→ Consider VA-ECMO implantation	

SBP: Systolic blood pressure, MAP: Mean arterial blood pressure, CI: Cardiac index, S(c)vO2: Mixed/central venous saturation, LVEF: Left ventricular ejection fraction, VTI: Velocity time integral, SaO2: Arterial oxygen saturation, IABP: Intra aortic balloon pump.

Table 3. Clinical and biological signs of cardiogenic shock as well as therapeutic measures leading to VA-ECMO implantations.

A. Refractory CS post myocardial infarction

Refractory CS post myocardial infarction is the main cause of death in hospitalized patients with acute myocardial infarction. It occurs in 5–10% of patients [19]. The use of early PCI in those patients was associated with improved survival [11]. No randomized controlled trials compare VA-ECMO with other mechanical supports, but non-randomized studies show a survival benefit with the early use of VA-ECMO. One study tested the hypothesis that early ECMO offered additional benefits in improving 30-day survival in patients with acute myocardial infarction complicated by profound CS undergoing primary percutaneous coronary intervention. The VA-ECMO group had a significantly lower 30-day mortality (39.1% versus 72%, p=0.008). This study was limited by the fact that the two cohorts were enrolled in two different periods (Non-VA-ECMO Group: 1993–2002, versus VA-ECMO group: 2002–2009) and also because coronary stents were unavailable until 1998 [20]. To date, only case reports or case series showed a benefit in implanting VA-ECMO in refractory cardiogenic

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shock. It appears essential to implant VA-ECMO before multiorgan failure but no defined criteria are yet available to decide exactly when the device should be implanted. Randomized controlled trials are needed to determine if there is a true benefit in the use of VA-ECMO in CS post myocardial infarction to determine if early VA-ECMO in conjunction with optimal medical treatment would improve clinical outcomes at 30 days as compared with optimal medical treatment alone.

B. Electrical storm induced CS

In electrical storm induced CS, appropriate and timely VA-ECMO support helps to maintain and preserve vital organ perfusion. The period of stability offered by VA-ECMO support can allow optimization of anti-arrhythmic medication particularly the use of anti-arrhythmic agents most of whom have profound negative inotropic and hypotensive effects, and prevents left ventricular dilation [15]. It also prevents the low flow syndrome and multi-organ failure. VA-ECMO implantation should be considered early when conventional maneuvers fail to control the cardiac rhythm [21]. Early-onset VA-ECMO support may be lifesaving and should be considered in the management of hemodynamically unstable arrhythmias when conventional therapy fails to convert refractory ventricular tachycardia [16, 22]. While recommendations for VA-ECMO to handle refractory ventricular tachycardia remain to be set, success in using VA-ECMO in this case rely upon the correct selection of patients in the emergency department, and the prompt implantation before multiple organ failure occurs. Prompt institution of VA-ECMO support achieves the best outcome [21].

C. Fulminant myocarditis

Fulminant myocarditis is a non-ischemic, clinical manifestation of cardiac inflammation with rapid onset and severe hemodynamic compromise. Infective etiologic process is usually the most frequent finding. Inotropic therapy and intra-aortic balloon pump might not be sufficient to treat the pump failure. VA-ECMO support may be required to provide time to enhance heart recovery in this normally self-limiting disease. A recent 5-Year Multi-Institutional Experience showed a VA-ECMO weaning rate of 81% and discharge rate of 72% in the overall patient population [13]. Mirabel et al. shows that patients with fulminant myocarditis, who would have died without emergent initiation of circulatory support, had favorable short- and long-term outcomes with 68% hospital survivors and 46% partial or complete native heart function recovery [14]. In both studies, VA-ECMO implantations were performed when maximal medical therapy failed to improve hemodynamic status. In the study of Lorusso et al., pre-ECMO patient characteristics showed a systolic blood pressure at 61.8 ± 30.4 mmHg, pH at 7.2 ± 0.1 and lactate levels at 12.0 ± 4.6 mmol/L, corresponding to severe cardiogenic shock states [13].

D. Massive pulmonary embolism

A pulmonary embolism (PE) is a common illness that can cause death [23]. Massive acute PE (MAPE) results in CA in 41% of cases and is associated with a high mortality rate [24, 25]. Clinical practice guidelines recommend fibrinolytic therapy for patients with MAPE and CA,

although few data are available to guide decisions about the agent, dose, rate, and frequency of administration [26, 27]. Fibrinolysis offers a rapid onset of action and ease of administration, and it is readily available in most hospital settings. The use of fibrinolysis during CPR in patients with presumed pulmonary embolism may improve survival [28, 29]. Fibrinolytic therapy is the first-line treatment in patients with high-risk pulmonary embolism presenting with CS in absence of contraindications. However, in several cases, there are absolute contraindications for this therapy. Catheter-based intervention is recommended for patients with circulatory collapse due to MAPE and is equivalent to surgical embolectomy [30]. Emergent VA-ECMO provides an opportunity for improving the prognosis of an otherwise near-fatal condition and should be considered in the algorithm for managing MAPE in an unstable patient [31]. The survival rate in patients with MAPE who receive VA-ECMO and anticoagulation or surgical embolectomy was 62% [31]. Thus, ECMO can provide lifesaving hemodynamic and respiratory support in critically ill patients with MAPE in patients hemodynamically unstable to support any other interventions or have not responded to medical therapies. Success in ECMO for MAPE is determined by the return of sufficient RV function [32]. ECMO may be considered in early management of patients with MAPE unresponsive or contraindicated to pharmacological treatment [33].

E. Pulmonary arterial hypertension

In addition, VA-ECMO is also a supportive option for patients with decompensated pulmonary arterial hypertension. In fact, pulmonary arterial hypertension is associated with high morbidity and mortality, particularly in patients with progressive RV failure. In this case, VA-ECMO can be used as a bridge to lung transplant or bridge to recovery when medical therapy is not sufficient to prevent cardiopulmonary failure in the acute setting [34].

F. Post-cardiotomy CS

Post-cardiotomy CS (PCCS) is very rare, but is a lethal complication in post cardiac surgery. PCCS occurs in 2–6% of patients undergoing surgical revascularization or valvular surgery [35, 36]. Approximately 0.5–1.5% of patients is refractory to maximal inotropic and intra-aortic balloon pump (IABP) support [37]. Post-cardiotomy CS occurs in perioperative cardiac surgery in patients with normal preoperative myocardial function as well as those with pre-existing impaired function [38]. Refractory PCCS leads rapidly to multi-organ dysfunction and is nearly always fatal without the use of advanced mechanical circulatory support [35]. VA-ECMO is used to salvage patients who develop refractory PCCS [39]. However, even if outcomes in patients requiring such support for PCCS continue to be poor [40], VA-ECMO may be used as temporary post-operative cardiovascular support.

G. Primary graft failure

Primary graft failure (PGF) after heart transplantation is a detrimental complication, and carries high morbidity and mortality. In a study involving 114 consecutive patients receiving orthotopic heart transplantation, 18 (15.7%) developed PGF requiring VA-ECMO support. Thirteen patients (72.2%) were able to be weaned from the support, and eight of them (44%)

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were discharged [41]. Thus, as in PGF recovery is usually more frequent than in other cases of PCCS, due to the more probable reversibility of the damage, ECMO support could be used as bridge to graft recovery [42, 43].

H. Septic cardiomyopathy

Septic cardiomyopathy occurs with severe myocardial depression in septic shock. In a retrospective observational study, 14 patients with septic shock refractory to conventional treatment all had a severe myocardial dysfunction at VA-ECMO implantation. Mean LV ejection fraction (LVEF) was 16% and cardiac index was 1.3 L/min/m^2 in these patients. At ECMO implantation, mean pH was 7.16 and blood lactate was 9 mmol/L. Twelve patients were weaned off VA-ECMO. Ten patients survived after a follow-up of 13 months and recover a normal LVEF [44]. VA-ECMO may provide benefit to patients with a cardiac failure in the setting of a septic shock, but larger studies are needed.

I. Refractory cardiac arrest

Increasing number of papers has reported encouraging results on the use of VA-ECMO for refractory CA. Extracorporeal circulation ensures an adequate blood flow, time to perform diagnostic and therapeutic interventions even before a return of spontaneous circulation is achieved [43]. For patients with whom conventional advanced life support maneuvers are insufficient and/ or to make specific interventions possible (e.g., coronary angiography and percutaneous coronary intervention (PCI) or pulmonary embolectomy for MAPE), extracorporeal CPR (eCPR) has to be considered as a lifesaving therapy [45]. This practice is evolving and is used for both in-hospital (IHCA) and out-of-hospital (OHCA) CA despite few observational statistics. Observational studies suggest that eCPR for CA is correlated with enhanced survival [46] in case of reversible cause of CA, few comorbidity, witnessed CA, immediate high-quality CPR, and eCPR early implanted (e.g., within 1 h of CA) as well as when VA-ECMO is implanted by emergency physicians and intensivists [47–50]. eCPR involves significant resource and training. It has been correlated with enhanced survival after IHCA in selected patients [47, 51] when compared with manual or mechanical CPR. After OHCA, survival after eCPR is less favorable [52]. However, when deployed during and/or soon after resuscitation attempts, despite variations in practice and heterogeneity of outcomes, these interventions yield a good neurological survival in 12% of adults suffering a refractory OHCA [53]. In a retrospective observational study dividing CA patients in two groups (shockable rhythm and non-shockable rhythm), the authors found that non-shockable rhythms could be considered as a formal contraindication allowing a concentration of efforts on the shockable rhythms, where the chances of success are substantial. They conclude that VA-ECMO for refractory OHCA should be limited due to a very poor neurological outcome [54]. Indications for eCPR are detailed in **Table 2**. However, there is an urgent need for randomized studies of eCPR and large eCPR registries to identify the circumstances in which it works best, establish guidelines for its use and identify the benefits, costs and risks of eCPR.

4. Complications

Not surprisingly, VA-ECMO is associated with a lot of possible complications that can be lethal. This is why VA-ECMO must be done by well-trained teams in reference centers.

The most common complications listed with the use of VA-ECMO are: major or significant bleeding, re-thoracotomy for bleeding or tamponade, vascular complications as lower limb ischemia, lower limb ischemia requiring fasciotomy or compartment syndrome, lower extremity ischemia requiring amputation, neurologic complications like stroke, acute kidney injury requiring renal replacement therapy, and significant infection.

A. Bleeding

In a recent meta-analyze, 20 studies were analyzed including 1866 patients. Bleeding was the most frequent complications with an estimated rate of 41%. The most frequent source of hemorrhage is the femoral cannula insertion site [55]. In central ECMO, the rate of re-thoracotomy for bleeding or tamponade was 42%. The average number of units of packed red blood cells transfused ranged from 12.7 to 29.0 units. Indeed, bleeding, thrombosis, and hemolysis remain the most common causes of morbidity and mortality for patients receiving ECMO therapy. These adverse effects have to be considered and should be monitored during ECMO therapy. Apart from surgical hemostasis problems, coagulation and inflammatory systems are immediately activated when blood comes in contact with the ECMO circuit, which necessitates systemic anticoagulation [56]. In a recent single center prospective randomized study on adult patients requiring ECMO therapy, hemostasis, anticoagulation, hemolysis, and inflammatory parameters were monitored. The results showed that median platelet count had dropped, prothrombin fragment 1.2, thrombin-antithrombin complex, and D-dimers increased, whereas fibrinogen values dropped [57]. However, antithrombotic therapy is necessary to maintain patency with the ECMO circuit and ultimately reduce the risk of clotting while decreasing the probability of hemorrhage. Currently, the most commonly used antithrombotic therapy is systemic anticoagulation with unfractionated heparin, which is associated with its well-known complications inclusive of bleeding (patient) and clotting (circuit). Systemic anticoagulation complications in ECMO support have not really reduced despite developments in technology and monitoring methods over the last few years.

Moreover, bleeding and thrombosis comprise majority of all side effects that can occur on ECMO, and the inability to mediate and control this effectively can lead to catastrophic complications and increases mortality. Heparin monitoring is very challenging on ECMO. There are actually no universal protocols concerning anticoagulation management; however, some centers propose to target 45–60 s for aPTT and 0.2–0.3 IU/ml for heparinemia (anti-Xa activity) [58]. Hemoglobin threshold for red cell transfusion should be 7–8 g/dl and only severe thrombocytopenia complicated by bleeding should be corrected. There is no single test that correctly monitors all of the factors influencing the anticoagulation, including the heparinization. As a result, over time and experience, a variety of tests are used. More recently, the Extracorporeal Life Support Organization (ELSO) proposed guidelines for management of the anticoagulation with ECMO. The main parameters monitored during ECMO are the activated

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coagulation time (ACT), the antifactor Xa assay (anti-Xa), and the activated partial thromboplastin time (aPTT). More recently, the thromboelastography (TEG) or the thromboelastometry (ROTEM) have been introduced to monitor ECMO patients. These tests add information about the phases of coagulation, platelet function, and fibrinolysis, which is very relevant in ECMO patients as they have coagulation abnormalities. While many centers have integrated those tests into their ECMO anticoagulation guidelines, more research is needed to understand the place of TEG and ROTEM monitoring in ECMO patients [59].

B. Vascular complications

Vascular issues are the second more frequent complication. The cumulative rate of lower extremity ischemia is around 17%. The cumulative rate of lower extremity fasciotomy or compartment syndrome is around 10%. The cumulative rate of lower extremity amputation occurs to 7 of 192 (5%) [60]. In another retrospective study, statistics of 100 patients with VA-ECMO inserted via percutaneous femoral approach for CS or refractory CA were examined. A 7-9 Fr percutaneous reperfusion catheter, distal to the arterial cannula, was positioned into the artery, if the leg showed sign of under-perfusion. Thirty patients with early ischemia benefited from a reperfusion cannula to improve perfusion of the limb and it succeeded in 26 of them. Seven patients suffered a compartment syndrome of the leg necessitating urgent fasciotomy. In two of those patients, the ischemia moved to irreversible ischemia necessitating amputation of the limb. The authors concluded that the majority of ischemic episodes were resolved with the insertion of a distal perfusion catheter. They did not observe any mortal vascular complication, nor was any of the observed complications related to increased mortality [61]. However, in another recent study, 84 peripheral VA-ECMO patients were separated into two groups depending on the presence of major vascular complications, defined as patients who required surgical intervention. The authors found that vascular complications negatively affect survival in patients receiving VA-ECMO support by means of femoral cannulation and that distal perfusion catheter can decrease the incidence of complications [62].

C. Hemolysis

Hemolysis during ECMO therapy remains of concern with a reported incidence between 5 and 18% [63–65]. Major contributors are technical-induced hemolysis that may consist of sub lethal damage to erythrocytes by shear stress, high ECMO blood flow particularly high flow velocity through small cannulas, cavitation particularly in case of hypovolemia, pressure changes within the oxygenator particularly in case of fibrin/thrombosis upon the membrane [66–72]. Free plasma hemoglobin (fHb) and lactate dehydrogenase can increase significantly during ECMO support [73, 74] because of red blood cell (RBC) destruction. fHb is cytotoxic causing cell necrosis [73, 75]. It also scavenges nitric oxide, leading to vasoconstriction, endothelial dysfunction, and platelet aggregation [76, 77]. Consequently, renal insufficiency or multiple organ failure can appear [78–80]. Then, prevention and rapid identification of hemolysis are crucial for ECMO patients.

D. Neurological complications

Neurological complications are rather common in patients on VA-ECMO [81]. These complications are generally related to thrombosis with cerebral infarction and intracranial hemorrhage [82]. Intracranial hemorrhage (ICH) in particular has been associated with higher rates of mortality [83]. A review on a large, multihospital database, the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project of the Agency for Healthcare Research and Quality reviewed patients between 2001–2011 receiving ECMO [84]. The authors showed that 10.9% suffered from neurological complications including seizure (4.1%), stroke (4.1%), and intracranial hemorrhage (3.6%). The outcome between seizure patients and patients without neurological complications did not differ. Patients with stroke or hemorrhage have a higher hospital length of stay, higher probability of discharge to a long-term facility, and patient who suffered of intracranial hemorrhage have a higher mortality rate. More research is still needed to prevent neurologic complications.

E. Infections

The ELSO registry found an overall prevalence of infection of 11.7%, ranging from 7.6% in neonates to 20.9% in adults, with little variation during the 11-year span of the registry data [85]. An increased rate of death was found in patients who acquired infection during VA-ECMO. Bloodstream infections were predominant in most studies that reported the site of infection, followed by surgical site infections, urinary tract infections, and respiratory tract infections [86]. A fungal infection developed in 12% of patients, with surgical site infections reported most commonly [87]. Currently, the ELSO Infectious Disease Task Force does not recommend routine antimicrobial prophylaxis during ECMO. This is confirmed by a recent review stating that there is no evidence to defend prophylactic antibiotics in most patients, even if infections during ECMO are serious complications. Infections should be prevented [86].

F. Refractory pulmonary edema

In case of peripheral VA-ECMO for refractory CS, patients with very low residual cardiac contractility and elevated afterload due to the ECMO can lead to an inadequate decompression of the left ventricle resulting in a refractory pulmonary edema, fatal pulmonary hemorrhage, and left ventricle (LV) clotting [88]. Various methods for left heart decompression are known, but there is no consensus about the appropriate method and timing of decompression. However, in this situation, the first therapeutic measures are the introduction of inotropic drugs associated with an intra-aortic balloon pump to help increase LV contractility allowing the opening of aortic valve, to decrease left ventricular afterload, and thus to unload the LV. Minimally invasive strategies such as percutaneous transseptal left atrial decompression [89] and subxiphoid surgical approaches to drain the left ventricle [90] have been described to reduce LV distension. The residual atrial defect may require correction once the patient has been weaned from mechanical support. Use of a percutaneously inserted VAD (Impella™; Abiomed, Aachen, Germany) to decompress the left ventricle has also been reported in this setting [91], alleviating the need for a high-risk septostomy or surgical venting. However, in

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some circumstances depending of the patient's state and local resources, central cannulation with left ventricular decompression may be indicated [92].

G. Harlequin syndrome

Harlequin syndrome is a hypoxemia of the upper body due to a competition of the VA-ECMO flow with the systolic function of the native heart. In a femoro-femoral VA-ECMO, when the heart function recovers, there is a competition between VA-ECMO flow and native cardiac flow in the aorta. In case of significant impairment of pulmonary gas exchange leading to an upper body hypoxemia, despite optimization of the ventilator settings, ECMO configuration has to be adapted. VA ECMO flows can be increased in an attempt to better perfuse the aortic root with retrograde arterialized blood. In addition, the arterial outflow cannulation site can be switched from the femoral artery to the axillary or carotid artery. As they are in closer proximity to the aortic arch, these cannulation sites may be more effective in washing the root with oxygenated blood. However, cannulation of these smaller vessels will require a smaller cannula, which will decrease the maximum achievable flows. A VA-V-ECMO circuit can also be created where a portion of arterialized blood from the arterial outflow cannula is diverted via the right internal jugular artery to the right heart. This enriches the blood traveling through the pulmonary circulation and to the left ventricle to provide better oxygen delivery to the coronary and cerebral circulations. Finally, if cardiac function has recovered sufficiently, VA-ECMO can be converted to VV-ECMO to provide only gas exchange support until the lungs fully recover its function [93].

5. Weaning

After a few days of mechanical assistance, patients implanted with VA-ECMO for CS or CA can sometimes be successfully weaned from the device, when they have partially or fully recovered from the condition that indicated ECMO use. Hemodynamic parameters such as invasive arterial pressure and heart rate, intravenous inotropes and vasoactive drugs, blood lactate and blood gas analyses should be monitored. A daily echocardiography should be performed and those criterions are evaluated: LVEF; aortic time–velocity integral (VTI); transmitral early peak (E) and late diastolic velocities; spectral tissue Doppler lateral mitral annulus peak systolic (TDSa); and early diastolic (Ea) annular velocities. LV filling pressures are estimated with the E/Ea ratio. First of all, the patient has to be considered as hemodynamically stable: baseline MAP > 60 mmHg with no or low-dose vasoactive agents and a pulsatile arterial waveform present for at least 24 h, and no compromising of the pulmonary blood oxygenation. Only in these conditions, an ECMO weaning trial can be attempted. ECMO flow is gradually reduced to 66% for 10–15 min, then to 33% and/or to a minimum of 1–1.5 L/min for another 10–15 min. If the patient begins to present hemodynamical instability (MAP dropped under 60 mmHg), the trial is stopped, and ECMO flow has to return to the initial flow. In a study upon 51 patients, the authors assessed a weaning strategy following support for refractory CS to recognize clinical, hemodynamic, and Doppler echocardiography parameters predictive for efficacious ECMO removal. Patients who were considered as hemody-

namically stable underwent ECMO flow decrease trials to <1.5 L/min under clinical and Doppler echocardiography monitoring. Patients with partially or fully recovery from severe cardiac failure, weaning trial tolerance, LVEF >20–25% and VTI >10 cm under minimal ECMO support, had ECMO support removed. In this study, 38 patients endured the weaning trial and 20 were finally weaned of the ECMO support.

This study showed that echocardiographic parameters determine weaned and non-weaned patients more than all other factors examined. The authors concluded that patients who tolerate a full ECMO weaning trial and have aortic VTI ≥10 cm, LVEF >20–25%, and TDSa ≥6 cm/s at minimal ECMO flow can be weaned [94].

6. Predictors of survival and outcome

Survival after VA-ECMO for refractory CS depends on etiology and severity of the patient at the implantation of the VA-ECMO support.

Mirabel et al. described factors associated with unfavorable outcomes in myocarditis related CS as higher body mass index; severe comorbidity; ICU admission Simplified Acute Physiology Score II, Sepsis-Related Organ Failure Assessment, and Glasgow Coma Scale; VA-ECMO placed under cardiopulmonary resuscitation; elevated sodium, troponin Ic and blood lactate; and low hematocrit and arterial pH [14].

Health-related quality of life was also evaluated in those survivors and revealed persistent difficulties with work or other daily activities. Mental health and vitality were deemed satisfactory. Severe anxiety, depression, and PTSD symptoms were reported by 27–38% of the patients after a median follow-up of 18 months.

Despite the high number of refractory CS requiring VA-ECMO, predictive survival modeling has not been reported till 2015 with the SAVE Score: Predicting survival after VA-ECMO for refractory CS [95]. Using a large international cohort of 3846 patients treated with VA-ECMO for CS (Extracorporeal Life Support Organization: ELSO), prognostic factors were identified for hospital survival and created a well-calibrated and reasonably discriminatory in-hospital survival prediction score comprising 13 pre-VA-ECMO variables. Parameters are Acute CS diagnosis group (myocarditis, arrhythmias, post heart of lung transplantation, congenital heart disease or others diagnoses leading to refractory CS), age, weight, acute pre-VA-ECMO organ failure, chronic renal failure, and time of intubation before VA-ECMO implantation. All of them determine a 5-class survival risk with survival rate. A SAVE-score of zero is approximately equivalent to 50% survival with positive scores representing higher chances of survival [95].

While inappropriate VA-ECMO use raises resource utilization and hospital costs and is associated with unacceptably high mortality, early identification of mortality risk factors and detailed analyses of survivors' long-term outcomes are needed. A two-center retrospective study was designed to identify pre-ECMO factors associated with in-ICU death and then

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derive a practical mortality risk score that might help physicians to select appropriate acute myocardial infarction (AMI) patients for VA-ECMO.

A study concerning 138 ECMO supporting AMI patients analyzed long-term survivors' health-related quality of life (HRQOL) and frequencies of anxiety, depression, and post-traumatic stress disorder (PTSD). The survivors were evaluated for HRQOL, psychological and PTSD status 6 months after discharge of ICU. This study showed that nearly 50% of all patients were still alive. The authors developed the ENCOURAGE score on the basis of multivariable logistic regression analyses including seven pre-ECMO parameters: age >60, female sex, body mass index >25 kg/m2, Glasgow coma score < 6, creatinine >150 μmol/L, lactate (<2, 2–8, or >8 mmol/L), and prothrombin activity < 50%. Six months after ECMO, probabilities of survival were 80, 58, 25, 20, and 7% for ENCOURAGE score classes 0–12, 13–18, 19–22, 23–27, and ≥ 28, respectively. The ENCOURAGE score ROC AUC (0.84) was significantly better than those of the SAVE, SAPS II, and SOFA scores. Survivors' HRQOL evaluated after median follow-up of 32 months revealed satisfactory mental health but persistent physical and emotional related difficulties, with 34% anxiety, 20% depression, and 5% PTSD symptoms reported. The authors concluded that the ENCOURAGE score might be a useful tool to predict mortality of severe CS in AMI patients who received VA-ECMO. However, it now needs prospective validation on other populations than AMI patients [96].

Prognosis is quite different regarding refractory CA patients. Early VA-ECMO implantation has been shown to give a better outcome in patient with CA. Low flow longer than 90 minutes offers a very bad prognosis [47].

In 2008, a French group proposed recommendations to limit the VA-ECMO implantation in case of refractory CA [97]. Our local ECMO alarms criteria for refractory cardiac arrest are shown in **Table 4**. Patients are evaluated according to these criteria by a multidisciplinary team including emergency physicians, intensivists, anesthesiologists, cardiologists, and cardiac surgeons. A consensual decision to implant a VA-ECMO or not is taken.

ECMO alarm criteria	
Indications	**Contraindications**
No-flow ≤ 3 min	No-flow > 5 min
OR immediate CPR by professional **OR** signs of life per CPR **OR** hypothermia	
Age ≤ 65 years	Obvious sign of death
First rhythm ≠ asystole	Comorbidities +++ → Futility
$EtCO_2$ ≥ 10 mmHg (≥ 1.3 kPa) under CPR	Time from cardiac arrest to ECMO > 100 min
Projected arrival at the hospital ≤ 60 min	

Table 4. E-CPR Geneva University Hospitals: refractory cardiac arrest algorithm (CPR ≥ 30 min).

Finally, some papers are now published about the ethical dimension of ECMO support [98]. In fact, ECMO technology now allows prolonged support with decreased complications, and

the need of early implantation, have led to a significant increase in the use of ECMO worldwide. This increasing use of a technology that is not a destination device in itself introduces many ethical dilemmas specific to this technology.

7. Conclusion

The use of VA-ECMO in patients with refractory cardiogenic shock and cardiac arrest is widely increasing and is now recognized as a standard technique because in these patients the mortality without the ECMO support would be dramatically higher. It seems essential to determine whether ECMO support should be initiated before organ dysfunction advances to preserve organ function. However, even if data in the literature show a progressive increase in the overall outcome, these devices are associated with serious complications such as bleeding, lower limb ischemia, infections, and CNS irreversible damage that remain problematic issues. Efforts to reduce or prevent them are necessary and strongly recommended to improve the outcome. Finally, as inappropriate VA-ECMO use raises resource utilization and hospital costs and is associated with unacceptably high mortality, early identification of mortality risk factors and detailed analyses of survivors' long-term outcomes are needed.

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Chapter 7

Extracorporeal Membrane Oxygenation Support for Complex Percutaneous Coronary Interventions in Patients without Cardiogenic Shock

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Additional information is available at the end of the chapter

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Abstract

It has been shown that extracorporeal membrane oxygenation (ECMO) may provide cardiopulmonary support during percutaneous coronary interventions (PCI) in patients with refractory cardiogenic shock. Current guidelines consider ECMO and implantable left ventricular assist devices in selected non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients. High-risk PCI remains a viable revascularization strategy for those patients who are not suitable for surgery or those refusing it. However, such a subset of patients is considered to be at an extremely high risk of PCI complications as there is a risk of hemodynamic collapse during balloon inflations or complex procedures, particularly, if coronary dissection with vessel closure or no reflow occurs. This chapter is devoted to the use of ECMO support for high-risk complex PCI in NSTE-ACS patients without cardiogenic shock based on the theoretical rationale, observational retrospective single-center studies and clinical case examples.

Keywords: ECMO, high-risk PCI, multivessel disease, non-ST-elevation acute coronary syndrome, stable hemodynamics patients

1. Introduction

In this chapter, we will try to justify the use of extracorporeal membrane oxygenation (ECMO) support for high-risk complex percutaneous coronary interventions (PCI) in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) patients without cardiogenic shock

based on the theoretical rationale, observational retrospective single-center studies and clinical case examples.

Cardiogenic shock complicates up to 8% of ST-segment-elevation (MI) and up to 3% of non-ST-segment-elevation myocardial infarctions. For cardiogenic shock patients, who fail pharmacological treatment, mechanical circulatory support devices can be introduced to augment myocardial performance and systemic perfusion. It has been shown that ECMO may provide cardiopulmonary support during PCI in patients with refractory cardiogenic shock [1–6]. Nichol et al. reviewed 84 studies of 1494 patients with cardiogenic shock, cardiac arrest or both, who were treated with PCI supported by ECMO, and showed an overall survival of 50% [3]. A similar more recent analysis found 49% survival rate either in the setting of mechanical circulatory support devices or ECMO and concluded that, in the current era, roughly half of the patients, who need a mechanical circulatory support device for refractory cardiogenic shock, survive, and roughly half of these survivors require an implantable ventricular assist device [4]. As there are no large randomized controlled trials with the use of ECMO for cardiogenic shock patients, the opinion of European experts on revascularizing this patient setting with ECMO support is not clear: "In younger patients with no contraindication for cardiac transplantation, left ventricular assist device therapy can be implemented as a bridge to transplantation. In patients not eligible for transplant, left ventricular assist devices may be inserted as a bridge to recovery or with the goal of destination therapy" [2]. At the same time, there is not enough evidence regarding safety and efficacy of ECMO during PCI in high-risk patients with NSTE-ACS without cardiogenic shock. Therefore, current guidelines consider ECMO and implantable left ventricular assist devices in selected NSTE-ACS patients [7].

Based on the United States registry data, there were ~0.4 million NSTE-ACS discharges in 2010 [8], which makes approximately1250 discharges per 1 million of the population per year. Additionally, it is well known that NSTE-ACS prognosis is unfavorable. Despite the fact that hospital mortality rate in NSTE-ACS is lower than in ST-segment-elevation myocardial infarctions, mortality at 6 months is comparable and, furthermore, mortality at 4 years is two-fold higher [9–11]. Based on our experience, we have had the evidence of an extremely poor prognosis in NSTE-ACS patients with multivessel disease that often undergo high-risk PCI [12]. Thus, this is a significant medical and social issue.

What do we know about NSTE-ACS with multivessel disease? First of all, this patient settings make up to 50% of all NSTE-ACS patients [13]. Secondly, no contemporary randomized clinical trials comparing PCI with coronary artery bypass surgery (CABG) in patients with NSTE-ACS and multivessel disease are available. Therefore, the selection of the optimal revascularization modality continues to be controversial. What is the right way to revascularize patients with NSTE-ACS and multivessel disease? Should we use CABG or PCI? Should we perform a complete or target vessel procedure? Should we choose stand-alone revascularization or a staged approach? When is it suitable to perform the procedure in relation to perioperative antithrombotic therapy and very high-risk NSTE-ACS? What is the place of staged (PCI-CABG) strategy? Currently, all these questions do not have answers apart from the point of view on complete revascularization: a complete revascularization strategy for significant

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lesions should be pursued in NSTE-ACS with multivessel disease patients [7]. This statement is based on the results of several trials which demonstrated, on the one hand, the benefit of an early complete revascularization approach irrespective of the possibility to identify the culprit lesion and; on the other hand, data show a poor 1-year outcome in NSTE-ACS patients with multivessel disease, who had a residual SYNTAX Score >8 [14–17].

There are limitations for CABG and PCI revascularization. Surgeons refuse CABG for high STS score or EuroScore II patients [18–21]. Factors associated with surgical mortality after CABG surgery include acute coronary syndrome, low left ventricular ejection fraction (EF), obesity, prior CABG and significant comorbidity (diabetes mellitus, cerebrovascular disease, peripheral artery disease, chronic obstructive pulmonary disease and renal failure) [22]. The rejection could be also based on the difficulties in balancing ischemic and bleeding risks (P2Y12 inhibitors loading) [23, 24].

The reason for PCI refusal is a high risk of death or major complications during or after PCI. At present, variables that contribute to a higher risk during PCI have been well defined by 2015 SCAI/ACC/HFSA/STS clinical expert consensus statement [1] and can be categorized into three major groups: (1) patient specific, (2) lesion specific and (3) clinical presentation specific. The statement demonstrates patient-specific (age, left ventricular function, symptoms of heart failure, diabetes mellitus, chronic kidney disease, prior myocardial infarction, peripheral vascular disease) and lesion-specific data (multivessel or left main disease, saphenous vein grafts) for high-risk PCI. There is no doubt that the clinical setting (acute coronary syndrome, cardiogenic shock) can increase a risk of PCI-related adverse events. A PCI is more high risk if we deal with a combination of factors, i.e., a large amount of myocardium at risk, complex PCI, low global left ventricular function, comorbidities and, finally, if we deal with acute coronary syndrome. For instance, if we are treating a complex coronary stenosis that affects a large amount of the left ventricle (Jeopardy score ≥ 8/12 [25] or the last patent coronary vessel) in patient with ejection fraction less than 40%, it can result in a quick hypotension or cardiovascular collapse. All of these factors may lead to a high incidence of death and major complications during and after PCI and require a personalized approach to treatment. One of the right ways to exclude a risk of hemodynamic compromise during and after a complex high-risk procedure is to use percutaneous mechanical circulatory support devices as an adjunct to PCI. Unfortunately, there are no risk calculators to assess the immediate need for mechanical circulatory support devices during PCI and this requires further investigation.

There are a lot of hemodynamically stable NSTE-ACS patients with multivessel disease in a real clinical practice. A surgical revascularization is not always feasible due to the criticality of the patient status (which is associated with a high mortality risk). Because of high surgical risk, CABG intervention could be refused either by the heart team or by a patient. Therefore, high-risk PCI remains a viable revascularization strategy for those patients who are not suitable for surgery or those refusing it. However, such a subset of patients is considered to be at an extremely high risk of PCI complications as there is a risk of hemodynamic collapse during balloon inflations or complex procedures, particularly, if coronary dissection with vessel closure or no reflow occurs. Nowadays, the development of cardiac support devices has allowed a safer approach for high-risk patients.

The next part of this chapter will discuss the number of NSTE-ACS patients with multivessel disease and the results of their treatment based on the single-center registry data reflecting real clinical practice.

2. Single-center experience in the management of NSTE-ACS patients with multivessel disease

We have observed NSTE-ACS patients consecutively admitted to our hospital in 2012. All patients had multivessel coronary disease (stenoses of two or more significant epicardial arteries and /or large branches (≥2.5 mm) ≥70% and / or stenosis of the left main coronary artery (LMCA) ≥50%). In general, NSTE-ACS patients (n = 150) had a high risk of adverse cardiovascular outcomes (mean GRACE Score 135±47.6, 40% patients had GRACE ≥140) and a significant surgical risk: mean EuroScore II was 5.7±6.4. Significant LMCA stenosis was diagnosed in 16% of patients and mean SYNTAX Score was 21.3 ± 9.9. Diabetes mellitus was presented in every fourth patient, 45% had a history of myocardial infarction, and peripheral artery disease was observed in 42% of patients of the study population (**Table 1**).

NSTE-ACS patients	***n*** **=150**
Mean age	61.6 ± 9.8 (35–82)
Male	89 (58.9%)
Mean left ventricular ejection fraction	55.9 ± 11.2 (21–73)
Mean GRACE Score	135 ± 47.6 (63–328)
GRACE ≥140	60 (40%)
LMCA stenosis ≥50%	24 (16%)
Chronic kidney disease	14 (9.3%)
Diabetes mellitus	36 (24%)
Prior myocardial infarction	68 (45.3%)
Arterial hypertension	134 (89.3%)
Peripheral artery disease	64 (42.6%)
Prior stroke	9 (6%)
EuroScore II	5.7 ± 6.4
SYNTAX Score	21.3 ± 9.9

Table 1. Baseline characteristics of the study population.

After coronary angiography all the cases were discussed by the multidisciplinary team and were divided into three groups depending on the treatment strategy: (1) PCI (n = 91, 60.6%); (2) CABG (n = 40, 26.6%) and (3) pharmacological treatment (n = 9, 6%). In addition, 10 patients

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(6.6%) required PCI followed by CABG. The mean hospital stay was 15.3±4.2 days (from 10 to 32 days). There was a conversion of treatment strategies for some patients. As a result, the treatment groups were made as follows: PCI/CABG/pharmacological treatment: 107 (71.3%)/25 (16.6%)/18 (12%), respectively. The comparison of clinical and demographic characteristics of the patient groups is presented in **Table 2**.

Variables	PCI* (n = 107)	CABG (n = 25)	Pharmacological treatment (n = 18)	$p \leq 0.05$ (PCI vs. CABG)	$P \leq 0.05$ (PCI vs. pharmaco)	$P \leq 0.05$ (CABG vs. pharmaco)
Mean age	60.5 ± 9.9	62.1 ± 7.9	67.4 ± 10.2		0.05	
Male	66 (61.7%)	17 (68%)	6 (33%)		0.04	0.05
Mean left ventricular ejection fraction	56.4 ± 10.8	56.3 ± 10.8	51.9 ± 14.1			
Mean GRACE Score	130.4 ± 41.7	133.7 ± 49.3	180.5 ± 72.9		0.004	0.02
LMCA ≥ 50%	9 (8.4%)	9 (36%)	6 (33%)	0.0005	0.009	
Chronic kidney disease	10 (9.3%)	2 (8%)	2 (11.1%)			
Diabetes mellitus	25 (23.4%)	5 (20%)	6 (33%)			
Prior myocardial infarction	44 (41.1%)	12 (48%)	12 (67%)			
Arterial hypertension	94 (87.9%)	23 (92%)	17 (94.4%)			
Peripheral artery disease	40 (37.4%)	15 (60%)	9 (50%)	0.06		
Prior stroke	4 (3.7%)	2 (8%)	3 (16.6%)			
EuroScore II	5.2 ± 6.0	5.0 ± 5.4	9.8 ± 8.4		0.03	0.03
SYNTAX Score	18.7 ± 8.8	26 ± 10.8	29.5 ± 7.6	0.001	0.001	

Table 2. Baseline characteristics of the groups.

The largest number of conversion strategy cases (n = 15) have been reported among patients who were initially selected for CABG. Seven patients were moved to the PCI group and eight patients to the pharmacological treatment group. The main reason for the strategy conversion was an extremely high risk of surgery associated with older age, female sex, severe concomitant diseases, obesity, reduced global contractility of the left ventricle, valvular pathology and a poor condition of the distal parts of the coronary arteries. It is important that hospital mortality in patients initially planned for CABG, but finally having received only pharmacological treatment was extremely high (20%). If any strategy of revascularization (PCI or CABG) was substituted with a pharmacological treatment, every third of such cases was associated with in-hospital mortality.

There were significant differences between the CABG and PCI groups in the incidence of LMCA stenosis (36% vs. 8.4%, respectively, p = 0.009) and peripheral artery disease (60% vs. 37%, respectively, p = 0.06). Patients receiving pharmacological treatment compared with the

PCI and CABG groups had older age (67.4 ± 10.2 years), higher number of females (67%) and a high risk of adverse cardiac outcomes (mean GRACE Score 180.5±72.9), significantly greater SYNTAX Score (29.5±7.6) and EuroScore II (9.8±8.4), which reflected the greatest risk of surgical and endovascular treatment.

During the first day after admission to hospital, 62.6% (n = 94), patients underwent revascularization (93 PCI and 1 CABG). Thus, in the first day of hospitalization PCI was performed for 86.9% of patients of the PCI group (93 of 107), whereas only 4% of CABG-group patients underwent CABG in this period (1 of 25). The absolute majority of the patients remaining free of revascularization in the first day received PCI within 7 days, whereas CABG was performed during 2–3 weeks after hospital admission.

Variables	**PCI* (n = 107)**	**CABG (n = 25)**	**Pharmacological treatment (n = 18)**	**NSTE-ACS (n = 150)**	**$p \leq 0.05$ (PCI vs. CABG)**	**$p \leq 0.05$ (PCI vs. pharmaco)**	**$p \leq 0.05$ (CABG vs. pharmaco)**
Death	10 (9.3%)	2 (8%)	6 (33.3%)	18 (12%)	–	0.015	–
Myocardial infarction	16 (15%)	1 (4%)	5 (27.7%)	22 (14.7%)	–	–	–
Stroke	3 (2.8%)	0	1 (5.5%)	4 (2.7%)	–	–	
Revascularization (all)	35 (32.7%)	1 (4%)	6 (33.3%)	42 (28%)	0.008	–	–
Revascularization (elective)	27 (25.2%)	1 (4%)	5 (27.8%)	33 (22%)	0.04	–	–
Combined endpoint (death + non-fatal MI)	18 (16.8%)	2 (8%)	6 (33.3%)	26 (17.3%)	–	–	–

Table 3. Long-term out comes of various treatment strategies.

The study endpoints included significant adverse events such as death, myocardial infarction, stroke and unplanned revascularization, which occurred during the follow-up period (15.3 ± 4.2 days and 27.6 ± 3.5 months). A comparative analysis of the hospital outcomes showed the worst results in the pharmacological treatment group. Hospital mortality among patients, who did not receive revascularization, was 27.7% (n = 5), compared with 5.6% and 8% in the PCI and CABG groups, respectively.

Long-term outcomes (27.6 ± 3.5 months) of the study are presented in **Table 3**. Twelve percent mortality was observed in the long-term follow-up in the overall patient population. The

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pharmacological treatment group kept leadership in the number of deaths. Mortality and the incidence of the combined endpoint (death + non-fatal MI) in patients who did not receive revascularization in the hospital period significantly exceeded mortality in the PCI and CABG groups. It is important to note that 33% of patients in the pharmacological treatment group received revascularization in the long-term follow-up period. This might have prevented a dramatic mortality increase in this group.

Myocardial infarction in the long-term follow-up period was predominantly due to the complicated hospital period in the pharmacological treatment group and a significant number of post-PCI myocardial infarctions. In the long-term follow-up period, the general incidence of repeat revascularizations was 28%. The majority of these cases (78.6%) were elective as part of the staged procedure in patients with multivessel coronary artery disease.

It is important that hospital mortality (15.3 ± 4.2 days) in the pharmacological treatment group was 27.7% and 30% among the patients converted to pharmacological treatment. The outcomes in the pharmacological therapy group could have been improved by increasing the availability of early revascularization. There are the two most important treatment strategies for these patients: early CABG or PCI with left ventricular assist device, which can be used for severe patients, representing a very high risk for CABG.

In summary, the results of the presented study showed that the majority of NSTE-ACS patients with multivessel disease required PCI. Nevertheless, for a significant number of patients, CABG is an optimal revascularization strategy. An essential proportion of patients, who require CABG, do not receive it in the early hospital period due to a high surgical risk, and this leads to poorer hospital outcomes among acute coronary syndrome patients. Patients of the pharmacological treatment group have the highest rate of hospital mortality. This fact suggests a need to increase the availability of early CABG or PCI with left ventricular assist device in high-risk PCI patients. A rationale for the choice of ECMO as support for a high-risk PCI in NSTE-ACS patients will be presented in the next section of this chapter.

3. Why did we choose ECMO to support a high-risk PCI in patients without cardiogenic shock?

To rule out the risk of hemodynamic compromise during and after the high-risk PCI, we can use percutaneous mechanical circulatory support devices. There has been a significant increase in the utilization of mechanical circulatory support devices from 1.3% of all PCIs in 2004 to 3.4% in 2012 (p trend < 0.001) in patients undergoing PCI in the United States [26]. Historically, the intra-aortic balloon pump (IABP) has long been used as a percutaneous hemodynamic support [27, 28]. Nowadays, a number of new devices have become available and have entered clinical practice. These include left ventricle to aorta assist devices, such as Impella (microaxial flow pumps); left atrial to the iliofemoral arterial system bypass pumps, specifically the TandemHeart; and extracorporeal membrane oxygenation [1].

The IABP provides modest ventricular unloading and enhances cardiac output, but does increase mean arterial pressure and coronary blood flow. A trigger from electrocardiographic

rhythm or arterial pressure ensures balloon inflation and deflation. Based on the BSIC-I randomized trial, Perera et al. [29] concluded that routine elective use of IABP did not reduce the incidence of major adverse cardiac and cardiovascular events following high-risk PCI. There was no difference between the two groups in the 6-month mortality rate (IABP 4.6% vs. no IABP 7.4%; $p = 0.32$). These results do not support a strategy of routine IABP placement before PCI in all patients with severe left ventricular dysfunction and extensive coronary disease.

The Impella moves blood from the left ventricle to the aorta, thereby unloading the left chambers of the heart and increasing the cardiac output. A sufficient right ventricular performance or additional right ventricular assist devices are necessary to maintain left ventricular preload and hemodynamic support during Impella pumping [1]. Only 14-F (CP device) or 21-F cannula (5.0 and LD devices) can provide an output of 5 L/min. The biggest experience to date has been gained with the Impella 2.5 device which can provide the flow rate only up to 2.5 L/min. CE mark approves the use of Impella up to 6 days. The PROTECT II study represents the largest prospective, randomized trial comparing hemodynamic support with Impella 2.5 ($n = 226$) versus IABP ($n = 226$), initiated prior to planned high-risk PCI in symptomatic patients with complex three-vessel disease or unprotected LMCA coronary artery disease, and severe ventricular dysfunction [30]. Although Impella provided better hemodynamic support with a maximum decrease in the cardiac power output from the baseline (0.04±0.24 W for Impella 2.5 in comparison with 0.14±0.27 W for IABP ($p = 0.001$)) and was required for a shorter duration, no significant difference in 30-day major adverse event rate was observed between the two groups (35.1% for Impella vs. 40.1% for IABP; $p = 0.227$). However, at 90 days, a strong trend toward lower major adverse event rate was observed in Impella 2.5L supported patients in comparison with IABP (40.6% vs. 49.3%; $p = 0.066$). Cohen et al. have published the article [31], analyzing the use of percutaneous left ventricular assist device to support high-risk PCI. The authors performed retrospective observational analysis of 339 patients included in the USpella registry, who were supported for high-risk PCI with a micro-axial rotational pump (Impella 2.5). There were patients who have met the eligibility criteria for the Impella arm of the PROTECT II trial [2]. In-hospital outcomes of the USpella registry patients were compared with the results of 216 patients treated in the Impella arm of the PROTECT II randomized trial. The authors concluded that despite a higher risk in the registry patients, clinical outcomes appeared to be favorable and consistent compared with the randomized trial.

The TandemHeart pumps blood from the left atrium to the iliofemoral arterial system through a transseptally placed cannula, thereby bypassing the left ventricle. The device reduces left ventricular preload, left ventricular workload, filling pressures and myocardial oxygen demand [1]. The TandemHeart provides an option of including an oxygenating membrane within its circuit. CE mark approves the use of the TandemHeart up to 30 days. No contemporary comparable large-scale randomized clinical trials of high-risk PCI with the TandemHeart device are available. Several observational studies have reported centers' experience of elective implantation of the TandemHeart device prior to high-risk PCI [32–34]. Although these latter small studies confirmed that the TandemHeart is technically feasible and may provide excellent hemodynamic support, the device use continues to be associated with significant

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complications such as stroke, limb ischemia and bleeding around the cannulation site. More recently, in 54 patients with extensive CAD (mean SYNTAX Score 33), undergoing high-risk PCI with the TandemHeart device for support, Alli et al. [35] reported 97% of success and 13% of major vascular complications, with survival rates at 30 days and at 6 months, as high as 90% and 87%, respectively. Finally, a small study compared the Impella 2.5 versus the TandemHeart to support high-risk PCI [36]. The 30-day major adverse cardiac event rate (death, myocardial infarction and target lesion revascularization) was 5.8% and was similar between the two groups with 99% of the PCI success rate in the both groups.

ECMO uses a centrifugal pump to drive blood from a patient through an oxygenator system before returning to the patient's arterial system. Cannulation sites include the femoral artery and the femoral vein (venoarterial ECMO) or the internal jugular vein/right atrium and the common femoral vein (venovenous ECMO). In addition to blood oxygenation, venoarterial ECMO can provide systemic circulatory support, augment cardiac output and unload both the right and left ventricles. The advantages of ECMO include the possibility of cannulation at the bedside. Currently, we have very few data on the use of ECMO to support high-risk PCI without cardiogenic shock as adjunct modality. The data are limited to single report. Galassi et al. [37] reported the successful use of ECMO for a high-risk NSTE-ACS patient with low ejection fraction (<20%) who underwent three-vessel total occlusive antegrade revascularization by PCI. Tomasello et al. [38] demonstrated a single-center experience of ECMO support for complex high-risk elective PCIs. Twelve patients underwent elective high-risk PCI with ECMO support. All PCI procedures were successful and no in-hospital major adverse cardiac or cardiovascular events were observed. At 6 months, neither death nor MI was observed. Two patients (17%) required further revascularization, and one patient required chronic hemodialysis. The authors concluded that elective high-risk PCI supported by ECMO is a viable therapeutic alternative for patients with severe coronary artery disease and left ventricular dysfunction, who are at a very high risk for CABG and able to ensure good immediate and mid-term outcome.

Our single-center registry data showed extremely poor prognosis if the revascularization for high-risk multivessel NSTE-ACS was refused [10]. As shown in the previous part of this chapter, hospital mortality rate is 28% if we choose a pharmacological strategy versus 5.5% for PCI and 8% for CABG. The pharmacological strategy group patients were refused any kind of revascularization and, of course, there were predictors of high-risk PCI (the mean SYNTAX Score 32, the mean GRACE Score 180 and unprotected left main stenosis in 33% of patients, all patients had signs of high-risk NSTE-ACS). At that moment we asked ourselves: What can we do with such multivessel high-risk NSTE-ACS patients? Could we help such patients with PCI supported by ECMO?

Why did we choose ECMO support for high-risk PCI in patients without cardiogenic shock? As compared with other devices, IABP provides a relatively modest augmentation of cardiac output (0.3–0.5 L/min). Conversely, the TandemHeart and ECMO may provide up to 3.5 and 5 L/min of cardiac support, respectively, whereas the Impella catheter can increase the cardiac output up to 2.5, 3.8 or 5 L/min, according to the selected size. Notably ECMO, TandemHeart and Impella 5L devices, often required a surgical cut-down, whereas IABP, Impella 2.5L and

3.8L could be exclusively managed percutaneously. In comparison with other ventricular assist devices, ECMO has the advantage to provide a more comprehensive circulatory support as it is responsible for both cardiac pump function and pulmonary gas exchange. For example, with ECMO, even if we deal with a cardiac arrest, a patient is still alive, and we can continue the high-risk PCI procedure. Importantly, the TandemHeart provides an option of including an oxygenating membrane within its circuit, thus, creating an ECMO-type circuit. However, despite their encouraging results, the expensive cost of both TandemHeart and Impella devices represents a major problem to extend their use.

It is believed that ECMO is limited by its complexity and the need for perfusion expertise and is rarely used in the cath-labs. These restrictions are not significant for Russian cath-lab teams as there is a widespread use of Prostar XL devices and 24/7 on-duty anesthesiologist (a member of the cath-lab team) who can provide ECMO perfusion. On the other hand, usually, these NSTE-ACS patients without cardiogenic shock do not need immediate revascularization, which means that a calm perfusion preparation and performing PCI on an elective basis is possible. Additionally, one of the main limitations of ECMO is that the left ventricle is not decompressed and this leads to a higher left ventricular wall stress. Theoretically, this has negative consequences on myocardial protection that can be decreased by a combination of ECMO and Impella (IABP) support [1, 39].

Thus, based on our single-center real-life registry data, there are up to 12% of the hemodynamically stable multivessel disease NSTE-ACS patients who were refused any kind of revascularization and had extremely poor prognosis with pharmacological approach [10]. PCIs for this setting have an extremely high risk of hemodynamic collapse so they need to be performed with hemodynamic support. A number of devices have been used for this purpose but we consider ECMO to be the best device. ECMO is able to provide the cheapest complete circulatory support (both oxygenation and circulatory support). However, randomized trials are necessary to establish effectiveness of percutaneous mechanical circulatory support devices in adjunction with high-risk PCI. Since 2012, we have begun to perform PCI with ECMO support for extremely high-risk multivessel NSTE-ACS patients who have been refused any form of revascularization. To evaluate the results, we decided to compare them with the outcomes of CABG for multivessel NSTE-ACS patients. The next part of this chapter will show the analysis of our single-center retrospective observation.

4. Extracorporeal membrane oxygenation support for complex high-risk percutaneous coronary interventions in patients without cardiogenic shock: a single-center experience

PCI with ECMO support and high-risk CABG for NSTE-ACS patients with multivessel disease will be presented in this section. It was a single-center registry, which compared 30-day outcomes of PCI with ECMO support and CABG in high-risk NSTE-ACS patients.

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Variables	PCI + ECMO (n = 22)	CABG (n = 53)	p
Demographic			
Age	64.2 ± 9.7	63.5 ± 7.5	0.4
Male	68.2% (15)	66% (35)	0.4
Body mass index	31.9 ± 6	27.1 ± 4.7	0.0002
Clinical			
Diabetes	31.8% (7)	15% (8)	0.05
Arterial hypertension	100% (22)	90.5% (48)	0.07
Hypercholesterolemia	81.8% (18)	39.6% (21)	0.0007
Prior MI	40.9% (9)	50.9% (27)	0.2
Prior stroke	9.1% (2)	7.5% (4)	0.4
Prior CABG	0	1.9% (1)	0.3
Chronic obstructive pulmonary disease	9.1% (2)	1.9% (1)	0.08
Peripheral artery disease	63.6% (14)	30.2% (16)	0.004
Glomerular filtration rate	91.5 ± 31.7	75.2 ± 28.4	0.05
Left ventricular ejection fraction, %	38.8 ± 12.7	53.6 ± 10	0.0001
GRACE	148 ± 22.9	95.6 ± 16.4	0.0001
EuroScore II, %	4.7 ± 3.7	3.61 ± 1.9	0.05
Angio			
Multivessel disease	100% (22)	100% (53)	0.5
Unprotected LMCA	81.8% (18)	39.6% (21)	0.0007
Mean LMCA stenosis %	78.1 ± 21.5	69.7 ± 18.1	0.1
Right dominance	68.2% (15)	92.4% (49)	0.02
SYNTAX Score	34±9.7	30±8.2	0.04
Jeopardy Score	11.2±1.7	8.4±1.9	0.0001

*Cockroft–Gault formula.

Table 4. Baseline characteristics and angiographic data.

High-risk CABG was based on a high-risk logistic EuroSCORE II (>5) and included one of the following: obesity (body mass index (BMI) > 30); severe concomitant disease (diabetes, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease and renal dysfunction); and dual antiplatelet therapy within the past 24 h.

High-risk PCI was defined as (1) the presence of impaired left ventricular function (ejection fraction < 30% on echocardiography); (2) a large amount of myocardium affected by stenosed vessels (Jeopardy Score ≥ 8), characterized by LMCA stenosis or by a target vessel that provided collateral supply to the occluded second vessel that, in turn, supplied > 40% of the myocardium; and, additionally, technical difficulties with the PCI procedure; and (3) intervention for bifurcation and/or left main and/or chronic total occlusion.

The study included 75 patients (PCI + ECMO, n = 22; and CABG, n = 53). All patients had multivessel disease with Syntax Score >25. PCI + ECMO group had more patients with obesity, hypercholesterolemia, diabetes, low ejection fraction, unprotected LMCA and peripheral artery disease, compared with the CABG group. In addition, the PCI group had a higher risk of the deterioration in the following scores: GRACE, EuroScore II, SYNTAX Score and Jeopardy Score. Thus, PCI + ECMO group had a potentially poorer prognosis (**Table 4**).

For PCI + ECMO, 21–23 Fr venous cannula was inserted in the right common femoral vein to the right atrium using a surgical technique. The 17–18 Fr arterial cannula was placed in the iliac artery. The mean cardiopulmonary support flow was 2.2–2.7 L/min/m^2. The mean bypass duration was 95.4 ± 25.2 min. The medications during PCI included unfractionated heparin and acetylsalicylic acid. The loading dose of clopidogrel before PCI received 42% of patients. The remaining 58% of patients had a loading dose of clopidogrel immediately after the surgical cannulation wound closure.

ECMO began immediately prior to PCI. We used the "RotaFlow System," developed by the MAQUET Getinge Groupe, Hirrlingen, Germany. The study endpoints were the success of the intervention, death, myocardial infarction, stroke, repeated revascularization and bleeding, as well as the combined endpoint of death, myocardial infarction, stroke and revascularization.

The mean revascularization waiting time was about 2 weeks in the both groups. In all the cases, the revascularization was successful in the both groups. Most of the CABG patients (94.3%) had a complete revascularization compared with 54.5% in the PCI + ECMO group (p = 0.0001). The mean length and diameter of implanted stents were 49 ± 16.7 mm and 3.5 ± 0.5 mm, respectively.

There were two fatal cases (9.1%) in the PCI + ECMO group and four patients died (7.5%) in the CABG group at 30-day follow-up (p = 0.2). Two patients (3.8%) of the CABG group had myocardial infarction as a complication of the postoperative period. One of these cases led to death. A major bleeding was observed in seven patients (13.2%) in the CABG group versus two patients (9.1%) in the PCI + ECMO group (p = 0.3). There were no significant differences in the incidence of endpoints at 30-day follow-up (**Table 5**).

Variables	**PCI + ECMO (n = 22)**	**CABG (n = 53)**	p
Successful revascularization	100% (22)	100% (53)	0.5
MACE	9.1% (2)	9.4% (5)	0.15
Death	9.1% (2)	7.5% (4)	0.2
Myocardial infarction	0	3.8% (2)	0.2
Repeated revascularization	0	0	0.5
Stroke	0	0	0.5
Major bleeding (TIMI)	9.1% (2)	13.2% (7)	0.3

Table 5. Thirty-day outcomes of revascularization.

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The present study included patients with high risk of adverse outcomes for any kind of revascularization (CABG and PCI). The main hypothesis of the study was that PCI + ECMO may be an alternative strategy of revascularization for NSTE-ACS patients at a high risk for CABG.

All the patients had an extremely severe diffuse coronary artery disease with LMCA stenoses, bifurcation lesions and chronic total occlusions (CTO) and underwent challenging PCI with ECMO support, which allowed to carry out a successful revascularization in stable hemodynamic conditions.

Despite the fact that CABG is a preferred method of revascularization for complex multivessel coronary disease patients, PCI with ECMO as a hemodynamic support can be successfully performed in a high-risk cohort of NSTE-ACS patients. Therefore, PCI with ECMO support may increase revascularization availability for this severe group of patients with a very high risk of in-hospital fatal outcomes, reaching 27% in the absence of the procedure.

The present study had several limitations. First of all, it was not randomized and the groups were not comparable. Nevertheless, the PCI +ECMO patients group had a more severe clinical and angiographic status, which made it possible to test PCI with ECMO as a method of revascularization in extremely high-risk cohort of NSTE-ACS patients. Second of all, a small number of patients included in the study did not allow to make definitive conclusions. Thus, in order to answer the question on the role of ECMO for high-risk PCI NSTE-ACS patients, randomized trials are required.

5. Clinical case examples of high-risk PCI supported by ECMO in NSTE-ACS patients

5.1. Clinical case example 1

The first case is presenting a successful antegrade recanalization of a 67-year-old male who survived cardiopulmonary resuscitation after non-ST-segment-elevation myocardial infarction. The patient experienced a cardiac arrest due to ventricular fibrillation after admission to hospital and he was stabilized after 25 min of cardiopulmonary resuscitation. After the resuscitation no neurological symptoms were detected. Coronary angiography revealed CTO in three vessels with severe coronary calcifications (**Figure 1A–C**); the patient was not considered to be a surgical candidate due to his poor clinical condition (very low EF <20% and ACS at presentation) and to his angiographic characteristics (very small coronary arteries without visualization of distal coronary segments). ECMO (ECMO for the circulatory failing heart system in real clinical patient setting after epidural anesthesia and surgical cannulation of the femoral vein and artery; the pump maintained a minimum flow of 2.0 L/min/m^2) and PCI, with the use of new composite dual coil guidewire Fielder XTR (Asahi Intecc Co., Japan) 48h after acute MI, were used to fully recanalize the left anterior descending artery (LAD), circumflex artery (CX) and right coronary artery (RCA). Excellent angiographic results were

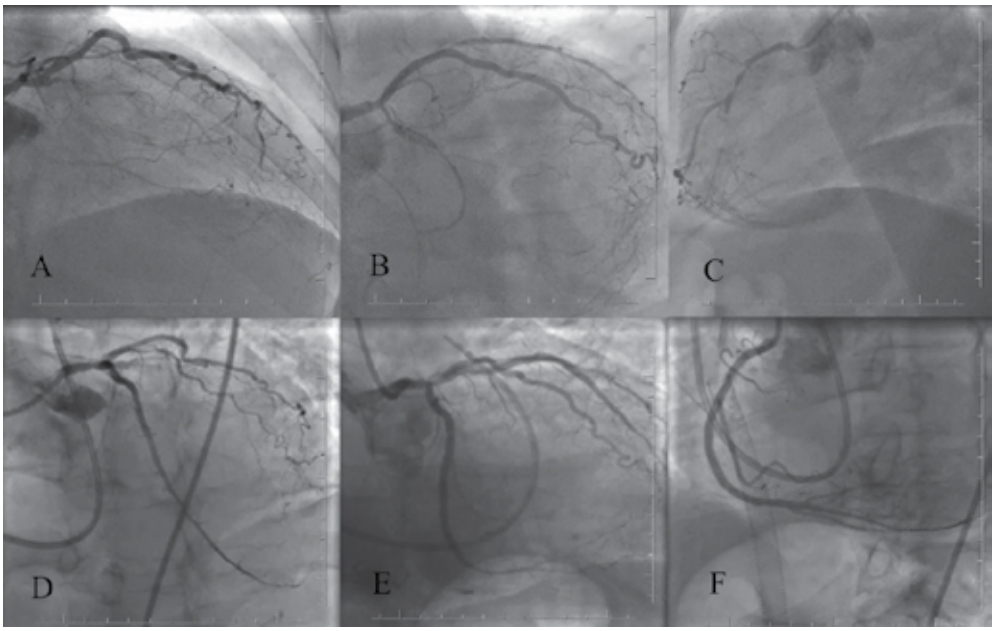

Figure 1. A successful antegrade recanalization of three CTOs in the NSTE-ACS patient supported by ECMO.

obtained by the use of three, two and four drug eluting stents (DES) in the LAD, CX, and RCA, respectively (**Figure 1D–F**), and ECMO was terminated at the end of the procedure.

In the search of technical solutions to improve the results of PCI in CTO, intracoronary guide wires represent, probably, the most advanced class of devices. The recent setup of the so-called "composite core, dual coil" guidewires can be considered an absolute turning point, especially when the complexity of CTO, patient clinical conditions and the use of an antegrade technique might limit procedural success.

To the best of our knowledge, this is the first case presentation of a three-CTO PCI executed in a single procedure and supported by ECMO in a patient in critical clinical condition. Percutaneous coronary intervention was considered the last remaining option to improve the outcome, and ECMO was used to guarantee circulatory assistance during the procedure. Indeed, CTO lesions and a critical hemodynamic patient condition due to ACS are considered the worst revascularization scenario taking into account that these patients are not suitable for cardiac surgery. Nevertheless, based on the excellent results of CTO revascularization already demonstrated in less complex clinical conditions, we believe that, by minimizing the risk of intra-procedural adverse events with the use of ECMO, revascularization of CTOs is possible even in the case of severe clinical conditions, by offering a patient an opportunity of revascularization therapy, the survival could be improved. Notably, the patient did not have any periprocedural adverse events, the EF improved up to 32% at 1-week follow-up, and he was discharged 9 days after the procedure.

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5.2. Clinical case example 2

The second case is presenting a successful high-risk multivessel PCI of a 58-year-old NSTE-ACS patient with a hemodynamic support by ECMO. The patient was presented with high-risk ACS (GRACE = 173). Coronary angiography revealed a three-vessel disease with significant severe thrombotic LMCA stenosis (85%) and RCA stenosis (75% of prox. part and 90% of mid. part) (SYNTAX Score = 23) (**Figure 2A** and **B**). The patient was obese with a body mass index of 35 kg/m^2. According to the echocardiography assessment, left ventricular ejection fraction was 50%. Before the admission to hospital, the patient received a loading dose of clopidogrel (300 mg) and acetylsalicylic acid (250 mg). At the time of angiography, the patient had severe chest pain associated with hemodynamic instability (hypotension, bradycardia), requiring analgesia and cardiotonic infusion. There was a very high risk for emergency CABG (hemodynamic instability, dual antiplatelet therapy, obesity), and the multidisciplinary team decided to carry out multivessel PCI supported by ECMO. Using artificial lung ventilation and multicomponent anesthesia, the puncture of the common femoral artery and the common femoral vein with closure device placement of ("Pro-Star" system) was performed (**Figure 3**). A venous cannula was positioned in the right atrium and an arterial cannula in the infrarenal part of the aorta. The pump maintaining a flow of 2.4–2.7 L/min was used. The middle and proximal RCA stenting was performed in ECMO conditions. Two DES were implanted with a diameter of 4 mm and a length of 22 mm (**Figure 2C** and **D**). As the next step kissing-predilation of LMCA-LAD and LMCA-IMA was performed. DES with a diameter of 4 mm and a length of 23 mm was implanted to LMCA-LAD. At the end of PCI T-provisional technique with kissing-dilatation of LMCA-LAD (balloon catheter 4.5–20 mm) and LMCA-IMA (balloon catheter 3.5–20 mm) was used (**Figure 2E** and **F**). ECMO was terminated at the end of the procedure. The arterial and vein cannulas were removed. The vascular access was successfully closed with the "Pro-Star" system. The patient was transferred to the intensive care unit. The patient was extubated when awake. The hemodynamics remained stable and

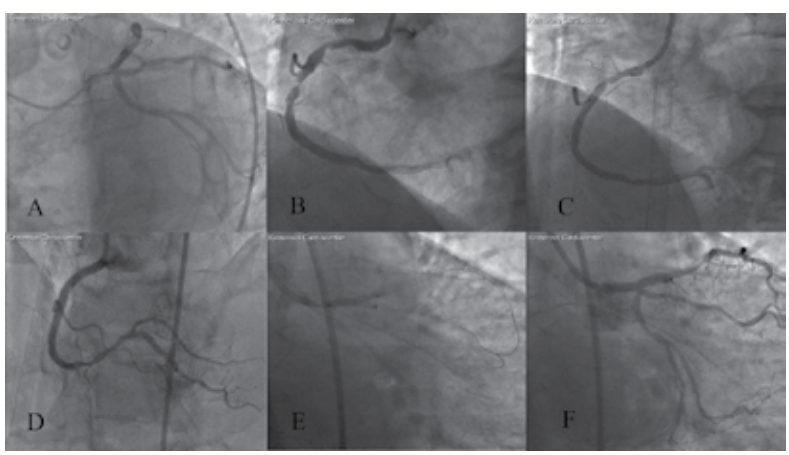

Figure 2. High-risk multivessel PCI with hemodynamic support by ECMO in the NSTE-ACS patient.

ischemia did not recurred. After 10 days, the patient was discharged from the clinic. Therefore, the use of ECMO allowed to perform a high-risk multivessel PCI in the NSTE-ACS patient in stable hemodynamic conditions.

Figure 3. Using the "Pro-Star" system for arterial and venous vascular access closure.

Thus, these clinical cases showed efficacy and safety of high-risk PCI with ECMO support in the treatment of NSTE-ACS patients, unsuitable for CABG and having extremely poor prognosis in the absence of revascularization. It is possible to use ECMO cannulas with a surgical or a puncture method and the Pro-Star system as a vascular access closure device. A local anesthesia in combination with an epidural block or total intravenous anesthesia can be used.

6. Conclusions

The current status of ischemic heart disease patients is characterized by an increase in the prevalence of advanced coronary disease, poor distal targets, severe comorbidities, reoperation, advanced age or impaired left ventricular function, which make surgical revascularization unattractive. PCI may be an alternative for these so-called high-risk PCI patients. Given aging population, increasing morbidity, technical advantages of percutaneous revascularization and improved quality of medical care, the number of such patients will grow.

Multivessel NSTE-ACS patients are one of the high-risk PCI groups based on such predictors as advanced complex coronary disease, a large amount of myocardium at risk, low global left ventricular function, comorbidities and high GRACE Score. The prevalence of multivessel NSTE-ACS (up to 50% of all NSTE-ACS patients [13]) and extremely poor prognosis with a pharmacological approach (hospital mortality rate of 28% [12]) make the issue of these patients

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treatment very important. PCI supported by ECMO is an unexplored strategy for this patient setting. Current recommendations suggest performing PCI with ECMO support for cardiogenic shock or cardiac arrest patients [1, 2]. There are limited data on the use of ECMO for high-risk PCI as well as for complex PCI in NSTE-ACS patients without cardiogenic shock [37, 38]. However, elective application of the device has a theoretical rationale, showed encouraging results based on the results of our single-center retrospective observation and was demonstrated by the presented clinical case examples.

There are two main unresolved issues related to the use of percutaneous mechanical circulatory support devices for high-risk elective PCI that will represent a challenge for the future progress. When should we use them? Which device is the best? The expert consensus statement suggested a schema for the support device use in high-risk PCI, which provides a clear solution only in the case of a combination of two risk factors: severe left ventricular dysfunction and an anticipated technically challenging PCI [1]. One of these makes it necessary to use the approach with IABP/Impella as a backup, which creates issues in case there is a need for emergency complete circulatory support. Clearly, the main disadvantage of this scheme is that it does not take into account an important adverse prognostic factor such as acute coronary syndrome. Thus, there is a necessity to further investigate the risk calculators to assess the online need for mechanical circulatory support devices during high-risk PCI. Finally, device selection is a matter of a personalized approach and the results of subsequent large randomized comparative studies.

Thus, in the current chapter, we attempted to provide the rationale for the hypothesis that a very high-risk complex PCI facilitated by ECMO can provide successful myocardial revascularization in patients ineligible for CABG. PCI with ECMO support is a feasible approach for high-risk interventions in hemodynamically stable NSTE-ACS patients with multivessel disease who were refused any kind of revascularization. Further research is needed to define precise indications for the use of ECMO and its priority role in high-risk PCI patients.

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Appendices

Appendix A.

The GRACE (2.0) Acute Coronary Syndrome Risk Calculator

The GRACE (Global Registry of Acute Coronary Events) 2.0 Acute Coronary Syndrome (ACS) Risk Calculator is a tool to help clinicians assess the future risk of death or myocardial infarction (MI), as a guide to treatment options, in a patient with ACS. It includes clinical findings at admission that have been shown to have predictive power for adverse events. These factors include age, pulse rate, systolic blood pressure, renal function, congestive heart failure, ST-segment deviation, cardiac arrest and elevated biomarkers, which together provide more than 90% of the accuracy of the complete multivariable prediction model. Outputs are given in terms of probability of dying (as a percentage) while in hospital, and at 6 months and 1 and 3 years after admission. The combined risk of death or MI at 1 year is also given. The GRACE Score at 6 months is also provided as guidelines have categorized patients into low (≤108 GRACE Score), medium (109–140 GRACE Score) and high risk (>140 GRACE Score) [7].

The updated calculator is derived from the original GRACE Score. The work on the updated calculator was supported by the British Heart Foundation, the Chief Scientist in Scotland and an educational grant from AstraZeneca to the University of Edinburgh. Professors Frederick

A. Anderson, Jr. and Gordon FitzGerald of the Center for Outcomes Research, University of Massachusetts Medical School, analyzed the GRACE population risk factors and created the algorithms. The algorithms were implemented, and the app and website were created by AS&K Communications.

GRACE is an international observational program of outcomes for patients who were hospitalized with ACS in a period of 10 years from 1999. GRACE includes nearly 250 hospitals in 30 countries, and enrolled a total of 102,341 patients. Participating physicians receive confidential quarterly reports showing their outcomes side by side with the aggregate outcomes of all participating hospitals. The GRACE Risk Score has been extensively validated prospectively and externally.

The GRACE 2.0 ACS Risk Calculator is available online on the Internet (http://www.gracescore.org). To calculate the GRACE risk for any patient with documented or suspected ACS, enter the patient data by selecting from the ranges given or by using the yes/no toggle switches. Press "Calculate" to obtain risk of event probabilities or "Reset" to clear all entered data. On the results screen, use "Edit input" to change individual parameters for the same patient or "New calculation" to reset the calculator and start over. The results are given first as a probability (expressed as a percentage) of either death alone, or death/MI, occurring up to given time points after admission. The original GRACE Score is also provided for 6-month results (**Figure A1**).

Figure A1. The Global Registry of Acute Coronary Events 2.0 Acute Coronary Syndrome Risk Calculator (http://www.gracescore.org).

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Appendix B.

The SYNTAX Score calculator

The SYNTAX Score is an angiographic tool used to characterize the coronary vasculature and predict outcomes of coronary intervention based on anatomical complexity. The SYNTAX Score was developed in connection with the SYNTAX (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial, which compared percutaneous coronary intervention (PCI) using Taxus Express paclitaxel-eluting stents (Boston Scientific Corporation, Natick, MA) to cardiac surgery in complex, high-risk patients with left main and/or three-vessel disease. A heart team (cardiac surgeon and interventional cardiologist) assessed each patient for suitability for both revascularization modalities, and consequently calculated the patient's SYNTAX Score based on coronary lesion complexity prior to the revascularization procedure. The Syntax Score and related materials were developed under the direction of the SYNTAX Steering Committee, and it was made possible by the support from Boston Scientific Corporation and Cardialysis BV.

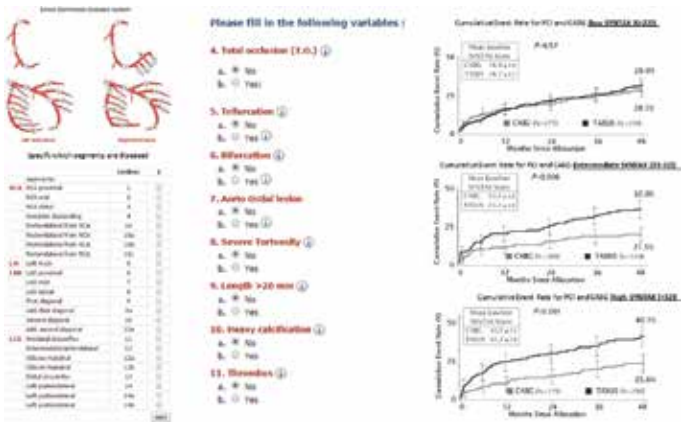

Figure B1. The SYNTAX Score Calculator (http://www.syntaxscore.com).

A computer program calculates the SYNTAX Score after answering a set of interactive, self-guided questions. The online SYNTAX Score calculator consists of 11 questions. Two questions determine the coronary artery dominance and diffuse disease/small vessels and will be asked only once per patient. The remaining questions refer to detailed adverse lesion characteristics and will be repeated for each lesion separately. The SYNTAX Score calculates a point value for each lesion, which will be summed to generate the patient's overall SYNTAX score. For patients with three-vessel disease and/or left main disease (SYNTAX trial population), the cumulative MACCE outcomes by SYNTAX score will be illustrated on a Kaplan–Meier curve. The patient's name, ID number and date of birth can be added, and the SYNTAX score document can be saved or printed for the patient's file. The SYNTAX Score Calculator is available online on the Internet (http://www.syntaxscore.com) (**Figure B1**).

Chapter 8

Cardiac Catheterisation and Intervention on ECMO

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Vikram Kudumula, Elved B. Roberts and
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Additional information is available at the end of the chapter

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Abstract

Cardiac catheterisation is an essential tool to evaluate patients who require ECMO support for severe haemodynamic impairment. In the first part of this chapter, we describe the equipment, teamwork, expertise, techniques and precautions that are necessary to carry out safe and effective cardiac catheterisation on ECMO. We have moved on from an early pioneering era to a stage where the multidisciplinary team approach has been worked out in detail, using operational procedures that deal with the technical challenges and minimise the risks of ECMO catheterisation and intervention. In the second part of the chapter, we explain in detail how cardiac catheterisation and intervention on ECMO contribute to the management of (1) post-operative congenital heart disease patients, (2) cardiac patients who suffer sudden haemodynamic deterioration, (3) patients with low cardiac output who require left heart decompression because of extracorporeal support, (4) patients with haemodynamically unstable arrhythmias and (5) haemodynamically unstable patients who require percutaneous coronary intervention. We also provide state-of-the-art information on the elective use of ECMO to support congenital and structural catheter interventions. Acute survival and long-term outcome are now related to the underlying conditions rather than complications of the catheterisation procedure itself.

Keywords: ECMO, cardiac catheterisation, catheter intervention, congenital heart disease, myocarditis, cardiomyopathy, balloon septostomy, atrial septal stent, arrhythmia, radiofrequency ablation, percutaneous coronary intervention, structural intervention

1. Introduction

Since cardiac catheterisation and transcatheter intervention in patients on ECMO was pioneered in the late 1980s, interventional cardiologists and ECMO teams have learned to work together to provide rapid accurate diagnosis and safe interventional solutions for patients with the most challenging anatomical problems and the most fragile physiologies. In the current era, experienced teams provide excellent results. The aim of this chapter was to describe state-of-the-art practice in this area.

Catheterisation is most commonly required in the setting of extracorporeal support in the following scenarios:

a. Following surgery for congenital heart disease

b. When acute haemodynamic collapse occurs in a cardiac patient unrelated to surgery

c. To decompress the left heart in patients with poor left ventricular function

d. Patients with haemodynamically unstable refractory arrhythmias

e. Percutaneous coronary intervention in patients with severe haemodynamic instability

f. Elective ECMO support for high-risk congenital and structural transcatheter interventional procedures

The first part of this chapter will address the practical issues related to carrying out cardiac catheterisation in patients on ECMO. The second part of the chapter will focus on up-to-date knowledge and practice in each of the clinical scenarios listed above.

2. Practical tips for ECMO catheterisation

2.1. Staffing

To maximise the safety of ECMO support, the entire team should be familiar with all local ECMO protocols and experienced in moving patients on ECMO. When out of the intensive care unit, the patient is accompanied by the bedside ECMO specialist, ECMO coordinator and a perfusionist. Surgical expertise is available in the event of a cannulation issue, and an anaesthetist or intensive care specialist always accompanies the patient. The circuit is maintained as if it were in the intensive care unit with the same routine circuit checks and monitoring of anticoagulation. The ECMO specialist needs to ensure that there is an adequate supply of syringes and ACT cartridges close by and that the ECMO emergency box containing spare connectors and pigtails accompanies the patient at all times. Each member of the team is tasked with surveillance of a different part of the circuit or patient during the transport.

2.2. Transport between intensive care and the catheter laboratory

The ECMO system should be mounted on a mobile cart. As most modern ECMO systems are capable of operating on battery power for extended periods, the patient and circuit can be

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transferred in a slow and steady manner to the catheter suite. The patient must be fully monitored and sufficient gas supply must be carried to provide oxygen both to the ECMO circuit, as sweep gas, and to the ventilator. All drug infusions should be continued. The ECMO circuit often represents the safest and most reliable access point as pre-existing central lines may need to be rewired and upsized to permit the procedure. It is, however, recommended that at least one well-functioning peripheral cannula is available in case there is a circuit-related complication. As with most critical care transfers, the ECMO patient should be appropriately sedated or anaesthetised prior to leaving the unit. All studies that have assessed the process of patient transport have described excellent outcomes with no cannula displacement, morbidity or mortality [1–3].

2.3. Cannulation

The exact method of ECMO cannulation is largely dictated by patient factors, mainly the weight and age of the patient, but consideration needs to be given to any anatomical variation or loss of vessels either secondary to prolonged ITU stay, surgery or previous catheter interventions. In children below 10 kg in weight, the carotid artery and the jugular vein are the vessels of choice. For most patients, a right-sided cut-down centred on the medial border of the sternocleidomastoid muscle approximately 1.5–2 cm above the clavicle provides excellent access to both of these vessels. Cannulas between 8 and 14 Fr may be inserted depending on the size of the patient and vessels and the amount of support required. In children over 10 kg, cannulation of a femoral vein and artery are preferred. This approach avoids damage to the carotid artery and alterations to flow of blood to the brain. It must be remembered that the femoral artery is an end vessel and the distal perfusion of the leg needs careful consideration in order to prevent limb ischaemia. An additional small cannula either placed antegradely into the superficial femoral artery or retrogradely into the posterior tibial artery can be used satisfactorily to prevent critical limb ischaemia. Once inserted, the cannulas should be firmly secured with at least two sutures.

Occasionally, a patient who is cannulated centrally through an open chest may need treatment in the catheter laboratory. This is almost exclusively in the post-operative patient and although possible carries a significantly higher risk than the patient cannulated peripherally. Centrally placed cannulas are usually shorter and therefore much more prone to being dislodged on patient movement or during the procedure. For such patients, a surgeon capable of reinserting the cannula is essential and additional caution must be exercised by the entire team.

2.4. In the catheter laboratory

A briefing is essential so that the cardiologist understands the ECMO set-up but also so that the ECMO team may fully appreciate what the diagnostic or interventional procedure involves. It is relatively straight forward to position the ECMO circuit to the side of the patient if the catheter procedure can be achieved utilising simple antero-posterior imaging. However, for more complex procedures, requiring imaging through a wide range of planes, we have found it preferential to position both the ECMO pump and the oxygenator on the catheter table, away from the traditional ECMO cart (**Figure 1**). By securing the circuit on the table, the

cardiologist can move the patient and position the C-arm without fear of inadvertent decannulation or damage to the circuit components. It is essential to ensure that the circuit is connected to a main's power supply and that the ECMO heater unit is running to prevent unwanted cooling of the patient throughout the procedure. When possible, oxygen should be connected to the wall supply.

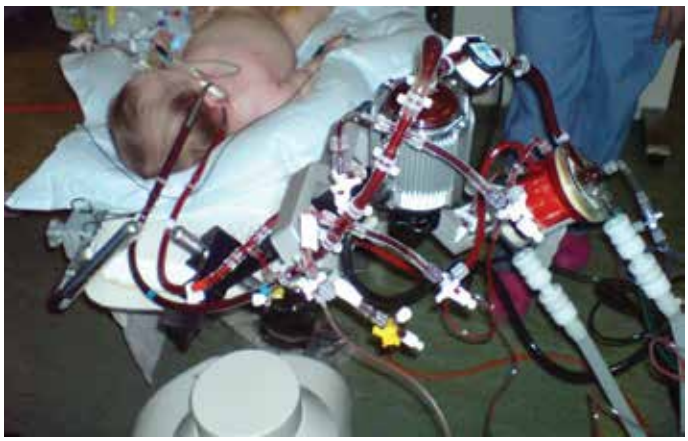

Figure 1. The ECMO circuit secured to the catheter table.

2.5. Vascular access

As the patient is heparinised, it is preferable to avoid new punctures. Existing central venous lines or arterial pressure monitoring lines are therefore exchanged over a wire for a sheath whenever possible. However, new punctures are required in the majority of procedures and complications are surprisingly rare [2, 4, 5]. Only one study described complications, in 13% patients, including venous thrombosis, lower extremity oedema without thrombosis, transient loss of peripheral pulses and lower extremity compartment syndrome requiring fasciotomy [3]. Patients often have a history of previous operations, interventions and prolonged intensive care. It is therefore important to check in advance whether any vessels are known to be occluded and to confirm vessel patency with vascular ultrasound before attempting new access. It is preferable to use vascular ultrasound during puncture attempts to minimise complications [2].

Draping the patient and maintaining sterility can be challenging, as old lines are being exchanged for sterile sheaths, requiring extra care to lift the line that is being removed away from the patient without contaminating the sterile field. Changing gloves after removing the old line and a second pair of hands to assist the exchange are advisable.

To avoid the morbidity of additional vascular access, angiography can be carried out by injecting contrast directly via the ECMO cannula, using a three-way adaptor in the connector [2]. This manoeuvre requires a coordinated sequence of transient flow cessation, contrast injection, saline flush, image acquisition and recommencement of flow [2]. With this technique,

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it is possible to get good images of the aortic root and coronary arteries, particularly if the aorta distal to the cannula is transiently occluded in patients with an open chest [2]. It is also possible to cut a Y-connector into the arterial limb of the ECMO circuit, through which catheters can be inserted [6–9]. The blind end of the Y-connector is closed with a haemostatic valve (Check-Flo Performer accessory adapter, Cook Medical, USA). Although this allows direct access to the heart, without the need for further punctures, catheters are more difficult to manipulate and torque takes longer to transmit because of friction inside the cannula and Y-connector. This loss of feel may hamper the procedure. For this reason, we reserve this approach for simple diagnostic procedures and for cases where vessels are absent or thrombosed or attempts to gain alternative access have failed. When the catheter is completed, the Y-connector must be removed. One study describes similarly placing a Y-connector in the venous limb of the ECMO circuit to obviate the need for venous puncture [2]. We remain concerned that this approach has the potential to rapidly entrain air into the venous circulation because of the negative pressure generated by the centrifugal pump.

2.6. Angiography

The ECMO circuit will normally be positioned to the right of the patient's head with neck cannulation. This usually makes it impossible to bring in the lateral camera C-arm, so most ECMO catheters are carried out with single plane fluoroscopy and angiography. Before starting the case, the image intensifier should be moved through a full range of right and left

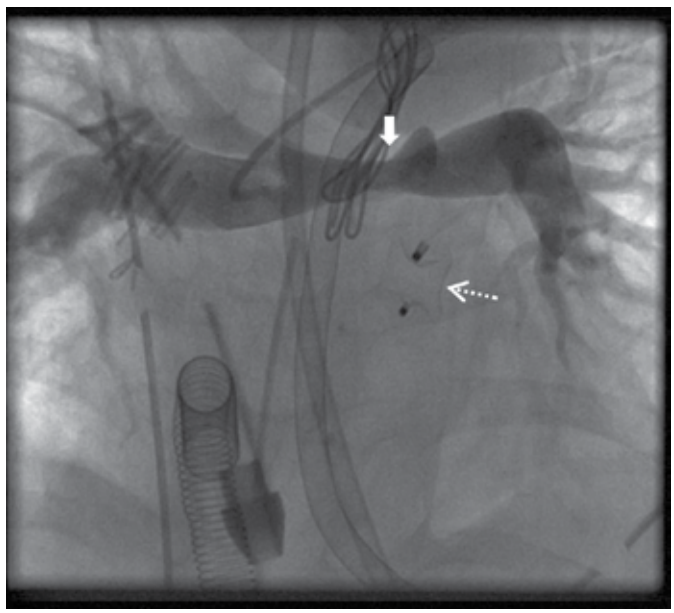

Figure 2. Clutter in the X-ray field. Legend—The image includes ECMO cannulas, chest drains, surgical clips, swabs, a nasogastric tube, a cardiac catheter and a vascular occlusion device (dashed arrow). There is a significant stenosis at the pulmonary artery bifurcation (solid arrow) following cardiac surgery (superior cavopulmonary shunt).

anterior oblique angles, to check whether any equipment is impeding the movement of the C-arm. The ECMO circuit and ancillary equipment should be positioned to maximise the range of camera angles. Test screening is carried out to check that equipment does not encroach on the field of view in the camera angles that are likely to be used during the case. ECG leads and electrodes that are not radiolucent may need to be removed, saturation probes repositioned, chest drain tubing moved and bundles of epicardial pacing wires taped over the abdomen rather than the chest. If it is anticipated that angles approaching the lateral plane may be required, the arms should be lifted up and supported either side of the head, taking care not to displace the ECMO cannulas. Sometimes items of equipment that cannot be moved, for example ECMO cannulas, chest drains, pacing leads, swabs with radio-opaque markers, chest spreaders and clamps, clutter the X-ray field and overlie the area of interest (**Figure 2**). Unusual camera angles may therefore be needed to properly visualise the area without hardware encroaching on the image. For angiography, 1 ml/kg contrast, or even lower volumes for low flow states, gives good image quality [2].

2.7. Catheter technique

Catheter manipulation is not usually any more difficult because of the extracorporeal support, though appreciation of catheter position is sometimes limited by single plane fluoroscopy. ECMO flow may need to be diminished or temporarily discontinued to document cardiac haemodynamics. ECMO can actually facilitate intervention, as it offers a stable haemodynamic platform to carry out interventions that might otherwise cause significant haemodynamic derangement. Furthermore, if the chest is open and a surgeon is close at hand, it is justifiable to accept a greater risk of vessel rupture during balloon angioplasty or stenting as the area is rapidly accessible for surgical repair. Complications during catheterisation are rare. One study reported myocardial perforation in 2 patients (3%), dealt with by inserting a pericardial drain without the need for surgery [5]. Another study reported retroperitoneal haematoma secondary to arterial trauma when removing an embolised coil [4]. Even in the earliest study, transseptal puncture was carried out in a fully anticoagulated state without complication [10]. The safety of transseptal puncture can now be enhanced by intraprocedural transoesophageal echocardiography, even in small children, using a micro-TOE probe.

2.8. Return to the intensive care unit

On completing the catheter, the circuit is resecured to the ECMO trolley if needed and the patient is returned to the intensive care unit. If additional vascular access was utilised for the procedure, this should be left in place until the patient returns to ICU. In this way, the clotting status of the patient can assessed prior to line removal. Although some have recommended that sheaths should be left in place until the patient is weaned from ECMO, most sheaths can be safely removed and bleeding controlled by manual compression [2, 4]. The ongoing need for anticoagulation and inherent platelet dysfunction mean that pressure needs to be applied for longer than would be expected for non-ECMO patients. Alternatively, venous sheaths can be exchanged for a central line of equal outer diameter, venous puncture sites can be closed with a Z-suture or the vessels can be repaired surgically.

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3. Clinical scenarios where catheterisation on ECMO is required

3.1. ECMO catheterisation following surgery for congenital heart disease

3.1.1. Why is ECMO required following surgery?

ECMO support may be required following surgery for congenital heart disease in the following circumstances: (a) failure to separate from cardiopulmonary bypass; (b) ventricular dysfunction with low cardiac output in the immediate post-operative period; (c) unexpected cardiac arrest requiring extracorporeal CPR; (d) lung disease; (e) pulmonary hypertension; and (f) refractory arrhythmias [11]. In such cases, it is important to quickly assess the integrity of the surgical repair and establish whether there are any residual anatomical problems that require correction, as studies have shown between 6% and 28% of post-operative patients requiring ECMO have residual lesions [11–14].

3.1.2. Why is cardiac catheterisation required following surgery?

In the majority of cases, echocardiography does not provide complete information because ventilation, dressings, pacing wires, chest drains, air in the anterior mediastinum and an open chest restrict the available echocardiographic windows. In one study, where ECMO was established using central cannulation with the chest open, only 17% of residual lesions were identified by echocardiography [11]. Other studies confirm that echocardiography has clear limitations in this context, with residual problems detected in at best 41% and at worst 19% of patients [1, 5]. Echocardiography is particularly poor at identifying problems with branch pulmonary arteries and systemic to pulmonary artery shunts. In contrast, in one of the largest studies on post-operative ECMO, cardiac catheterisation identified 78% of residual lesions. About 91% of cardiac catheterisation procedures yielded unexpected diagnostic information of clinical importance [11]. Both surgeon and cardiologist therefore need to remain open to the fact that something may have been missed. In 70–83% of cases, management is altered by the results of cardiac catheterisation [1, 2, 4, 5, 11]. The findings may result in redo surgery, cardiac intervention or elective withdrawal of ECMO in patients with severe neurological impairment or lack of myocardial recovery. Cardiac catheterisation is therefore mandated whenever there is any doubt about the cause of the patient's poor haemodynamic status.

3.1.3. Survival after catheterisation on ECMO

Table 1 shows how outcomes for patients who require cardiac catheterisation on ECMO have improved over time. The studies listed describe a mixed group of paediatric cardiac ECMO patients, not just patients who required ECMO in the post-operative period. Nevertheless, the trend towards improved survival is impressive.

Outcome	1990–1995 Desjardins et al. (1999) [4]	1984–2001 Booth et al. (2002) [5]	2009–2012 Panda et al. (2014) [2]	2004–2013 Callahan et al. (2015) [3]
Weaned from ECMO	53%	72%	82%	86%
Discharged from hospital	29%	48%	68%	72%
Survival on follow-up	14%	43%	64%	69%

Table 1. Outcomes in patients who have cardiac catheterisation on ECMO.

In a study that included only children on ECMO following paediatric cardiac surgery, children with residual lesions had 87% survival to decannulation when lesions were detected within 3 days of the operation, compared with 36% survival when the lesions were detected later. Most lesions were detected by cardiac catheterisation. Survival to discharge was 58% and 18%, respectively, in the two groups [11]. These findings reinforce the 2011 recommendations of the American Heart Association that cardiac catheterisation with potential for intervention is indicated early in the post-operative period in any patient who requires mechanical cardiopulmonary support without a clear cause [15].

3.1.4. The timing of cardiac catheterisation

Although there is a natural tendency to attribute the need for extracorporeal support to myocardial stun following cardiopulmonary bypass and cross-clamping, if patients fail to wean from ECMO within 3 days, cardiac catheterisation is strongly advised. Catheterisation should be carried out earlier if haemodynamic measurements made on PICU or echocardiography suggest a residual problem. In cases where the surgeon suspects a residual problem or coronary artery issues could result in permanent myocardial damage, it is preferable to proceed straight from theatre to the cardiac catheterisation laboratory. In our centre, it is routine to carry out a detailed assessment of every surgical repair in theatre either by TOE or by epicardial echocardiography. Intracardiac problems are therefore usually identified early and repaired immediately. In view of this, when a patient fails to wean from ECMO on PICU, it is likely that any residual lesion will be beyond the reach of echocardiographic imaging. Branch pulmonary artery problems, aortic problems and distortion, stenosis and thrombosis of cavopulmonary and aortopulmonary shunts remain a blind spot for the echocardiographer.

3.1.5. Types of catheter procedures required in the post-operative period

Indications for catheterisation include the evaluation of coronary arteries (**Figure 3**), pulmonary arteries (**Figure 4**), pulmonary venous obstruction, aortic obstruction, shunts and aortopulmonary collaterals. The surgeon who carried out the operation is usually present in the catheter laboratory at the time of the study. If a residual lesion is identified, our practice is to convene a short meeting in the catheter laboratory control room with surgeons, cardiologists and intensivists represented. An immediate decision is made whether the patient should return to the operating theatre or should proceed to have catheter intervention. About 20–50% of residual lesions can be dealt with in the catheter laboratory [2, 11, 16]. Interventions include

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duct stenting (**Figure 5**), shunt angioplasty or stenting, branch pulmonary artery angioplasty or stenting, coronary stenting, stent fenestration of Fontan circulation, balloon atrial septostomy, ASD device closure, VSD device closure, coil occlusion of collaterals and catheter-directed thrombolysis [3, 5, 11, 17]. Complications are rare [2–5, 11, 16]. As the circulation is fully supported, hybrid procedures are possible, particularly when the chest is open. For example, branch pulmonary artery stenting can be carried out with a sheath introduced through the anterior wall of the main pulmonary artery or right ventricular outflow tract. A greater risk of vessel rupture during angioplasty or stenting can be accepted when the chest is open, the patient is draped for a surgical procedure and the whole theatre team are scrubbed and on standby in the catheter laboratory, as the surgeon can quickly control bleeding and repair even major damage to blood vessels (**Figure 4**).

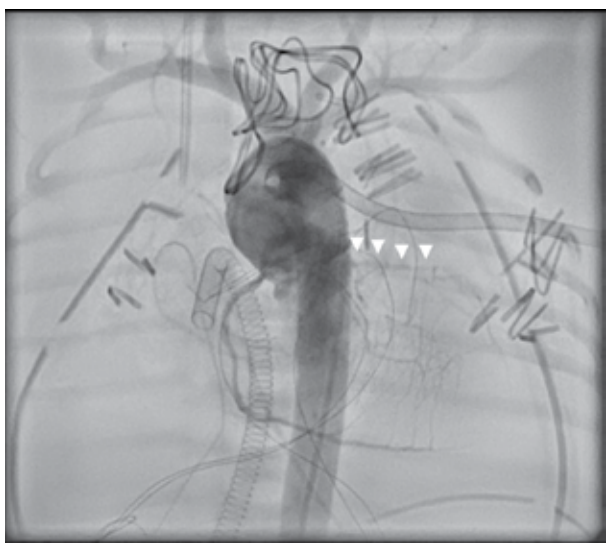

Figure 3. Partial occlusion of the left coronary artery post-repair of common arterial trunk. Legend—The arrowheads show weak opacification of the left coronary artery.

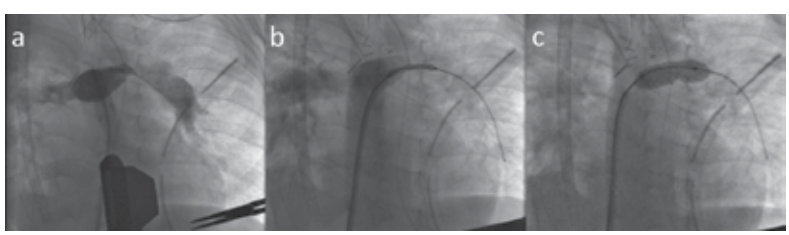

Figure 4. (a) Torsion of the left pulmonary artery following unifocalisation surgery for pulmonary atresia with VSD and MAPCAS (major aortopulmonary collateral arteries); (b) A premounted stent is positioned across the site of stenosis; (c) The stent is deployed but has a residual waist. As the balloon is inflated to higher pressure, the pulmonary artery ruptures at the stenotic anastomotic site and has to be repaired immediately by the surgeon who is on standby.

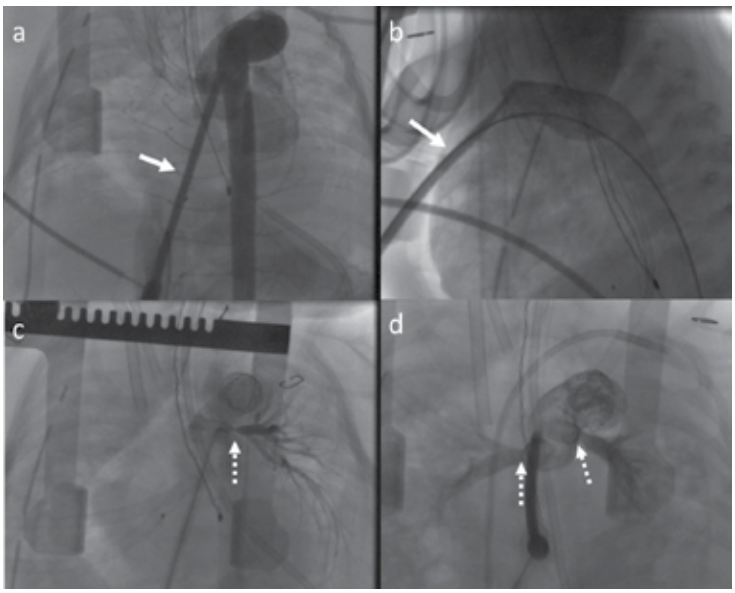

Figure 5. Stenting the arterial duct and altering pulmonary artery bands in a hybrid Norwood procedure. (a) Angiography is carried out via a sheath introduced through the anterior wall of the pulmonary artery (solid arrow). The pulmonary arteries are not opacified as the bands are too tight; (b) Lateral view showing flow into the aorta after stenting the arterial duct; (c) Very tight left pulmonary artery band (dashed arrow); (d) Good flow into the pulmonary arteries with mild proximal narrowing (dashed arrows) after loosening the pulmonary artery bands.

3.2. The cardiac patient with acute haemodynamic collapse unrelated to surgery

3.2.1. When is diagnostic catheterisation indicated?

Neonates who present moribund with shock or profound cyanosis may require urgent extracorporeal support before a full cardiac evaluation can be carried out. When congenital heart disease is present, a full diagnosis is usually then secured with transthoracic echocardiography alone. However, it may be difficult to diagnose obstructed total anomalous pulmonary venous drainage, as its clinical presentation mimics lung disease and pulmonary venous drainage can be hard to define once VA ECMO has been commenced, even when ECMO flows are reduced to encourage flow through the pulmonary circulation. In view of this, ECMO patients have sometimes required cardiac catheterisation to establish or exclude TAPVD [18, 19]. However, in the current era, every effort is made to establish pulmonary venous drainage echocardiographically before sick neonates are placed on ECMO. When this is not possible, contrast CT may offers a less invasive alternative.

3.2.2. Catheter intervention in children on ECMO

When ECMO is initiated to treat shock or cyanosis in cardiac patients, cardiac catheterisation is normally only necessary when intervention is planned. A wide array of interventions have

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been described following emergency ECMO in paediatric patients, including balloon angioplasty of critical aortic stenosis [1, 20], balloon angioplasty of a restrictive cor triatriatum membrane [21], balloon atrial septostomy in the context of hypoplastic left heart syndrome with a restrictive atrial septum [4] and radiofrequency ablation of incessant tachycardia [22, 23].

3.2.3. ECMO salvage as an alternative to balloon atrial septostomy for moribund patients with transposition of the great arteries

Patients with transposition of the great arteries deserve special mention. When such patients present profoundly hypoxic and acidotic, the team is under great pressure to perform balloon atrial septostomy quickly. However, it may sometimes be difficult and time-consuming to gain vascular access. In such circumstances, it is occasionally easier and quicker to cannulate the neck vessels for ECMO. Once the patient is on ECMO, balloon atrial septostomy can be undertaken or the patient can proceed to theatre for an arterial switch procedure after a period of stabilisation [24].

3.2.4. Catheter intervention in adults on ECMO

Adult patients may also require emergency ECMO support followed by catheter intervention. Patients with massive pulmonary embolism may need to be resuscitated using extracorporeal support, following which catheter-directed thrombolytic therapy, catheter embolus fragmentation or percutaneous thrombectomy can be carried under stable conditions [25–27]. As structural intervention gains momentum, patients who need ECMO support because of shock or cardiac failure caused by severe valvar stenosis or regurgitation may increasingly be treated using transcatheter therapy on extracorporeal support. TAVI has already been carried out following emergency ECMO [28] and one patient with severe mitral regurgitation requiring ECMO has been successfully treated with a MitraClip [29]. However, results are likely to better if ECMO is used to electively support interventional procedures in high-risk patients, before acute haemodynamic decompensation occurs [28].

3.3. Left heart decompression in patients with poor ventricular function

3.3.1. Why is left heart decompression necessary?

When VA ECMO is commenced to support patients with severe myocardial dysfunction, the heart may stop ejecting completely because of the increased afterload caused by the extracorporeal circulation. In these circumstances, left ventricular end-diastolic pressure rises sharply because of acute left heart distension, and the increased wall stress, reduced myocardial perfusion and subendocardial ischaemia that occur as a consequence compromise recovery of ventricular function. Left atrial pressure increases, causing pulmonary venous hypertension, pulmonary oedema and in severe cases pulmonary haemorrhage. Left heart decompression is necessary to decrease pulmonary oedema, avoid pulmonary haemorrhage and allow myocardial recovery [30–32].

3.3.2. Making the decision to decompress the left heart

Approximately 10–20% patients who require ECMO for poor left ventricular function will require left heart decompression [31–33]. The decision to decompress the left atrium is usually made within 24 h of commencing ECMO, on the basis of left heart dilation on echocardiography and pulmonary oedema on chest X-ray [32]. Direct surgical left atrial cannulation is possible in post-operative patients [31, 32]. However, a non-surgical approach is preferable in patients with myocarditis and post-operative patients where there is a plan to switch to neck cannulation in order to close the chest.

3.3.3. Percutaneous decompression using drains incorporated into the ECMO circuit

Percutaneous decompression may be achieved by introducing a transseptal left atrial drain from a femoral venous approach [32, 34–37] or passing a pigtail catheter into the left ventricle from a femoral artery approach [38, 39]. The return from these drains is incorporated into the venous limb of the ECMO circuit. However, there are concerns about systemic thromboembolism when hardware remains in the left heart for a prolonged period of time. Also, transseptal drains have become less popular in recent years because of problems with kinking, poor flow and drain movement with patient care [32].

3.3.4. Percutaneous left atrial decompression by opening the atrial septum

In the majority of patients, left atrial decompression is achieved by balloon atrial septostomy [30, 32, 40]. If prolonged extracorporeal support is anticipated or balloon septostomy fails to achieve an adequate interatrial communication, atrial septal stenting is carried out [32, 41]. Transseptal puncture is required as a first step in approximately 90% of patients, as only about 10% have a pre-existing interatrial communication [30, 32]. Most transseptal punctures are carried out using a Brockenbrough needle. Accidental left atrial perforation is a particular concern as the patient is fully anticoagulated. However, the largest series reported only one left atrial perforation, which closed without requiring pericardial drainage [32]. Needle position may be guided by transthoracic or transoesophageal echocardiography to minimise complications [40, 42]. Radiofrequency transseptal perforation is an alternative and may be preferable when the septum is very thick, but there is some concern that an accidental burn hole in the atrial wall may be less likely to close spontaneously. In young infants, it is possible to perform a Rashkind balloon atrial septostomy, rapidly jerking a septostomy balloon from the left to the right atrium in order to tear a hole in the atrial septum. Older patients require a static balloon septostomy, as the septum is too thick for the Rashkind technique to be effective.

3.3.5. Static balloon septostomy

To perform a static balloon septostomy, a long sheath is advanced over the transseptal needle into the left atrium. A catheter is then advanced through the transseptal sheath and directed into the left upper pulmonary vein. A wire is passed through the catheter into the pulmonary vein and the catheter and sheath are withdrawn. A balloon is advanced over the wire until it is centred across the atrial septum. Balloons are usually in the 12–18 mm range, but smaller

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and larger diameters may be required, depending on patient size [32, 33]. The balloon is then inflated to tear a hole in the septum (**Figure 6**). Historically, blade atrial septostomy was carried out after transseptal puncture to ensure that a large hole could be created, but blade septostomy has now almost disappeared from practice. If the hole is not big enough to reduce left atrial pressure to less than about 20 mmHg, a larger balloon can be used, a second hole can be created by a separate transseptal puncture, a cutting balloon (Boston Scientific, Natick, USA) can be used to create blade cuts in the margins of the defect to allow more effective balloon dilation, or atrial septal stenting can be carried out.

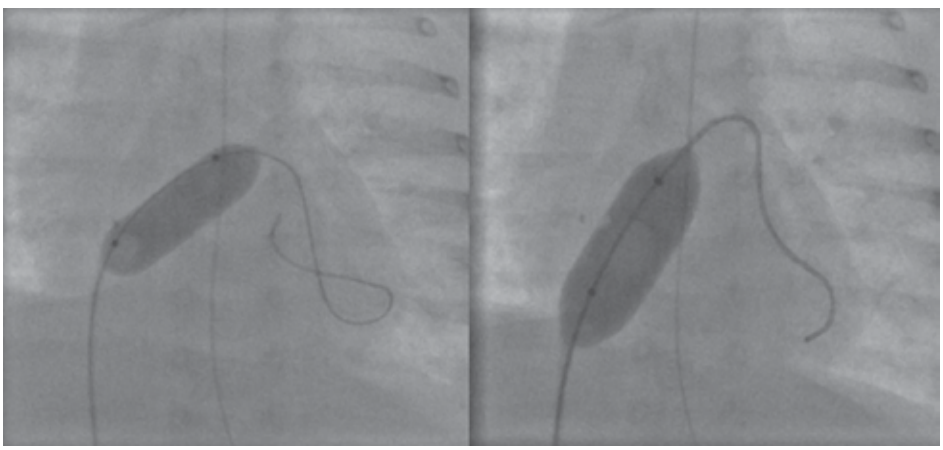

Figure 6. Static balloon dilation of the atrial septum with progressively larger balloons.

3.3.6. Stenting the atrial septum

Stenting can be carried out using the 'dog-bone' technique described by Stumper et al. (**Figure 7**) [43] or simply by implanting a straight stent across the septum (**Figure 8**) [42]. Echocardiography is used to measure the distance from the inferior vena cava to the atrial septum and from the septum to the pulmonary veins to guide what length of stent should be chosen. The stent should not project more than about halfway across the atrial cavity, to avoid the risk of puncturing the atrial wall, particularly when the heart size reduces as the patient recovers. Transoesophageal echocardiography can be used to check that the stent is accurately centred on the septum before the balloon is inflated. A hole with a diameter of about 4–5 mm is usually adequate [33]. To achieve this, when a straight stent is implanted, it is usually mounted on an 8- to 10-mm-diameter balloon, which is inflated at low pressure to leave a waist at the septum. In the current era, premounted stents are often used [42]. When the dog-bone technique is used, a 15-mm balloon should be used with a 4- to 5-mm constraining loop that prevents the centre of the balloon expanding. If a larger communication is required, the stent can be post-dilated. If the communication is too large, the centre of the stent can be constricted with a gooseneck snare [43].

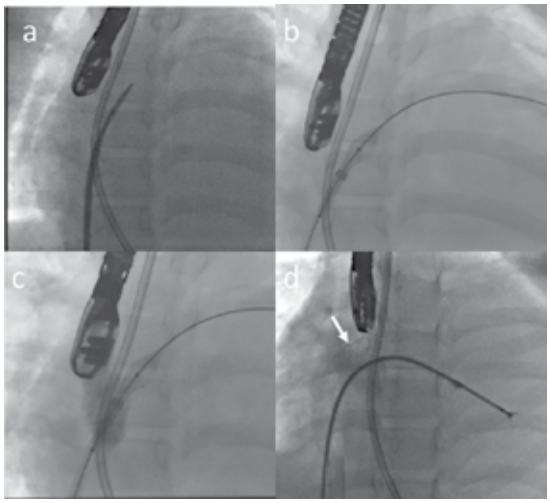

Figure 7. 'Dog-bone' stenting the atrial septum. (a) Brockenbrough needle transseptal puncture; (b) A wire is introduced into the left pulmonary vein, and a stent mounted on a balloon is advanced through a long sheath. The stent balloon assembly is half-unsheathed so that the distal half of the stent can be inflated and pulled back against the atrial septum; (c) As the sheath is pulled back to the right atrium to expose the whole stent, contrast injected through the side arm of the sheath defines the plane of the atrial septum and shows the stent is well centred; (d) The stent has been deployed across the atrial septum (arrow). There is a central waist which stabilises the stent on the septum. The waist was produced by tying a loop of prolene around the middle of the balloon before the stent was mounted. Myocardial biopsy is also shown.

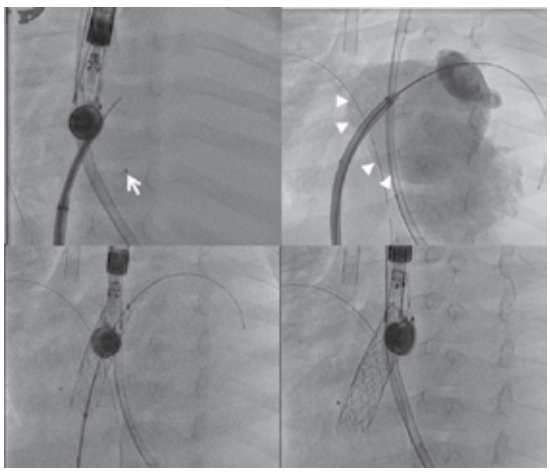

Figure 8. Implanting a straight stent across the atrial septum. (a) Brockenbrough needle transseptal puncture. The arrow highlights the small radio-opaque marker at the tip of the ECMO cannula. Most of the distal cannula is radiolucent; (b) The tip of the transseptal sheath is in the left atrium. Contrast injected into the left atrium defines the plane of the atrial septum (arrow heads); (c) A balloon mounted stent was deployed, but was not well centred on the septum. A second stent was therefore implanted overlapping the first stent to prevent embolisation; (d) The balloon and wire have been removed, leaving the 2 overlapping stents in a stable position.

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3.3.7. Does the atrial communication need to be closed after the patient recovers?

Patients who survive ECMO after left atrial decompression should have routine follow-up echocardiography to check whether the atrial septal defect has closed. One study found that 80% of such patients had a residual defect and 44% required either transcatheter or surgical closure [33]. However, this may be an overestimate, as less than 20% of patients in another series had residual defects, and only one of those patients needed device closure [32].

3.4. Patients with haemodynamically unstable refractory arrhythmias

3.4.1. Why is ECMO required in arrhythmia patients?

Patients with haemodynamically unstable arrhythmias fall into two main categories:

(1) Adults with ventricular arrhythmias; (2) infants with tachycardia mediated cardiomyopathy secondary to incessant supraventricular tachycardia [44]. Such patients may require ECMO because (a) there is an abrupt haemodynamic deterioration; (b) there is no therapeutic window for drug treatment, because antiarrhythmic drugs have caused an unacceptable deterioration in the patient's haemodynamics; (c) catheter ablation is indicated but cannot proceed without extracorporeal support, either because the patient cannot maintain cardiac output in tachycardia or because the patient's haemodynamics are so precarious that there is a significant risk of cardiac arrest during the procedure.

3.4.2. ECMO support of VT ablation in adult patients

It is debatable whether adult patients with haemodynamically unstable VT benefit from ablation with ECMO support. ECMO certainly provides a stable platform to carry out activation mapping of VT where the arrhythmia is not haemodynamically tolerated [45]. However, VT ablation can now be carried out by substrate mapping, which does not require the patient to remain in the unstable tachycardia. The authors of a leading article in 2009 that advocated VT ablation with ECMO support have now retreated from that position [45]. They point out that greater experience with substrate mapping and the widespread availability of three-dimensional mapping systems have allowed the vast majority of haemodynamically unstable VTs to be successfully treated during sinus rhythm with very reasonable long-term success rates and very low morbidity. Their use of ECMO support for VT ablation therefore fell from 9% (2003–2007) to 0.5% (2007–2012) [46]. There will inevitably be cases where patients with VT require extracorporeal CPR or urgent ECMO for critically compromised haemodynamics. In such patients, who are small in number, it is sensible to proceed to ablate the VT whilst on mechanical support [47]. However, the era of elective ECMO support to allow activation mapping seems to have passed.

3.4.3. When is radiofrequency ablation on ECMO necessary in infancy?

In infants with tachycardia-related cardiomyopathy, ECMO is commenced when drug refractory incessant tachycardia causes progressive deterioration in haemodynamics or when antiarrhythmic drugs cause cardiovascular collapse requiring extracorporeal CPR [23, 48].

Once the patient is receiving extracorporeal support, approximately 2/3 should be treatable with antiarrhythmic drug therapy alone. However, catheter ablation may be required in about 1/3 patients [44]. Ablation may be necessary because the tachyarrhythmia is truly drug resistant. However, ablation is also reasonable when the tachycardia is very difficult to control on ECMO, requiring high-dose or multiple antiarrhythmic medications, as invasive treatment can shorten the duration of ECMO support and minimise the risk of tachycardia recurrence [23, 48]. It is important to avoid tachycardia recurrence following decannulation as it is may be very difficult to recannulate the neck vessels if the child becomes unstable again.

3.4.4. Elective use of ECMO to support paediatric ablation procedures

ECMO can be used to electively support paediatric ablation procedures when patients cannot maintain an adequate cardiac output in tachycardia, either because of congenital heart disease or poor ventricular function, and mapping in tachycardia is an essential part of the procedure [49]. In such procedures, the length of time the patient will need to spend in tachycardia, the degree of haemodynamic impairment this will cause, the size of the patient, the technical difficulty of the ablation and the possibility of extracorporeal CPR being required all factor into the decision to use ECMO pre-emptively.

3.4.5. Technical aspects

Very few publications focus on catheter ablation of arrhythmias in children on ECMO. Although some of the larger series dealing with paediatric cardiac catheterisation on ECMO include a few patients who had ablation, only basic information is provided [2, 5]. The sum total of published information consists of 13 patients described in a multicentre review [44] and 16 patients described in various case reports and case series [2, 5, 22, 23, 48–54], with possible overlap between these sources.

Atrial septostomy may be needed at the same time as ablation when left heart distension has developed on ECMO, as ventricular function and cardiac output may take several days to improve after the tachycardia is successfully ablated [22, 23, 44, 51]. Left atrial decompression may speed up resolution of pulmonary oedema, improve function and shorten the time to decannulation.

Most infant ablation procedures on ECMO are carried out with 2 vascular access points. A single diagnostic catheter and a 5 Fr 4-mm tip ablation catheter are usually used [44]. An oesophageal bipolar electrode can be added for atrial sensing and stimulation [48]. The largest study described an average of two ablation substrates per patient. Right-sided accessory pathways and left-sided ventricular tachycardia were the most common ablation targets. About 69% were successfully treated with radiofrequency ablation alone. In 29% cases, there were problems with convective cooling of the catheter tip, resulting in inadequate lesion formation. Energy delivery and thermodynamics were not improved by reducing ECMO flow to increase blood flow through the heart. After converting to cryoablation, the tachycardias were successfully ablated. Although this series described a procedural success rate of 100%, the complication rate was 15%, with one patient suffering transient heart block and one mitral

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valve damage that ultimately required valve replacement [44]. The desire to produce effective lesions to avoid tachycardia recurrence must be tempered by caution. Lesion depth should be kept at a minimum to reduce the risk of perforation and damage to adjacent cardiac structures, such as valves or coronary arteries, which are particularly close to the endocardium of the atrioventricular junction in infants. There are no robust data to suggest how much energy should be delivered to achieve this balance. Although successful ablation has been described with energy as low as 5 W [23], we recommend initially setting up the ablator to deliver 20 s lesions at a power of 10 W with a temperature limit of 50° when treating infants. Where convective cooling does not allow delivery of an effective lesion, successful ablation can also be achieved with a cooled tip ablation catheter [23].

3.5. Percutaneous coronary intervention on ECMO in critically ill patients

3.5.1. Types of mechanical support available for percutaneous coronary intervention

There are occasions when percutaneous coronary intervention (PCI) cannot be carried out without additional haemodynamic support. The characteristic scenarios are cardiac arrest, cardiogenic shock and global critical coronary perfusion status. In these circumstances, various types of mechanical circulatory support are available, including VA ECMO, intra-aortic balloon pump, Impella (Abiomed, Danvers, MA) and Tandem Heart (Cardiac Assist, Inc., Pittsburgh, PA). Impella uses an axial flow pump to propel blood from the left ventricle to the aorta. Tandem Heart pumps blood extracorporeally from the left atrium to the femoral artery via a transseptally placed left atrial cannula. Current evidence on the utility of these devices is summarised in the 2015 SCAI/ACC/HFSA/STS consensus statement on mechanical circulatory support [55]. Choice between these various modalities is dictated by the patients' haemodynamic status, availability of equipment and local expertise. In our centre, where there is a large ECMO programme and considerable experience with emergent use of ECMO,

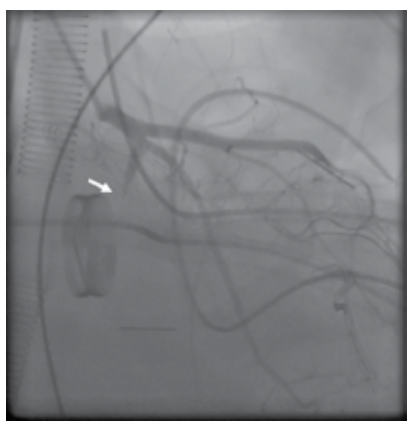

Figure 9. Circumflex occlusion (arrow) following mitral valve replacement. Stent implantation successfully opened the occluded segment.

patients are more likely to receive ECMO support when their haemodynamic status is critically compromised. ECMO should be chosen in preference to other ventricular assist devices when there is impaired oxygenation or right ventricular failure. Post-operative patients on ECMO may occasionally require PCI when there is an unexpected coronary lesion (**Figure 9**).

3.5.2. PCI on ECMO in patients who have a cardiac arrest

Patients who have cardiac arrest before or during PCI present the greatest challenge to the interventional team. To carry out PCI while there is no spontaneous cardiac output is extremely difficult. Manual CPR in this setting, even if performed to perfection, requires pauses for X-ray imaging and soon becomes ineffective in most cases. When extracorporeal CPR is instituted soon after cardiac arrest, it provides a haemodynamically stable platform for PCI that allows the operator to focus on the technique itself, rather than dealing with volatile haemodynamics and a jerky, mobile X-ray view of the target vessel. There are reports of excellent outcomes from PCI in patients on ECMO following cardiac arrest [56–61]. However, Kagawa et al. described only 29% 30-day survival in 61 patients with acute coronary syndrome who received emergency ECMO coupled with PCI to treat cardiac arrest unresponsive to manual CPR [62]. Arlt et al. described 40% survival to hospital discharge in a cohort of patients who received PCI coupled with extracorporeal CPR using a miniaturised ECMO system [63]. Better results were described in the CHEER trial, which included 26 patients with resistant cardiac arrest who were treated with emergency ECMO, combined with 30 ml/kg of intravenous ice-cold saline to induce therapeutic hypothermia. Eleven of these patients proceeded to have PCI on ECMO. Six patients survived with full neurological recovery [64]. A well-organised extracorporeal CPR service is important to achieve the best outcomes in this context. Patients should be established on ECMO quickly by an expert team, following high-quality CPR without severe metabolic disturbance or tissue hypoxia, to maximise their chance of survival with intact neurology.

3.5.3. PCI on ECMO in patients with profound cardiogenic shock

When patients who require PCI present with severe cardiogenic shock (usually defined as systolic blood pressure less than 75 mmHg on high-dose inotropic support), extracorporeal support can be used to offload the left ventricle and boost cardiac output during revascularisation. Recent studies have suggested that survival is improved when ECMO is used as an adjunct to PCI in this patient group. Esper et al. [65] showed an impressive 67% survival to discharge in patients with severe shock who received ECMO in the cardiac catheter laboratory. Good outcome has also been demonstrated following left main stem PCI in patients with cardiogenic shock supported by ECMO [66]. Data from true randomised comparison of outcomes with and without ECMO are absent. However, comparison between present and historic cohorts provides some insight. Sheu et al. [67] demonstrated a statistically significant reduction in 30-day mortality in PCI patients with profound shock, from 72% to 39%, following introduction of ECMO support in 2002. Tsao et al. [68] demonstrated a significant difference in 30-day (32% vs 67%) and 1-year (24% vs 64%) survival in PCI patients with severe shock when they compared cohorts treated without ECMO (2004–2006) and with ECMO (2007–2009),

respectively. Unai et al. [69] found similar results after introducing ECMO support for PCI patients with profound shock in 2010. Existing evidence therefore supports early ECMO intervention in this patient group, particularly to avoid the peak in mortality that normally occurs in the first few days after revascularisation [67]. A recent meta-analysis suggests that this positive effect on in-hospital mortality is found only in patients treated with ECMO and that treatment with percutaneous left ventricular assist devices, such as the Impella or Tandem Heart, does not confer a survival benefit [70].

3.5.4. Elective use of ECMO to support high-risk PCI

Percutaneous coronary intervention is regarded as high risk when there is moderate-to-severe left ventricular dysfunction, a large amount of myocardium is subtended by the stenosed vessels and, in addition, the procedure involves technical difficulties, such as the presence of bifurcation lesions, triple vessel disease, left main stenosis or chronic total occlusion. In such cases, where there is a significant risk that the intervention will precipitate haemodynamic decompensation, it is intuitive to suppose that elective extracorporeal support will reduce mortality. Yet, better outcomes have not been convincingly demonstrated in high-risk PCI procedures supported by intra-aortic balloon pump or Impella [71–73]. In contrast to this, a recent study using elective Tandem Heart support yielded promising results, with 30-day and 6-month survival rates of 90% and 87%, respectively [73]. From this study, it is tempting to extrapolate that elective ECMO may improve outcome in this patient group, where the safety margin is very small. Case reports have certainly described success in high-risk PCI using ECMO to produce a stable haemodynamic platform [74, 75]. One single-centre prospective study reported 100% PCI success with no in-hospital major adverse cardiac events in 12 consecutive patients who underwent high-risk PCI with ECMO support. At 6-month follow-up, neither death nor myocardial infarction were noted [76]. Notwithstanding this, there are at present no large volume conclusive multicentre trials of these techniques. It is possible that other means of haemodynamic support may be just as effective as ECMO in these situations. Technological advances in usability and further attempts at generating good scientific evidence for the role of ECMO in PCI will go hand in hand and hopefully provide strong evidence for guideline development in the longer term.

3.6. ECMO support for high-risk elective congenital and structural catheter intervention procedures

3.6.1. When has elective ECMO support been used for high-risk procedures?

Elective use of ECMO to support high-risk intervention is a new area of practice. There is little published information. The larger series that deal with paediatric catheterisation on ECMO do not include data on ECMO use in this context [2–5, 11]. One series dealing with extracorporeal CPR in the paediatric catheter laboratory included two patients with critically low cardiac output and one with severe hypoxaemia who had elective ECMO support before catheterisation [77]. The patients survived with no neurological damage. A handful of case reports have also shown that elective ECMO before catheterisation allows procedures to be

undertaken safely in patients with extremely fragile haemodynamics. Interventions included branch pulmonary artery stenting [78, 79], radiofrequency ablation of a Mahaim pathway [49], radiofrequency ablation of VT [52] and tricuspid valve implantation [80]. In adult patients, 100% procedural success and 0% mortality were described in a small very high-risk TAVI cohort where ECMO was instituted electively before the procedure. These results were clearly superior to those cases where high-risk TAVI patients were rescued by emergency ECMO during the procedure [28]. Such 'ECMO hybrid procedures' allow us to deal with increasingly complex interventional problems in sicker patients without increasing mortality.

3.6.2. The team approach to using ECMO in high-risk catheter procedures

In our catheter laboratory, the risks of procedures that could potentially have catastrophic complications are mitigated by collaboration with the ECMO team. Whenever there is a significant possibility of lethal complications, the case is discussed with the interventional team, the ECMO team, cardiac intensivists and cardiac surgeons. A joint plan is made in advance at a multidisciplinary team meeting. A detailed team briefing then takes place on the morning of the procedure, with all disciplines represented. Participants are encouraged to raise any potential issues in advance. It is important to plan as much as possible before the procedure, anticipating difficulties rather than reacting to them as they occur [81].

3.6.3. Our local 3 level strategy to support high-risk catheter procedures

Depending on the perceived level of risk, we have three different levels of ECMO support:

3.6.3.1. Level 1

The first level of support is used for cases where serious complications are possible but unlikely. We include duct stenting or right ventricular outflow tract stenting in this category, as it is possible that the patient's only source of pulmonary blood supply can be compromised by the intervention. In such cases, the ECMO team and surgical team are made aware that the procedure is taking place, but no special precautions are taken. Sharing information cuts down the response time, should extracorporeal CPR become necessary.

3.6.3.2. Level 2

The second level of support is used for cases where there is a significant possibility of a lethal complication. In this category, we include patients undergoing stenting and high-pressure balloon dilation of a calcific right ventricle to pulmonary artery conduit, particularly where aggressive dilation is planned at a site where rupture would be difficult to control with a covered stent, for example at the pulmonary artery bifurcation. If there is a massive rupture, the only possible rescue strategy may be to occlude the entire conduit with a balloon and place the patient on VA ECMO while preparations are made for cardiac surgery. In such cases, in addition to the vascular access that is required to perform the intervention, we place an extra sheath in the contralateral femoral artery and vein. These sheaths can be rewired and used for percutaneous ECMO cannulation in an emergency. An ECMO circuit is assembled and kept

http://dx.doi.org/10.5772/63978

in the catheter laboratory. Blood and products are prepared in advance as if the patient were going for cardiac surgery. The ECMO team, a cardiac surgeon and a theatre team remain in the catheter laboratory during the procedure, and a cardiac theatre is kept free. When the risk is particularly high and the response needs to be immediate, the ECMO circuit is primed with blood before the procedure starts. High-risk neonatal interventions in this category involve preparing the neck for cannulation rather than the groin. This may consist of prepping and draping the neck area and inserting a sheath that can be easily rewired into the jugular vein or may extend to cut down and exposure of the neck vessels for cannulation in very high-risk cases.

3.6.3.3. Level 3

The third level of support is reserved for patients with poor ventricular function and low cardiac output, where there is a high risk of cardiac arrest or acute haemodynamic decompensation during the catheter procedure (**Figure 10**). Also in this category are patients who have critically low oxygen saturation because of narrowed shunts or branch pulmonary arteries, where pulmonary blood flow will be further compromised during the intervention. In these patients, ECMO is electively instituted in advance of the case while the patient is on the intensive care unit. We have used this approach to carry out conduit stenting in an adult patient with gross right heart failure secondary to severe chronic right ventricle to pulmonary artery conduit stenosis. The patient, who had an excellent result, was decannulated on the

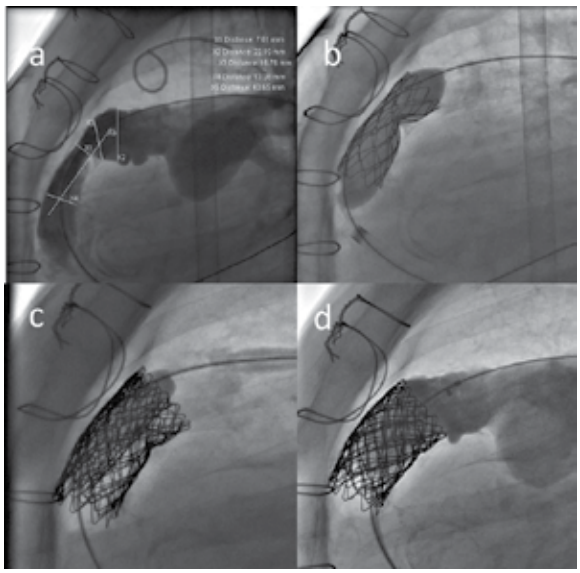

Figure 10. Elective ECMO support of right ventricle to pulmonary artery conduit stenting. (a) Angiography shows a tight stenosis in the right ventricle to pulmonary artery conduit; (b) A covered stent is implanted in the conduit. Further stents were subsequently implanted and dilated with a high-pressure balloon; (c) A Melody (Medtronic, Minneapolis, MN) percutaneous pulmonary valve is implanted in the prestented conduit at a second procedure 5 months later; (d) A well-expanded conduit with a competent pulmonary valve is ultimately achieved.

same day as the procedure and ultimately had successful percutaneous pulmonary valve implantation.

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Chapter 9

Extracorporeal Membrane Oxygenation During Lung Transplantation

Young-Jae Cho

Additional information is available at the end of the chapter

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Abstract

Lung transplantation is increasing as a widely accepted surgical treatment for certain type of end-stage lung disease. Recent technical improvements in extracorporeal membrane oxygenation (ECMO) have been able to expand the role of ECMO during lung transplantation. The evolution of oxygenators, introduction of the new-type pump and tube, and improvement of percutaneous cannulation including dual lumen single catheter resulted in the technical renaissance of ECMO for lung transplantation. Now, beyond the traditional support for patients with severe primary graft dysfunction, ECMO can be established as essential perioperative roles for patients undergoing lung transplantation, such as preoperative lung protective support as a bridge to transplantation, replacement cardiopulmonary bypass during intraoperative support, and rescue of various life-threatening situations after post-transplant. After all, ECMO will be a fundamental, life-saving modality for patients during lung transplantation.

Keywords: Perioperative procedures, lung transplantation, Perioperative procedures, Ventilator-induced lung injury, Intensive care unit

1. Introduction

Recent expanded role of extracorporeal membrane oxygenation (ECMO) is switching the paradigm of organ transplantation, especially in the lung. Traditionally, the role of ECMO in the area of lung transplantation was focused in supporting patients with severe primary graft dysfunction (PGD) after post-transplant; however, as the technical ECMO environments such as new type of pump, oxygenator, catheter and tubing are improving, ECMO is now applied to

the whole process of lung transplantation, from "bridge-to-transplant" to "rescue post-transplant" [1, 2].

The prevalence of lung transplantation has also increased over several decades especially in the specific end-stage lung diseases, such as cystic fibrosis, interstitial lung disease, and chronic obstructive lung disease. Contrary to successful early survival rate, the long-term survival rate of lung transplantation has still seen modest improvement. In addition, the mortality of patients on the waiting list is also concerning, consequently the interest in looking for alternative strategies for patients with end-stage lung disease who wait lung transplantation has risen considerably.

Mechanical ventilation has been applied to support the failing lung in peritransplant patients; however, per se can aggravate respiratory failure and hemodynamic instability by increasing the risk of ventilator-associated pneumonia and ventilator-induced lung injury [3]. Traditionally, mechanically ventilated pretransplant patients have been reported to have higher post-transplant mortality rates than nonventilated patients [4].

At this point, ECMO can be considered an alternative bridging strategy in lung transplantation, and now despite the complexity and side effects, the use of ECMO during lung transplantation has risen by 150% in the recent last 2 years compared to the previous decades (1970–2010; **Figure 1**). Besides the increase of amount, the characteristics of using ECMO are also evolving (**Table 1**) [5].

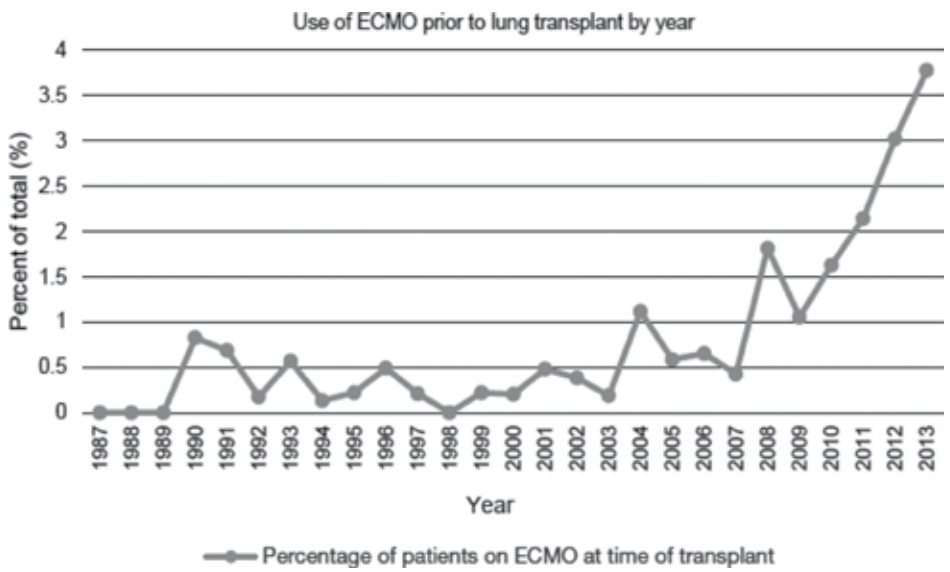

Figure 1. Percentage of patients on ECMO at the time of transplant by year. Data obtained from the United Network for Organ Sharing (UNOS) database 1987–2013. Adapted with permission from [1], © 2014 Gulack et al. Published under AME Publishing Company. DOI: 10.3978/j.issn.2072-1439.2014.06.04. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher AME Publishing Company.

	1970s	1980s	1990–2000	2000–2010	2010–June 2011
Patients listed for lung transplantation on ECMO	1	1	22	104	58
Modes of ECLS used	VA	VA	VA	VV, VA, iLA™	VV, VA, iLA™, hybrid
Pump configuration	CPB	Roller pump	Roller pump	Centrifugal	Centrifigual
Oxygenator membrane	Silicone membrane	Polypropylene and silicone	Polypropylene	PMP	PMP
Cannulation approach innovation	Central	Central	Central	Peripheral Novalung®	Peripheral Avalon™

CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ILA™, interventional lung assist; PMP, polymethylpentene; VA, venoarterial; and VV, venovenous.

Table 1. Evolution of ECMO as a bridge to lung transplant by decade. Adapted with permission from [5], © 2013 Diaz-Guzman et al. Published under Wolters Kluwer Health, Inc. DOI: 10.1097/MAT.0b013e31827461c2. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health.

2. Extracorporeal membrane oxygenation as a bridge to lung transplantation

The first report of the use of ECMO as a bridge-to-transplant was published in the 1970s [6]. The patient was successfully transplanted and wean from ECMO, he died at 10 days of post-transplant. Successful cases were reported in 1993 [7]; however, still controversies of using ECMO as a bridge-to-transplant were noted at that time because of poor clinical outcomes, for example, the estimated 1-year survival for the transplant of ECMO was only 40%. In addition, the resources have been considerable for a successful transplant through ECMO bridge, such as prolong intensive care and hospital stays, need of tracheostomy, substantial blood requirement, and consequent neuromuscular complications that also required prolonged periods of postoperative rehabilitation.

The lung allocation scoring (LAS) system, begun in 2005, can be attributable to increase the use of ECMO as a bridge-to-transplant. Contrary to it patients before 2005 would receive lungs only based on the length of time on the waiting list, both medical urgency and net benefit from transplantation were incorporated to create a standardized scoring system. Since the adoption of LAS system, patients receiving continuous mechanical ventilation get higher scores, more likely to receive a transplant. Simultaneously, issues were arisen that ventilator-dependent patient before transplantation may be too sick for transplantation, which may affect the post-transplant outcomes. Direct or indirect risk factors could be considered in these patients: one is the increased risk of "ventilator-induced lung injury (VILI)" or "ventilator-associated pneumonia" during waiting period, and the other is "ICU-acquired weakness."

ECMO has been associated with avoidance of mechanical ventilation and it facilitates perioperative rehabilitation. As far as minimizing VILI when using ECMO as a bridge-to-transplant, ECMO may be beneficial for the patients waiting lung transplantation who have refractory hypercapnic respiratory failure, which was followed by most patients with end-stage lung disease combined with hypoxic respiratory failure. Extracorporeal CO_2 removal (ECCO2R), more commonly called as this concept instead of ECMO, reduces mechanical ventilation requirements, enabling the use of low tidal volume and high PEEP at relatively lower respiratory rates. Recently, technological improvements, such as interventional lung-assisted device pumpless venovenous ECMO (NovalungGmbH, Germany), a low-resistance oxygenator that offers good decarboxylation, and the CardioHelp venovenous ECCO2R device (Maquet, Germany), have led to remove CO_2 selectively including partial or full oxygenation support [8].

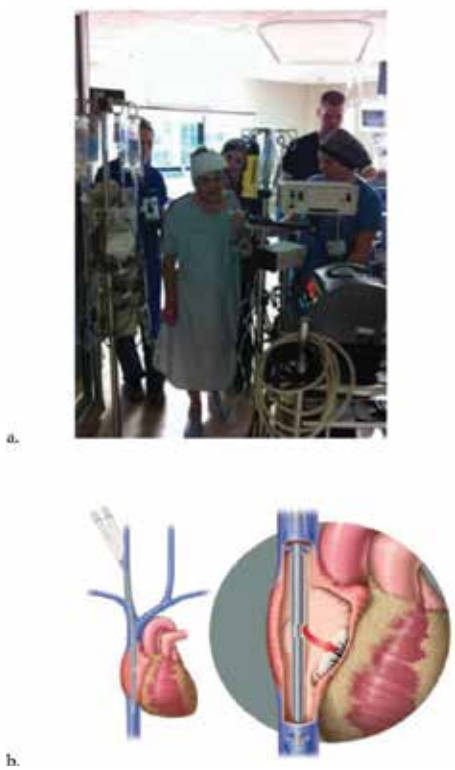

Figure 2. (a) Patient ambulating on venovenous-ECMO, (b) Avalon Elite Double lumen catheter and catheter placement. Adapted with permission from [5], © 2013 Diaz-Guzman et al. Published under Wolters Kluwer Health. DOI: 10.1097/MAT.0b013e31827461c2. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health.

Compared to the conventional mechanical ventilation strategy, patients who received "awake" ECMO as a bridge-to-transplant can be liberated from bed and participate in a preoperative "active" rehabilitation program, which consequently mitigated ICU-acquired weakness

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(**Figure 2a**). For this purpose, new-type single catheters, configured by double lumen, such as "Avalon" (**Figure 2b**) or "Novatwin" cannula, can be preferable, which facilitate easier patient mobilization to prevent decline in skeletal muscle dysfunction in postoperative period. Although a direct causal relationship between preoperative rehabilitation enhanced by a bridge-to-transplant using ECMO and postoperative exercise tolerance with ultimate clinical outcomes has not been established, it is generally considered a standard of care to enlist all patients into an active pulmonary rehabilitation program before transplantation or a "destination therapy" like that seen with left ventricular-assisted devices in the area of heart transplantation. There appears to be a benefit even in a common selected group of extremely sick conditions before transplant despite the scarcity of data currently [9].

Until now, there are no randomized controlled trials showing the beneficial effect of ECMO as bridge to lung transplant, several retrospective studies reported acceptable survival and its feasibility. Because most of these analyses were composed of many heterogeneous patients' feature, whether ECMO as an alternative, rather than an adjunction, to invasive mechanical ventilation is a better bridging strategy during lung transplantation still remains an unresolved issue. A meta-analysis of 14 retrospective studies [10–23] reported from 50 to 90% of the post-transplant 1-year survival rate, which was significantly better in spontaneously breathing patients or when the ECMO bridge duration was shorter than 14 days.(**Tables 2** and **3**) [4].

Author, year	Patients, number	Age (years)	Sex male, *n* (%)	Diagnosis	Ventilation strategy	Bridge time (days)	Severity score prebridge
Mason, 2010 [19]	51	39±22	25 (49%)	PF 27%; COPD 1996; CF 12%; PH 9.8%; sarcoidosis 2%; other 20%	na	na	LAS 54±21
Bermudez, 2011 [11]	17	40±14	7 (41%)	PF 35%; Re-LTx 35%; CF 23%; COPD 6%	MV	3.2 (0–49)	na
Hammainen, 2011 [15]	16	41±8[a]	7 (58%)	PF 37%[a]; PH 15%[a]; CF 8%[a]; ARDS 8%[a]; IP 8%[a]; PVOD 8%[a]; BOS 8%[a]; PGD 8%[a]	na	12 (1–59)	na
Shafii, 2012 [21]	19	44 (23–60)	10 (53%)	IP 68%; CF 16%; PH 16%	MV 13	6±5	LAS 87 (64–95)
Nosotti, 2012 [20]	11	34±13	5 (45%)	na	Awake 7 MV 4	12.1±14.7	SOFA 4.9±1.4
Javidfar, 2012 [17]	18	34 (22–50)	8 (45%)	CF 44%; PF 33%; PH 11%; Other 11%	Awake 6	11.5 (6–18)	LAS 93(90–94)
George, 2012 [14]	122	48±16	74 (60%)	PF 29.5%; CF 11.5%; COPD 10.7%; PH 2.5%; other 45.8%	na	na	LAS 73.9±21.4
Fuehner, 2012 [13]	26	44 (23–62)	21 (81%)	PF 35%; PH 27%; CF 19%; BOS 12%; sarcoidosis 4%	Awake 19 MV 7	9 (1–45)	SOFA 7 (6–12)

Author, year	Patients, number	Age (years)	Sex male, *n* (%)	Diagnosis	Ventilation strategy	Bridge time (days)	Severity score prebridge
Hoopes, 2013 [16]	31	45±15	21 (67%)	PF 29%; CF 23%; ILD 13%; ARDS 10%; PVOD 10%; PH 6%; BOS 3%; IP 3%; CWP 3%	Ambulatory 18 13 VM	11 (2–53)	LAS > 50
Anile, 2013 [10]	12	na	na	CF 92%; histiocytosis 8%	Awake 2 MV 10	6±2.1	na
Toyoda, 2013 [22]	31	46±15[a]	10 (43%)[a]	Pf 33%[a]; CF 21%[a]; Re-LTx 13%[a]; scleroderma 13%[a]; bronchiectasis 8%[a]; COPD 4%[a]; sarcoidosis 4%[a]; PH 4%[a]	MV[a]	7.1±10	Las 87±9 [a]
Weig, 2013 [23]	26	36 (30–51)[a]	14 (54%)	PF 62%; CF 23%; COPD 4%; Re-LTx 4%; lung cancer 4%; sarcoidosis 4%	na	16 (88–25)[a]	SOFA 9 (8.5–10.5)[a]
Crotti, 2013 [12]	25	41±12	na	PF 52%; CF 16%; PH 16%; Re-LTx 12%; ARDS 4%	Awake 10 MV 15	5.8±4.5 versus 29.8±11.5[a]	SOFA 5.6±1.9
Lafarge, 2013 [18]	36	31 (22–48)	19 (53%)	CF 56%; PF 30%; other 14%	MV	3.5 (2–7)	na

Data presented in this table refer to patients underwent ECMO support with the intention to bridge to lung transplantation.
[a]Transplanted patients (when data for all enrolled patients are not available; Hemmainen et al., all data; Toyoda, all data; Weig et al., ECMO bridge time and SOFA; Anile, diagnosis). ECMO bridge time (days) and the prebridge severity score are expressed as mean± standard deviation or median and range. When no descriptive cumulative data for the overall population are provided, they are calculated from raw data presented in the original papers.
[b]Data refer to patients divided according to waiting time on ECMO: up to 14 days or longer.
Pts, patients; ECMO, extracorporeal membrane oxygenation; PF, pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; PH, pulmonary hypertersion; Re-LTx, Re-lung transplantation; ARDS, acute respiratory distress syndrome; IP, interstitial pneumonia; PVOD, pulmonary veno-occlusive disease, bronchiolitis obliterans syndrome; PGD, primary graft dysfunctions ILD, interstitial lung disease; CWP, coal workers, pneumoconiosis; MV, mechanical vertilation; LAS, lung allocation score; SOFA, sequential organ failure assessment; and na, not available.

Table 2. Characteristics of patients who underwent ECMO bridge to lung transplant. Reproduced from [4], © 2015 Chiumello et al. Published under CC BY 4.0 license. DOI: 10.1186/s13054-014-0686-7.

Author, year	Ltx/total patients, *n*	Died before Ltx, *n* (%)	Type of bypass	Survival at 1 year post-LTx (%)	Length of stay post-LTx (days)	MV (days post-LTx)
Mason, 2010 [19]	51/51	na	na	50%	24 (9–55) H	na
Bermudez, 2011 [11]	14/17	3 (17%): neurologic dysfunction, thrombosis	W, VA	74%	16 (3–40) ICU)	12 (2–20)

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Author, year	Ltx/total patients, *n*	Died before Ltx, *n* (%)	Type of bypass	Survival at 1 year post-LTx (%)	Length of stay post-LTx (days)	MV (days post-LTx)
Hammainen, 2011 [15]	13/16	3 (19%): septic MOF	W, VA	92%	22 (3–63) ICU	na
Shafii, 2012 [21]	14/19	5 (26%): septic MOF 2, DC 2, and anoxic brain injury 1	W, VA	75%	42 (19–175) H	22 (5–125)
Nosotti, 2012 [20]	11/11	na	W	87% and 50%[b]	47.6±21.9 H 30±20.4 ICU	27.1±20.7
Javidfar, 2012 [17]	10/18[a]	8 (44%): pneumonia 1, MOF 6, and CA 1	W, VA	60%	22 (18–33) H 47 (41–52) ICU	na
George, 2012 [10]	122/122	na	na	57.6%	32 (16.5–60) H	na
Fuehner, 2012 [13]	20/26	6 (23%): CA 2, septic MOF 4	W, VA	6 months 80%	38 (20–87) H 18 (1–69) ICU	14 (0–64)
Hoopes, 2013 [16]	31/31	na	VA, W	93%	31 (12–86)[e]H	na
Anile, 2013 [10]	7/12	5 (41%)	W, VA	85.7%	29 (15–59) H	<5
Toyoda, 2013 [22]	24/31	7(22%)	W, VA	74%	46 median H	na
Weig, 2013 [23]	13/26	13 (50%): acute liver failure 7, thoracic bleeding 3, cerebral hemorrhage 1, and PE 2	W, VA	54%	na	na
Crotti, 2013 [12]	17/25	8 (32%): MOF 3, septic shock 2, cardiogenic shock 2, and intestinal ischemia 1	W, VA	82% and 29%[c]	na	12.2±11.9[d]
Lafarge, 2013 [18]	30/36	6 (17%): GI bleeding 1, DIC 1, cerebral hemorrhage 1, CA 1, septic shock 1, and therapeutic limitation 1	W, VA,CPB	66.5%	na	na

Data are expressed as mean±standard deviation or median and range. Mason et al., Nosotti et al., and George et al. enrolled transplanted patients.
[a]Three of the eight patients who died had transiently recovered their baseline function and were weaned from ECMO support; they subsequently died before LTx.
[b]ECMO group: 87% awake (7 pts); mechanical ventilation ECMO group: 50% (4 pts);
[c]82% patients on ECMO bridge <14 days (early); 29% patients on ECMO bridge >14 days (late);
[d]12.2±11.9 days (early group) −45.3±33.5 (late group).
[e]LTx, lung transplant; CA, cardiac arrest; MOF, multiorgan failure; DIC, disseminated intravascular coagulation; Gl, gastrointestinal; VV, venovenous; VA, venoarterial; CPB, cardiopulmonary bypass; MV, mechanical ventilation; LOS, length of stay; H, hospital; and na, not available.

Table 3. Summary of outcomes. Reproduced from [4], © 2015 Chiumello et al. Published under CC BY 4.0 license. DOI: 10.1186/s13054-014-0686-7.

3. Extracorporeal membrane oxygenation during lung transplantation

There is little evidence or protocol about how to manage ECMO during intraoperative situation; however, the intraoperative use of ECMO may be necessary at any stage of developing hypoxia, hypercapnia, and/or hemodynamic instability. In bilateral lung transplantation, ECMO can stabilize hemodynamic variables and prevent "first lung syndrome," the hyperperfusion of the first implanted lung during implantation of the second lung. In addition, it can also be used at every phase during lung transplantation to enhance a protective ventilation strategy and avoid 100% oxygen so as to mitigate the reperfusion syndrome especially during one-lung ventilation or to support when there was a lung size mismatch, auto-PEEP, and dynamic hyperinflation [8].

Because of many advantages mentioned earlier, ECMO has replaced CPB as the first option for intraoperative support during lung transplantation in many transplant centers. A recent published study from Germany showed 5-year experience with intraoperative ECMO in lung transplantation since April 2010 [10]. Compared with patients who underwent lung transplantation without ECMO, overall survival at 1 and 4 years was not inferior in patients in whom the indication for ECMO support and the intraoperative use of ECMO did not emerge as a risk factor for mortality. Though small numbers were included, many studies showed overall clinical beneficiary of ECMO over CPB during lung transplantation, such as lesser intraoperative blood transfusion requirement, lesser mechanical ventilation requirement, shorter ICU stay, and higher postoperative complications.

Bermudez et al. [11] compared 49 VA-ECMOs with 222 CPBs using intraoperative lung transplantation. In this study, there was a higher requirement for reintubation, tracheostomy, and dialysis in the CPB group; however, the lack of significant differences in perioperative blood transfusion requirement and hospital length of stay may have been caused by the ECMO group including a sicker population, such as the higher LAS (73.3 vs. 52.9) and higher pretransplantation ECMO requirement (42.8% vs. 7.2%). Though most of these studies did not show any difference in the survival curve between two groups, one study [12] revealed the hospital mortality gain of CPB over ECMO (39% vs. 13%); however, it should be considered that there were more planned ECMOs than CPBs (61% vs. 28%) in this study, which may not be ignored showing the different mortality between two groups.

4. Extracorporeal membrane oxygenation as a rescue postlung transplant

In the postopertative setting of lung transplantation, early primary graft dysfunction (PGD), which is a syndrome consisting of lung injury during the first 72 hours following lung transplant defined as a physiologically decreased oxygenation and radiologically diffuse infiltrates, continues to be a major situation of morbidity and mortality. There is no doubt that ECMO has been applied as a pivotal management strategy to support severe PGD because none of interventions to ameliorate the effects of PGD on transplanted lung have been

successful, including inhaled nitric oxide and prostaglandins. Although about 5% of lung transplantation requires ECMO support for PGD, this remains the most common indication for ECMO use as a rescue strategy and consequently it is reasonable that the concept of "bridge-to-transplant" has been arisen from the intermittent successes of a bridge to redo transplant in selected patients [1].

The goal of ECMO for severe PGD after lung transplant, same as mentioned in bridging-to-transplant, should be to minimize ventilator-induced lung injury such as elevated airway pressures or high inspired oxygen concentration by mechanical ventilation with positive pressure. While about this no uniform guidelines exist, one recommendation how to use ECMO to support PGD after lung transplant consists of initiating it when peak inspiratory pressure reaches up to 35 cm H_2O or 60% FiO_2 [13]. In addition, if possible, it could not be delayed greater than 48 hours to initiate ECMO after transplantation because of alleged worse outcomes. Hartwig et al. [14] reported surprising survival result in this group patients supported with VV-ECMO. Of the recipients from VV-ECMO following transplant, 96% weaned successfully with a 1-year survival of 64%.

Promisingly, *ex vivo* lung perfusion (EVLP), a novel technique used to evaluate and recondition marginal or rejected grafts, is also adapted during lung transplantation. The retrieved donor lung can be perfused in an *ex vivo* circuit, providing an opportunity to reassess its function before transplantation for the purpose of increasing successful transplantation with high-risk donor lungs. Cypel et al. [15] showed physiologically stable donor lung during 4 hours of *ex vivo* perfusion and its feasibility regarding less PGD event. Although the result was statistically not significant, this was the first report that demonstrates the possibility of *ex vivo* using ECMO for lung transplantation, remained and cited as the reference protocol. Recently, Boffini et al. [16] also revealed that the use of initially rejected grafts treated with EVLP did not increase severity of PGD after lung transplantation, suggesting a protective role of EVLP against PGD.

5. Conclusions

Recently, Biscotti et al. suggested the decision algorithm of how to use ECMO during entire lung transplantation (**Figure 3**) [2]. Though the details are not described in this chapter, the interhospital transport of lung transplantation candidate during ECMO is also feasible and this is opening a kind of new future episode [17].

Modern experience with ECMO and reported institutional experience on survival challenge historical assumptions about the treatment of end-stage lung disease and suggest that "bridging" to transplant with ECMO is both technically feasible and logistically viable. It is clear at this point that continued advances in the technologies and further research will help determine how best to include ECMO as a bridging strategy for lung transplantation.

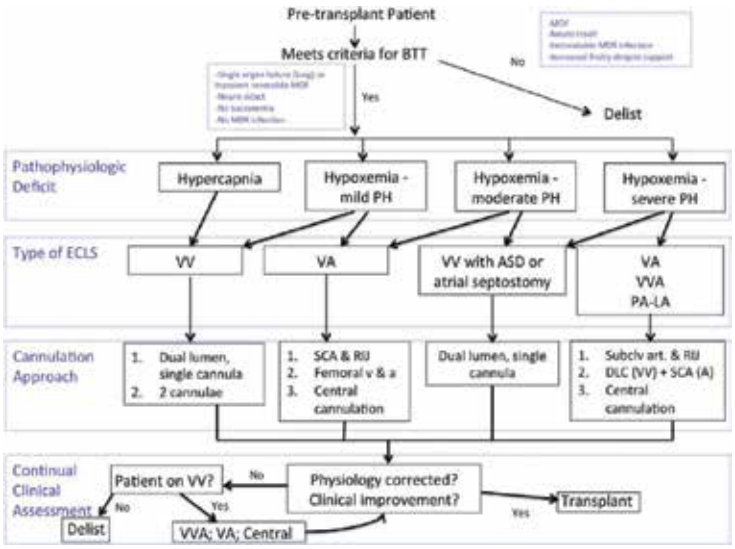

Figure 3. Decision algorithm of ECMO for lung transplantation. DLC, double lumen cannula; MDR, multidrug resistant; MOF, multiorgan failure; PALA, pulmonary artery to left atrium; PH, pulmonary hypertension; RIJ, right internal jugular vein; and SCA, subclavian artery. Adapted with permission from [2], © 2015 Biscotti et al. Published under Elsevier. DOI: http://dx.doi.org/10.1016/j.thorsurg.2014.09.010. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Elsevier.

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Chapter 10

Extracorporeal Membrane Oxygenation Support as Treatment for Early Graft Failure After Heart Transplantation

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Abstract

Early graft failure (EGF) is a major risk factor for death after heart transplantation (Htx) accounting for >40% of deaths within 30 days postoperatively. According to the last International Society for Heart and Lung Transplantation (ISHLT) consensus statement, the graft dysfunction (GD) is to be classified into primary (PGD), in case of an unknown triggering factor or secondary (SGD) where there is a discernible cause such as acute rejection, pulmonary hypertension, or known surgical complications. The diagnosis of GD is to be made within 24 h after completion of Htx surgery and a severity scale for GD should include mild, moderate, or severe grades based on specified criteria. Mechanical circulatory support (MCS) for GD should be considered when medical management is not sufficient to support the newly transplanted graft. Currently, extracorporeal membrane oxygenation (ECMO) is widely accepted as treatment of severe EGF, given its easy and quick setup, the system versatility, the optimal end-organ perfusion provided, and the possibility of both biventricular and lung assistance by usage of a low-cost single pump.

Keywords: heart transplantation, early graft failure, cardiogenic shock, mechanical circulatory support, extracorporeal membrane oxygenation

1. Introduction

A recent examination of early mortality after heart transplantation (Htx), documented in the International Society for Heart and Lung Transplantation (ISHLT) Registry, reveals that >40% of deaths within 30 days post-operatively are due to early graft failure (EGF) [1, 2]. Results get even worst in the pediatric transplant population where an early mortality of 88% after diagnosis has been reported [3]. To better define the classification, diagnosis and management of this condition, a Consensus Conference was organized on April 23, 2013 during the 33rd Annual ISHLT meeting. There were 71 specialists on this field including cardiologists, immunologists, pathologists, and surgeons, representing 42 heart centers worldwide. According to the consensus statement [1], graft dysfunction (GD) has been classified into primary (PGD), in case of an unknown triggering factor or secondary (SGD) when a discernible cause such as hyper-acute rejection, pulmonary hypertension, or known surgical complications [1] can be identified. The diagnosis of GD is to be made within 24 h after completion of heart transplantation (Htx) surgery and a severity scale for GD should include mild, moderate, or severe grades based on specified criteria. Risks are often multifactorial and usually include donor, recipient, and surgical variables. Before the advent of short-term ventricular assist devices (VADs) and extra-corporeal membrane oxygenation (ECMO) support after transplant, severe EGF was likely considered to be fatal. Currently, the use of mechanical circulatory support (MCS) devices as treatment of GD is more widely well accepted and adopted whenever maximal medical management is not sufficient to support the newly transplanted graft. In this chapter, we will focus on actual indications, surgical strategies, and future perspectives of veno-arterial ECMO as a bridge to graft recovery in both pediatric and adult populations.

2. Clinical background and epidemiology

The exact incidence of PGD has been unknown until 2013 due to the lack of standardization of diagnostic criteria according to the historical observational studies as stated by the above mentioned ISHLT consensus paper [1]. However, the ISHLT registry data always offered specific information concerning epidemiology and clinical characteristics of PGD by time. The examination of early mortality after heart transplant documented in the registry shows that 66% of the death that occurs in the first 30 days after transplant are due to “graft failure” and “multi-organ dysfunction” [1]. Most of these events are probably the result of fatal PGD. An analysis of the United Network for Organ Sharing (UNOS) database was conducted for transplants occurring from 1999 to 2007 (n = 16,716) [3]. For this analysis, PGD was defined by “hard outcomes,” meaning postoperative death or retransplant, where the incidence of PGD was 2.5%. In this PGD group, 85% were due to deaths and 15% were due to retransplants [3]. A closer look at early mortality from the ISHLT revealed that more than 100,000 patients who received Htx between 1982 and 2011 shows that approximately 10% of patients dies within 30 days of transplant, and this number increases to 14% after 90 days [1]. The risk of 30-day and 90-day mortality was the highest in retransplant (18% and 22%) and congenital heart disease (17% and 21%), intermediate in valvular cardiomyopathy (14% and 18%), and the

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lowest in ischemic (10% and 14%) and non-ischemic (8% and 12%) cardiomyopathy patients [1]. Increasing recipient age is a known risk factor associated with intermediate-term and long-term mortality after heart transplant; however, 30-day and 90-day mortality varies little in patients of different age groups, including patients older than 70 years. Sizable majority of early post-transplant deaths likely results from PGD. The recent reduction of early post-transplant mortality might have resulted from lower incidence and/or better treatment of PGD. There are considerable differences in early post-transplant mortality in patients who receive transplants for different heart disease etiologies, and early post-transplant mortality continues to represent a significant problem despite better survival. Concerning epidemiological data of Htx in children a retrospective review showing ECMO need in the early post-transplant period at Denver Children's Hospital, Aurora, Colorado. From 1990 to 2007, 310 children underwent Htx, and 28 children who underwent transplantation (9%) were placed on ECMO for postoperative primary graft failure [4]. They conclude that primary graft failure requiring mechanical circulatory support in the early period after transplantation is not uncommon in children (9%), and a long ischemic time is a major risk factor of graft dysfunction [4]. Pediatric cardiac allografts can be successfully salvaged by ECMO in a reasonable proportion of patients (54%) [4].

2.1. Pathogenesis

The transplant process may lead to donor heart graft several kinds of insults due to:

– Brain death and its sequelae in the donor.

– Hypothermic ischemia during transport.

– Warm ischemia during implant surgery.

– Reperfusion injury after release of the aortic cross-clamp in the recipient.

Systemic factors in the recipient determine a "hostile" environment that further compromises donor heart function after reperfusion. Associated with brain death in the donor, there is a series of events that result in impaired myocardial contractility and sensitize the heart to ischemia-reperfusion injury. An example is the intense release of myocardial norepinephrine immediately after brain death that causes cytosolic and mitochondrial calcium overload [5]. Mitochondrial calcium overload may activate autophagy, apoptosis, or necrosis [6]. During donor resuscitation, administration of exogenous catecholamines may determine a reduction of myocardial β-receptor sensitivity and an activation of multiple pro-inflammatory mediators, including complement [7–9]. Referring to hypothermic ischemia, during transport most donor hearts are stored in a cold preservation solution and transported on ice. Hypothermia slows but does not stop cellular metabolism, so progressive ischemic injury is an inevitable consequence of prolonged static storage. In addition, the absence of normal aerobic metabolism arrests the activity of transmembrane Na^+/K^+ adenosinetriphosphatase pump consequently the switch to anaerobic metabolism during cold storage causes a rapid decline in high-energy phosphates and development of lactic acidosis [10]. Na^+/H^+ exchanger is activated by intracellular acidosis and it exchanges H^+ for Na^+ across the cell membrane. The increasing of intracellular Na^+ determines an accu-

Donor risk factors	Recipient risk factors	Surgical procedural risk factors
• Age	• Age	• Ischemia time
• Cause of death	• Weight	• Donor-recipient mismatch
• Trauma	• Mechanical support	• Weight mismatch
• Cardiac dysfunction	• Congenital heart disease	• Experience of procurement team and center volume
• Inotropic support	• Multiple reoperation	• Cardioplegic solution
• Comorbidities: (diabetes, hypertension)	• LVAD explant	• Increased blood transfusion
• Drug abuse	• Comorbidities: (renal/liver dysfunction)	• Elective vs. emergency transplant
• LV hypertrophy	• Ventilator dependent	
• Valvular disease	• Multiorgan transplant	
• Hormone treatment	• Elevated PVR	
• CAD	• Allosensitization	
• Sepsis	• Infection	
• Troponin trend	• Retransplant	
• Hypernatremia		

Table 1. Risk factors for EGF.

mulation of intracellular Ca^{2+} by activation of the Na^{+}/Ca^{+} exchanger [11]. Other factors, recipient related, contribute to early graft dysfunction. It is possible to find two clinical conditions. The first is the presence of a high pulmonary vascular resistance in the recipient [12, 13]. In this case, the graft failure is considered secondary (to a known recipient factor) rather than primary. However, even with recipient pulmonary pressures and resistances within the accepted ranges for heart transplantation, a lower degree of pulmonary hypertension correlates with a lower incidence of PGD. The second scenario is characterized by activation of the systemic inflammatory response in the recipient, which causes vasodilated systemic circulation that is not responsive to medical therapy [14]. This "vasoplegic" response is associated with risks factors such as mechanical circulatory support before transplantation, large transfusion requirements, and prolonged cross-clamp time. In this circumstance, the "hostile environment" of the recipient results in PGD. The pathophysiology of PGD in this setting is not so clear, but it could involve the multiple action of many pro-inflammatory cytokines leading to upregulation of inducible nitric oxide synthase or indoleamine dioxygenase, with overproduction of nitric oxide or other endogenous vasodilators [14, 15]. The multiple risk factors for PGD include not only donor and perioperative factors but also recipient characteristics, confirming the multifaceted nature

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of PGD. The risk factors (**Table 1**) for PGD related to recipient are: age, parameters reflecting pulmonary hypertension and more severe pre-transplant condition, including dependence on intravenous inotropic support, mechanical support and mechanical ventilation. Donor factors include age, female donor, and cause of brain death. Procedural factors are represented by ischemic time and donor-to-recipient weight mismatch. The RADIAL score (**Table 2**) is today the only validated scoring system for the prediction of PGD [16]. This predictive model was obtained after multivariate analysis of independent risk factors for PGD in a single-center derivation cohort of 621 heart transplants performed from 1984 to 2006. Six factors with similar influence were chosen to form the acronym RADIAL: four of these are related to the recipient: right atrial pressure (4–10 mmHg), age (4–60 years), diabetes and inotropic support dependence; and two are associated with the donor: age (4–30 years) and length of ischemia time (4–240 min). The presence of each of these factors in an individual patient adds one point to the final score. According to the RADIAL model, there are three groups with low (0–1 points), medium (2 points), and high (>3 points) risk for PGD.

R (recipient)	**Right atrial pressure**	**>10 mmHg**	**1**
A (recipient)	Age	>60 years	1
D (recipient)	Diabetes	Diagnosis/treatment	1
I (recipient)	Inotropic support dependence		1
A (recipient)	Age	>30 years	1
L (recipient)	Length of ischemia	>240 min	1
Low risk for PGD		**(0–1) points**	
Medium risk for PGD		(2) points	
High risk for PGD		(>3) points	

Table 2. Radial score.

2.2. Classification

According to the consensus statement [1], graft dysfunction should be classified into PGD or secondary graft dysfunction (SGD) where there is a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications (e.g., uncontrolled bleeding; **Table 3**). It is necessary to made the diagnosis of PGD within 24 h after completion of the cardiac transplant surgery. There is an important difference between treatment of patients with RV failure and LV failure, so it was decided to divide PGD into two entities: PGD-LV, which includes LV and biventricular failure, and PGD-RV alone (**Table 3**). Finally, it was created a grading system for PGD-LV, which includes the descriptors of mild, moderate, and severe dysfunction. These were carefully defined with the use of hemodynamic variables, echocardiography results, level of inotropic support, and need for mechanical circulatory support. Because RV failure can often be more difficult to quantify, there are no grades for the severity of PGD-RV.

Primary graft dysfunction (PGD)		Secondary graft dysfunction
a. PGD-left ventricle (PGD-LV): includes [21] left and biventricular dysfunction b. PGD-right ventricle (PGD-RV): includes right ventricular dysfunction alone		Occurs when there is a discernible cause for graft dysfunction (e.g., hyperacute rejection, pulmonary hypertension, known surgical complication)
PGD-left ventricle (PGDLV):	*Mild PGD-LV: one of the following criteria must be met*	LVEF < 40% by echocardiography, or hemodynamics with RAP > 15 mmHg, PCWP > 20 mmHg, CI < 2.0 L/min/m^2 (lasting more than 1 h) requiring low-dose inotropes
	Moderate PGD-LV: must meet one criterion from I and another criterion from II:	I. One criteria from the following: left ventricular ejection fraction < 40%, or hemodynamic compromise with RAP > 15 mmHg, PCWP > 20 mmHg, CI < 2.0 L/min/m^2, hypotension with MAP < 70 mmHg (lasting more than 1 h). II. One criteria from the following: *High-dose inotropes—Inotrope score > 10[a] or **Newly placed IABP (regardless of inotropes)
	Severe PGD-LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP
PGD-right ventricle (PGDRV):	*Diagnosis requires either both I and II, or III alone:*	I. Hemodynamics with RAP > 15 mmHg, PCWP < 15 mmHg, CI < 2.0 L/min/m^2 II. TPG < 15 mmHg and/or pulmonary artery systolic pressure < 50 mmHg, or III. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient.

[a]Inotrope score = dopamine(x1) + dobutamine(x1) + amrinone(x1) + milrinone(x15) + epinephrine(x100) + norepinephrine(x100) with each drug dosed in μg/kg/min [k2].

Table 3. Classification of graft dysfunction.

2.3. Pharmacologic and mechanical management

Before the introduction of short-term VAD support and ECMO after Htx, PGD was frequently fatal except for that cases where emergency salvage retransplantation was possible. D'Alessandro et al. from La Pitié-Salpétrière in Paris retrospectively evaluated the use of ECMO temporary support as a treatment for PGD [17]. They studied 394 patients, who underwent cardiac transplant between 2000 and 2006. In 90 patients, PGD after transplant occurred. In this study, PGD was defined as the need for inotrope support with epinephrine and/or the

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necessity for mechanical circulatory support in the postoperative 48 h. Of these 90 patients, 54 received ECMO, 8 used other assist devices, and 28 were treated only with maximal inotropes [17]. Of those medically treated (i.e., on maximal inotropes only), survival was 46% compared with a survival of 50% for those on ECMO [17]. These data confirm that ECMO is becoming a safer and more effective technique to manage patients with PGD. A retrospective analysis of short-term VAD use after transplantation found that in 38 patients from 2003 to 2008 who have been implanted with the CentriMag device (Levitronix, Waltham, MA) for PGD survival was 50% at 30 days and 32% at 1 year [18]. Earlier implantation of the device after transplant seemed to correlate with improved survival, and all survivors were supported with the device for no more than 30 days [18]. In summary, medical treatment of PGD consists of inotrope and vasodilator support and these are considered the first line therapy for PGD and may be helpful for milder cases of PGD. ECMO and other mechanical circulatory support are the only effective options for more severe cases, appearing to reduce mortality compared with other treatments. From the data, early intervention and short-term support appears to be associated with improved survival.

3. Indication of ECMO in EGF

EGF is the main cause of early mortality after transplantation. Hemodynamic deterioration caused by cardiogenic shock due to the pump failure unresponsive to inotropes has a catastrophic progression if not corrected in time [2]. As the pathophysiology of EGF is often unclear, specific treatment remains still challenging and the choice of the most suitable support option (e.g., ventricular assist device [VAD] or extracorporeal membrane oxygenation [ECMO]) remains controversial. In particular, ECMO support, even if associated with mortality and a high rate of morbidity (such as bleeding, ischemic or thromboembolic events and infections), is considered a valid therapeutic route [19, 20].

3.1. Adult population

Actually, there is not a real or unique indication for ECMO implanting in case of EGF. What we can consider are the single centers experience. Routinely, after exclusion of surgical problems, the first line treatment starts using inotropic drags such as milrinone, epinephrine, and dopamine. In case of hard weaning from CPB machine because of unstable, hemodynamics should be considered the use of intra-aortic balloon pump (IABP) and prepare the patient for ECMO implantation (**Figure 1**). In the Cedars-Sinai Heart Institute, for example, they place on ECMO if cardiac index remains <2.5 L/min/m^2 with central venous pressure and left atrial pressure >12 mmHg and a mean arterial pressure <65 mmHg. The approach of the Columbia University at the management of PGD has evolved: most patients now receive BiVAD support, usually a C-Mag BiVAD with left apical cannulation. More recently ventricular-arterial ECMO has also become a more common mode of support. The median length of device support at their transplant center was 7 days, with an in-hospital mortality of 51%. Only 5.7% survived to re-transplantation [1].

3.2. Pediatric population

ECMO represents the most commonly used method of mechanical circulatory support in the post-transplantation period of pediatric patients [21]. In the same way of the adult, also for the pediatric population, the indications for the ECMO implantation are not clear. In almost all centers, the extracorporeal membrane oxygenation is started in the operating room because of the inability to wean from cardiopulmonary bypass, and only a few cases required ECMO in the first 48 h after transplantation requiring a cannulation in the cardiac intensive care unit [4]. In particular, as reported by Tissot et al. [4], the timing of ECMO cannulation is not predictive of outcome. In their population, in fact, the survival is not significantly different between patients started on ECMO in the operating room with those cannulated in the first 48 h after transplantation for hemodynamic instability or cardiac arrest in the cardiac intensive care unit. This is in contrast with Galantowicz et al. [22], who reported no chance of survival if the cardiac allograft could not support the patient after cardiopulmonary bypass.

4. Surgical approach

Mechanical circulatory support has evolved markedly over recent years even in terms of surgical techniques. In particular, ECMO support can be deployed peripherally or centrally, using a traditional or minimally-invasive approach. There is still a great debate about the cannulation site strategies (**Table 1**). The central cannulation has several advantages such as full antegrade outflow and avoidance of peripheral ischemic complications [23]. However, it

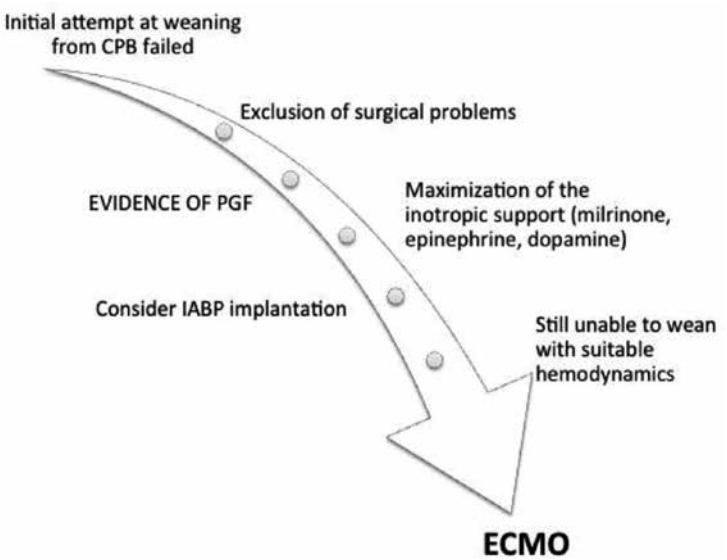

Figure 1. Decision algorithm for ECMO implantation for EGF.

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leads to an high risk for bleeding, tamponade, and infection [24]. These are the main reasons why a lot of centers adopt a peripheral setting.

4.1. Peripheral cannulation

For veno-arterial ECMO installation, a femoral vein and a femoral artery are usually used for vascular access. The correct position of the venous cannula tip is the mid-right atrium to have an homogenous drainage of venous blood from both caval veins. The femoral arterial cannula should be fully introduced till its tip reaches the common iliac artery, in adults (**Figure 2**). Commonly, in our center, we use a DLP Biomedicus 15–19 Fr (Medtronic Inc., Minneapolis, MN) cannula for the femoral artery, and a DLP Biomedicus 17–23 Fr (Medtronic Inc.) cannula inserted into the femoral vein for the venous drainage [25]. Both insertions are performed using the Seldinger technique after anterior vessel wall exposure and secured with pledgeted, reinforced purse string prolene sutures. Combined IABP support is additionally adopted in the peripheral ECMO population to indirectly "vent" the left ventricle and avoids the pulmonary edema. For peripheral cannulation, a continuous-wave Doppler image of the tibial artery flow and pulsatility should be acquired every 2 days, in the presence of a consultant vascular surgeon, to evaluate and provide a correct distal leg perfusion.

Although, as described above, the peripheral cannulation reduces the risk of bleeding and of infection, it can lead to important lower limb ischemia and the so-called "watershed phenomenon." The "native" flow meet the retrograde blood flow from the arterial cannula somewhere between the ascending aorta and the renal arteries at a point called the "watershed." All areas distal to this zone received blood oxygenated by the ECMO; meanwhile, the upper part receives blood from the left ventricle depending on respiratory function of the lung which can be severely compromised [26]. In an effort to minimize these matters, some centers reported on the use of a side graft sutured on the axillary artery as arterial return for ECMO peripheral setting. The advantages include: a low grade of atherosclerosis vessel disease, an antegrade flow into the aorta, and a preferential delivery of oxygenated blood into the heart and brain [27].

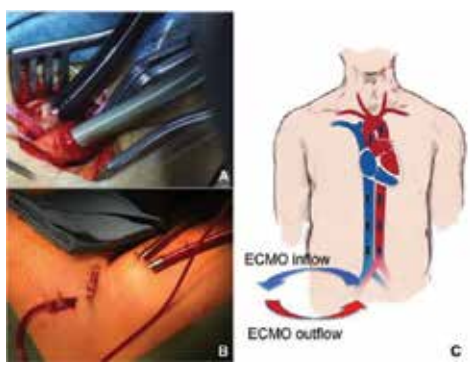

Figure 2. Peripheral ECMO setting (A: intra-operative direct cannulation; B: intra-operative percutaneous approach; C: setting).

4.2. Central cannulation

The easiest way to perform a central approach for ECMO implantation after Htx is to re-utilize the cannulas adopted for aortic arterial return and atrial venous drainage during the cardio-pulmonary bypass (CPB). Usually, the aortic cannula is left in situ to avoid new aortic puncturing, while the venous cannula is placed into the right atrium through its lateral wall. At our center, the central cannulation is performed using the right atrium, through its lateral wall as access, and the left atrium, between the right pulmonary veins as access, for venous drainage [25]. The employed cannulae are two 28-Fr wire-reinforced angled veno-atrial cannula (Jostra Venous Catheter OD; Maquet Cardiopulmonary AG, Hirrlingen, Germany) for both atria. The outflow cannula is always positioned into the ascending aorta [straight aortic perfusion cannula (22 or 24 Fr); Edwards Lifesciences LLC, Irvine, CA]. All cannulas are secured with pledgeted, reinforced purse string prolene sutures, tunneled through sub-costal incisions to allow chest closure, and then connected to the circuit, avoiding air in the system. In case of graft isolated right ventricular failure (RVF) and pre-transplant recipient severe pulmonary hypertension, the extracorporeal right-to-left atrium bypass (ECRLAB) ECMO setting may be adopted (**Figure 3**) [25]. Briefly, the cannulation is performed centrally, using the right atrium for venous drainage and the left atrium, between the right pulmonary veins, for arterial return. The cannulae are two 28-Fr wire-reinforced angled veno-atrial cannula (Maquet) for both atria. The conventional circuits, with the inflow cannula in the right atrium and the outflow cannula in the pulmonary artery, could not completely decompress the right heart in case of high pulmonary arterial pressures, presumably because no blood entering the chamber can be ejected across the pulmonary valve. ECRLAB improves the right-sided pressures, showing that the component of the right ventricular afterload is "reversible" [25]. ECRLAB appears as well, by increasing both cardiac output and return to the left atrium and ventricle, to improve end organ function avoiding any eventual multiple organ failure syndrome (MOF).

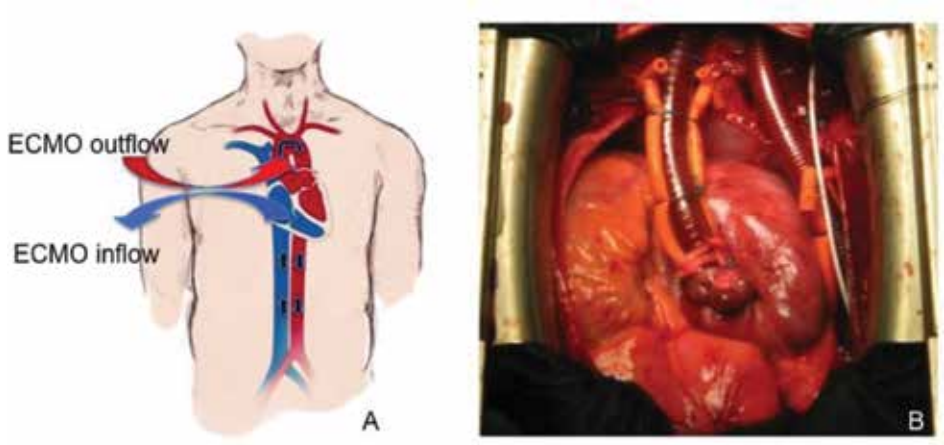

Figure 3. Central ECMO setting (A: setting; B: intra-operative picture).

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4.3. Minimally invasive

A challenging option to reduce the ECMO-related risk of complications is the adoption of minimally invasive surgical approaches. There are few reports in the literature. In a recent paper, Weymann et al. describe their technique [28]. After a small right-sided thoracotomy at the eighth intercostal space, flexible arterial and venous cannulas are tunneled. A sewing ring is secured to the right atrium and a tube graft is anastomosed to the ascending aorta. Following full-dose heparinization, the arterial cannula is inserted with the tip into the vascular graft for the ascending aorta and the venous cannula via the ring into the right atrium. After de-airing, the central extracorporeal life support is set at full flow. So far, this surgical approach has not been described in patients who underwent ECMO implantation as treatment of early graft failure, but it might be considered a valid idea for future implantations.

5. Weaning protocol

There are no standardized methods or techniques with regards to weaning ECMO. Usually, the factors indicating cardiac recovery, and so the possibility of weaning from the ECMO, are: increasing blood pressure, falling central venous and/or pulmonary pressures, and improving of cardiac contraction [23]. It is so useful reassess the myocardial function every 24/48 h with TTE, trans-thoracic echocardiography / TEE, trans-esophageal echocardiography in addition to daily hemodynamics. It would be reasonable to reduce pump flows in 0.5 L decrements to 2 L/min over 36–48 h checking the above mentioned variables. The weaning protocols change from center to center according to the personal experience. Lima et al. [29], for example, routinely use the intra-aortic balloon pump for ECMO weaning. At our institution, full ECMO flow is instituted for at least 72 h [25]. Criteria for weaning include an $SvO_2 \geq 70\%$, a hematocrit of 28–30%, the absence of bleeding or tamponade, the absence of left heart distension, improvement in contraction of both ventricles, normal blood lactate levels (<1.5 mmol/L), and a normal urine output (>80 mL/h). A gradual weaning by reducing the ECMO flow by 10% every ~12 h is our main strategy, together with close TEE and Swan-Ganz catheter examinations. Once an ECMO flow of 1.5 L/min/m^2 is reached, in the presence of two or more consultant surgeons, the pump flow is radically reduced at 0.5 L/min/m^2 for ~30 min. If the hemodynamics in terms of systemic arterial pressure (mean pressure >60 mmHg), LV contractility (EF >40%), aortic blood flow time-velocity integral >10 cm, central venous pressure (10–12 mmHg), wedge pressure (10–12 mmHg) and SvO_2 (>70%) show no significant changes without the addition of new inotropes, the heparin is stopped, and ECMO support is removed in the operating room within the next 3 h [25].

6. Outcomes

In case of primary graft failure, when all pharmacological options fail, ECMO system represents surely a good option in cardiac surgeon's hands to secure a valid circulatory

support. Outcomes in both subtypes, adult and pediatric population, vary among the different centers (**Table 4**). This may be related to several aspects such as the time of implantation and surgical techniques.

Transplantation center	Year	ECMO in PGF/ total cardiac transplants	Surgical approach
Cedars-Sinai Heart Institute [1]	2005–2012	8/555	—Central cannulation: 100% —Peripheral cannulation: 0
Instituto de Cardiologia do Distrito Federal, Brasília [29]	2007–2013	11/71	—Central cannulation: 81.8% —Peripheral cannulation: 18.2%
Heart Center Leipzig [35]	1997–2011	28/298	—Central cannulation: 0 —Peripheral cannulation: 100%
Cardiac surgery and Heart Transplant Unit (ISMETT), Palermo [30]	2006–2013	18/114	—Central cannulation: 77.8% —Peripheral cannulation: 16.7% —Central arterial cannulation and peripheral venous cannulation: 5.5%
Cleveland Clinic [36]	1990–2009	43/1417	—Central cannulation: 0 —Peripheral cannulation: 100%
The Alfred Hospital, Melbourne [37]	2000–2009	39/239	—Central cannulation: 66.6% —Peripheral cannulation: 41%
Groupe hospitalier Pitié-Salpétrière [17]	2000–2006	54/394	—Central cannulation: 48.1% —Peripheral cannulation: 51.9%
S. Orsola-Malpighi Hospital [38]	2002–2007	11/188	—Central cannulation: 54.6% —Peripheral cannulation: 45.4%

Table 4. Outcomes of ECMO support as treatment of EGF.

6.1. Adult

In literature, the successful ECMO weaning rate ranges from 68% to 82% and corresponds to a hospital mortality rate of 50%. In the experience reported by Santise et al. [30], 13 patients (72.2%—13/18) were weaned from the mechanical circulatory support, and eight of them (44%) were discharged home. The causes of death of the patients weaned from ECMO were multi-organ failure, sepsis and acute mycotic rupture of pulmonary artery. Also the group of La Pitié-Salpétrière [17], in an older paper, report good results after ECMO implantation. Among the 54 patients supported with ECMO, 36 were weaned from the assistance and 27 were discharged. In this study, patients treated with ECMO had the same 1-year conditional survival as patients not having suffered EGF: 94% at 3 years.

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6.2. Pediatric

Early primary graft failure after Htx in children is associated with significant rates of mortality and morbidity. Extracorporeal membrane oxygenation is widely used and is well established to support circulatory function in children with post-cardiotomy low cardiac output syndrome [31]. The manuscript with the largest series on pediatric heart transplantation is that of Tissot from Denver Children's Hospital, Aurora, Colorado [4]. They retrospectively analyzed the indications and outcome of extracorporeal membrane oxygenation for early primary graft failure and determined its impact on long-term graft function and rejection risk. From 1990 to 2007, 28 (9%) of 310 children who underwent transplantation for cardiomyopathy or congenital heart disease required ECMO support. Fifteen children were successfully weaned off ECMO and discharged alive (54%). This is comparable to what has been previously reported in the pediatric population [21, 32, 33].

Mean duration of ECMO was 2.8 days for survivors (median 3 days) compared with 4.8 days for non-survivors (median 5 days). The duration of cannulation was so important in this series, with no child surviving ECMO support for >4 days. The long-term outcome in those patients supported by ECMO for primary graft failure and surviving to hospital discharge was excellent. There was, in fact, 100% 3-year survival in the ECMO survivor group, with 13 patients (46%) currently alive at a mean follow-up of 8.1 ± 3.8 years.

7. Conclusions and perspectives

PGD is the main cause of early mortality after Htx. Hemodynamic deterioration caused by cardiogenic shock due to pump failure unresponsive to inotropes has a catastrophic progression if not solved in time. Early institution of ECMO allows myocardial graft function recovery despite multifactorial insults and prevents the development of an eventual multisystem organ failure which would otherwise occur in case of a prolonged period of uncorrected cardiogenic shock [34]. In addition to the short-term effects, it has been observed that ECMO implantation, as a bridge to graft recovery after transplantation, can be used without influencing the long-term outcome of this high-risk postoperative cohort of patients. Currently, we take advantage from a wide available range of surgical options for ECMO setting. However, we are still too far from the ideal mechanical support device as routine and well-accepted treatment strategy.

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Chapter 11

Extracorporeal Membrane Oxygenation in Traumatic Injury: An Overview of Utility and Indications

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Additional information is available at the end of the chapter

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Abstract

Severe respiratory failure may develop in the trauma patient as a consequence of direct lung injury, in response to trauma-associated systemic inflammatory response syndrome (SIRS), as a result of infection, or at times as an unintended consequence of the life-saving management of the acute traumatic injury. Approximately 0.5% of all adult trauma patients develop some form of pulmonary dysfunction along the acute lung injury (ALI) – acute respiratory distress (ARDS) spectrum, with the incidence of severe respiratory failure reaching 10–20% in multisystem trauma victims. Of concern, mortality in patients with acute respiratory failure who go on to develop severe pulmonary dysfunction can be as high as 37–50% with the use of conventional therapeutic modalities. Extracorporeal membrane oxygenation (ECMO) has been proposed as a rescue strategy when less invasive primary or adjunctive attempts fail. Numerous case reports and single-center studies demonstrate potential benefits of early implementation of veno-venous (VV)-ECMO for the treatment of severe respiratory failure associated with trauma or sequelae of trauma. In this clinical context, VV-ECMO can be employed to correct for both ventilatory and oxygenation failure while allowing the treating physician to provide much needed rest to the patient's lungs and permit healing to take place. The use of ECMO (mainly veno-venous, with limited use of veno-arterial circuits for cardiac indications) has been described in patients with severe chest injuries, traumatic pneumonectomy, bronchopleural fistulas, and various forms of respiratory failure refractory to conventional therapies.

Keywords: VV-ECMO, VA-ECMO, ALI, ARDS, acute respiratory failure, trauma, indications, contraindications

1. Introduction

Approximately 0.5% of all adult trauma patients develop some form of pulmonary dysfunction, with the incidence of severe respiratory failure reaching 10–20% in multisystem trauma victims [1]. Mortality may be as high as 50% in trauma patients with acute respiratory failure who go on to develop severe pulmonary dysfunction [2]. Novel approaches to mechanical ventilation and adjunctive strategies may help improve outcomes, but continue to fall short of the desired paradigm change [3–6]. Extracorporeal membrane oxygenation (ECMO) has been proposed as a rescue strategy when less invasive primary or adjunctive attempts fail [7–9]. Due to ample case-based literature on the topic of ECMO use in the trauma patient, the goal of this chapter is to provide the reader with a high-level overview of trauma-specific considerations, controversies, pitfalls, indications, and potential avenues for future development in the use of ECMO in the trauma patient.

2. ECMO: a synopsis

There are four major types of short-term mechanical circulatory assist devices used for cardiopulmonary support: (1) intra-aortic balloon pumps, (2) percutaneous ventricular assist devices, (3) extracorporeal membrane oxygenators (ECMO), and (4) non-percutaneous centrifugal pumps [10, 11]. The use of ECMO is limited largely to non-trauma applications, including respiratory (veno-venous or VV-ECMO) and mixed cardiac and respiratory support (veno-arterial or VA-ECMO) in pathophysiologic states considered refractory to maximal standard therapies [12–14]. Circuit characteristics, technical considerations, and other fundamentals of ECMO have been discussed elsewhere in this book. This chapter including the use of ECMO in trauma patients, including indications, contraindications, competing priorities, and practical clinical considerations.

Key considerations must first be addressed before continuing the discussion of ECMO in trauma. Cardiopulmonary support was initially introduced to facilitate and assist cardiac surgical interventions [12, 15]. Subsequent evolution of this technology included device miniaturization and clinical translation to environments outside of the operating room, such as the intensive care units (ICU) [12, 15, 16]. Consequently, it became much easier to deliver ECMO-based therapies, in the setting of acute, refractory respiratory failure, for extended periods of time [17]. Prolonged cardiopulmonary support based on ECMO is now considered a viable option in risk-appropriate, carefully selected non-cardiac surgery patients [18, 19]. At the same time, other non-interventional treatment options and adjuncts are being refined and potential new indications proposed which are actively and dynamically changing the landscape of clinical utilization of ECMO [20–25]. Finally, financial aspects of ECMO therapy must be recognized as well, with significant barriers to wider implementation due to healthcare institutions being increasingly focused on cost containment and value [26–28].

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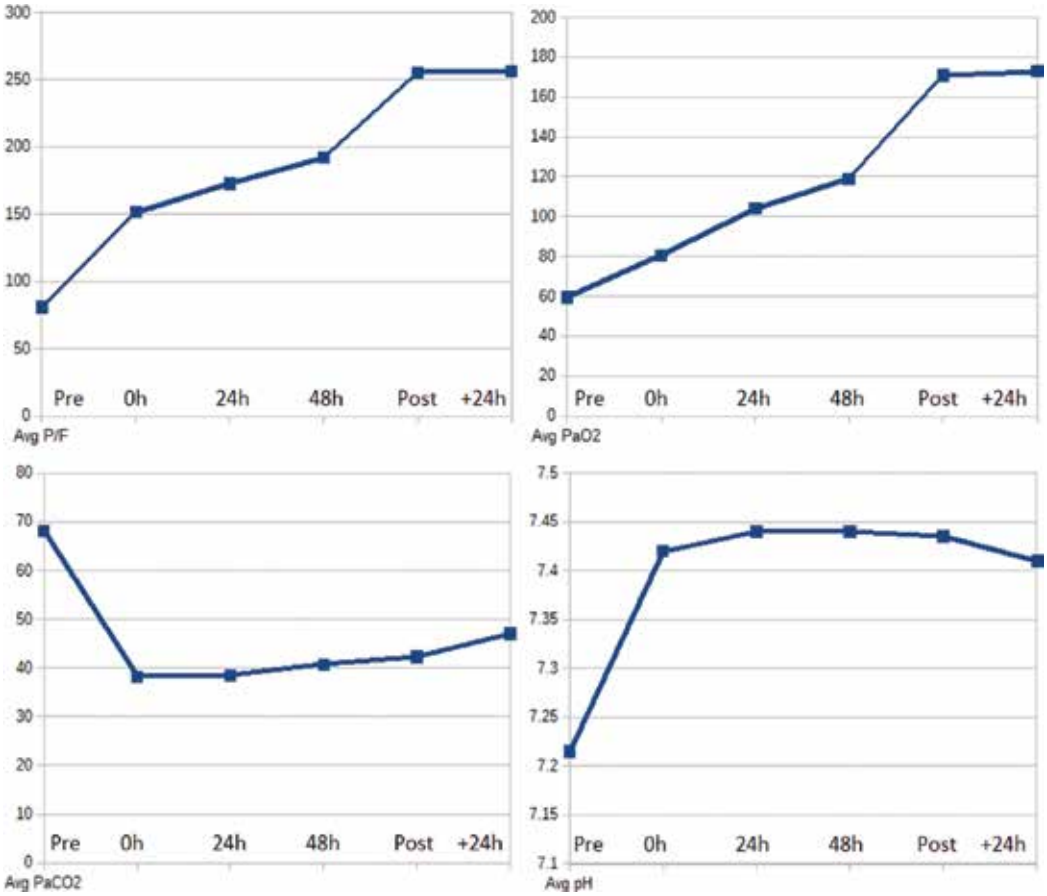

Figure 1. Simplified demonstration of the behavior of key physiologic parameters modifiable with the use of ECMO. Each graph above shows the baseline parameter value, followed by the initial post-ECMO, 24- and 48-h, and then immediate post-weaning measurements. The final value for each parameter represents average measurement for each corresponding variable at 24 h post-ECMO. (**Top left**) Average PaO_2/FiO_2 values; (**top right**) average PaO_2 values (mmHg); (**bottom left**) average $PaCO_2$ values (mmHg); (**bottom right**) average pH values. Data compiled from: Arlt et al. [33], Bonacchi et al. [110], Muellenbach et al. [89], Ried et al. [111], Wu et al. [45].

During ECMO, blood is drained from the patient's native vascular system, propagated by a mechanical pump device, and then re-introduced back into circulation [17, 29]. There are two major types of ECMO: (a) VV-ECMO and (b) VA-ECMO [30]. Both provide a support framework that is capable of essentially correcting systemic abnormalities related to catastrophic failure of pulmonary oxygenation and/or ventilation (**Figure 1**), with the main difference being the ability for VA-ECMO to actively augment systemic perfusion [30, 31]. As outlined above, systems capable of providing full pulmonary (but not cardiac) support in patients with severe hypoxemic respiratory failure are termed VV-ECMO devices [32]. Modern VV-ECMO systems take advantage of high flow rates in order to both maximize gas exchange capacity and decrease the risk of thrombotic complications, thus creating an additional potential benefit for patients with contraindications to heparin use [30, 33]. Because VV-ECMO accounts for the

majority of ECMO applications in trauma, we briefly discuss basic principles of venous cannulation required for the deployment of veno-venous ECMO circuits. Cannulation for VA-ECMO is beyond the scope of the current discussion and has been described in other parts of this text.

As outlined elsewhere in this book, the VV-ECMO "inflow catheter" is typically placed in the superior vena cava (SVC) by way of right internal jugular (IJ) central venous access [12, 34]. The "outflow catheter" is typically placed in the inferior vena cava (IVC) by way of femoral central venous access [35, 36]. At the bedside, the distinction between the two can be determined visually in most cases, as the "inflow catheter" blood is generally bright red and the "outflow catheter" blood is usually darker in appearance [37]. The care of the complex trauma patient is characterized by the presence of multiple competing clinical priorities [38, 39]. Thus, providers may need to be flexible in terms of vascular access options for ECMO. For example, cervical spine injury in the trauma patient may preclude internal jugular cannulation [40]. Moreover, significant pelvic or lower extremity fractures may preclude accessing the femoral vessels [41]. Finally, significant complications have been reported during and following ECMO catheter placement, highlighting the need for providers with appropriate level of expertise to be present throughout the entire ECMO delivery process [42, 43]. Image-guided approaches may provide an added degree of procedural safety during the cannula placement process [35, 44].

During its earliest applications, ECMO in trauma required the use of substantial amounts of heparin for anticoagulation due to the risk of clot formation and circuit occlusion [29]. This, in turn, limited ECMO's use due to the potential for hemorrhagic complications in patients with traumatic brain injury, solid organ injuries, or major vascular disruption related to trauma. ECMO circuits of the past were large, bulky, difficult to transport, and not as biocompatible as systems of today [29]. However, since then, ECMO circuits have evolved into essentially portable pump-driven devices that are compact, easy to transport, and carry a much lower risk of circuit clotting due to the synergies between device miniaturization, optimization of flow rates, and heparin-bonded circuits that are more biocompatible [29, 33]. Even when systemic heparinization is required during active ECMO therapy, mortality figures continue to be better than those for comparable non-ECMO trauma patients with equivalent injury severity [45]. In one study, 67.8% of trauma patients receiving ECMO with systemic heparinization survived [45]—a number comparable to non-heparinized trauma patients [46]. Later in the chapter, we discuss the application of ECMO *without* the use of anticoagulation, including important preconditions, indications, contraindications, and risks associated with such approaches.

When full cardiopulmonary support is required for patients in circulatory failure and/or cardiogenic shock, the VA-ECMO approach is utilized [12, 32]. Because the vast majority of trauma-related ECMO applications involve severe respiratory failure (e.g., VV-ECMO) and do not involve or require the need to augment systemic perfusion (e.g., VA-ECMO), we refer the reader to portions of this book that refer to VA-ECMO applications for specialized guidance regarding the patient with refractory cardiac failure. However, when applicable, VA-ECMO

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use in trauma will be outlined in the context of general ECMO applicability and clinically relevant aspects central to the current discussion.

3. ECMO in trauma: general considerations, indications, and contraindications

Broadly speaking, ECMO provides the ICU team with an opportunity to ameliorate a broad range of cardiorespiratory maladies, from cardiogenic shock to refractory pulmonary failure [47–50]. In fact, ECMO may be the only clinical "bridge" for patients who otherwise would not be expected to survive the acute phase of their critical illness [47–50]. The degree to which ECMO is able to facilitate various clinical objectives depends on the principal patient diagnosis (e.g., the primary reason for extracorporeal circuit support) and the type of ECMO circuit used [12, 51–53]. In addition to improvement in key oxygenation and circulatory parameters, the vicious cycle of metabolic acidosis, coagulopathy, and hypothermia (e.g., "the lethal triad") in the polytrauma patient can be limited and even reversed with early and aggressive use of ECMO [33, 54]. In the past, ECMO was utilized as a "last resort" or a salvage therapy when all other modes of intervention had failed. However, evidence is now emerging that early ECMO implementation can limit, or even reverse, the extent of multisystem organ failure resulting from trauma-related sequelae traditionally associated with high mortality, especially in the setting of severe chest injuries [29].

In terms of specific indications and contraindications, the literature pertaining to trauma in this evolving area of cardiopulmonary circulatory support remains scant. It has been proposed that indications for ECMO in the setting of trauma should generally mirror indications in non-trauma settings, as outlined in the Extracorporeal Life Support Organization (ELSO) guidelines (**Table 1**) [55, 56]. Typically, ECMO is indicated in the setting of severe hypoxemia and/or hypercarbia with anticipated mortality in excess of 80% using conventional ventilation strategies [56]. Consequently, patient eligibility should be determined utilizing a case-by-case, highly individualized selection process [57]. The overall risk–benefit equation must be taken into careful consideration, with general contraindications to ECMO being advanced age, the presence of significant comorbid conditions, and recent intracranial hemorrhage [56]. This selection process must also consider initiation of therapy prior to irreversible pulmonary damage and the emergence of non-preventable mortality. A delay in therapy due to stringent inclusion criteria may make any attempt at salvage moot [58]. Additional potential contraindications include the prospect of irreversible end-organ failure despite timely initiation of ECMO support, pre-ECMO ventilator support duration of >7 days, uncorrected coagulopathy, contraindication to anticoagulation, active systemic infection, recent stroke, severe peripheral arterial disease, inability to cannulate due to patient factors, and severe aortic regurgitation [57, 59, 60]. Because many of the above contraindications are viewed as being "relative" as opposed to "absolute," each patient's case must be considered individually. Perhaps more importantly, outcomes appear to be better in centers that support dedicated, highly experienced ECMO and perfusion teams (optimally able to support at least six ECMO cases per year) [56].

Inclusion criteria

Anderson et al. [46]

- Total static lung compliance <0.5 mL/cm H_2O/kg.
- Transpulmonary shunt <30% on FiO_2 >60%
- Reversible respiratory failure
- Time on mechanical ventilation ≤5 days (10 day absolute maximum)

Biderman et al. [8]

- Injury severity score (ISS) >16
- Conventional mechanical ventilation failed to control:
  - Hypoxemia
  - Hypercapnia/respiratory acidosis

Cordell-Smith et al. [75]

- Severe, but potentially reversible, respiratory failure
- Murray lung injury score >3.0 or uncompensated hypercapnia with pH <7.20

Gothner et al. [40], p. 1–6

- Hypoxemia, with PaO_2/FiO_2 of <200; FiO_2 between 0.8 and 1.0; and ventilation time >8 h
- Tidal volume >4–6 mL/kg ideal body weight
- Inspiratory pressure (P_{insp}) >32–34 mmHg
- Respiratory acidosis (pH <7.25) and/or
- Arterial oxygen saturation <90%

Michaels et al. [108]

- Potentially reversible respiratory failure
- Mechanical ventilation <7–10 days
- PaO_2/FiO_2 of <100
- Shunt fraction >30%
- Static lung compliance <0.5 mL/cm H_2O/kg or <30 mL/cm H_2O at tidal volume 10 mL/kg
- Failure to resolve the above indicators despite aggressive conventional management

Muellenbach et al. [89]

- Optimization/maximization of lung-protective ventilation strategy (tidal volume 6 mL/kg and high PEEP prior to ECMO)
- PaO_2/FiO_2 of <80, and FiO_2 >90%

Wu et al. [112]

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Inclusion criteria

Anderson et al. [46]

- Severe hypoxemia, with PaO_2/FiO_2 of <60, and PEEP >10 cm H_2O despite maximal ventilator support
- Initial PaO_2/FiO_2 of <60, with rapidly deteriorating pulmonary and hemodynamic status despite maximal ventilator support
- Irreversible CO_2 retention in the presence of hemodynamic instability

Exclusion criteria

Anderson et al. [46]

- Potential for severe bleeding
- Duration of mechanical ventilation >10 days ("11 days or greater")
- Necrotizing pneumonia
- Poor quality of life (e.g., patients with metastatic malignancy, major central nervous system injury, or quadriplegia)
- Age >60 years

Biderman et al. [8]

- Age >60 years
- Prolonged mechanical ventilation (>7 days) with
  - Peak airway pressures >30 cm H_2O and/or
  - FiO_2 >80%
- Septic shock and multi-organ failure
- Non-commitment of staff/family to full treatment

Michaels et al. [108]

- Mechanical ventilation >7–10 days
- Age >60 years
- Excessive risk of central nervous system bleeding with heparinization
- Septic shock
- Advanced multi-organ failure
- Severe pulmonary hypertension (mean pulmonary artery pressure >45 mmHg or >75% systemic pressure)
- Pre-existing terminal disease

Table 1. Compilation of parameters used during the determination of ECMO suitability in various literature reports pertaining to trauma population.

After an indication for ECMO has been met, the decision regarding percutaneous cannulation versus open central cannulation has to be made [61, 62]. In addition, the provider team needs to determine whether to use anticoagulation or to proceed without anticoagulation [63–65]. This decision must consider issues not only related to initiation and maintenance but also weaning of ECMO support (e.g., ability to maintain clot-free circuit with lower flow rates) [65]. The choice of anticoagulation is also important, with alternative options available (e.g., argatroban, bivalirudin) for patients with a contraindication to heparin use (e.g., heparin-induced thrombocytopenia) [64, 66]. Some additional considerations include potential/relative contraindications to ECMO, such as severe aortic regurgitation, severe peripheral arterial disease, uncontrolled sepsis, bleeding diathesis, recent cerebrovascular accident (CVA), or an irreversible cause for the end-organ failure being treated [59]. Previous studies show short-term survival rates between 35% and 83% among patients who appropriately receive ECMO, depending on patient population and primary disease characteristics [67–71]. Additionally, the **C**onventional Ventilation or ECMO for Severe Acute Respiratory Failure (CESAR) trial showed that patients referred to an ECMO center had a significant increase in survival without disability at 6 months compared to conventional management (63% versus 47%, respectively) [72]. Of note, the CESAR study included a small subset of trauma patients [72]. From this point forward, this chapter focuses on the use of ECMO as a supportive therapy in critically ill trauma patients with respiratory failure.

4. ECMO for refractory respiratory failure in trauma

Approximately 0.5% of all adult trauma patients may be at risk of developing severe respiratory failure or ARDS, with the incidence increasing to 10–20% in multiply injured, high-risk patients [1]. The list of potential causes for trauma-related respiratory distress is heterogeneous and includes pulmonary contusions, fat emboli from long bone/pelvic fractures, thermal injuries, massive transfusion, traumatic brain injury, infection/sepsis, and severe pancreatic trauma, among other etiologies [73–77]. Veno-venous ECMO can be employed to improve systemic physiologic parameters while facilitating pulmonary rest and promoting healing of the lung in patients with the most severe chest injuries and worsening/refractory respiratory failure. Among some of the reported clinical scenarios where VV-ECMO has been successfully utilized are post-traumatic pneumonectomy, bronchopleural fistulas, tracheal injury, and severe/refractory respiratory failure associated with various primary causes [29, 54, 78–81]. For more cardiac-specific indications, including traumatic cardiac injury, VA-ECMO has been utilized [54, 82–84].

As suggested in previous sections of this chapter, early use of ECMO in trauma-related severe respiratory failure may improve outcomes and limit the extent of the post-injury "lethal triad" of acidosis, hypothermia, and coagulopathy that ultimately leads to multisystem organ failure and mortality [29, 46, 58, 85]. In order for VV-ECMO to produce optimal outcomes, a high degree of clinical vigilance, early diagnosis, and prompt management of refractory respiratory failure are required. Clinicians must be familiar with, and recognize the "vulnerable phase" of lung injury. The typical time frame during which pulmonary injury peaks in severity is

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between 48 and 96 h [86]. Thus, it is logical that pre-ECMO mechanical ventilatory support of >7 days portends poor outcome [46, 57].

The majority of traumatic pulmonary contusions improve with conservative treatment alone; however, patients with involvement of >20% of the lung volume have been shown to progress to more severe respiratory failure in as many as 80% of cases [87]. Moreover, severe pulmonary contusions may be associated with findings of blood-filled pneumatoceles, lung lacerations, and multiple fractured ribs; the presence of which may further increase the already elevated mortality of the polytrauma patient [29, 88, 89].

Another special consideration is the clinical scenario of traumatic pneumonectomy, with the potential to cause severe acute right heart failure, potentially leading to refractory hypoxemia and very high mortality rates [29, 78]. In this setting, VV-ECMO may be considered as a life-saving therapy that helps minimize various post-trauma pneumonectomy physiologic derangements [29]. In other reports, ECMO was used to facilitate successful repair of ruptured mitral papillary muscle [90], resection of post-traumatic ruptured lung abscess with empyema [91], and postoperative cardiorespiratory support following repair of traumatic aorto-right atrial fistula and tricuspid valve rupture [92].

5. ECMO in the setting of neurologic (brain and spinal cord) injury

Ensuring adequate tissue oxygenation remains a basic tenet of neurologic injury management. The ability to maintain adequate arterial oxygen saturation can prevent secondary brain injury and mitigate against poor outcomes [93]. Due to the simultaneous presence of significant pulmonary injury and brain trauma, the risk of mortality and morbidity may be greater than that of each individual organ system failure in isolation. The need for systemic anticoagulation with ECMO has historically precluded the use of this modality in patients with traumatic brain injury. However, advances in the circuit flow characteristics and oxygenator technology now allow for heparin bonding of the circuit [94]. This in turn reduces the need for anticoagulation during VV-ECMO therapy, thus decreasing the odds of hemorrhagic complications such as cavitary or intracranial bleeding [89].

Firstenberg et al. [95] published a case report of a 27-year-old male involved in a motor vehicle collision. The patient was intubated at the scene and upon hospital arrival was hypothermic with severe mixed respiratory and metabolic acidosis. Due to refractory nature of the patient's respiratory failure, salvage VV-ECMO was utilized as a life-saving “bridge” to pulmonary recovery. Of note, the patient had massive pulmonary contusions, multifocal intraparenchymal brain hemorrhages, as well as intraventricular and subdural blood on computed tomography (CT) imaging [95]. Repeat head CT scans on post-trauma days 1 and 5 showed no significant intracranial changes following the initiation of VV-ECMO [95]. It should be pointed out that due to the concerns for intracranial hemorrhagic complications, the patient received only 10,000 units of heparin systemically before percutaneous femoral-femoral VV-ECMO cannulation and no heparin for 48 h thereafter. Because the lack of heparin anticoagulation posed concerns for clotting of the circuit, frequent evaluations of the VV-ECMO circuit (e.g.,

every 6–8 h) were instituted, with no evidence found of clot formation within the circuit. There were no apparent inefficiencies of gas exchange noted [95]. Following a 96-h course of VV-ECMO, the patient underwent decannulation. On post-trauma day 23, he was transferred to an inpatient rehabilitation facility [95]. Muelenbach et al. likewise reported successful application of VV-ECMO without continuous anticoagulation and only heparin-coated cannulas and circuits for up to 5 days in patients with ARDS and traumatic brain injuries [89].

In another report, a 31-year-old male suffered severe bilateral pulmonary contusions, a right pneumothorax, traumatic frontal brain contusions, subdural hemorrhage, and right main bronchus disruption [96]. Definitive repair of bronchial disruption was feasible utilizing ECMO as "bridge" therapy. Although VV-ECMO was the preferred "bridge" to bronchial repair, due to concerns for right heart failure, VA-ECMO was chosen in this particular case. Because the cannulation catheter used was not heparin coated, low-dose heparin was used during pre-cannulation and VA-ECMO, without worsening of the patient's traumatic brain injuries [96].

Veno-venous ECMO has also been used in a patient with spinal cord injury [44]. An 18-year-old victim of a vehicular crash sustained multiple traumatic injuries, including left hemothorax, intracerebral bleeding, and complete paraplegia. After developing severe respiratory failure, the patient was placed on VV-ECMO "rescue" therapy. Interestingly, the cannulation was performed using fluoroscopy, without anticoagulation, and involved a double-lumen catheter inserted via the right IJ vein. The patient subsequently improved, was successfully weaned from VV-ECMO after 1 week, and was eventually transferred to a rehabilitation facility [44]. In another report, a small subset of patients with spinal cord injury underwent VV-ECMO for post-traumatic ARDS, without reported neurologic sequelae [40].

6. ECMO in polytrauma: managing the risk of traumatic hemorrhage

The use of ECMO has been reported in trauma patients with a range of severe blunt and penetrating injuries [14, 97]. Polytrauma, in turn, presents the treating physician with a number of competing priorities [38, 39]. Wen et al. [98] reported on successful use of VV-ECMO in a 19-year-old motorcyclist with severe hypoxia on presentation. His subsequent trauma evaluation showed significant right-sided lung contusions, pulmonary aspiration, as well as a grade IV liver laceration (without evidence of active bleeding) [98]. A non-heparinized VV-ECMO circuit was used for 5 days without major complications [98].

Fortenberry et al. [97] described five children and three adults with median duration of pre-ECMO mechanical ventilation of 6 days. Reported injuries included four liver lacerations, three pulmonary contusions, as well as renal trauma. Four patients underwent pre-ECMO laparotomies, including three splenectomies. Of note, the majority of patients (seven of eight) in that series underwent VV-ECMO, and significant bleeding was reported in seven patients while on ECMO [97]. The authors classified hemorrhagic complications of ECMO as "manageable." Survival in the pediatric subset of patients was 80% [97]. Similarly, Madershahian et al. [54] described successful ECMO use in patients with severe blunt injuries including pulmonary

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contusions, bronchial rupture, multiple fractures, and abdominal trauma. The authors encourage prompt institution of ECMO for the temporary management of gas exchange in trauma patients with refractory respiratory failure [54].

In another report, a patient with grade III liver laceration and blunt chest trauma complicated by endobronchial hemorrhage was treated with VV-ECMO [99]. The patient was maintained on low-dose heparin to maintain the activated partial thromboplastin time (aPTT) around 1.5–2.0 times normal, with no complications noted. The reported duration of VV-ECMO therapy in this case was 10 days [99]. Diffuse pulmonary hemorrhage may result from massive pulmonary contusions. In such cases, hemostasis may be difficult to achieve, even with surgical resection. Employment of single lung ventilation may be used, coupled with VV-ECMO and frequent bronchoscopic lavage [95]. Skarda et al. [14] reported on ECMO use in children with severe traumatic injuries, including open reduction and internal fixation and endoscopic procedures while on active extracorporeal support.

7. ECMO as bridge to definitive surgical management

Across various scenarios outlined in previous sections of this chapter, ECMO was believed to be the main factor contributing to patient survival in potentially futile situations. At times, patient survival is possible without the use of ECMO; however, definitive surgical repair may not be possible without extracorporeal support. Finally, ECMO may be necessary for both survival and definitive repair of injuries.

Gatti et al [9] published a case of a 27-year-old man who sustained a 4-cm-wide stab wound to the fifth left intercostal space, resulting in cardiac injury evidenced by a massive left hemothorax and a pericardial effusion. The patient experienced acute clinical decompensation, developed pulseless electrical activity (PEA) arrest, and underwent an emergency department implementation of VA-ECMO (using left internal jugular vein inflow and right femoral artery outflow) at flow rates between 4.5 and 5.0 L/min [9]. A median sternotomy was then performed, with drainage of a pericardial effusion, repair of a right ventricular injury and repair of an injured branch of the right coronary artery. This was followed by return of adequate cardiac function [9]. Overall, the patient underwent >40 minutes of cardiopulmonary resuscitation and was cannulated on VA-ECMO for approximately 120 minutes, with 350 units/kg of heparin administered during the duration of extracorporeal support [9]. Other than a mild postpericardiotomy syndrome, the patient recovered from his injury without neurological sequelae [9]. Other scenarios where ECMO was instrumental to satisfactory clinical outcomes following major cardiac trauma includ repair of ruptured mitral papillary muscle [90] and postoperative cardiorespiratory support following repair of traumatic aorto-right atrial fistula and tricuspid valve rupture [92].

Major airway trauma, including bronchopleural fistulae, has an associated mortality in excess of 30% [100]. In one case, VV-ECMO was used in the setting of severe hypoxemia as a bridge to surgical management of major bronchial injury [101]. A 31-year-old male sustained multiple injuries following an automobile collision, including a right-sided hemopneumothorax,

cerebral contusion, subarachnoid and subdural hemorrhages, bilateral pulmonary contusions, and a right main stem bronchial tear that was immediately repaired operatively. On postoperative day 5, the patient developed complete occlusion of the right main stem bronchus, with severe respiratory failure and hemodynamic instability. Consequently, the patient was placed on a VA-ECMO circuit utilizing low-dose heparin to help facilitate the definitive surgical airway repair. The authors reported that they would have considered VV-ECMO if the patient was hemodynamically stable [101].

Ballouhey et al. [102] utilized ECMO in a 32-month-old girl who sustained major tracheobronchial trauma after being struck by a vehicle. Initial diagnostic imaging showed the endotracheal tube to be outside of the trachea. Due to the presence of hemodynamic instability, VA-ECMO was selected for the surgical repair. Of note, the authors did point out that in the presence of hemodynamic stability, VV-ECMO can be used to support patients in need of surgical correction of major tracheobronchial disruptions [102]. In some cases of unilateral pulmonary or bronchial trauma, either single-lung (e.g., selective ventilation of only one lung) or differential-lung (e.g., each lung managed independently via separate ventilator-tracheal tube circuits) ventilation can be coupled with ECMO to ensure adequate oxygenation while the healing of contralateral traumatic injury is taking place [103]. Following surgical repair of the airway, postoperative continuation of ECMO may be deemed appropriate because (a) healing of operatively repaired tissue may be otherwise affected or compromised [29] or (b) the patient may not be able to immediately wean off the extracorporeal support [92].

8. ECMO: summary of single-center experiences

A number of valuable single-center experiences have been reported, demonstrating successful use of VV-ECMO in trauma. Key findings from these studies are presented in **Table 2** and **Figure 2**. The subsequent discussion focuses on the most important "take-home" messages from this cumulative body of literature. In addition to supporting the notion that in carefully selected trauma patients ECMO can improve survival, there is emerging evidence that the performance of surgical procedures on extracorporeal support is safe, including repeated damage control operations [104–106].

Back in mid-1990s, Anderson et al. [46] presented a single-institution experience with 24 multiply injured patients treated with ECMO for refractory respiratory failure. Both VV-ECMO and VA-ECMO was utilized, with all patients receiving systemic heparinization. Hemorrhagic complications were reported in 75% of patients. The overall survival to hospital discharge was 63%, with early initiation of ECMO (<5 days) being associated with better outcomes [46]. In another early experience, Senunas et al. [107] reported on 14 multiply injured patients who sustained severe skeletal trauma and progressed to refractory respiratory failure. Consistent with data provided by others [46, 108], this study also showed improved survival when ECMO was initiated early (87% survival for <6 pre-ECMO ventilator days versus 16.7% survival for >6 pre-ECMO ventilator days) [107]. Michaels et al. further quantify the importance of early ECMO initiation in a series of 30 trauma patients, with associated odds ratio of 7.2 for patient survival when the duration of pre-ECMO ventilator support was ≤5 days [108].

Study	Patient data	ELS data	Complications	Mortality/survival	Comment
Anderson et al. [46]	*N* = 24 Mixed pediatric and adult population	**Duration of ELS**: 287 ± 43 h (12 ± 1.8 day) **Heparinization**: All patients **Circuit-related complications:** Oxygenator failure: 8.3% **Raceway/tubing rupture**: 8.3% **Pump failure**: 4.2% **Circuit change**: 25%	**Hemorrhage**: 75% **Renal failure**: 21% **Cardiac**: 12.5% **Stroke or intracranial bleeding**: 21% **Pneumothorax**: 8.3%	**Survival to discharge from hospital**: 63% **Time to ELS**: Survivors 3.8 ± 0.8 days Deceased 10 ± 1.4 days	Both VV-ECMO and VA-ECMO was utilized Early intervention (e.g., ≤5 days to ECMO) was associated with better outcomes Reduced anticoagulation levels were utilized in a patient with closed head injury and depressed skull fracture
Senunas et al. [107]	*N* = 14 (4 male; 10 female) **Survivors**: Mean ISS 19 (9–34) Mean GCS 14.5 (12–15) **Non-survivors**: Mean ISS 18 (11–29) Mean GCS 13.3 (6–15)	**MV prior to ECMO**: 6 days (1–19 days) **Duration of ECMO**: 240 h (50–624 h)	**Hemorrhage**: 57.1%	**Overall survival**: 57.1% **Survival for patients with <6 pre-ECMO ventilator days**: 87.5% **Survival for patients with >6 pre-ECMO ventilator days**: 16.7%	The study involved 14 multiply injured patients with major orthopedic trauma 5 of 14 patients underwent surgical procedures while on ECMO Consistent with experience reported by Anderson, et al., early initiation of ECMO was associated with better survival
Michaels et al. [108]	*N* = 30 (15 male; 15 female) Age 26.3 ± 2.1 years (15.59 years) Mean ISS 19.8 ± 2.2 Mean PaO_2/FiO_2 56.9 ± 5.4	**Duration of ECMO**: 237.8 ± 36.9 **Circuit-related problems**: Oxygenator change: 24% Pump complication: 7% Tubing change: 21%	**Acute renal failure**: 55% **Hemorrhage**: 59% **Infection**: 28% (positive cultures) **Pneumothorax**: 31% **Neurologic**: 14%	**Survival to discharge**: 50% Early use of ECMO (≤5 vent days) was associated with odds ratio of 7.2 for survival	Fewer ventilator days and more normal SvO_2 were associated with survival Numerous patients underwent surgical procedures while on ECMO, including tracheostomy (50%), laparotomy (13%), thoracotomy (3%), femoral artery repair (3%), and open reduction of lower extremity fracture (3%)
Cordell-Smith et al. [75]	*N* = 28 Age 27 years Mean ISS 18 Mean PaO_2/FiO_2 62 Lung injury score 3.1 (Murray)	**Pre-ECMO MV**: 69 h **Duration of ECMO**: 141 h **Heparinization**: All patients received systemic heparin, with activated clotting time targets between 180 and 220 s	Complication data not provided	**Overall survival**: 71.4% Of interest, survivors had higher mean ISS (19) than non-survivors (14)	Mean time to ECMO was 61 h for survivors versus 87 h for non- survivors
Huang et al. [109]	*N* = 9 Age 35.1 ± 9.7 years (18–47 years) Mean ISS 44.56 ± 4.93 (35–50) Mean SOFA 12.1 ± 3.67 (7–16) Mean PaO_2 49.04 ± 9.82 mmHg (31–64) Mean PaCO2 66.4 ± 15.72 mmHg (45–86)	**Time from injury to ECMO**: 33 h (4–384 h) **Duration of ECMO**: 145 h (69–456 h)	**Colonic rupture with sepsis**: 1 patient (11%) **Liver failure**: 11%	**Survival to discharge**: 77.8%	**VA-ECMO**: 2 patients **VV-ECMO**: 7 patients 6 patients (66.7%) received additional surgeries while on ECMO
Arlt et al. [33]	*N* = 10 (8 male; 2 female) Age 34.8 years (21–62 years) Mean ISS 73 ± 4 $PaCO_2$ 67 (36–89) Median norepinephrine demand 3 mg/h (1.0–13.5)	**Duration of ECMO**: 5 days (0.5–11 days) The authors report on the use of a new miniaturized ECMO device, with initial therapy performed without heparinization	**Sepsis/ Multi-organ failure**: 30%	**Overall hospital survival**: 60%	**VV-ECMO**:7 patients **VA-ECMO:** 3 patients The study describes the use of ECMO in actively hemorrhaging patients
Biderman et al. [8]	*N* = 10 (6 male; 4 female) Age 29.8 ± 7.7 years (19–42) Mean ISS 50.3 ± 10.5 (29–57) PaO_2/FiO_2: ECMO 62 (35–82) iLA 92 (78–140) $PaCO_2$: ECMO 62 (48–95) iLA 85 (65–150) (+) Traumatic brain injury	**Time to ECMO**: 3 days (1–7 days) **Time to iLA**: 5 days (3–8 days) **Duration of ECMO**: 9.5 ± 4.5 days	**Cannula related:** Bleeding: 10% Accidental removal: 10% Pressure ulcer: 30% Sepsis: 20% Cardiogenic shock: 10%	**ECMO survival**: 60% **iLA survival**: 80%	**iLA Circuit**: 5 patients **ECMO**: 5 patients iLA is a pumpless extrapulmonary gas exchange system (http:// www.novalung. com/en/home)

Study	Patient data	ELS data	Complications	Mortality/survival	Comment
Bonacchi et al. [110]	*N* = 14 (10 male; 4 female) Age 47 ± 17.6 years Mean ISS 46.5 ± 16.3 (+) Damage control surgery	**Time from trauma to ECMO**: 351.8 ± 242 min (145–950 min) **Duration of ECMO**: 128.7 ± 113 h (24–384 h) **Heparin-free time on ECMO**: 20.7 ± 19.8 h **Blood transfusion**: 11.9 ± 5.3 units **rfVIIa administration during ECMO**: 50% **Heparinization**: ECMO circuit used was heparin-coated; systemic heparin was held in cases of bleeding (mean delay of 16.7 ± 19 h, range 2.5–72 h); Titration to mean aPTT of 40–50 s / activated clotting time of 160–180 s Initially, 18 patients were considered for ECMO; however, due to inability to maintain adequate circuit flow and perfusion on VA-ECMO, only 14 patients were successfully treated	**Renal failure requiring VV hemofiltration**: 50% cases **Hepatic insufficiency**: 14.2% **Sepsis**: 21.4% **Leg ischemia**: 7.1% **Oxygenator failure**: 7.1%	**ECMO survival**: 35.7% **Organ donation**: 42.9% **Death (w/o organ donation)**: 21.4% All cases (*n* = 4) with inability to establish or maintain circuit flow/ perfusion died	**VV-ECMO**: 4 patients **VA-ECMO**: 10 patients Cardiac index, mean arterial pressure, blood lactate, PaO_2, $PaCO_2$, and pH normalized within 3.5 ± 1.5 h of ECMO initiation Intra-aortic balloon pump was used in 2 patients
Ried et al. [111]	*N* = 52 (49 male; 3 female) Age 32 ± 14 years (16–72 years) Mean BMI 28.2 ± 6.1 Mean ISS 58.9 ± 10.5 Mean LIS 3.3 ± 0.60 Mean SOFA 10.5 ± 3.0 PaO_2/FiO_2 63 (49–101) $PaCO_2$ 67 (50–87) Lactate 28 (14–49) mg/dL	**Pre-ELS MV**: 3.2 ± 4.1 day (0–21 days) **Time to ELS**: 5.2 ± 7.7 days (0–38 days) **Duration of ELS**: 6.9 ± 3.6 days (<1–19 days) **ELS flow rate (L/min)**: 2.3 ± 0.9 (0.7–4.6) **Duration of MV**: 18.4 ± 10.6 days (1–51 days) **ICU/ hospital stay**: 22 days (14–32)/ 25 days (16–41) **Surgical procedure**: 86.5% **Thoracic procedure**: 15.4% **Surgery with ELS**: 30.8%	**Cannula-related**: PECLA 19% VV-ECMO 12% **RRT**: 30.8%	8 (15.4%) during ELS support 3 (6%) after ELS weaning **Hospital mortality**: 21% **Overall survival**: 79%	**VV-ECMO**: 26 patients **pECLA**: 26 patients **pECLA**: Pumpless extracorporeal lung assist
Tseng et al. [104]	*N* = 9 (8 male; 1 female) Age 37 years (IQR 26.5–46 years) Median ISS 34 (IQR 15.5–41) (+) Damage control surgery	**Median time to VA-ECMO**: 6 h (IQR 4–47.5) **Median duration of ECMO**: 91 h (IQR 43–187)	**Hemorrhage**: 22%	**Survival to discharge**: 33%	**VA-ECMO**: 9 patients
Wu et al. [45]	*N* = 20 Age 38 years (22–61 years) Median ISS 35 (19–75) (+) Intracranial hemorrhage (+) Damage control surgery	**Time from trauma to ECMO**: 64 h (IQR 12–230) **Median duration of pre-ECMO ventilation**: 45 h (IQR 8–148) **Median ECMO duration**: Survivors: 144 h (74–196 h) Deceased: 232 h (36–575 h) **Post- ECMO intubation**: 231 h (61–476 h) **Hospital days**: Survivors: 69 days (27–81 days) Deceased: 32 days (4–46 days)	**Hemorrhage**: 35% **CVVH**: 35% **Tracheostomy**: 40%	**Overall survival**: 70% **Age (survivors)**: 41 years (29–57) **Age (non-survivors)**: 30 years (22–61 years) **ISS (survivors)**: 29 (19–43) **ISS (non-survivors)**: 63 (26–75) **Mortality from sepsis**: 15%	**VV-ECMO**: 20 patients "Heparin-minimized" strategy was utilized in 55% of patients
Wu et al. [112]	*N* = 19 (17 male; 2 female) Age 38 years (25–58 years) Median ISS 29 (25– 34) Median APACHE II 25 (21–36) PaO_2/ FiO_2 60 (48–65) (+) Brain hemorrhage	**Median blood transfusion**: 5500 mL (3,500–13,000) **Heparinization**: 16 patients (84.2%) **ICU duration**: 16.8 ± 9.37 days	**Pneumonia**: 15.8% **Coagulopathy**: 10.5% **Need for CVVH**: 37%	**Overall survival**: 68.4% **Age (survivors)**: 30 years (21–39) **Age (non- survivors)**: 53 years (48–63 years)	**VV-ECMO**: 9 patients **VA-ECMO**: 10 patients Five patients had pre-ECMO traumatic brain hemorrhage (3/5 or 60% survived) Mortality in heparin group was 5/16 (31.3%) Gothner et al. [40]
Gothner et al. [40]	N = 6 (all male) Age 45 years (31–54 years) Mean ISS 31 (20–48) (+) Spinal cord injury (+) Minor brain injury	**Time to ELS**: 3 ± 5 days (0–13 days) **Duration of ELS**: 7 ± 5 days (6–18 days) **ICU stay**: 21 ± 7 days (13–30 days) **Hospital stay:** 60 ± 34 days (21–105 days) **Blood transfusion**: 8 Units (2–20 U) PRBC	**Cannula related:** 17% (thrombosis) **Urethral bleeding**: 17% **Acute renal failure**: 17% **VAP**: 83%	**Overall survival**: 100%	**VV-ECMO**: 6 patients Authors describe the use of double lumen cannula placed via right IJ approach

Table 2. Important characteristics of major clinical studies of ECMO in trauma (1994–2015).

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Cordell et al. [75] treated 28 multiply injured patients suffering from severe respiratory failure with VV-ECMO. In that series, patients received "limited anticoagulation" using intravenous heparin, with activated clotting times between 180 and 220 s [75]. The overall survival was 71.4%, with shorter "time to ECMO" associated with better survival (e.g., 61 h for survivors versus 87 h for non-survivors) [75]. Huang et al. describe 78% survival in nine trauma patients undergoing ECMO [109]. In that series, two-thirds of patients underwent additional surgeries while on extracorporeal support [109]. Arlt et al. [33] treated 10 multiply injured patients with hemorrhagic shock using a miniaturized ECMO circuit, without initial systemic heparinization. The 60% reported survival is very impressive given the mean ISS of 73 for the study cohort [33]. Others have found that independent predictors of mortality in trauma patients undergoing ECMO include ISS >63, pH <7.01 (mean of last three evaluations), and blood lactate of >14.4 mmol/L (mean of last three evaluations) [110].

Gothner et al. [40] published clinical experience based on six patients with major trauma (mean injury severity score [ISS], 31) and post-traumatic severe respiratory failure who were supported with VV-ECMO using a double lumen cannula. The authors reported mean pre-ECMO hospitalization of 3 days, mean ECMO run times of 7 days, mean hospital stays of 60 days, and 100% survival for the 6 study patients [40]. It was noted that the double lumen cannula utilized was not heparin coated and thus heparin dosages had to be adjusted to maintain the prothrombin time (PTT) in the range of 50–60. As such, this approach in patients

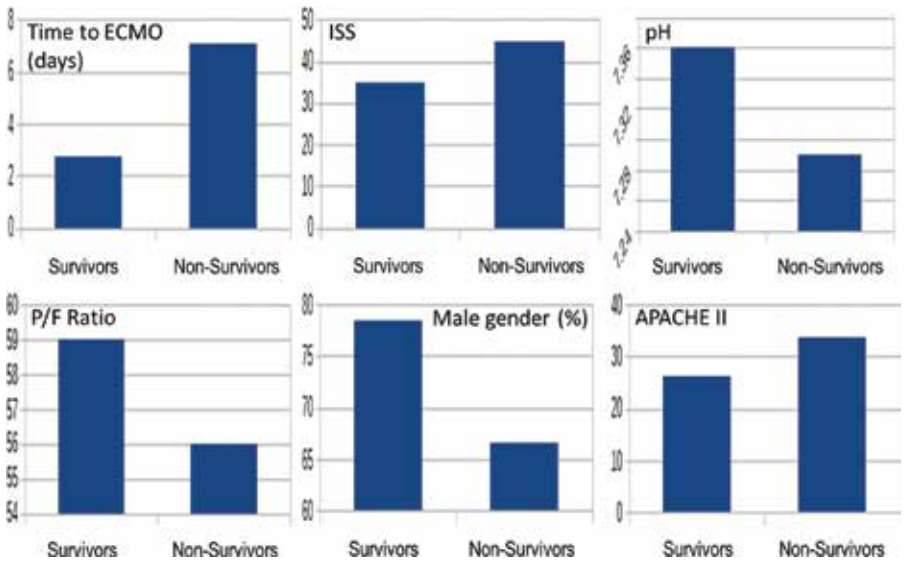

Figure 2. Comparison of important baseline parameters for trauma survivors and non-survivors, compiled from key single-center ECMO experiences. (**Top left**) Time from injury to ECMO (days); (**top middle**) injury severity score (ISS); (**top right**) pH values; (**bottom left**) PaO_2/FiO_2 ratio; (**bottom middle**) male gender (%); (**bottom right**) APACHE II score. Data compiled from: Anderson et al. [46], Arlt et al. [33], Biderman et al. [8], Cordell-Smith et al. [75], Michaels et al. [108], Senunas et al. [107], Wu et al. [45, 112].

who are at elevated risk of bleeding is controversial, despite the report finding no substantial elevation in the risk of bleeding among study patients [40].

Another study retrospectively looked at a single-center experience with VV-ECMO over a 10-year period. The authors focused on critically injured trauma patients with mean ISS of nearly 59 and the sequential organ failure assessment (SOFA) scores of 10.5 [111]. Within the sample of 52 patients, 26 received pumpless extracorporeal lung assist (PECLA) and the other 26 underwent VV-ECMO [111]. In this series, mean time to extracorporeal support was 5.2 days, average support duration of was 6.9 days, many patients underwent surgery while on extracorporeal support, and cannula-related complications occurred in 15% of patients (19% PECLA; 12% VV-ECMO) [111]. Overall survival was 79% compared to predicted survival of 59% (estimated from ISS data). The authors additionally noted that patients with elevated risk of hemorrhagic complications or evidence of intracranial bleeding were not started on heparin during the initial 48 h. After securing evidence that bleeding is controlled (e.g., repeat CT scan imaging), heparin was started slowly and target PTT set at approximately 40–50 s [111].

Wu et al. [112] studied 19 patients treated with ECMO for severe lung injury and respiratory failure. The most common mechanism of pulmonary injury was blunt trauma, with median patient age of 38 years, median ISS of 29, median Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 25, and median blood transfusion volume of 5.5 L [112]. The overall survival within this cohort was 68% (13 of 19 patients), with survivors being younger (30 years) than non-survivors (53 years) [112]. There were five patients (26% of total) with traumatic brain hemorrhage, of whom three survived (60% of brain trauma group) [112]. Sixteen out of 19 patients (84%) received heparin during VV-ECMO therapy, with 5 mortalities noted in that group (31%). In addition to demonstrating potential benefits of VV-ECMO in multiply injured patients, the authors also emphasize the value of timely ECMO intervention [112].

Biderman et al. [8] published another important single-center experience using ECMO in trauma. A total of 10 patients (mean age 30 years; mean ISS of 50; 60% male) received ECMO therapy. Within this group, all patients suffered from blunt trauma and severe thoracic injuries, with vascular and abdominal solid organ injuries being the most common. Mean ECMO support time was 9.5 days [8]. Seven patients within the group had traumatic brain injury, with four exhibiting active intracranial hemorrhage. Coagulopathy was prevalent before institution of VV-ECMO in this group. Consistent with other reports outlined in this chapter, the authors point out that complications related to the extracorporeal support therapy were manageable and non-lethal [8]. Reported complications included bleeding from the cannulation site, dislodged cannula, and pressure ulcers. Mortalities were attributed to sepsis (two cases) and cardiogenic shock (one case) [8]. Of importance, the authors were able to demonstrate clinical success of high-flow ECMO technique without anticoagulation, especially in patients with coagulopathy or traumatic brain injury. This experience shows that even in patients with acute and active hemorrhage, meaningful benefits can be gained from utilizing ECMO [8].

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9. ECMO: weaning and liberation

Because the increasing duration of ECMO support is associated with greater mortality, extracorporeal support weaning should be a constant consideration for patients undergoing this therapy [113]. Thus, as soon as a patient is identified as a candidate for ECMO wean, the process should begin promptly and follow a protocolized course toward the goal of liberation from dependence on extracorporeal oxygenation [113]. In general, weaning for patients on VV-ECMO for severe respiratory failure should be considered based on improvements in pulmonary compliance, chest radiography characteristics, and arterial oxygenation indices [12, 57]. This can be followed by a "weaning trial" where blood flow through the circuit is maintained, but gas transfer is temporarily (up to several hours) stopped [12, 57]. For patients on VA-ECMO for cardiac failure, important considerations prior to weaning therapy should include echocardiographic findings (preferably transesophageal), aortic pulsatility, and a successful "off-ECMO trial" that consists of temporary clamping of the drainage and infusion lines while maintaining a temporary bridge between the arterio-venous conduits [57, 114, 115].

10. The financial impact of ECMO

Due to resource utilization and the overall level of intensive care afforded to affected patients, ECMO is recognized as a labor intensive and costly intervention. In 1993, Schumacher et al. [116] demonstrated that early ECMO in infants was cost-effective when compared to late ECMO or "no ECMO" controls. In 2005, Mahle et al. [117] reported on the cost utility of salvage ECMO following surgery for congenital heart abnormalities. Based on their financial analysis, the authors concluded the calculated cost-utility for salvage extracorporeal membrane oxygenation in this population was $24,386 per quality-adjusted life-year saved, which would be considered within the range of acceptable cost-efficacy. The CESAR trial evaluated cost based on in-hospital expense, as well as the economic burden of services required during follow-up for ECMO patients and their families [72]. The authors reported that mean costs per patient in the group who underwent ECMO were £73,979 (approximately $116,502) over a period of 6 months. Based on cost-benefit analysis, the United Kingdom National Health Service declared ECMO treatment, at a referral center, to be cost-effective even though the mean costs of patients receiving ECMO were higher compared to the control arm. A caveat to this conclusion is that dollar-for-dollar cost in a non-single party payer system (e.g., the USA) may vary considerably [72].

11. Miscellaneous topics

11.1. Analgo-sedation

ECMO applications mandate the ability to control patient activity and ensure adequate analgesia and sedation [118, 119]. It has been noted that VA-ECMO is associated with signif-

icantly greater doses of sedation than VV-ECMO [119]. The current understanding of how different ECMO circuits affect pharmacokinetic characteristics of certain drugs (e.g., antibiotics, sedatives, analgesics) is incomplete [118, 120]. Over the past few years, evidence has emerged that periodic sedation and analgesia interruptions, and even allowing patients to remain awake may be beneficial to both short- and long-term ECMO outcomes [118, 121]. In fact, such daily interruptions help facilitate patient mobilization and even ambulation [17, 122, 123]. However, this is not without risks. The importance of adequate analgo-sedation optimization is highlighted by a case of major hemorrhage requiring cardiopulmonary resuscitation following ECMO cannula dislodgement in a conscious, spontaneously breathing patient [124]. The applicability of the "awake ECMO" concept in trauma is probably limited, mainly due to the generally transient requirement for extracorporeal support in this population, as well as the significant analgo-sedation requirement secondary to multiple injuries (e.g., not directly related to ECMO).

11.2. Organ donation

Trauma is one of the leading causes of death, with traumatic brain injury being a major contributor to the overall trauma mortality [39, 125]. Brain death following trauma is numerically one of the major sources of organs donated for transplantation [125]. Balsorano et al. [126] reported on successful use of VA-ECMO as a tool for organ preservation prior to organ procurement. The authors pointed out the myriad of complex physiologic disturbances that occur following brain death, emphasizing potential barriers to organ recovery such as cardiac arrest and refractory cardiopulmonary collapse [126, 127]. The use of ECMO to optimize organs from non-heart-beating donors (e.g., donation after cardiac death) is not a new concept [128]. Gravel et al. [129] describe the use of ECMO to facilitate renal transplantation from organ donors following cardiopulmonary death.

11.3. Multidisciplinary approach to ECMO

The authors of this chapter feel strongly that promotion of a multidisciplinary approach to trauma patients undergoing ECMO therapy is essential. In most of the published literature, patients enrolled in the ECMO arms of the trial were at tertiary referral centers that were replete with expertise in cardiac surgery, perfusion, advanced ventilator strategies, and specialized critical care. Trauma centers embarking on an ECMO program need to ensure that these specialties have reviewed pertinent treatment protocols and safety standards involved in the implementation of extracorporeal support. Also, we recommend involving the ELSO to help with credentialing and performance improvement initiatives for any center considering ECMO as a treatment option. As outlined earlier in this chapter, one of the most significant advantages of modern ECMO circuits is their portability. This facilitates ECMO implementation in a variety of settings, including the emergency department, the operating room, and the ICU [110]. Consequently, multidisciplinary participation in institutional ECMO programs should include representation from all key departments and stakeholders, from cardiovascular surgery to emergency medicine.

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12. Conclusions

Improvements in biocompatibility, miniaturization, and portability of modern ECMO circuits have increased the safety profile and clinical utility of this extracorporeal support option. In turn, this has resulted in an expanding range of clinical applications of ECMO, including its increasing use in the trauma patient with refractory circulatory and respiratory failure. Clinical approaches once considered to be futile and controversial are now available as life-saving strategies for patients who otherwise would not be able to survive. Important challenges remain to greater ECMO implementation in the trauma population, including the use of anticoagulation and better optimization of patient selection. Trauma centers contemplating an ECMO program should seek buy-in from the services who will be intimately involved in the care of the patient as well as organizations dedicated to ensuring the quality and efficiency of extracorporeal support program.

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Patient Management

Chapter 12

Anesthetic Management of Patients on ECMO

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Additional information is available at the end of the chapter

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Abstract

The management of a patient placed on extracorporeal membrane oxygenation (ECMO) is a team effort. The anesthesiology team plays an integral part during cannulation and oftentimes as well during decannulation. In addition, the management of a patient taken to the operating room on ECMO requires a degree of expertise. This chapter will review monitors, echocardiography, medications, fluid and blood management protocols, and ventilation strategies to help the anesthesiology team provide best care for this patient population.

Keywords: anesthesia, monitoring, echocardiography, anticoagulation, ventilation

1. Introduction

The anesthetic management of patients on extracorporeal membrane oxygenation (ECMO) continues to evolve as the indication for ECMO use expands. The anesthesiology team has to care for these patients during the critical period prior to ECMO placement, during cannulation, for surgeries while on ECMO, and then finally during decannulation. A keen understanding of the physiology, pharmacokinetics, and pharmacodynamics of the patient on ECMO is needed in order to appropriately care for this delicate patient population.

2. Monitoring

2.1. Invasive blood pressure monitoring

Mean arterial pressure (MAP) should be monitored during ECMO with an invasive blood pressure catheter. End-organs typically require a MAP greater than 65 mmHg in order to

maintain an adequate perfusion pressure. Hypotension may be corrected by increasing ECMO flows and/or administering volume. If the hypotension is secondary to a decreased systemic vascular resistance, then vasopressor agents may be needed to increase MAP.

There should be a degree of pulsatility even while on higher levels of ECMO support. Lack of pulsatility may point toward stagnation, which can cause overdistension of the left ventricle (LV) and lead to thrombosis. LV decompression is imperative to prevent ventricular ischemia and allow ventricular recovery. In these cases, ECMO flow can be reduced, or a vasodilator may be administered to attempt afterload reduction or inotropic agents may be added [1]. If the LV is not adequately decompressed, a left-heart vent, a percutaneous left ventricular assist device (LVAD; Impella®, Abiomed Corp., USA), or a balloon atrial septostomy can be performed to decompress the LV [2, 3]. Decreased pulsatility may also be a sign of hypovolemia, a mechanical obstruction, right ventricular failure, and/or dysrhythmias [1].

2.2. Interpretation of arterial blood gases from different anatomical sites

The location of the arterial inflow cannula determines the best site for arterial blood sampling and/or monitoring of SpO_2. With axillary cannulation, radial artery catheters should be avoided on the ipsilateral side, as the values obtained are not reflective of the net gas exchange [1]. With femoral cannulation, the right radial artery should be monitored. If heart function is poor, then arterialized blood flow to the coronary and cerebral circulations will occur through retrograde flow in the aorta. As heart function begins to recover, the mixing point within the aorta travels distally, and perfusion will be provided by the native cardiac output. The degree of oxygenated perfusion will also be determined by lung function, with poor lung function in the setting of good cardiac output leading to poorly oxygenated blood being supplied to the coronary and upper body circulations. Placement of a radial artery catheter on the right will allow detection of this condition, referred to variably as Harlequin syndrome, North–South syndrome, or upper body hypoxemia [1].

If the patient is on venovenous (VV) ECMO, the infusion blood will mix with the systemic venous return blood. The typical ratio of infusion to deoxygenated blood is approximately 3:1. As a result, blood analysis will demonstrate approximately a PO_2 40, PCO_2 41, and saturation of 80% [4]. A minimum saturation of 80% is adequate to support systemic oxygen delivery as long as the hematocrit is greater than 40% and cardiac function is decent [4]. As the lung begins to recover, the saturation will increase over 80%.

If the patient is on veno-arterial (VA) ECMO, the infusion blood will mix with the blood in the aorta. This leads to a typical ratio of infusion to native blood of 8:1 [4]. If lung function is normal, then blood analysis will demonstrate approximately a PO_2 of 200, PCO_2 of 40, and saturation of 100% (on FiO_2 of 0.2) [4]. If there is no native lung function, then PO_2 will be approximately half at 100.

2.3. Mixed venous blood saturation and other hemodynamic monitors

An arterial oxygen saturation (SaO_2) greater than 80% may be sufficient to monitor appropriate systemic oxygen delivery during ECMO [5, 6]. SaO_2 alone, though, may not always be a suitable

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monitor, as various variables including hemoglobin, degree of recirculation, membrane oxygenator function, extracorporeal blood flow to cardiac output ratio, and venous oxygen saturation contribute to systemic oxygen delivery (DO_2) and oxygen consumption (VO_2) [7]. Systemic perfusion is best measured by mixed venous blood saturation (SVO_2), with a goal to maintain it greater than 75% [4]. If mixed venous saturation is less than 75%, then pump flow may need to be increased or volume may need to be given in the form of blood and/or crystalloid solution.

Pulmonary artery catheters (PACs) can be difficult to place once ECMO has been initiated and may not be a valuable monitor. The minority of blood flows through the lungs while on ECMO, and SvO_2 from a PAC will probably not be accurate. SvO_2 can be estimated however by blood gas analysis or saturation probe at the level of the venous cannula leading to the membrane oxygenator [1]. Other markers of anaerobic metabolism such as lactate may be useful to monitor when SvO_2 appears to be inaccurate [8].

Central venous pressure (CVP) can be used as a trend monitor as ECMO flow also affects exact measurements of this monitor. A rising CVP pressure due to mechanical obstructive processes such as tension pneumothorax, tamponade, or abdominal compartment syndrome can be detected with a central venous catheter.

Newer flow-based hemodynamic monitoring devices such as the Flotrac™ and NICOM™ (Edward life sciences, USA) are currently being investigated in the ECMO patient population.

2.4. Cerebral oximetry

A high percentage of ECMO patients unfortunately suffer a neurological complication. These complications can run the gamut from seizure, intracranial hemorrhage, ischemic stroke to encephalopathy [9]. Neurological complications increase the rate of mortality [10]. Methods to monitor for neurological complications include electroencephalogram, transcranial Doppler, and cerebral oximetry.

Upper body hypoxemia can be detected by a decrease in cerebral oximetry values, either unilateral or bilateral. A differential cerebral desaturation may occur when the right brain becomes hypoxemic, but perfusion of the left brain is preserved because of retrograde oxygenated blood flow from the descending aorta [11]. Central aortic saturation may be improved by increasing venous drainage, increasing blood oxygen content, and/or placing additional outflow arterial cannulas.

3. Echocardiography for ECMO

In ECMO-supported patients, soft-tissue ultrasound for vascular access guidance, transthoracic (TTE) and transesophageal (TEE) cardiac ultrasound are complementary technologies that

can guide safe cannula placement, initiate therapy, monitor progress of therapy, detect complications, and help determine ultimate recovery and weaning strategies.

3.1. ECMO patient selection

A comprehensive TEE or TTE is important to help guide therapy in critically ill adults who may benefit from ECMO therapy. Patients may demonstrate refractory hypoxemia, despite maximal ventilator support or hemodynamic instability even with resuscitative efforts. Echocardiography can identify potentially reversible pathological states, which may account for the patient's hypoxic or hemodynamic condition. Findings may include tamponade, acute severe mitral or aortic insufficiency, severe pulmonary hypertension, intracardiac shunts, and/or severe right or left ventricular dysfunction. Alternative resuscitative maneuvers may be undertaken before ECMO is initiated to alleviate potentially reversible conditions. Significant conditions identified by echocardiography that may complicate VV or VA ECMO include a prominent patent foramen ovale, atrial septal defect (ASD), intra-atrial septal aneurysm, pacer and defibrillator leads, or tricuspid valvular disease. Echocardiography may also provide information regarding aortic dissections, which is a contraindication to VA ECMO. Finally, echocardiography allows prompt assessment of cardiac function to guide VV versus VA ECMO therapy.

3.2. Echocardiography for cannulation

Surface ultrasound guides the correct placement of guidewires and cannulas into vessels within the neck, thorax, axillary and/or femoral areas, and into their final correct positions within the right atrium (RA) and inferior vena cava (IVC) to allow proper flow and limit recirculation between cannulas [12–14]. TEE can be used to guide central versus peripheral arterial cannula placement. Prior to placement of the arterial cannula, echocardiography should exclude a preexisting aortic dissection, which is a contraindication to VA ECMO. After placement, echocardiography should evaluate the aorta for an iatrogenic dissection, which may be a complication of the cannulation and initiation sequence. All cannulas should be properly placed before initiating ECLS to optimize initiation time and eliminate repositioning, which introduces bleeding and infection risk.

Echocardiography also allows confirmation of proper positioning of the single Avalon Elite® Bi-Caval Dual Lumen catheter (Maquet Holding, Germany), which is inserted typically via the right internal jugular vein (IJ), but may be inserted via the left IJ if the right side is inaccessible [13]. The cannula body should span the RA and encompass both the superior vena cava (SVC) and IVC for drainage. The return lumen should be positioned in the center of the RA and directed to allow return flow of oxygenated blood to cross the tricuspid valve. Utilization of saline microbubble contrast through specific lumens of the dual lumen catheter may help guide correct placement and orientation within the RA in relation to the tricuspid valve [15]. Comparison of dual-lumen cannulation to conventional cannulation for VV ECMO demonstrated that dual-lumen cannulation required more materials, more technical and physician experience, and higher costs, but allowed better patient mobilization, including prone

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positioning and potentially lighter sedation and shorter duration of mechanical ventilation [16].

Use of the Avalon Elite® bi-caval dual lumen catheter has also been described in adults with secundum ASDs and Eisenmenger's syndrome as a bridge to recovery or transplant. The right atrial infusion port is positioned echocardiographically to infuse oxygenated blood across the ASD as opposed to the traditional tricuspid valve position. Placement improves oxygenation, decreases pulmonary artery pressure, and unloads the right ventricle. Patients without an ASD who have pulmonary hypertension or Eisenmenger's syndrome requiring VV ECMO may benefit by having an atrial blade septostomy performed prior to bicaval cannula placement [17].

TTE can also be utilized to place and monitor the position of the Avalon Elite® using the subcostal sagittal plane view, which provides imaging of the RA and both venae cavae. All three of the catheter ports can be identified and confirmed in their correct anatomical locations using TTE. A survey demonstrated that TEE (67%) was utilized more frequently to place the Avalon Elite® catheter than TTE (25%) or fluoroscopy (4%) with a mean insertion and orientation time of 26 ± 13 min [18]. It is recommended during the initial provider training period that placement of the Avalon Elite® Bi-Caval dual-lumen catheter occurs under both fluoroscopy and TEE guidance. As proficiency with cannula placement improves, TEE alone provides excellent image guidance for correct placement and orientation [14].

3.3. ECMO maintenance

On VV ECMO, venous cannula malposition, with inflow and outflow cannula positioned in close proximity leads to recirculation of returned oxygenated blood back to the ECMO pump. Recirculation undermines effective treatment and occurs with both single-lumen and dual-lumen cannulas. Traditionally, two-dimensional (2D) and three-dimensional (3D) echocardiography with confirmation of proper venous cannula position were used to exclude significant recirculation. Research using dilution techniques with ultrasonic probes attached to the arterial inlet and venous outlet lines of the cannulas allows calculation of a recirculation percent. Surveillance TTE with serial quantification of the recirculation percent can help determine malposition and diagnose cannula migration [19].

On VA ECMO, echocardiography can be utilized to define myocardial contractility, left ventricular end diastolic volume (LVEDV), mitral regurgitation, aortic valve systolic excursion, and LV decompression. For patients supported with VV or VA ECMO, volume management is critical to prevent volume overload and worsening lung injury. A positive fluid balance on hospital day 3 has been shown to be an independent predictor of 90-day mortality in patients supported with either VA or VV ECMO [20]. In a study evaluating utilization of echocardiography to guide fluid therapy optimization, measurements of LV stroke volume using the aortic valve area and aortic velocity time integral were performed at baseline. Passive leg raise was then performed with elevation of the lower extremities to a 45-degree angle, while the trunk was lowered from a semirecumbent to a supine position. Repeat measurement of LV stroke volume was then performed, and an increase in 10% or greater of the passive leg raise stroke volume (PLRSV) from baseline predicted a greater than 15% increase in stroke volume after

volume expansion (500 ml saline administered over 15 min). This simple diagnostic procedure can reliably identify patients with ARDs supported with VV ECMO who may benefit from fluid loading [21].

3.4. Detection of extracorporeal life support complications

Patients supported by ECMO are at increased risk for complications due to their underlying critical illness and the complex support techniques being utilized. Complications that may occur during ECMO that can be diagnosed by echocardiography include thrombosis, cannula malposition, tamponade, SVC or IVC syndrome, RV overload, hepatic congestion, and/or cannula thrombus casting [2, 22].

3.5. Recovery and weaning

Evaluating pulmonary and ventilator parameters help identify pulmonary recovery for patients on VV ECMO. Estimation of cardiac or cardiopulmonary recovery can be more complicated for VA ECMO. Historical metrics include a left ventricular ejection fraction (LVEF) of greater than 35–40%, right ventricular ejection fraction (RVEF) greater than 40% in the absence of moderate-to-severe tricuspid regurgitation, LV outflow tract velocity time integral greater than 10 cm, and/or the absence of LV dilatation with serial decreases in the ECMO flow rate. Multiple weaning protocols have been published, but ultimately ECMO flow is gradually decreased by set amounts, with periods of full support for recovery between trials. During the weaning phase, serial comprehensive echocardiographic examinations with a focus on qualitative and quantitative measures of RV and LV function can help guide the weaning process. Other more sophisticated applications of echocardiography to assess LV function during ECMO weaning include two-dimensional strain rate and Doppler tissue myocardial velocities [23].

TTE can be utilized to evaluate suitability for weaning, although contrast-enhanced TTE may be necessary to improve image quality. While contrast microspheres are hydrodynamically labile and demonstrate increased bubble destruction with passage through the ECMO circuit, the reduced signal persistence does not typically impair adequate image optimization with contrast-enhanced TTE [2].

Weaning protocols using a continuous hemodynamic TEE (hTEE®; Imacor, Garden City, NY) have been described to successfully manage separation of patients from ECMO in the ICU. The benefit of the hTEE® over conventional TEE or TTE is device placement and utilization in a continuous fashion over the 4–6 h weaning period, allowing multiple assessments and interventions over time. Timely determination of ventricular function recoverability is critical, secondary to the significant resources involved in caring for these complex, critically ill patients. Patients who demonstrate a low likelihood of ventricular recovery may have ECMO discontinued or transitioned to a longer term support solution, such as a LVAD or cardiac transplantation.

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4. Drug administration

4.1. Pharmacokinetics and pharmacodynamics

The body's relationship between the drug dosage and the drug concentration over time is pharmacokinetics (PK). Pharmacodynamics (PD) is the relationship between drug concentration and the associated pharmacological response. PK and PD are linked via the dose–effect relationship. The goal of drug therapy is to maximize efficacy and minimize toxicity. Critical illness and ECMO alter the PK and PD of medications significantly, and therefore, the risk of therapeutic failure or toxicity is heightened in this patient population [24, 25]. Clearance of medications in critically ill patients is typically dependent upon renal or hepatic function, and clearance can increase or decrease depending upon the underlying disease process [26]. Complex changes in PK parameters occur with ECMO initiation and maintenance with an increased volume of distribution, altered clearance, and sequestration of drugs in the ECMO circuitry [27]. Failure to account for these alterations in PK can lead to therapeutic failure, and drug monitoring is critical for appropriate treatment outcomes when feasible.

ECMO alters the PK of sedative, analgesic, and antibiotic drugs, and their metabolites, independent of other associated patient and pathological factors. Drug molecular size, degree of ionization, lipophilicity, and plasma protein binding, all contribute significantly to adult, pediatric, and neonatal ECMO PK studies. Drugs with a high lipophilicity or protein binding have greater degradation or loss in the ECMO circuitry [25, 27–30]. Significant sequestration occurs primarily in the oxygenator due to its large surface area. The type and age of the components (oxygenator, pump, and tubing) also contribute to the degree of sequestration [25, 31].

4.2. Sedatives and analgesics

Sedatives and analgesics are necessary in the critically ill ECMO patients to provide optimal and safe care. A balance between light sedation and avoidance of muscle relaxants and the specific needs of the ECMO patient needs to be considered. Deeper sedation with muscle relaxants may be needed to optimize flows and ventilation strategies and minimize oxygen consumption. Adequate sedation minimizes catheter movement and dislodgements, and prevents patient coughing, which can create a “suck down” event and lowers ECMO flows and may cause hemolysis [25]. ECMO patients typically undergo total IV anesthesia during surgery with anesthetic agents including sedatives, hypnotics, analgesics, and muscle relaxants. Clinical teams with expertise in infusion therapy and total IV anesthetic techniques can be helpful to guide therapy and prevent underdosage or overdosage of medications. Significant and rapid increases in midazolam, morphine, and propofol doses immediately after ECMO initiation may be necessary to maintain pre-ECMO sedation levels. These “supranormal” elevations may be required for the entire ECMO support period and may warrant additional neuromonitoring to ensure adequate sedation levels [32, 33]. A survey of international ECMO centers identified that medications were used in the following frequencies: midazolam (79%), fentanyl (45%), morphine (43%), dexmedetomidine (41%), propofol (36%), and clonidine (25%) [33]. Muscle relaxants were used in only 35% of centers, and differences

in sedation and neuromuscular blocking agent use varied between experienced and less experienced centers. Critical care best practices can be extended to ECMO patients who should have consideration of daily cessation of sedation, analgesics, and avoidance of neuromuscular blockade.

Due to longer recognized indications for ECMO support in newborn patients compared to adults, most of the studies of PK exist in this patient population. Due to differences in physiology and circuit design between newborns and adults, translation of studies between patient populations may not be applicable [34]. Large PK studies in adult patients on ECMO focused upon antibiotics, antifungals, antivirals, sedatives, and analgesics are currently being performed [35, 36].

Variability in studies regarding drug sequestration in neonates exists for both morphine and fentanyl, and some advocate morphine use over fentanyl due to reduced drug withdrawal and length of stay in morphine-treated patients [25, 37, 38]. In vitro modeling has demonstrated that the tubing and membrane oxygenator of the ECMO circuit extract 67% of fentanyl over 48 h, but morphine demonstrated no extraction; therefore, higher fentanyl dosing but not morphine is needed to maintain adequate plasma levels [38]. Other in vitro studies examining morphine and fentanyl demonstrated significant sequestration of both agents by the ECMO circuit with 40% dose extraction by the PVC and membrane oxygenator [31, 39]. Some recommend using fentanyl for short-term pain relief and to avoid long-term fentanyl use in ECMO patients due to significant uptake by the tubing. Morphine may also be affected by uptake and may not be the best agent for long-term pain relief. IV acetaminophen, with lower lipophilicity and protein binding, may prove to bind less to the circuit components. An in vitro study of IV acetaminophen concentration over 6 h demonstrated relatively constant concentrations over time, irrespective of circuit age [40]. Based upon this study, use of IV acetaminophen in place of opioids may be preferable in patients requiring analgesia, undergoing ECMO therapy.

Pharmacokinetic and dynamic studies of midazolam in newborns supported with ECMO demonstrate an increase in the volume of distribution and an increased clearance of midazolam and its active metabolite 1-hydroxymidazolam. Over time, the active 1-hydroxymidazolam accumulates and may contribute to a greater proportion of the sedative effects seen clinically. The clinical significance of the active metabolite is unclear, because typically after 5–7 days of ECMO, infusion rates of midazolam need to be increased substantially to maintain sedation levels despite accumulation of the active metabolite. Others are concerned that 1-hydromidazolam accumulates and must be accounted for when the infusion is discontinued and the sedative effect remains. Careful titration based upon sedation scores are recommended to guide sedative therapy [41]. In vitro experiments demonstrate that sequestration is higher in older circuits than newer circuits and suggest that sequestration may be a time-dependent process. This phenomenon, in conjunction with increased clearance, contributes to the need to increase drug doses over time [25]. Benzodiazepines, as a class, demonstrate sequestration with 46–89% of midazolam and 50–59% of a dose of lorazepam being extracted by the PVC tubing and membrane oxygenator in a time-dependent fashion [31, 38, 39, 42].

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Dexmedetomidine has demonstrated decreases in concentrations over time during in vitro ECMO analysis related to PVC circuit adsorption, and dosing adjustments to maintain appropriate serum concentrations are recommended [43]. Use of propofol in patients on ECMO has been debated over concerns of propofol damaging the ECMO circuit or membrane oxygenator. For cardiac surgical cases, it is not recommended to administer propofol directly into the cardiopulmonary bypass circuit with a membrane oxygenator due to poor blood mixing and propofol separation in the reservoir [44]. Administration is recommended via a dedicated peripheral intravenous line as opposed to a central line to prevent prompt venous cannula uptake and direct routing to the pump. Despite theoretical concerns, injection of propofol into the pump does not cause alteration in gas exchange nor oxygenation to patients on cardiopulmonary bypass [45]. Use of propofol in patients on ECMO has been debated. Propofol, a highly lipophilic medication, demonstrates significant sequestration with up to 98% concentration loss due to tubing binding, which limits drug efficacy [46]. Propofol-induced hypertriglyceridemia with associated hemolysis has been reported in ECMO patients [47]. Surveys indicate that propofol use for sedation is not common and may stem from concerns regarding poor mixing and poor gas exchange from the oxygenator, despite these findings not having been found specifically in ECMO patients [33]. Propofol may be utilized in patients on ECMO, but concerns regarding extremely high dose requirements, limited effect, propofol infusion syndrome, hypertriglyceridemia, and hemolysis exist.

4.3. Antibiotics

Antibiotics are commonly given to patients on ECMO for surgical prophylaxis and/or to treat the underlying pathology of the respiratory failure or associated infection occurring during the critical illness. Bloodstream infections are common in ECMO patients, occurring in 14.4% of patients supported for greater than 48 h, with Gram-negative bacilli being the most frequent pathogen [48]. The success of ECMO may rely on the success of the antibiotic therapy, and therapeutic failure secondary to inadequate drug concentrations must be avoided. PK features and dosing requirements of vancomycin, cephalosporins, and carbapenems are unclear with some studies suggesting significant sequestration with resultant lower concentrations, while others suggesting no change in concentration in ECMO patients [31, 42, 49, 50]. Antifungal agents, caspofungin and voriconazole, have been studied, with caspofungin demonstrating maintained peak and trough levels but voriconazole being significantly sequestrated. Limited data exist for antivirals; there is no significant change in concentration across the oxygenator for oseltamivir given for influenza A infections to ECMO patients [51]. For patients with H1N1 disease, standard dosing of enteral oseltamivir in ECMO patients is recommended and produces concentrations necessary to inhibit the neuraminidase activity of the H1N1 virus [52]. Therapeutic drug monitoring is recommended for all antibiotics, antifungals, and antivirals when available, and is critical to guide therapy to optimize outcomes [25].

4.4. Inotropes and vasopressors

ECMO is initiated for a variety of life-threatening respiratory or cardiac issues, and can be used to support patients and organ recovery for extended periods of time. Many patients are

critically ill when ECMO is initiated and are supported with cardiovascular adjuncts (96.2%) prior to ECMO support, including inotropes (95.8%), vasopressors (83.5%), IABP (40.1%), cardiopulmonary resuscitation/defibrillation (31.1%), and ventricular assist devices (9.0%) [9]. Patients who were on cardiovascular adjuncts at the initiation of ECMO have a worse outcome than patients not supported on these agents [9]. Pharmacological agents are typically required to provide support to recovering organs during the weaning and separation phases, as these organs are still recovering from recent intervention and/or injury. Weaning of ECMO occurs commonly in the intensive care unit or the operating room and requires collaboration of a team of professionals. Hemodynamic instability in the separation phase may be secondary to vasodilation, RV or LV dysfunction, left ventricular outflow tract obstruction, pulmonary hypertension, respiratory failure, and/or acidosis. Specific therapy should be initiated prior to separation to improve weaning and separation success rates, as failed weaning is associated with organ injury or failure [53]. Predictors of successful weaning are improved pulse pressure, decreased inotropic score, and improved LVEF and RVEF.

5. Anticoagulation

5.1. Heparin

Initiation of ECMO requires the consideration of anticoagulation and associated risk of bleeding versus thrombosis due to blood exposure to nonnatural surfaces. Exposure of blood to the artificial surfaces of the ECMO circuits initiates a complex inflammatory response and the coagulation pathway. Multiple biochemical pathways are activated, which lead to procoagulant activity as well as fibrinolytic activity, which can lead to circuit thrombosis and patient hemorrhage. Unfractionated heparin is the most widely used anticoagulant and works via two endogenous anticoagulants—antithrombin (AT) and tissue factor pathway inhibitor (TFPI). A survey of 121 ECMO centers determined that unfractionated heparin is the preferred anticoagulant for most cases and that alternative anticoagulants are used only 8% of the time [54].

Standard anticoagulation protocols for VV and VA ECMO include a bolus of unfractionated heparin (2500–5000 IU) administered intravenously during guidewire placement immediately prior to cannulation. After ECMO institution, heparin is administered via a central line by continuous infusion to maintain an ACT between 180 and 220 s. Small case series, however, suggest that lower goal ACT values between 140 and 160 s lead to less major bleeding and bleeding-induced death and transfusions without an increase in oxygenator changeovers or thrombotic events [55].

Studies have investigated ECMO patients supported without anticoagulation in order to minimize bleeding complications. In one study of 32 patients (24 post cardiotomy, 8 eCPR) on VA ECMO without anticoagulation during maintenance of ECMO, no neurologic or hemorrhagic complications occurred [56]. In certain high-risk patients for hemorrhagic complications supported on ECMO, it may be reasonable to withhold systemic anticoagulation during VA ECMO. VV ECMO patients may also tolerate no anticoagulation, as a case report described a

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successful 32-day heparin-free VV ECMO support period for a patient who suffered a retroperitoneal hematoma during initial cannulation [57]. Another case report described a weaning strategy in a patient on VV ECMO who required cessation of heparin therapy due to persistent thoracic and mediastinal bleeding by maintaining a normal blood flow (62.5 ml/kg/min) and weaning the gas flows only [58]. Based upon these small series of studies, interruption or cessation of systemic anticoagulation may be considered if necessary to manage bleeding risk.

Bleeding is a common complication in ECMO patients, occurring in up to 22–32% of patients [59]. In the presence of hemorrhage, or traumatic bleeding, heparin may be held temporarily to control bleeding sources. Patients with traumatic brain injury have historically been a relative contraindication due to concerns about anticoagulation and intracranial bleeding. Two published case reports indicate that these patients may be managed successfully on ECMO with low-dose anticoagulation (heparin 2000 unit bolus at initiation) and goal aPTT of 40–60 s [60]. Although studies are small, historical contraindications such as severe septic shock, traumatic brain injury, polytrauma patients, pregnancy, and patients requiring frequent surgical intervention are now being treated with ECMO without full-dose anticoagulation and broadening the indications for ECMO significantly [61–65].

Patients on ECMO may require surgery, with tracheostomy, extremity, and vascular and abdominal exploration being the most common procedures performed. Heparin infusions may be held during the surgical procedure and immediately resumed postoperatively. Postoperatively, ECMO patients requiring noncardiac surgery have been shown to have statistically significant higher blood transfusion requirements (73.3 vs. 25.5%), higher average number of units transfused (2.8 vs. 0.8%), and higher perioperative mortality (46.7 vs. 6.4%) in comparison to LVAD patients undergoing similar noncardiac surgical procedures [66]. The use of blood products increases mortality in both ECMO and LVAD patients undergoing noncardiac surgery, and meticulous surgical technique, interrupting anticoagulation, and minimizing blood transfusions may improve overall mortality. Mortality may be decreased if 81 mg of aspirin is continued preoperatively in both ECMO and LVAD patients undergoing noncardiac surgery.

5.2. Direct thrombin inhibitors

Bivalirudin (Angiomax®, The Medicines Company, USA) has been proposed as an alternative anticoagulant to heparin for patients on ECMO. According to guidelines, ECMO patients with heparin-induced thrombocytopenia (HIT) should be anticoagulated with direct thrombin inhibitors (DTIs) such as bivalirudin or argatroban [67]. Dosing of bivalirudin for ECMO patients ranges from 0.025 to 0.5 mg/kg/h, although no standard dose exists due to limited use. Monitoring of the anticoagulation effect for patients on DTIs is difficult, with ACT, aPTT, and ecarin clotting time all being recommended [68]. A retrospective study of 21 patients (12 adults and 9 children) undergoing postcardiotomy ECMO receiving heparin versus bivalirudin demonstrated a better coagulation profile, less bleeding and less transfusions, and overall lower costs in the bivalirudin group [69]. In this study, bivalirudin-treated patients had significantly longer ACT, aPTT, and TEG®r times at different specific time intervals. A study

comparing aPTT in patients receiving heparin versus bivalirudin on VV and VA ECMO demonstrated more frequent aPTT variations greater than 20% of the previous value in the heparin-treated group [70]. Based upon these variations, the number of drug dose corrections was higher in the heparin-treated group. Although not statistically significant, both major and minor bleeding were higher in the heparin group. Bivalirudin may be superior to heparin due to more consistent aPTT levels with less drug dose alterations.

Avoidance of blood stagnation with bivalirudin anticoagulation is critical due to a short half-life and rapid cleavage of bivalirudin by proteolytic enzymes. This may lead to inadequate anticoagulation and increased risk of thrombosis, especially in stagnant flow areas. Cardiac chambers can become natural reservoirs for stagnant flow on ECMO when chambers are enlarged, and poor cardiac function limits forward cardiac flow. In bivalirudin-anticoagulated patients, echocardiography findings of a dilated atrium, poor ventricular function, and/or no aortic valve opening are concerning and increase the risk of thrombosis. If present, partial ECMO, institution of improved drainage, venting, or inotropic support should be performed urgently. If unsuccessful, conversion to a different anticoagulant should occur [71].

Argatroban (Argatroban, GlaxoSmithKline, USA), a DTI, is also indicated as an anticoagulant for prophylaxis or treatment of thrombosis in patients with HIT. In vitro analysis of circuits primed with argatroban suggests that thrombin generation may be lower [72]. Utilization in patients undergoing VV ECMO was studied in nine patients with the suspicion of HIT, eight of which were also on renal replacement therapy [73]. The first patient received argatroban infusion of 2 mcg/kg/min as recommended in the product information. Significant bleeding requiring transfusion occurred in this patient, and the subsequent eight patients received 0.2 mcg/kg/min continuous infusions to minimize bleeding. This dosing was sufficient to increase the aPTT and thrombin time (TT) to goal within 4 h in the majority of the patients. In this small study, the maintenance dose of argatroban was 0.15 mcg/kg/min, and no adjustment in dosing was necessary for patients in renal failure. It is recommended that dosages of argatroban should be decreased in the critically ill patients, patients with hepatic dysfunction, and ECMO patients. Several successful case reports using full-dose argatroban dosing in patients with HIT exist, but adequacy of standard anticoagulation monitoring remains a concern [74–76]. DTIs can be used safely in patients on ECMO, but limited experience and concern over a consistent monitor of adequacy of anticoagulation limit widespread acceptance of these agents for all ECMO patients. Currently, DTIs are typically reserved for patients with severe AT-III deficiency or HIT.

5.3. Heparin-induced thrombocytopenia

HIT is a complication of heparin therapy with a mortality of 10–30%. Antibodies bind to a complex of heparin and platelet factor 4 and cause thrombocytopenia and thrombosis. Within 4–5 days of heparin exposure, platelet counts fall but symptoms may present sooner in patients who have been previously exposed to heparin. If HIT is suspected, discontinuation of heparin should occur, and continuation of anticoagulation with an alternative agent should be considered to prevent thrombosis. As thrombocytopenia is common in critically ill patients due to a variety of other illnesses, HIT should be ruled out by lab testing with PF4 ELISA

analysis [73]. A study of 119 patients supported on ECMO demonstrated that by day 4, 60% of the patients had a 50% or greater decrease in platelet counts [77]. In patients suspected of having HIT (19%), a reduction of platelet count by 71% was present with a median platelet count of 43 × 10^9/l. One patient had laboratory-confirmed HIT; yet, all patients suspected of having HIT, warranting a change in anticoagulation therapy, demonstrated a higher hospital mortality rate (61 vs. 32%).

Once HIT is suspected, unfractionated heparin should be stopped and conversion to a nonheparin anticoagulant should be considered. Warfarin should be avoided until thrombocytopenia resolves, and prophylactic platelet transfusions should not be administered. DTIs or factor Xa inhibitors should be used for anticoagulation. Bivalirudin is the recommended agent for patients with HIT requiring urgent cardiac surgery and ECMO [67, 78]. Recommended dosing for ECMO is 0.5 mg/kg/h IV, which is closer to the thrombosis prophylaxis dose of 0.25 mg/kg/h versus the bypass-dosing regimen (1.75–2.5 mg/kg/h). A short half-life and absence of renal or hepatic clearance make bivalirudin a preferred alternative to other DTIs for ECMO patients [79, 80].

5.4. Monitoring of anticoagulation

Activated coagulation time (ACT) is the most commonly used measure of anticoagulation for patients maintained on ECMO. Experiences extrapolated from the cardiac operating room form the decision to use this technology for patients on ECMO. ACT is a simple, quick, and crude measure of anticoagulation for patients on high-dose heparin therapy (300 units/kg), but is less reliable at standard rates of heparin infusion (<50 U/kg/h). ACT levels do not correlate with either activated partial thromboplastin time (aPTT) or with anti-Xa activity, especially at lower levels of heparin dosing with ECMO [78]. Despite these limitations, ACT can be used for patients on ECMO with goal values between 150 and 220.

Antifactor Xa assay can be used to monitor and manage unfractionated and low molecular weight heparin therapy. Antifactor Xa levels between 0.3 and 0.7 IU/ml reflect a heparin effect; yet, some ECMO centers advocate higher target ranges between 0.7 and 1.1 IU/ml. ACT and antifactor Xa measure two distinct components of the coagulation process. ACT measures whole blood clotting and is therefore affected by heparin, thrombocytopenia, and inflammation. Antifactor Xa assay measures heparin effect or heparin concentration. Antifactor Xa assay is specific to the anticoagulant effect of unfractionated heparin and is unaffected by coagulopathy, thrombocytopenia, or dilution. aPTT is unreliable in the initial management of ECMO patients. Once ECMO is established, aPTT can be used as a measure of anticoagulation, with goal aPTTs between 1.5 and 2.5 times normal [81]. When comparing therapeutic ACT values to therapeutic aPTT levels, a poor correlation exists between ACT and aPTT, and ACT testing alone may not be enough to optimize heparin dosing [82]. Despite these limitations in ACT monitoring, a survey of ECMO centers reported the preferred method of anticoagulation monitoring was ACT, as reported by 97% of the respondents [54]. Most respondents reported using more than one test to guide therapeutic decisions, with 82% utilizing AT testing, 65% anti-factor Xa testing, and 43% thromboelastography monitoring. Utilization of ACT to manage ECMO patients can be complicated by limitations intrinsic to the ACT test. ACT values

are affected by heparin therapy as well as patient characteristics, including coagulopathy, platelet dysfunction, hypothermia, AT level, and hemodilution [78]. The use of ACT alone to monitor the degree of anticoagulation on ECMO is too insensitive, and therefore, the addition of other coagulation tests may prove beneficial to the patient [83]. Limited studies have been performed with heparin concentration (Hepcon® HMS Plus, Medtronic, USA) management in ECMO patients, and therefore target heparin concentration levels for ECMO patients are undetermined [84]. Thrombosis and clot formation within circuits, membrane oxygenators, and patients is a significant complication of ECMO therapy and can occur despite full anticoagulation with heparin. Clot formation in the oxygenator is reported to occur in 13–19%, and reported rates of serious patient complications include GI bleeding (4%), cardiac tamponade (10%), neurological events (3.5–11%), and surgical bleeding (21–24%) [78, 85].

6. Fluid management

Goals of fluid management include maintaining a normal blood volume while achieving an adequate hematocrit and keeping a normal body weight. Blood volume should be maintained at a level needed to maintain right atrial pressure between 5 and 10 mmHg [4]. A net negative fluid balance should be achieved, and volume overload should be avoided as this in itself can lead to further heart or lung injury. This balance can be difficult to achieve in patients with capillary leakage and inflammation. Pharmacological diuretics or continuous hemofiltration in patients with renal failure may be needed to achieve a fluid balance.

"Chattering" of the cannulas may be an indicator of intravascular volume depletion. Administration of fluid and/or blood is indicated when this occurs. Similarly, a fluctuating flow rate of the centrifugal pump may be due to hypovolemia, but may also occur due to excessive pump speed or malposition of the cannulas [86].

Fluid management is also of critical importance when weaning and decannulating from ECMO. Due to the change in the volume of distribution, fluid overload and right ventricular failure may occur during this period [8].

7. Blood management

7.1. Transfusion thresholds

Surgical procedures in the United States account for 15 million units of packed red blood cells (pRBCs) being transfused annually, with cardiac surgery consuming 10–15% of the U.S. blood supply [67]. Studies in ECMO patients demonstrate even higher utilization of blood products, most likely secondary to critical illness and alterations in hemostasis. Current transfusion practices for cardiac surgery support transfusion when hemoglobin (Hgb) is less than 7 g/dl. A study of 158 patients on VV and VA ECMO established that 97% of patients received transfusions, and bleeding occurred in 17% of VV ECMO patients and 33% of VA ECMO

patients [48]. Patients on VA ECMO received more transfused units of pRBCs than patients on VV ECMO, and transfusion rates were higher in patients who subsequently died [48, 87, 88]. Platelet volume requirement was an independent risk factor of mortality for VV ECMO patients, while the volume of blood transfused was an independent risk factor for mortality on VA ECMO [48].

7.2. Red blood cells

Volume of pRBC transfused varies in ECMO patients based upon underlying indications for support with the greatest volume transfused in cardiac patients, intermediate for eCPR patients, and least for noncardiac indications. Volume of RBCs transfused remains an independent predictor of in-hospital mortality among ECMO patients for noncardiac indications and postcardiotomy patients [89]. A retrospective study of 38 patients on VA, VV, or VAV ECMO, utilizing a transfusion trigger of 7 g/dl, a low dose anticoagulation strategy with a targeted aPTT of 40–60 s and autotransfusion following decannulation demonstrated an overall transfusion rate of 63.2% [90]. Median hemoglobin was 8.2 g/dl, and a median of 1 unit was transfused over a median duration of 9 days. Bleeding occurred in 26.3% of patients, with severe bleeding in 5.3%. Survival to hospital discharge occurred in 73.7%. This study suggests a restrictive transfusion practice in critically ill patients with ARDs supported with ECMO with a favorable and comparable outcome to studies using a higher transfusion trigger. A study of 18 patients on VV ECMO maintained with a hemoglobin concentration between 7 and 9 g/dl and transfused when Hgb was less than 7 g/dl demonstrated no increase in mortality (38.9%) [91]. A restrictive transfusion approach, which is well supported in the critically ill, may also be applicable to patients on ECMO, but large randomized control trials have not been conducted to compare restrictive versus liberal transfusion practices.

7.3. Platelets

Initiation of ECMO causes profound changes in coagulation parameters. Platelet counts, factor XIII, and fibrinogen all fall within the first 5 days of ECMO support, while thrombin–AT complex, D-dimer, and AT levels rise [92, 93]. Platelet counts typically fall during ECMO, and remain low and only recover after cessation of ECMO therapy [92]. Platelet transfusions remain a frequent occurrence on ECMO due to both patient factors and extracorporeal circuit factors. Severe thrombocytopenia occurs with ECMO initiation, especially in neonates and infants. Adults placed on ECMO post cardiotomy may have underlying thrombocytopenia and platelet dysfunction due to recent bypass support. Some experts recommend maintaining platelet counts between 45 and 65 × 10^9/l, with mandatory transfusion recommended when platelet counts are less than 20 × 10^9/l [84, 93]. Thromboelastometry can help define platelet function, and transfusion of platelets may be necessary despite a normal platelet count due to platelet dysfunction.

7.4. Fresh frozen plasma and fibrinogen

Transfusion of clotting factors also occurs frequently to support coagulation in ECMO patients. Maintenance of an INR less than or equal to 1.3 is recommended by transfusion guidelines.

While FFP contains most of the clotting factors, concentrations of specific components vary widely per unit of FFP transfused. Fibrinogen levels should be checked, and maintenance of fibrinogen levels greater than 100 mg/dl is recommended. When supplementing fibrinogen with cryoprecipitate, concomitant administration with platelets may increase the risk of thrombus and thromboembolic complications. Fibrinolysis, documented by thromboelastography, may be treated with antifibrinolytic therapy. Treatment should be undertaken cautiously as case reports exist of fatal thrombosis associated with antifibrinolytic therapy in ECMO patients.

7.5. AT-III levels

Unfractionated heparin binds with AT, and this complex increases the efficacy of AT. AT levels affect heparin PD, and measurements of AT levels can be helpful, especially in patients with elevated unfractionated heparin requirements. Acquired AT-III deficiency occurs commonly during ECMO, especially in pediatric patients and can create anticoagulation issues. Supplementation of AT is currently available from three sources, if AT levels fall below 0.5–0.7 U/ml: FFP, concentrated pooled human AT (Thrombate III®, Grifols Therapeutics, USA), and/or recombinant AT (ATryn®, rEVO Biologics, USA). Use of Thrombate III® has been shown to be safe in pediatric patients on ECMO without increasing bleeding complications or pRBC transfusions [94]. Recombinant AT (rAT) has the greatest concentration among the three products and has also been used successfully to elevate AT levels in pediatric ECMO patients. Frequent monitoring of AT levels is recommended due to prolonged rAT pharmacokinetics in ECMO-supported patients [95]. In conjunction with AT supplementation, heparin dosing should be decreased by 25% to prevent over anticoagulation. Recombinant AT is preferred over FFP for AT supplementation in ECMO patients due to low levels of AT in FFP and unpredictable responses to replacement with FFP. Conversion from heparin to a DTI has been used successfully in patients with low AT-III and concerns over supplementation with AT-III or FFP [68].

7.6. Recombinant factor VIIa

Concern exists for using recombinant factor VIIa (rFVIIa) on ECMO patients, despite successful case reports for bleeding cessation, due to overwhelming patient or circuit thrombosis. A study of 30 VA and VV ECMO patients who received recombinant factor VIIa (rFVIIa) for refractory bleeding demonstrated an efficacy rate of 93.3% in stopping bleeding, but a patient thrombotic rate of 3.3% and a circuit thrombotic rate of 16.7%, which were not statistically significant when compared to controls [96]. Recombinant FVIIa should only be considered as a "last resort" to stop bleeding in ECMO patients [67, 78, 84, 96].

7.7. Transfusion protocols

Utilization of a comprehensive ECMO anticoagulation monitoring protocol in children can result in fewer bleeding complications, reduced blood product usage, and increased circuit life [97]. In a small study of 10 patients using a proposed transfusion algorithm incorporating thromboelastometry and platelet function assays, less than 20% of the

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transfusions corresponded to the algorithm, and transfusions were noted to be in excess of those recommended [98]. This finding suggests poor adherence to algorithm-based transfusion practices. Consensus guidelines for blood component therapy in ECMO patients suggest transfusing to ensure adequate oxygen carrying capacity, normal AT-III activity (80–120% control), fibrinogen levels of 250–300 mg/dl, and a platelet count greater than 80,000/μl [67].

7.8. Bloodless ECMO

Refusal of blood products by patients should not contraindicate ECMO support as a case report describes a successful 44-day period of ECMO support in a patient with hemoglobins between 4.5 and 6.0 g/dl who refused transfusion on religious ground [99]. A multimodal approach to stimulate erythropoiesis and minimize blood loss was utilized to manage the anemia. Another case report described a successful 15 days of bloodless VV ECMO support in a 17-year Jehovah's Witness patient [100]. Experience with bloodless cardiac surgery including circuit miniaturization, reduction from the standard ECMO lab sampling protocol, retrograde priming the ECMO circuit following cannulation, erythropoietin administration, hemostasis, and cell saver reinfusion during decannulation and separation was performed.

7.9. Thromboelastometry

Thromboelastometry [(ROTEM®, TEM/Pentapharma, Germany)(TEG®, Haemonetics, USA)] are point of care testing devices to examine the viscoelastic properties of whole blood. Different activators and inhibitors are utilized to examine clotting via the different pathways and components of the coagulation cascade. These devices evaluate from initiation of clot formation to clot lysis and can diagnose factor deficiencies, fibrinogen deficiencies, clot strength, heparin effect, platelet function and fibrinolysis. Interpretable information is provided within 10 minutes with a full analysis of clot formation and lysis within 60 minutes. Thromboelastography is however a poor guide to monitor and manage heparin anticoagulation in ECMO patients. A 5-year retrospective study of 20 heparinized patients on ECMO investigated the correlation between ACT, aPTT, and thromboelastrography [101]. Analysis demonstrated poor correlation between aPTT, ACT and INTEM clotting time with unfractionated heparin infusion rates. Approximately 50% of patients in this study demonstrated normal INTEM tracings despite an elevated aPTT, questioning the sensitivity of INTEM clotting time to heparin dosing. Reliance on INTEM clotting times only for heparin dosing could lead to heparin overdosing due to the association of normal INTEM clotting times despite therapeutic aPTT in heparinized ECMO patients. Thromboelastography has a role in ECMO patients, not for heparin dose management, but to evaluate the hemostatic balance in these complex patients. Transfusion algorithms exist for cardiac surgery patients based upon thromboelastography patterns, and these algorithms can be extrapolated to ECMO patients to guide medication and transfusion therapies [98].

8. Ventilation strategies

Prior to initiation of ECMO, lung strategies that may be undertaken beyond lung protective ventilation include use of neuromuscular blockade [102] and/or prone positioning [103]. Another rescue therapy for patients with severe acute respiratory distress syndrome (ARDS) and refractory hypoxemia includes high levels of positive end-expiratory pressure (PEEP) [104].

Whether on VV or VA ECMO, the patient's lungs should be allowed to rest and hence the ventilator should be managed at low settings. Ventilator-induced lung injury (VILI) also needs to be minimized [105]. In order to reduce VILI, alveolar strain, atelectrauma, and oxygen lung toxicity have to be prevented, and this can be achieved with ECMO [106]. According to Extracorporeal Life Support Organization Guidelines [4], standard rest settings consist of a low rate with a long inspiratory time, low plateau inspiratory pressure (under 25 cm H_20), low FiO_2 (under 30%), and PEEP between 5 and 15 cm H_2O. For patients with VV ECMO, especially those with ARDS, tidal volume should be targeted to less than 4 ml/kg predicted body weight, and plateau pressures should be kept ≤25 cm H_2O, a concept referred to as ultraprotective ventilation [106]. This ventilation strategy is associated with the use of high PEEP levels and extracorporeal carbon dioxide removal ($ECCO_2R$) [107–109]. Higher PEEP is needed in order to prevent ventilation/perfusion mismatch [110]. High PEEP should not be used however in patients with low lung recruitability, as this may increase alveolar strain and impair hemodynamics [111].

Manipulating ventilator settings to improve oxygenation is not recommended. Unfortunately, the best mode of ventilation for patients on both VA and VV ECMO have yet to be determined. Only 27% of ELSO-registered centers have a mechanical ventilation protocol for ECMO patients [112]. About 77% of these centers report “lung rest” to be the primary goal for ventilation. Pressure-controlled ventilation is the most popular mode for patients with ARDS, and airway pressure release ventilation (APRV) is being used more in recent clinical trials [106, 113]. Specific large randomized trials that focus on mechanical ventilation with ECMO are needed.

Monitoring the lung during ECMO can be challenging. Daily monitoring of plateau pressure, compliance, and tidal volume may offer valuable information [106]. Transpulmonary pressure can be estimated by an esophageal balloon in order to titrate PEEP [114].

The ventilator should be turned off in cases of interstitial emphysema or severe air leak syndromes [4]. This will result in atelectasis, and aggressive lung recruitment will be needed when resuming mechanical ventilation.

If the patient develops a pneumothorax during ECMO, a significant risk/benefit analysis should be undertaken in order to decide on best management. If it is a small pneumothorax (<20%) without hemodynamic compromise, then it is best to treat conservatively [4]. An enlarging pneumothorax or one causing hemodynamic compromise will require external drainage. Caution should be made in placing a chest tube, as this may lead to significant bleeding potentially requiring a thoracotomy. A small catheter should alternatively be placed.

The timing of tracheostomy on mechanical ventilation is controversial, with most centers performing early tracheostomies, even though evidence has demonstrated that there is no benefit in performing this procedure in the first 10 days on ECMO [115, 116].

Certain patients can be extubated while on ECMO and allowed to breathe spontaneously. Awake ECMO is recommended, if possible, for patients awaiting lung transplants or suffering from hypercapnic respiratory failure [117–119]. Also, if the patient is on VA ECMO for cardiac support and the lungs are adequate, these patients may be extubated and managed awake.

As the patient begins to recover, lung recruitment maneuvers consisting of sustained inflation at 25–30 cm H_20 should be undertaken. In addition, sedation should be titrated to allow spontaneous breathing while adjusting the sweep gas to maintain a PCO_2 between 40 and 45 mmHg [4]. Additional lung recovery strategies include diuresis, pleural drainage, therapeutic bronchoscopy, and positional therapy [8].

9. Conclusions

The usage of ECMO continues to evolve faster than the literature can support. Large randomized trials need to be undertaken in order to support clinical practice and define best anesthetic management. Until then, literature from other specialties such as emergency medicine and critical care should be carefully evaluated in order to guide management of this unique patient population.

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Chapter 13

Management of Mechanical Ventilation During Extracorporeal Membrane Oxygenation

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Additional information is available at the end of the chapter

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Abstract

This chapter explores the best practices of mechanical ventilation during extracorporeal membrane oxygenation (ECMO) through a detailed discussion of the physiologic theory and clinical evidence. Future areas of study and unanswered questions about mechanical ventilation during ECMO are also delineated.

Keywords: mechanical ventilation, venovenous extracorporeal membrane oxygenation, venoarterial extracorporeal membrane oxygenation, ECMO, lung protective ventilation, positive end expiratory pressure

1. Introduction

Extracorporeal membrane oxygenation (ECMO) has been used as rescue therapy for hypoxemic, hypercarbic, and cardiogenic respiratory failure for decades, despite high complication rates [1, 2]. Venovenous (VV) ECMO was implemented internationally to great success during the recent H1N1 pandemic, and continues to be used as a last hope in refractory hypoxemia [3, 4]. Venoarterial (VA) ECMO is often employed when respiratory failure is secondary following hemodynamic collapse (most commonly cardiogenic in origin).

In a global effort to improve both the application and outcomes of VV and VA ECMO, all aspects of ECMO patients' care have been called into question. In this chapter, we explore both the theory and data behind specific mechanical ventilation (MV) strategies used in patients receiving ECMO to better understand current practice and propose areas of future study.

2. Ventilator associated lung injury

The landmark studies of lung protective ventilation in acute respiratory distress syndrome (ARDS) were published nearly 20 years ago, but the goal of lung protective ventilation remains to avoid ventilator associated lung injury (VALI) while permitting healing from the initial pathologic state [5, 6]. VALI is commonly described as a series of related injurious phenomena.

Barotrauma was the first, distinct aspect of VALI to be described. It can be defined as alveolar injury resulting from elevated transpulmonary pressures [7, 8]. Volutrauma is a related process where overdistension of alveolar volume results in lung injury [7, 8]. Barotrauma and volutrauma are both clinical explanations to approximate the physiologic principles of lung stress and strain using commonly measured variables including tidal volume, plateau pressure and positive end expiratory pressure (PEEP) [9]. MV strategies commonly aim to prevent barotrauma or volutrauma by limiting plateau airway pressures to ≤30 cm H_2O or tidal volumes to ≤6 ml/kg predicted body weight (PBW) [5].

Atelectrauma, conversely, occurs when low (or negative) end-expiratory transpulmonary pressures result in cyclic opening and closing of alveoli, generating disruptive forces on the basement membrane, resulting in lung injury [7, 10]. PEEP is commonly used to prevent atelectrauma by minimizing alveolar closure at the end of exhalation. Mechanical activation of the lung creates a biological reaction (e.g., neutrophil recruitment, cytokine release) known as biotrauma [8, 10–12]. Evidence of biotrauma may serve as a surrogate marker of the response to mechanical ventilation, and is often employed as an outcome measure when comparing MV strategies.

3. Mechanical ventilation strategies during venovenous extracorporeal membrane oxygenation

Guidelines for MV during ECMO are sparse. The Extracorporeal Life Support Organization 25 (ELSO) has published guidelines that include pressure assist-control ventilation (PCV) with low inflation 26 pressures (10 cm H2O), higher PEEP (15 cm H2O), low respiratory rate (5 bpm), and FiO2 of 0.5 27 or less [13]. The European Network of Mechanical Ventilation had similar guidelines in a 2009 response to the H1N1 pandemic recommending tidal volumes to obtain a plateau pressure of 20–25 cm H_2O, PEEP above 10 cm H_2O and with a respiratory rate of 6–20 cycles per minute and an FiO_2 between 0.3 and 0.5 [14]. However, in practice, there is significant variation in the mode of mechanical ventilation used in patients receiving ECMO [15, 16].

In the past 20 years, significant progress has been made in identifying the specific mechanical ventilation strategies that benefit patients with ARDS and acute respiratory failure [5, 17–20]. However, during this time, little progress has been made on the optimal method of mechanical ventilation in ECMO patients [14]. While volume assist-control ventilation (VCV) remains the most common mode of MV in ARDS, an observational study of current practice demonstrated

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pressure controlled modes of ventilation to be the most common mode of MV during ECMO [16, 21]. In many circumstances, ECMO may even facilitate ultraprotective MV, loosely defined as ventilation with tidal volumes below 4 ml/kg PBW. Although surrogate outcomes such as inflammatory markers may be improved by using this strategy, clinical benefit has not been demonstrated [22–24].

Experts continue to advocate for particular variations of VCV, PCV, or airway pressure release ventilation (APRV) predominantly based on physiologic 7 rationale and surrogate outcome studies demonstrating the avoidance of VALI [13]. However, there is a growing body of clinical evidence to guide the use of MV during ECMO [25, 26].

3.1. Lung rest: prevention of barotrauma or volutrauma

In a 2014 survey of ELSO centers, the majority (77%) reported "lung rest" to be the primary goal of mechanical ventilation during ECMO [15]. Although the definition of lung rest was not prespecified, one can assume that an intended goal was to limit both tidal volume and inspiratory airway pressures in that 81% of participants used tidal volumes ≤6 ml/kg PBW, including 34% who used ultraprotective tidal volumes ≤4 ml/kg PBW [15].

Initial studies of very low tidal volume ventilation in lung-injured rats demonstrated that tidal volumes of 3 ml/kg decreased pulmonary edema formation and improved pulmonary epithelial fluid clearance even when compared to 6 ml/kg [27]. Decreased levels of pulmonary inflammatory markers have also been found in humans ventilated with very low tidal volumes [22, 28]. These findings parallel a *post hoc* analysis of five large ARDS trials, which demonstrated a continuous mortality benefit to very low tidal volumes even when plateau pressures were less than 30 cm H_2O [29]. Case reports of tidal volumes as low as 1.9 ml/kg PBW have also shown positive outcomes [30]. However, prospective studies have failed to show a mortality benefit to ultralow tidal volume ventilation [24]. The Xtravent study compared very low tidal volume ventilation (~3 ml/kg PBW) plus $ECCO_2R$, to conventional low tidal volume ventilation (~6 ml/kg PBW) without $ECCO_2R$ in 79 patients with ARDS and did not find a difference in ventilator-free days or mortality at 60 days [24]. There was, however, an improvement in ventilator-free days in the more hypoxemic subgroup ($PaO_2/FiO_2 \leq 150$) [24].

Although it is generally accepted that limiting tidal volumes and plateau pressures with controlled ventilation modes should minimize VALI in the population requiring VV ECMO, preferences for volume control vs. pressure control ventilation vary significantly [4, 16, 25]. Advocates of volume control ventilation cite the ease of setting and studying a pre-specified tidal volume, as well as the added benefit of preventing large tidal volumes as lung compliance improves. However, VCV requires manually checking plateau pressures to analyze the compliance of the respiratory system. PCV has the benefit prespecifying a maximal inspiratory pressure and of being able to visually observe improving lung compliance by noting the change in tidal volume for a given driving pressure.

The most likely reason for the abundant use of PCV during ECMO is its use during the CESAR trial, the largest and most widely accepted comparison of ECMO to conventional ventilation in patients with potentially reversible respiratory failure [25]. In the CESAR trial, PCV settings

included a peak inspiratory pressure of 20–25 cm H_2O, PEEP of 10–15 cm H_2O, respiratory rate of 10 bpm, and FiO_2 of 0.3. Similar settings were used in 54% of ECMO patients in a recent observational study in three major centers [16]. Only 10% of patients received a volume controlled mode of ventilation again suggesting the widespread acceptance of the CESAR trial and the ESLO guidelines [16]. However, it remains unclear how these potential risks and benefits of VCV versus PCV translate into clinical outcomes.

The disadvantage to lung protective ventilation is primarily hypercarbia (and subsequent effects of increase $PaCO_2$) that can often be mitigated by ECMO or $ECCO_2R$. Right ventricular (RV) heart function must be considered in this setting as pulmonary vascular resistance and right ventricular stroke work index is likely to increase significantly even with relatively small (10 mm Hg) increases in $PaCO_2$ [31]. Lung recruitment may result in decreased hypoxemic pulmonary vasoconstriction and increased available pulmonary vasculature which may offset some of the increase in pulmonary vascular resistance seen with hypercarbia [32]. Alternative therapies for refractory hypoxemia including aerosolized prostacyclin may also mitigate hypercarbia-induced pulmonary hypertension, but prospective studies have failed to demonstrate a mortality benefit [33].

Finally at the extremes of ultralow tidal volume ventilation (nearing or below physiologic dead space), high levels of PEEP are required to maintain convective ventilation and prevent small airway closure and progressive atelectasis as seen during apneic oxygenation [34, 35].

3.2. Lung recruitment: prevention of atelectrauma

Lung recruitment does not exist in a vacuum, isolated from lung protection. Some strategies designed to maximize lung rest may exacerbate atelectrauma, other strategies selected to prevent atelectrauma may worsen alveolar overdistension. Ideally, these strategies can be combined to balance lung rest with lung recruitment. For example, most studies of ultralow tidal volume ventilation use relatively high amounts of PEEP to prevent atelectasis and ventilation/perfusion mismatch [7, 22, 24].

The goal of lung recruitment is to prevent atelectrauma by maintaining open all available lung units. The primary strategy to accomplish this is through the use of PEEP. The optimal PEEP for acute respiratory failure remains unknown [17–20, 36]. Even less data exists about the optimal PEEP for patients receiving ECMO. One retrospective observational study demonstrated an increase in mortality for lower PEEP during the first 7 days of ECMO [16]. It is notable that "lower PEEP" in this study was <12 cm H_2O which would include all patients at the ELSO guideline-recommended PEEP of 10 cm H_2O [16]. The SOLVE ARDS study is currently enrolling to compare PEEP set for optimal lung compliance versus zero PEEP (ZEEP), in patients receiving ECMO [37].

One alternative strategy to maintain an open lung is the regular use of recruitment maneuvers [18, 38]. Recruitment maneuvers have not been systematically studied in the ECMO population. Data on their use in acute respiratory failure is conflicting. When incorporated into a multifaceted open lung strategy, recruitment maneuvers failed to show mortality benefit when compared to conventional low tidal volume ventilation [18]. The lack of benefit of recruitment

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maneuvers is often attributed to the bundling of many lung protective strategies in one intervention or to studies being underpowered to detect significant differences in outcomes [39]. Neither a systematic review nor the Cochrane meta-analysis demonstrated a mortality benefit to recruitment maneuvers [39, 40].

One downside of recruitment maneuvers relates to the heterogeneity of the lung in the setting of ARDS that may result in simultaneous alveolar overdistension and atelectasis during lung recruitment, particularly if PEEP is not adjusted or re-optimized following recruitment [41]. Alveolar overdistension may also be caused by excess use of PEEP with manifold negative consequences including decrease in venous return, decrease in cardiac index and increase in RV afterload [42].

Some centers have advocated the use of airway pressure release ventilation (APRV) during ECMO to augment lung recruitment. APRV is a "time-triggered, time-cycled, bi-level, pressure-regulated ventilation mode that allows a patient's spontaneous breathing pattern to be superimposed upon the mechanical ventilation pattern" [43]. Functionally, the patient is held at an inspiratory pressure level ($PEEP_{High}$) and with short "releases" to $PEEP_{Low}$ (typically less than 1.5 s) while able to breathe spontaneously throughout. Oxygenation is typically improved by increasing airway pressure (both $PEEP_{High}$ and $PEEP_{Low}$) or FiO_2, while ventilation is achieved through the number and duration of "releases" as well as by spontaneous ventilation. When the mode is adjusted so that the time spent at $PEEP_{High}$ is equal to, or less than $PEEP_{Low}$ the mode is often referred to as bilevel, bipap, or biphasic positive airway pressure.

Advocates of APRV assert that higher mean airway pressures improve both lung recruitment (decreasing microstrain) and functional residual capacity (FRC) (improving lung compliance) [43, 44]. They also add that facilitating spontaneous ventilation improves *V*/*Q* matching by increasing ventilation near the diaphragm in well-perfused areas, and may enhance venous return and cardiac output [43–46]. Alternatively, these benefits may simply reflect improved lung recruitment due to higher mean airway pressures, as similar beneficial effects are seen during lung protective ventilation with higher PEEP [44]. Furthermore, permissive hypercarbia during APRV either results in an increased work of breathing for the patient, or undesirably high release volumes, which likely offsets the benefits of lung recruitment by increasing tidal strain [43]. Given the lack of large trials comparing the use of APRV to conventional lung protective ventilation, the benefit of using APRV during ECMO remains theoretical at best. The in-progress EOLIA trial does permit APRV and subgroup analyses may delineate the role of APRV in the future management of MV during ECMO [26].

3.3. Additional concerns

In adults with acute respiratory failure undergoing MV, high plateau pressures due to decreased respiratory system compliance often trigger clinicians to limit tidal volumes (or driving pressures) and PEEP. In a subset of patients, however, the decrease in respiratory system compliance reflects a decrease in chest wall compliance rather than lung compliance. In these patients attempts to measure surrogates of pleural pressure such as esophageal manometry may facilitate further optimization of MV [47, 48]. Future studies, including the currently enrolling EPVent2 may help elucidate the benefits of esophageal pressure monitor-

ing in the management of MV in patients with acute respiratory failure [49]. Specifically, esophageal manometry may help select patients who can avoid VV ECMO, and those in whom atypical MV settings should be considered even during ECMO.

A high fraction of inspired oxygen increases shunt by increasing absorption atelectasis [50, 51]. In most settings, ECMO facilitates weaning of ventilator FiO_2 to ≤0.5. However, during ECMO weaning, ventilator FiO_2 is often increased. Given that ECMO weaning is a priority for 84% of ELSO centers surveyed, future studies should examine the optimal timing of ECMO weaning, including the necessary changes to MV to facilitate ECMO weaning and the negative effects of premature weaning [15].

4. Mechanical ventilation strategies during venoarterial extracorporeal membrane oxygenation

The lung protective principles described are generally applicable to all patients on ECMO. For VA ECMO patients, however, the cardiovascular effects of mechanical ventilation can be especially relevant. RV dysfunction is a predictor of poor outcomes and increased mortality for patients with left ventricular assist devices (LVADs) [52]. These devices are often the bridge/destination therapy for patients requiring VA ECMO [52]. Also, because VA ECMO may limit blood flow through the lungs, the optimal amount of alveolar ventilation may be different compared with patients requiring VV ECMO [53].

4.1. Lung volume and right ventricular afterload

The primary measurement of RV afterload is pulmonary vascular resistance (PVR) [54]. PVR is comprised of the resistance imparted by (1) alveolar vessels and (2) parenchymal vessels. PVR is altered significantly by increasing lung volumes and is minimized when the lung is at functional residual capacity (FRC). As lung volumes increase and alveoli become distended, alveolar pressure exceeds pulmonary arteriolar pressure, leading to vascular compression, and increased PVR. However, that same increase in lung volume also increases the radial traction on parenchymal lung vessels and improves their geometry; decreasing the contribution of parenchymal vessels to PVR [54]. Thus, generally, as lung volume increases, the contribution of alveolar vasculature to total PVR increases, while the contribution of parenchymal vasculature decreases. The net effect is a balance between these two phenomena in which PVR is relatively stable at normal lung volumes [54].

In normal individuals, PVR is optimized (at its lowest point) when the lung is at FRC [54]. It is important to note that lung volumes slightly below FRC may be more deleterious to PVR than lung volumes slightly above FRC. As alveolar units collapse, decreased oxygenation leads to hypoxic vasoconstriction, which further increases PVR above the expected increase from parenchymal lung vessels. Thus, one approach to decreasing RV afterload using MV would be ventilation with relatively low tidal volumes at or slightly above FRC. This would optimize pulmonary mechanics to decrease PVR while also minimizing volutrauma to the susceptible segments of the lung.

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4.2. PEEP and venoarterial extracorporeal membrane oxygenation

In the ideal physiologic scenario during VA ECMO, PEEP would be optimized to maintain FRC thus optimizing PVR, and minimizing the negative effects on RV preload (unless clinically desired). However, little is known clinically about the optimal PEEP in the setting of VA ECMO.

The use of PEEP to maintain FRC is clinically challenging. Helium dilution and other traditional methods of determining FRC are highly impractical in the clinical setting. While techniques involving nitrogen washout or partial CO_2 rebreathing have been proposed, and may be automated on some ventilators, they have not been widely adopted [55, 56]. Thus, "optimal" PEEP is often determined by the PEEP that maximizes oxygenation, improves lung compliance, or decreases lung stress [57]. Optimal PEEP has rarely been studied in the presence of ECMO, and is often extrapolated from studies of ARDS. For example, in animal studies of ARDS, optimal PEEP is often cited as the point at which thoracopulmonary dynamic and static compliance is maximized, which correlates with the PEEP value immediately above that at which FRC begins to decrease [58, 59]. In these studies, PEEP was incrementally decreased to determine the point at which respiratory system compliance decreased—thereby approximating the minimal amount of "open lung" PEEP required to maintain FRC. There is mixed evidence on whether optimal PEEP should be determined using this methodology [60, 61]. Others argue that incremental PEEP combined with dynamic compliance monitoring allows for the simultaneous evaluation of recruitment and compliance [61]. More recent studies using computed tomography-guided optimal PEEP have reported that lung recruitability and the amount of PEEP required to maintain alveolar recruitment are independent and therefore the optimal PEEP may not be related to lung recruitability [62].

PEEP, when it contributes to total intrathoracic pressure, affects venous return to the heart [63]. As PEEP increases above resting pleural pressure, intrathoracic pressure increases; decreasing venous return to the right heart and therefore decreasing RV preload [64]. These effects are often seen as negative, but in the correct setting may be beneficial [64, 65]. For example, patients with afterload-dependent left ventricular (LV) heart failure, including many patients on VA ECMO, may benefit from the decreased RV preload associated with the addition of PEEP, particularly if PEEP is helping to minimize PVR [64, 66]. Conversely, patients with a preload dependent cardiac output (CO) could potentially benefit from lower levels of positive pressure ventilation and PEEP. In this patient population, if PEEP is required, careful attention should be paid to minimizing the effects on cardiac preload.

Many argue that in the ARDS patient, true optimal PEEP does not exist, maintaining that it is not clinically realistic to expect all of the beneficial effects of PEEP to converge on a particular value for a given patient [67]. A similar argument could be extended to patients on ECMO. As such, given a lack of direct evidence, it remains in the hands of the clinician to determine which parameters are most important to optimize for their individual patients.

4.3. Inhaled pulmonary vasodilators and right ventricular function

RV dysfunction is common in patients receiving both VV and VA ECMO. In patients with moderate-to-severe ARDS (likely candidates for VV ECMO), the prevalence of RV dysfunction is approximately 20%. RV dysfunction is more common in patients with pneumonia, those with high driving pressures (≥18 cm H_2O), low PaO_2/F_iO_2 ratio (<150 mmHg), and high $PaCO_2$ (≥48 mmHg); patients who would also be more likely to meet criteria for VV ECMO [68]. Similarly, in LVAD patients (a cohort related to VA ECMO patients), RV dysfunction may be seen in up to 40% of cases [69].

While inhaled pulmonary vasodilators have long served as adjuvant therapies for patients with increased PVR receiving LVADs [69], the data supporting their use in ARDS and VV ECMO is less clear [70]. Inhaled nitric oxide (iNO) is commonly used in pediatric patients with persistent pulmonary hypertension [71], and adults with LVADs [69]. It may temporarily improve oxygenation in patients with acute respiratory failure [72, 73], but has not been shown to improve mortality [70], comes with substantial cost (**Table 1**) and at doses above 20 ppm has an escalating side effect profile [72, 74]. Inhaled aerosolized prostacyclin (iAP) has also been used in the treatment of pulmonary hypertension [75], as well as refractory hypoxemia [72]. Similar to iNO, no mortality benefit has been demonstrated for its noncardiac use [33], and drug delivery depends on delivery setup [74]. However, the cost savings compared with iNO may be as large as 17-fold [76]. Controlled studies on the use of inhaled vasodilators specifically on ECMO patients are currently lacking.

Medication	Administration methods	Dosing	Cost per day
Inhaled aerosolized prostacyclin	Nebulization	5–50 ng/kg/min (can be fixed or weight-based and delivered drug will vary according to setup)	$100–900
Inhaled nitric oxide	Direct gas delivery (diluted with nitrogen and oxygen)	5–20 ppm (range 1–80 ppm)	$2000–5000

Table 1. Inhaled vasodilators dosing and cost [75, 76].

Although inhaled nitric oxide and prostacyclins are well-established therapies for patients with RV dysfunction, associated with increased transpulmonary gradients, there are other agents that may be beneficial. Milrinone, a type III phosphodiesterase inhibitor, typically used intravenously as an inotrope with systemic vasodilatory effects, has been used successfully as inhaled pulmonary vasodilator [77, 78]. The use of inhaled sodium nitroprusside has also been reported [79]. Despite a lack of firm scientific evidence, these agents are often used as adjuvants in patients with RV dysfunction on ECMO (given a plausible physiologic benefit and lack of evidence of harm) and may be considered in patients with elevated transpulmonary gradients refractory to the MV maneuvers described.

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4.4. Venoarterial extracorporeal membrane oxygenation and ventilation of the lungs

Protective and ultraprotective MV settings can lead to hypercarbia. In patients on VV ECMO, this concern is mitigated significantly because of the ECMO circuit's ability to effectively clear CO_2. In the patient on VA ECMO, however, alveolar hypoventilation may be a therapeutic tool.

Patients on VA ECMO have a unique physiology where the pulmonary circulation (Q_p) is unlinked from, and is necessarily lower than, the systemic circulation (Q_s) because a significant amount of the total CO (Q_T) is shunted through the VA ECMO circuit (Q_{ecmo}). This decoupling of the pulmonary circulation from total cardiac output may lead to unusual ventilation and perfusion conditions in the lung. In patients on VA ECMO, the decrease in Q_p can be expected to decrease pulmonary arterial pressures (P_{pa}). This decrease in pulmonary perfusion should increase areas of relative dead space if ventilation is held constant. However, in the lung injured patient, pulmonary perfusion is likely to be heterogeneous worsening V/Q matching and increasing both shunt and dead space. This decreased Q_p and P_{pa} requires some additional considerations when selecting a ventilation strategy for patients on VA ECMO.

Patients on VA ECMO with "normal" alveolar ventilation but a relatively low flow through the pulmonary vascular system (low Q_p) may be at risk for significant localized pulmonary hypocapnia and alkalosis. In a rat lung model, hypocapnia, independently of pH, directly impaired alveolar fluid reabsorption [80]. Hypocapnia also has direct bronchoconstricting effects, demonstrated to decrease lung compliance in small studies of human subjects [81]. Although both impaired alveolar fluid reabsorption and bronchoconstriction have been noted to be reversible with a return to normocapnia, there is increasing evidence that hypocapnia is not innocuous and may exert directly harmful effects to the lungs [53]. Conversely, there is animal data to suggest that therapeutic hypercapnia may attenuate pulmonary inflammation and reduce free radical injury; there is also some support for the therapeutic use of hypercapnea [82, 83]. These positive effects need to be balanced against the increase in PVR and RV afterload that can be caused by hypercarbia. Therefore, while lung protective ventilation is recommended in patients receiving ECMO, the benefit of avoiding localized hypocarbia may make ultraprotective ventilation more enticing. Future studies into the therapeutic benefit of hypercapnia in these patients will be needed to offset the downsides of increased RV afterload.

4.5. Venoarterial extracorporeal membrane oxygenation and arterial blood gas measurements

Arterial blood gas measurements are not normally representative of pulmonary function for patients on VA ECMO. For patients who are on VV ECMO, oxygenated blood from the ECMO circuit is mixed with deoxygenated venous blood prior to entering the right ventricle. Therefore, the patient's lungs increase the oxygen content and clear CO_2 for all of the blood entering the patient's arterial circulation equally. If the ECMO flow is increased on VV ECMO, the oxygen content of all of the patient's blood is increased. Similarly, when native pulmonary CO_2 clearance improves all of the patient's arterial blood will reflect these changes.

For patients on VA ECMO, oxygenated blood from the ECMO circuit is returned to the patient distal to their native pulmonary circulation. Depending the patient's native cardiac output (Q_p), this effectively "isolates" the lung from interrogation via arterial blood gases. It is not unusual, for example, for a patient on VA ECMO to have Q_p equal to 20% of Q_s (with the other 80% coming from Q_{ecmo}). Pulmonary function would then accounts for, at most, 20% of the oxygen content found in the peripheral arterial blood. However, even this estimate may be misleading, as ECMO blood may not mix uniformly with blood ejected from the native heart at the site where it is sampled by as arterial blood gas. As a result, arterial blood gas analysis in a patient on VA ECMO may provide more information about the patient's native cardiac function then native pulmonary function. In other words, the arterial blood gas reflects the patient's native cardiac output (Q_p) relative to Q_{ecmo} more than the effects of pulmonary oxygenation or ventilation. Consequently, making decisions about MV based on arterial blood gas analyses in patients on VA ECMO should be done cautiously.

Ironically, when cardiac output improves in patients on VA ECMO it is normal to find a worsening PaO_2 on arterial blood gas measurement. While this should not occur in patients with satisfactory lung function, as Q_p increases in a patient with poor native lung function (and represents and increasingly higher percentage of Q_s) a lack of oxygenation from the native lung would be unmasked. At that point, it may become necessary to either escalate MV settings or transition to veno-venoarterial ECMO. Conversely, when arterial blood gases indicate a very high PaO_2 (approximating the PaO_2 found in the arterial limb of the ECMO circuit), it may indicate worsening cardiac function rather than improving lung function.

5. Conclusion

The primary goal of mechanical ventilation in patients on ECMO should be optimization of respiratory variables to permit healing from the pathologic state. Much of the data used to establish guidelines for mechanical ventilation strategies in ECMO patients is derived from studies of patients with ARDS. Similar to ARDS, the prevention of VALI remains of central importance to pulmonary recovery for patients on ECMO. Furthermore, by mitigating hypercarbia, ECMO may lift some of the previously encountered limits on MV permitting ultraprotective ventilation to be used.

Hemodynamic effects of MV are important considerations for patients on ECMO. Many patients on both VV and VA ECMO for ARDS have significant RV compromise and may benefit from optimized RV preload and afterload by closely attending to intrathoracic pressures and pulmonary lung volumes [84].

Finally, it is important to consider the possibility that patients on ECMO may not require invasive MV support at all. There has been at least one case report of a patient undergoing VA ECMO support without the need for mechanical ventilation and only minimal analgosedation [85]. Although additional data will need to be obtained before definitive guidelines can help improve the quality of MV during ECMO, it is important to consider that, for some patients, the best strategy for mechanical ventilation is to remove it entirely.

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Chapter 14

Sedation, Analgesia Delirium in the ECMO Patient

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Additional information is available at the end of the chapter

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Abstract

The goal of this chapter is to identify medications frequently utilized for sedation and analgesia in Extracorporeal Membrane Oxygenation (ECMO) patients. In addition to describing basic pharmacologic principles of these medications, we discuss their benefits and disadvantages and explain the effects the ECMO circuitry will have on pharmacokinetics of each drug. We also discuss need for various depths of sedation and the utility of neuromuscular blocking agents. Emerging techniques for achieving appropriate sedation will be identified. An explosion of literature in recent years has led to Intensive Care Unit (ICU) delirium increasingly being recognized as an indicator of poor outcomes in the general ICU population. We discuss strategies to manage this complex and multifactorial issues, and how they can be applied to our particular subpopulation of ECMO patients.

Keywords: sedation, analgesia, agitation, delirium, neuromuscular blocking agents, ECMO sequestration

1. Introduction

The basic principles of initiation and titration of sedatives and analgesics in the critically ill apply to those on Extracorporeal Membrane Oxygenation (ECMO). There are, however, some unique characteristics that pertain to the patient as well as the ECMO device itself that may help guide the intensivist in this particular subset. We will describe the basic pharmacologic principles of commonly used medications for providing sedation and analgesia and nonpharmacologic interventions. Emerging techniques for achieving appropriate sedation will be identified that include ECMO in the awake patient.

The ECMO circuitry has its own unique effects on the pharmacokinetics of each drug. We will also discuss the need for various depths of sedation and the utility of neuromuscular blocking

agents. This chapter also includes a discussion of monitoring and identifying the emerging techniques for management of sedation, analgesia, and delirium that include ECMO in the awake patients.

The reader should be able to identify the most commonly used analgosedation practices in ECMO patients after reading this chapter as well as the emerging techniques. They should understand the effect of the ECMO circuitry on pharmacokinetics of each drug described. We also hope to increase the understanding of the complex issue of Intensive Care Unit (ICU) delirium. The authors hope the readers will use the information to develop a systematic approach for delivering and titrating targeted analgosedation as well as for identifying and managing delirium in the critically ill ECMO patient.

2. Sedation and analgesia

The American College of Critical Care Medicine task force recently revised its clinical practice guidelines for the management of pain, agitation, and delirium in critically ill adult patients [1]. These guidelines recognize that pain is common in Intensive Care Unit (ICU) patients and may lead to both acute and long-term sequelae. In the acute setting, pain increases the proinflammatory balance of cytokines and may contribute to tissue hypoperfusion due to arteriolar vasoconstriction [2,3]. Opiates decrease this stress response and decrease tissue metabolic oxygen consumption [2]. Later, acute pain may lead to PTSD and Chronic Pain in patients who survive their critical illness [4,5]. Sedatives such as benzodiazepines may be used to decrease the stress response; however, they may have negative consequences that could worsen outcomes in ICU patients [1]. The 2013 guidelines thus advocate for pain assessment in ICU patients and an "analgesia-first" approach to sedation [1]. For patients undergoing ECMO, many considerations are similar to those encountered in other critically ill populations; however, certain factors will require additional consideration in this vulnerable group. Ultimately, the choice of medication for sedation and analgesia in a patient on ECMO will rely on multiple pharmacokinetic and pharmacodynamics considerations, clinical circumstances, patient's variables, and the goals of the team managing the patient [6].

Although intravenous opioids have been a mainstay of ICU analgesia for many years, much of the pharmacokinetic data comes from single-dose studies in healthy volunteers [7,8]. ECMO further complicates the situation by altering the pharmacokinetics of analgesics and sedatives [9,10]. The depth and duration of sedation as well as the titratability of the medication(s) selected must be considered. Often the level of sedation tolerated will depend on the patient's stability and sedation goals may vary considerably over time. This is especially true during the initial period after initiation of ECMO. At this stage, greater levels of sedation and sometimes chemical paralysis may be required. At the same time, the patient is frequently still in a state of hemodynamic or metabolic shock. Patients with an open chest due to central cannulation and those who require multiple painful procedures will require a greater degree of sedation to decrease movement and the consequent risk of cannula dislodgement. Medication interactions with the ECMO circuit itself must also be taken into account. Circuit seques-

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tration of highly lipophilic medications will decrease their bioavailability. This issue will be discussed in more detail in a later part of this chapter. Renal and hepatic functions are often impaired in patients requiring ECMO [11]; thus, the half-life of many medications can be prolonged; metabolites and compounding agents such as propylene glycol may accumulate leading to unwanted side-effects.

Route of administration is another concern with critically ill patients on ECMO. Enteral administration is cheaper and decreases reliance on parenteral access but may result in erratic and unpredictable absorption [6]. Submucosal and IM administration is generally unreliable in patients suffering from shock [8]. The 2013 Clinical Practice Guidelines from the Society of Critical Care Medicine consequently recommend intravenous opioids as the first-line drug class of choice to treat nonneuropathic pain in critically ill patients [1]. Intravenous administration provides faster onset, higher bioavailability, and rapid titratability [8]. This proves advantageous when administering medication prior to an invasive procedure or when following a sedation protocol. As the patient progresses in their course, lesser levels of sedation and analgesia may be required and minimal analgesia and sedation may be necessary [12]. At this point, continuous infusions may be discontinued and intermittent dosing of analgesics may prove sufficient.

All the available IV opioids can be titrated to achieve equally effective levels of analgesia [1]; thus the main difference between opiates comes down to cost, pharmacokinetic properties, and pharmacodynamic distinctions [6]. Opioids with agonist-antagonist properties should be avoided in critically ill patients in general due to decreased analgesic efficacy and the potential for triggering withdrawal in opiate dependent patients [6]. Meperidine is an undesirable choice because of potential drug interactions with serotonergic and dopaminergic agents, vagolytic side effects and the buildup of normeperidine, a metabolite which lowers the seizure threshold [8]. Fentanyl, a synthetic opioid with a rapid onset and short distribution half-life, is one of the most commonly used opioids in the ICU [13]; however, because fentanyl and its derivatives, sufentanil, alfentanil, and remifentanil, are highly lipophilic, they are extensively consumed by the ECMO circuit [10]. It has been demonstrated that within hours of administration, nearly the entire dose of fentanyl is lost in an ex vivo ECMO circuit primed with blood [14,15]. With such rapid absorption rates, exceedingly high doses of fentanyl would be required to maintain the desired level of analgesia. Furthermore, a patient previously exposed to high doses of opiates may experience withdrawal if placed on ECMO while already receiving fentanyl analgesia. Fentanyl may thus best play the role of a rapid onset analgesic used for brief but painful procedures.

From a pharmacokinetic standpoint morphine may be the preferred analgesic during ECMO. Because it is hydrophilic, it shows little absorption into the ECMO circuit [14,15]. Morphine was in fact considered the "preferred analgesic agent for critically ill patients" by the older 1995 guidelines for analgesia and sedation published by the Society of Critical Care Medicine [16]. Some of morphine's attributes however make it less desirable for use in the critically ill population. Histamine release from morphine may contribute to bronchospasm and hypotension [6]. In renal failure, accumulation of the active metabolite morphine-6-glucuronide may lead to prolonged sedation. Hydromorphone, a semisynthetic opiate, may thus prove a more

suitable option for IV analgesia in patients on ECMO. Although there is no specific study of hydromorphone's pharmacokinetics in an ECMO circuit, the drug's hydrophilic nature should keep sequestration at acceptable levels. There is no histamine release associated with large doses of hydromorphone, and although the parent drug may accumulate in renal and hepatic impairment, there are no active metabolites. The half-life of hydromorphone is 2–3 h, allowing for either intermittent bolus dosing or a continuous infusion to maintain the desired level of analgesia. Oxycodone, another semisynthetic opioid, may be given enterally for patients who are expected to have adequate absorption from their gastrointestinal tract. It is metabolized by the cytochrome P450 system, thus the dose should be reduced in hepatic dysfunction. Peak effect is reached after approximately 30 minutes to an hour and the duration of its effect is approximately 3–6 h. Oxycodone is relatively hydrophilic and so should not significantly bind to the ECMO circuit.

Analgesic adjuncts such as intravenous (IV) acetaminophen, gabapentin, ketamine, and dexmedetomidine may be used to decrease reliance on opioid analgesics and minimize their side effects. Unfortunately, many of these medications have only been studied on a limited basis in the ICU population, and data for patients receiving ECMO is remarkably limited. IV acetaminophen has been approved by the US Food and Drug Administration (FDA) for use along with opioids for pain management after major and cardiac surgery [17,18]. However, it has not been studied for extended periods of time or in a population with a high incidence of organ failure such as ECMO patients [19]. Additionally, the benefits of acetaminophen may not be as apparent or relevant in a population that requires long-term ICU level care. Neuropathic pain in settings such as burns, neuralgia, and neuropathy tends to be poorly treated by opioids [1]; however, it may respond to medications such as gabapentin and pregabalin that target calcium channels in the central nervous system [6,20]. If patients have been started on these medications due to pre-existing conditions, continuation of the therapy is prudent to avoid withdrawal. Unfortunately, pharmacokinetics can be complicated by unpredictable absorption from the GI tract, renal dysfunction, renal replacement therapy, and uncertain interactions with the ECMO circuit.

Since ECMO is frequently complicated by hemodynamic instability and rapidly escalating requirements for sedation and analgesia [9], ketamine infusions have been used to optimize patient comfort without increasing the depth of sedation or contributing to hypotension. Ketamine is an NMDA antagonist that has been shown to augment opiate analgesia without decreasing sympathetic tone [21]. Limited data exists on long-term ketamine use in critically ill patients; however, some trials have shown decreased opiate usage, improved gastrointestinal motility, and decreased vasopressor requirements in patients treated with ketamine [22]. Similarly, a retrospective review of ketamine in 26 ECMO patients treated at a single center demonstrated a decrease in vasopressor requirements and a decrease in sedation requirements while maintaining the same level of sedation [23]. The doses of ketamine used in the ECMO trial (50–150 mg/H) were substantially higher than those described for analgesia in other studies. Since ketamine is lipophilic, this may be attributable to circuit sequestration of ketamine. A possible concern with ketamine analgesia in patients, who have cardiogenic shock,

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is that the increase in blood pressure may come at the expense of a decrease in cardiac output and an increase in systemic and pulmonary vascular resistance [24].

When an analgesia-based regimen is insufficient to provide adequate patient comfort, or a greater depth of sedation is required due to clinical circumstances, a sedative may be initiated. Just as opiates have been the mainstay of analgesia in the ICU, benzodiazepines have traditionally been used for sedation in critically ill patients. Benzodiazepines activate -aminobutyric acid A receptors in the central nervous system leading to anxiolysis, amnesia, sedation, and an increase in the seizure threshold [8]. Recent evidence however has identified these agents as a leading, modifiable cause of delirium in hospitalized patients and implicated them in prolonging the duration of mechanical ventilation and ICU stays [25–27]. Other agents such as propofol and dexmedetomidine have shown superiority in comparison to benzodiazepines by reducing ICU stays and duration of delirium [26–28].

Of the benzodiazepines, midazolam is frequently used as an infusion for short to intermediate duration sedation of ICU patients [8]. It is water soluble, has a rapid onset of action, and a relatively shorter half-life of 2–5 h. However, with prolonged infusion, midazolam and its active metabolite 1-hydroxymidazolam glucuronide may accumulate, contributing to prolonged sedation and respiratory depression. Liver and renal failure may both prolong this effect. Lorazepam is metabolized by glucuronidation in the liver to an inactive metabolite and is thus less affected by renal and hepatic dysfunction. Since it has a longer half-life of 10–20 h, it may be given as an infusion or bolused on an as needed basis. Midazolam is highly lipophilic and is to a large extent absorbed by the ECMO circuit. In one study 50% of midazolam remained available after 30 min of in vitro ECMO circulation, and only 13% was detected after 24 h [29]. On the other hand, another study evaluated lorazepam and showed that 70% of lorazepam remained at 24 h [61]. Since lorazepam is somewhat less lipophilic, a lesser degree of sequestration would be anticipated.

Of the nonbenzodiazepine sedatives, propofol is extensively absorbed by the ECMO circuit [30]. This property and its tendency to cause hypotension would make propofol a less desirable agent for the sedation of patients on ECMO. Dexmedetomidine, a selective alpha-2 receptor agonist, with sedative and analgesic properties, has demonstrated substantial advantages over benzodiazepines in the care of critically ill patients. Patients sedated with dexmedetomidine are more easily aroused, have a reduced incidence of delirium, decreased sympathetic tone, and less respiratory depression [1,28]. A recent study showed that addition of dexmedetomidine to standard care of agitated, mechanically ventilated patients resulted in more rapid resolution of delirium and more ventilator free days [31]. Dexmedetomidine may not be appropriate in patients requiring a deep level of sedation or those with hypotension or bradycardia [6]. Dosage adjustments will likely be required for patients on ECMO due to significant interactions with the PVC tubing of the circuit [32].

Monitoring levels of sedation and analgesia is crucial in decreasing the likelihood of undesired outcomes [1]. Chanques et al. demonstrated that a protocol for systematically assessing and treating pain and agitation in critically ill patients not only decreased pain and agitation but also decreased the duration of mechanical ventilation and the incidence of nosocomial infections in a mixed medical-surgical population [33]. Although a patient's self-assessment

of pain is considered the "gold standard" for pain assessment, this is frequently difficult to obtain in the ICU setting. Hemodynamic indicators of pain are not validated or reliable [1]. Behavioral scales have been developed as an objective tool for measuring pain in patients unable to communicate. Two scales in particular, the Behavioral Pain Scale and the Critical Care Pain Observation Tool have been found to be both reliable and valid in patients who are unable to report pain but have intact motor function [34]. Although further validation and study is warranted, implementation of these scales has been shown to be feasible and to lead to improved pain management and clinical outcomes [33,35,36]. Whether such protocols of pain assessment and titration would improve outcomes in ECMO patients remains to be seen.

With regard to sedation, the Richmond Agitation-Sedation Scale (RASS) and the Sedation-Agitation Scale (SAS) are considered the most valid and reliable sedation assessment tools for measuring depth of sedation. They demonstrate high inter-rater reliability as well as convergent and discriminant validation in a relatively high number of subjects [1]. The RASS additionally provides a goal for the titration of sedation. In patients who are chemically paralyzed, as ECMO patients may be immediately after cannulation, one of several objective sedation monitors, such as the bispectral index (BIS), Narcotrend Index, Patients State Index or state entropy, should be used [1]. Electroencephalogram monitoring should be used in patients suspected of having nonconvulsive seizures.

3. Neuromuscular blockade and ECMO/ARDS

Neuromuscular blocking agents (NMBAs) have been controversial with regard to their efficacy in treating acute respiratory distress syndrome (ARDS) (we will not discuss the use of NMBAs for the initial intubation of the patient). Due to lack of evidence on a large scale, no clear recommendations exist regarding the use of NMBAs in ARDS. Early work suggested that anesthesia and paralysis cause a ventilation/perfusion mismatch and impair gas exchange [37]. The traditional view on NMBA use in the critical care setting is largely negative, with a number of potential complications associated with this therapeutic modality [38,39]. However, other work over the past 12 years has indicated that use of NMBAs in acute respiratory distress syndrome (ARDS) has been shown to improve oxygenation and decrease mortality in most hypoxemic patients [40]. What is applicable in ARDS is also applicable in ECMO because ECMO is just a further device extension beyond ventilators and high-frequency oscillators [41,42].

Gannier et al. asserted that the hypoxemia in ARDS reaches its worst levels in the first 48 h. In a study of 56 patients with ARDS, improved oxygenation was seen in patients randomized to NMBAs in the first 48 h while receiving volume assist control with a tidal volume of 6–8 ml/kg [43]. Another similar study reported that early NMBA use may contribute to modulation of the pro-inflammatory response [44]. Additionally, a third study of 340 patients where *cis*-atracurium was administered in the first 48 h of development of ARDS found that the NMBAs improved the adjusted 90-day survival and increased time off of the ventilator without increasing muscle weakness [45].

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Two recent meta-analyses based on randomized control trials analyzed the use of NMBAs in ARDS. Neto et al. performed a systematic review of the literature and meta-analysis of studies conducted between 1966 and 2012, and the three abovementioned studies were the only acceptable, high-quality trials performed [46]. The authors concluded, based on these three studies, that that the use of NMBAs in the early stages of ARDS leads to an improved outcome. Alhazzani et al., in a second meta-analysis, demonstrated a decreased mortality rate at 28 days among those receiving NMBAs in early ARDS [47]. They stated that nine patients need to be treated to save one life. They also found that there was a reduced risk of barotrauma and an increased number of days without mechanical ventilation during the first four weeks in those receiving NMBAs. Furthermore, they showed that the PaO2:FiO2 ratio was improved at one, two, and three days.

Physicians must be aware of the potentially important pathophysiological events that can occur with the use of NMBAs in hypoxemic patients [40]. These include increases in thoracopulmonary compliance, functional residual capacity, perfusion of ventilated spaces, and recruitment of portions of the lung that have little compliance. There can be decreases in pulmonary shunt, muscular O_2 consumption, overdistention of high-compliance areas, derecruitment, end-expiratory collapse, asynchronous patient-ventilator dynamics, barotrauma, volutrauma, biotrauma, and atelectrauma. The debate continues as to the best ventilation practices/strategy in ARDS. The problem with NMBAs is that they seem to eliminate the opportunity for the use of spontaneous modes [40].

Additionally, every practicing intensivist must be aware of ICU-acquired weakness (ICUAW), a polyneuropathy and/or myopathy, that occur in 34–60% of the patients with ARDS [48–50]. It was associated with independent risk factors such as organ dysfunction, female gender, length of time on a ventilator, and corticosteroid administration [51], and there is some evidence it is related to hypothermia, hyperglycemia, ICU length of stay, low albumin, and vasopressors [52–54]. While NMBAs have historically been associated with ICUAW, recent evidence contradicts this view, at least with nonsteroidal NMBAs [40].

It is of great importance to use a nerve stimulator for the monitoring of neuromuscular blockade [55]. If the dose of NMBAs is limited, there may be a decrease in the subsequent risks of ICUAW and complications from residual neuromuscular blockade [56]. Peripheral nerve stimulator use is mandatory in order to facilitate appropriate titration of NMBAs. Train of four (TOF) monitoring is the primary method for assessment of NMBA and generally involves the use of supramaximal electrical impulses every 0.5 s applied to the ulnar, facial, or posterial tibial nerve with a resultant identifiable pattern or response [55]. Instruction in TOF monitoring is beyond the scope of this chapter.

Hraiech et al. make the observation that based on the available evidence provided by randomized control trials, NMBAs can be integrated safely into the concept of protective ventilation [40]. The use of NMBAs should be confined to the acute phase of ARDS. Spontaneous breathing must be encouraged when the severe phase has passed and in those with mild and moderate ARDS from the outset. Finally, never forget to sedate a patient in which a NMBA is used. In some countries, such as the USA, this can be a cause of legal action or discipline [57]. While the above suppositions related to NMBAs were not directly related to ECMO, the difficulty in

oxygenating an ECMO patient should at least lead to the consideration of pharmacologic paralysis.

4. Drug sequestration in ECMO

Drug therapy while a patient is on ECMO may be affected by multiple pharmacokinetic alterations, including volume of distribution and protein binding. One of the reasons a patient's volume of distribution may be increased is due to sequestration of drug within the ECMO circuit. Sequestration of drugs into the ECMO circuit is a well-known phenomenon with certain drug properties predicting which medications may bind to the ECMO circuit [15]. Medications that are considered lipophilic, such as propofol, will have a high octanol/water partition coefficient (log *P*) and will be soluble in organic materials such as PVC tubing [15]. Conversely, medications that are considered hydrophilic may be unaffected by the ECMO circuit. In an ex vivo study performed by Lemaitre and colleagues, the concentration of propofol decreased to 11% of expected values after 24 h in a closed ECMO circuit [30], while concentrations of vancomycin, a relatively hydrophilic drug, remained unchanged.

In addition to lipophilicity, the degree of a drug's protein binding may affect sequestration in the ECMO circuit. Shekar and colleagues performed an ex vivo study and determined that drugs with significantly reduced concentrations at 24 h were either highly protein bound (>80%), highly lipophilic (log $P > 2.3$), or both [60]. For medications with the similar lipophilicity, the degree of drug recovery was based on protein binding. Both ciprofloxacin and thiopentone have similar lipophilicity (log *P* 2.3; however, greater reductions were seen in the drug with higher protein binding, thiopentone (88%), compared with ciprofloxacin (4%). This held true when comparing two hydrophilic drugs vancomycin and ceftriaxone. Circuit drug recovery at 24 h was higher for vancomycin (91%) compared with ceftriaxone (80%), which is more highly protein bound. It is unclear of why highly protein bound drugs bind to the ECMO circuit. It is postulated that proteins in the priming solution or in the patient's blood bind to the circuit and then the drug in turn binds to the protein sequestered in the circuit. Drugs that are both lipophilic and highly protein bound may be more prone to sequestration in the circuit. As an example, fentanyl a highly protein bound and lipophilic drug has been studied in ECMO with extreme reductions in concentrations (97%) at 24 h [14]. However, it is still unclear if the presence of both properties results in additive binding within the circuit.

In addition to considering drug properties to predict sequestration, it is imperative to evaluate the ECMO circuit components and their materials. Wildschut and colleagues showed significant differences in drug recovery for both fentanyl and midazolam in neonatal centrifugal pumps compared to neonatal roller pumps [15]. The neonatal centrifugal pumps had nearly one hundred fold increases in drug recovery for fentanyl and midazolam compared with the roller pumps, which may be due to the fact that roller pumps require more PVC tubing, potentially increasing the amount of drug-binding sites. The PVC tubing and membrane oxygenators used in ECMO have both been shown to sequester drug within the ECMO circuit; however, the PVC tubing is presumed to be responsible for the removal of a vast majority of

the drugs [61,62]. It is unclear if saturation of drug-binding sites on the PVC tubing occurs, as studies comparing drug recovery in new and used ECMO circuits show variable results [15,32,61]. The limitation of all of these studies is the short duration (<48 h) of drug exposure to the ECMO circuit. As ECMO has been used clinically for much longer periods of time, it is unclear if or when saturation of the ECMO circuit occurs and how this may impact drug therapy.

Once a patient is placed on the ECMO, drug sequestration is just one of the factors that can cause pharmacokinetic changes. Data for sequestration of drugs in the ECMO circuits are limited, and it is important to understand the majority of the data is derived from ex vivo experiments. When caring for a patient on the ECMO, it is imperative to consider the drug properties, type, and duration of ECMO, and patient's factors that influence drug dosing in order to prevent harm and/or therapeutic failure.

5. Delirium

Often used interchangeably with the term "acute brain dysfunction," delirium has consistently been shown to be an independent predictor of poor short-term outcomes in the critically ill. This includes increased mortality in mechanically ventilated patients as well as prolonged hospital and ICU stays [63,64]. There is now increasing evidence of delirium's ill effects in the long term as well. Long-term cognitive impairment has been linked to the development and duration of delirium in the ICU setting [65].

Delirium is defined as a disturbance in attention and awareness which is an acute change from baseline. Typically, it develops over a short period of time (over hours to days) and fluctuates throughout the course of the day. Patients often present with additional disturbances in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception) [66,67].

There are three subtypes of delirium that are based on the patient's level of alertness: "hyperactive," "hypoactive," and "mixed." Often hypoactive delirium goes unrecognized and has been linked to poorer outcomes [68].

Patients on the ECMO are particularly vulnerable to the development of delirium given their severity of illness and comorbidities. Four independent risk factors for transition to delirium have been identified: pre-existing dementia, history of hypertension, and/or alcoholism, and a high severity of illness at admission [6]. However, there are many other factors that have been associated with this form of acute brain dysfunction—these can be further stratified based on (1) illness (2) patient's factors, and (3) environmental or iatrogenic factors [69] **(Table 1)**.

Care of the delirious patient in the ICU should focus on a three-step approach of monitoring, preventing, and treating delirium. At this time, there is limited data on delirium in the ECMO patients. Further research is essential in determining an evidence-based algorithm in the ECMO patient as there are many unique patient- and equipment-related factors specific to these patients that need to be investigated. The Confusion Assessment Method for the

Intensive Care Unit (CAM-ICU) is the most frequently applied screening and monitoring tool in the ICU setting (**Figure 1**) [70]. Proper assessment will guide further interventions.

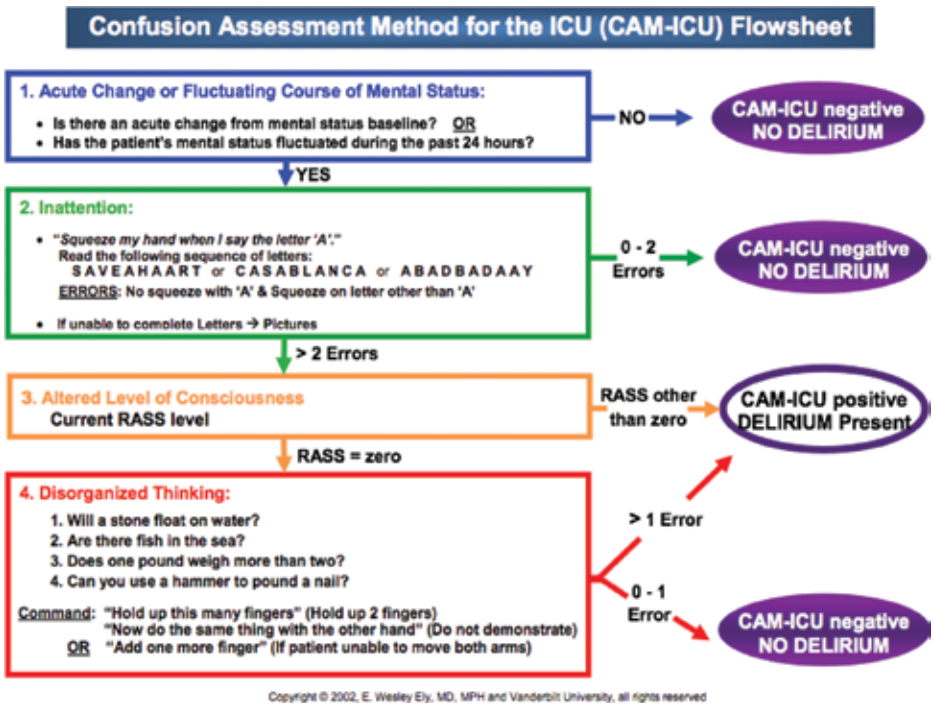

Figure 1. Confusion assessment method for the ICU (CAM-ICU) Flow sheet.

Illness	Patient's factors	Environmental/iatrogenic factors
Cardiovascular instability	Cognitive impairment, pre-existing dementia, and depression	Diagnostic procedures and therapeutic interventions
Acid base disorders	Age > 65	Use of restraints
Electrolyte abnormalities		Sensory deprivation: need for hearing aids and glasses
Sepsis		Sleep deprivation
Respiratory distress		
Acute CNS abnormalities		
http://www.mc.vanderbilt.edu/icudelirium/terminology.html		

Table 1. Factors that have been associated with delirium.

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Primary prevention should focus on decreasing the risk factors and minimizing iatrogenic causes known to increase the likelihood of transition to delirium. Management for both prevention and treatment can be further subcategorized into nonpharmacologic and pharmacologic interventions. These include minimizing loud noises and interruptions, a nonpharmacologic sleep protocol, stimulation during the day, and frequent reorientation to person, place, and time. Pharmacologic prevention of delirium has not been shown to decrease the likelihood of its occurrence [6]. The authors believe this practice may actually lead to over sedation and increase the likelihood of transition to delirium and do not recommend this approach based on existing evidence at this time. Daily assessment of analgesia and sedation requirements and deliberate choices in agents are an important part of the management (**Figure 2**).

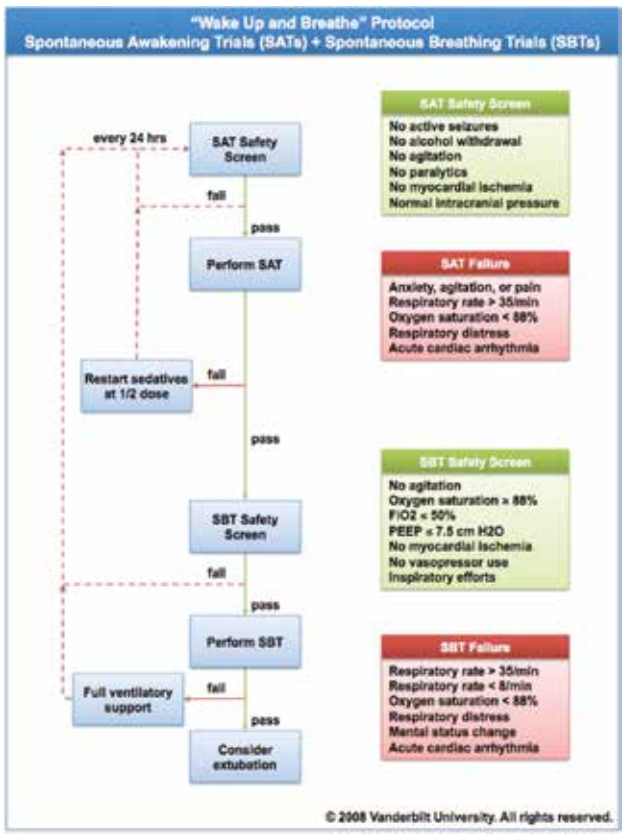

Figure 2. 'Wake up and breathe' protocol.

Benzodiazepines have been proven in multiple ICU settings to increase the likelihood of transition to delirium [71, 72]. Traditionally, they have been used for deep sedation in the ECMO patients because of their relative preservation of hemodynamic stability and unique pharmacologic property of lorazepam that would ensure adequate plasma concentrations in patients on the ECMO. In the future, the use of deep sedation with medications that remain in

the system long after titrating off may lead to this practice being called into question. Deep sedation may be provided with multiple other sedatives that were discussed in the section regarding sedation and analgesia.

As further evidence emerges, prevention and treatment of delirium in the ECMO patient will become more standardized. Early mobilization and liberation from mechanical ventilation should be included in goals for prevention and management of delirium in the ECMO patient. There is compelling evidence that protocol-based treatment with these goals in mind can improve clinical outcomes in the general ICU population [73].

In keeping with the goal of early liberation of mechanical ventilation, many centers are exploring strategies for the use of ECMO in the awake patient. This may decrease the morbidity and mortality associated with mechanical ventilation, deep sedation, and immobility that have traditionally accompanied the use of ECMO. Additionally, it is possible for patients to breathe spontaneously, which might prevent respiratory muscle atrophy. While this has been best documented in the pediatric population and adult VV-ECMO patients being bridged to lung transplantation, this could also be utilized in the VA-ECMO patient. In such a case, close monitoring would be essential to ensure that the patient's breathing pattern and neurologic status are not compromising the patient's hemodynamics and respiratory status [74–76].

6. Conclusion

Increasingly, complications related to sedation, analgesia, and delirium are being recognized as factors that may play a role in morbidity of the critically patient. The decision to initiate medications for sedation, pain control, or agitation should be made by a clinician with intimate knowledge of the most commonly used agents. The use of deep sedation, light sedation, or minimal sedation should be decided upon based on the clinical picture specific to each individual patient on VA or VV ECMO. Pain must be accurately assessed in patients who may or may not be able to verbally express pain scores and titrated to response. The initiation of medications for agitation or anxiety must be decided upon with careful consideration in this critically ill population and the need for these medications should be reviewed on a daily basis.

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Chapter 15

Weaning Strategy from Veno-Arterial Extracorporeal Membrane Oxygenation (ECMO)

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Additional information is available at the end of the chapter

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Abstract

Background: Significant advances in extracorporeal technology have led to the more widespread use of veno-arterial extracorporeal membrane oxygenation (VA ECMO) for cardiac failure. However, procedures for weaning from VA ECMO are not standardized. High death rate after successful weaning shows that many questions remain unresolved in this field.

Objectives: In this review, we discuss data from the literature and propose a strategy to optimize the weaning process.

Data synthesis and conclusions: It is especially important that the VA ECMO is not removed while the patient is still recovering from the condition that necessitated the use of VA ECMO implantation. Damaged organs need to recover before attempting weaning and the patient should be considered hemodynamically stable. The etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Finally, weaning trials using echocardiographic and hemodynamic assessments are indispensable to assess the behavior of the ventricles and to determine whether the VA ECMO can be removed.

Keywords: ECMO, weaning, echocardiography, load conditions

Abbreviations

LV EF	Left Ventricular Ejection Fraction
LV	Left Ventricle

RV	Right Ventricle
VA ECMO	Veno-Arterial Extracorporeal Membrane Oxygenation

1. Introduction

Veno-arterial extracorporeal membrane oxygenation (VA ECMO) is used to support patients with refractory cardiogenic shock [1, 2]. It has been successfully used as a bridge to myocardial recovery, cardiac transplantation, or implantation of a ventricular assist device in patients with overt cardiac failure of various causes, e.g., acute myocardial infarction, end stage dilated cardiomyopathy, viral or toxic myocarditis, complications of cardiac surgery, or cardiac arrest.

After a few days of mechanical assistance, the device can sometimes be successfully removed if the patient has partially or fully recovered from the condition that necessitated the use of ECMO. However, to date, only a few studies have reported strategies for weaning from VA ECMO [3, 4].

Moreover, weaning does not signify survival because 20–65% of patients weaned from VA ECMO support do not survive to hospital discharge.

This review will discuss the various factors influencing survival after weaning in addition to weaning strategies proposed in the literature. Based on this information, we will propose a strategy to optimize the weaning process.

2. Principles of VA ECMO

Patients with significantly impaired cardiac function (with or without impaired gas exchange) require venoarterial configuration for circulatory support. A venous cannula inserted into the right atrium drains blood from the patient into the pumping mechanism of the ECMO circuit. The blood is oxygenated through a membrane oxygenator and perfused in the aorta by a centrifugal pump via a second cannula [1, 2].

The typical configuration for VA ECMO involves femoral venous drainage and femoral arterial reinfusion. With this configuration, the reinfusion jet flows retrograde up the aorta and may meet resistance from antegrade flow generated by the left ventricle.

An ECMO circuit can be set up centrally through the right atrium and the ascending aorta, or peripherally through the femoral vein and the femoral or axillary artery. ECMO can support both heart and lung function and assists the two ventricles.

3. Indications for ECMO

The main indication for VA ECMO is medical cardiogenic shock, including that associated with acute myocardial infarction, fulminant myocarditis, acute exacerbation of severe chronic

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heart failure, drug intoxication, hypothermia, and acute circulatory failure due to intractable arrhythmia.

VA ECMO is also used in some particular situations for patients with postcardiotomy cardiac failure, after cardiac transplantation, or cardiac arrest requiring cardiopulmonary resuscitation [1, 2].

Furthermore, VA ECMO is starting to be used for patients with pulmonary embolism, sepsis associated cardiomyopathy, and pulmonary hypertension [1, 5].

4. Outcome of patients receiving VA ECMO

VA ECMO is used as a bridge to myocardial recovery and cardiac transplantation. It may also be used as "a bridge to a bridge", i.e., before implantation of a ventricular assist device [6]. No randomized controlled trials have compared VA ECMO to other mechanical support systems in patients with cardiogenic shock. However, several nonrandomized studies suggest that the early use of ECMO offers a survival advantage in such circumstances [1, 2, 5, 7–13]. 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 [7–14]. Patients successfully weaned from VA ECMO are defined as those having ECMO removed and not requiring further mechanical support because of recurring cardiogenic shock over the following 30 days [3].

However, 20–65% of patients weaned from ECMO do not reach survival to discharge [3, 7–11]. The most frequent reasons for death are cardiac and multisystem organ failure. These observations demonstrate the difficulties in predicting the future of patients after the removal of ECMO [8, 9].

5. Factors predicting death in weaned patients

Successful weaning from ECMO does not signify patient survival. Several studies have assessed the predictors of death after ECMO weaning in particular situations or settings, mainly in postcardiotomy shock and out-of-hospital cardiac arrest [10, 11, 15]. Markers associated with death after weaning include: door-to-VA 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, obesity, and SOFA score [10, 11, 15]. These death-associated factors reflected the severity and the progression of multiorgan failure at the time of ECMO implantation. They should be considered prior to weaning from ECMO.

6. Factors predicting successful weaning from VA ECMO

Few studies have aimed to identify criteria to predict which patients can be successfully weaned from ECMO.

Fiser et al. studied 51 postcardiotomy patients receiving ECMO to identify factors that could predict when to discontinue ECMO [7]. They found that patients aged over 65 years or with ejection fractions of less than 30% after 48 hours of ECMO were less likely to survive after weaning.

Aissaoui et al. assessed the ability of clinical and echocardiographic variables to predict successful weaning in 51 patients receiving VA ECMO due to medical cardiogenic shock or postcardiotomy shock [3]. Among these 51 patients, 38 hemodynamically stable patients underwent at least one ECMO flow reduction trial, in which the flow rate was reduced to 1.5 L/min under clinical and Doppler echocardiography monitoring. Twenty patients were ultimately weaned from ECMO. High values of arterial systolic and pulse pressure, aortic velocity-time integral, LVEF, and lateral mitral annulus peak systolic velocity were associated with successful weaning. All patients weaned from ECMO had an LVEF ≥ 20–25%, an aortic velocity-time integral of ≥12 cm and a lateral mitral annulus peak systolic velocity of ≥6 cm/s under minimal ECMO support. In this study, successful weaning-associated factors are simple and easy-to-acquire echocardiographic variables evaluating LV systolic function (LVEF and lateral mitral annulus peak systolic velocity) and LV flow (aortic velocity-time integral) (**Figure 1**).

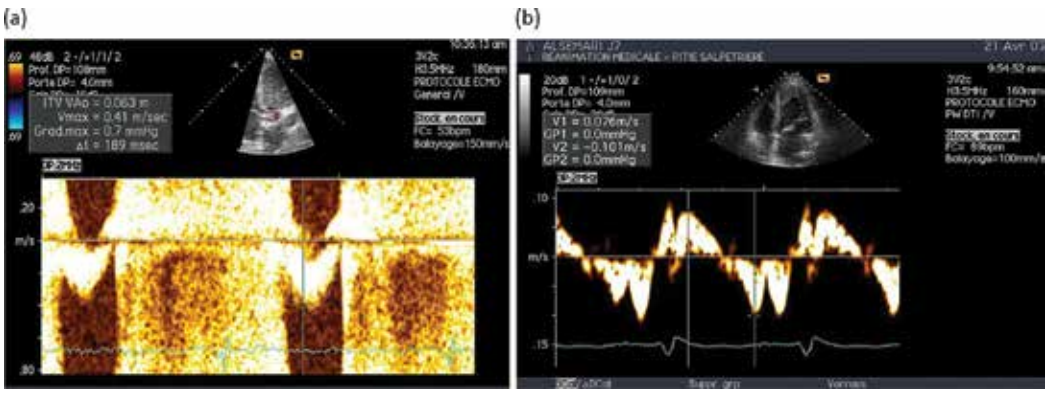

Figure 1. Echocardiographic variables measured by the Doppler method. A. Aortic velocity-time integration obtained by pulsed Doppler measured at the LV outflow tract. B. Lateral systolic peak obtained by spectral Doppler tissue imaging at the lateral mitral annulus.

Luyt et al. examined whether biomarkers could predict cardiac recovery in patients receiving VA ECMO [16]. They studied 41 consecutive patients with potentially reversible cardiogenic shock, and examined circulating concentrations of the N-terminal fragment of the B-type natriuretic peptide, troponin Ic, the midregional fragment of the proatrial natriuretic peptide, proadrenomedullin, and copeptin on days 1, 3, and 7 post-ECMO. There was no difference in

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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.

Thus, the current data suggest that echocardiography is an important tool to determine both the recovery of LV 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 [17,18].

7. Appropriate conditions to attempt weaning from ECMO

According to the Extracorporeal Life Support Organization (ELSO) guidelines, hepatic function should have recovered prior to any attempt to wean patients from ECMO, irrespective of the findings of cardiac assessment [19].

In addition, it is unusual to attempt weaning in the first 72 hours after VA ECMO implantation because damaged organs need time to recover. However, the duration of ECMO may be shorter in cases of drug intoxication, and VA ECMO weaning can be attempted earlier [20–22]. In most previous studies, the mean duration of support was at least of 3.3 ± 2.9 days and was even 8.0 ± 6.0 days in one study [3, 9–11 , 23]. This time period is also necessary to allow the recovery of a potentially "stunned" myocardium [7]. In these studies, the mean duration of support was longer for patients successfully weaned from ECMO than those who were not [3, 11].

It is not necessary to wait for the recovery of renal function. Restoration of acute renal injury after cardiogenic shock can take up to four weeks after the improvement of cardiac output, by which time significant decreases in elevated filling pressures may have occurred [23, 24]. Other considerations include pre-ECMO status (age, comorbidities, cardiopulmonary resuscitation) and the etiology of cardio-circulatory dysfunction, which must be compatible with myocardial recovery (acute myocarditis, acute myocardial infarction, post-cardiotomy, drug intoxication, septic cardiomyopathy) [1, 2, 6].

VA ECMO should not be removed if the patient has not recovered from the condition which necessitated VA ECMO implantation (high volume overload and high doses of inotropic agents). Volume overload must be managed by diuretic 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 [19]. The PaO_2/FiO_2 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% [25]. These measurements should be made with an ECMO flow rate of less than 1 L/minute and a sweep gas flow rate of 1 L/minute. In case of persistent severe respiratory failure despite cardiac recovery, VA ECMO should be switched to VV ECMO [5].

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 [19].

The patient should be considered hemodynamically stable, i.e., they should have a baseline mean arterial pressure (MAP) of >60 mmHg in the absence or at low doses of vasoactive agents, and a pulsatile arterial waveform maintained for at least 24 hours [3].

8. Utility of weaning trials

Weaning trials are essential to assess the behavior of the left ventricle during increases in preload, and to determine whether the ECMO can be removed.

Load conditions can be modified by varying the flow of the VA ECMO centrifugal pump. When ECMO flow is decreased, preload is increased, and afterload is decreased [18].

Aissaoui et al. varied ECMO flow and examined hemodynamic variables of the failed left ventricle in 22 patients receiving VA 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 [18].

A weaning trial is also very important to evaluate right ventricular (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 [3, 4, 17, 18]. 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 [4]. They showed that a weaning trial involving left and right ventricle assessment by transesophageal echocardiography could accurately predict both successful weaning from ECMO and successful left VAD implantation without the occurrence of right ventricular 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 [26].

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9. 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 trans-thoracic echocardiography (TTE) [3], and the second involves hemodynamic transesophageal echocardiography (hTEE) [4].

In the TTE study conducted by Aissaoui et al., an ECMO weaning trial was undertaken daily if: (1) the patient was considered hemodynamically stable, i.e., they had a baseline mean blood pressure of >60 mmHg in the absence or at low doses of vasoactive agents and a pulsatile arterial waveform maintained for at least 24 h; and (2) pulmonary oxygenation of the blood was not compromised [3]. The ECMO flow was decreased to 66% of the initial flow rate for 10–15 min. It was then decreased to 33% for 10–15 min and then to a minimum of 1–1.5 L/min for another 10–15 min.

If mean blood pressure dropped significantly and was constantly <60 mmHg 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 >20–25% and aortic VTI of >10 cm under minimal ECMO support.

In the TEE study conducted by Cavarocchi et al., the weaning trial consisted of four stages and involved hemodynamic transesophageal echocardiography [4]. 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), left and right ventricular function was assessed during the infusion of inodilators (dobutamine and/or milrinone). These drugs were used to assess right ventricle function in patients with LV dysfunction under consideration for LVAD placement. The definitive removal of the ECMO was considered if both LV and RV functions recovered. If LV dysfunction persisted without RV failure, LVAD implantation was considered. An external right VAD placement was considered in cases of isolated, persistent RV dysfunction. If biventricular dysfunction remained, total artificial heart replacement was considered if the patient was a candidate for heart transplantation.

10. Transthoracic echocardiography *versus* transesophageal echocardiography

The weaning assessment requires repeated measurements to be recorded over several days. Echocardiographic variables of LV systolic function (LVEF and lateral mitral annulus peak systolic velocity), LV flow (aortic velocity-time integral), and right ventricular diameters can be used to predict successful weaning. These parameters are factors that are simple and easy-to-acquire with transthoracic echocardiography. For these reasons, the transthoracic approach is a good option because it can be repeated many times [17, 18]. In case of poor echogenicity, the transesophageal echocardiography can be used [4].

11. Hemodynamic assessment during the weaning attempt

Hemodynamic assessment can be useful during the weaning trial. In particular, the presence of volume overload can be determined from measurements of pulmonary capillary wedge pressure and central venous pressure. Such measurements also enable the assessment of cardiac output (cardiac index). Hemodynamic measurements should be performed at full flow, after reducing the ECMO flow to 50% and after stopping the pump.

For patients to be considered for VA ECMO weaning, hemodynamic variables with the pump off should be as follows: cardiac index >2.4 liters/min/m^2, mean blood pressure >60 mmHg, pulmonary capillary wedge pressure <18 mm Hg, and central venous pressure <18 mmHg [13]. The absence of volume overload can also be verified from this hemodynamic assessment. Systolic RV and LV function have to be evaluated by echocardiography.

12. Anticoagulation during the weaning attempt

ECMO weaning and weaning trials are associated with a risk of thromboembolic complications due to blood stagnation during the reduction of ECMO flow. The ELSO recommends that anticoagulant drugs should be continued during the trial, and that the blood lines and access cannulas should be periodically unclamped to avoid stagnation [19]. The activated partial thromboplastin time should be between 1.5 and 2.5 times the normal value [19, 27].

13. Aids to optimize weaning

Some teams assessed the ability of some medications to facilitate weaning from VA ECMO [28, 29].

The Levosimendan was assessed in six VA ECMO patients with the hypothesis that its remaining effects could favor the weaning from ECMO. This inodilator drug was infused in

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the patients 24 h before the planned weaning. In this small study, the use of Levosimendan was associated with an increased rate of successful weaning [28].

In an animal study, the author studied if thyroid hormone supplementation in refractory cardiogenic shock pigs improved abnormalities induced by ischemia-reperfusion, cardiac function, and rate of weaning from ECMO. They found that it improved cardiac function during VA ECMO [29, 30].

These strategies were reported for very small populations or animals and must be confirmed in larger series.

The use of an intra-aortic balloon pump may improve survival in ECMO patients [8, 11]. In a recent study conducted by Petroni et al., the use of an intra-aortic balloon pump in patients receiving VA ECMO restored pulsatility and decreased left ventricular afterload, and was associated with small left ventricular dimensions and low pulmonary artery pressure [31]. No study has assessed the value of intra-aortic balloon pumps during VA ECMO weaning.

14. Proposed weaning strategy

In light of all these data, we propose a strategy to optimize weaning from VA ECMO (**Figure 2**) [32].

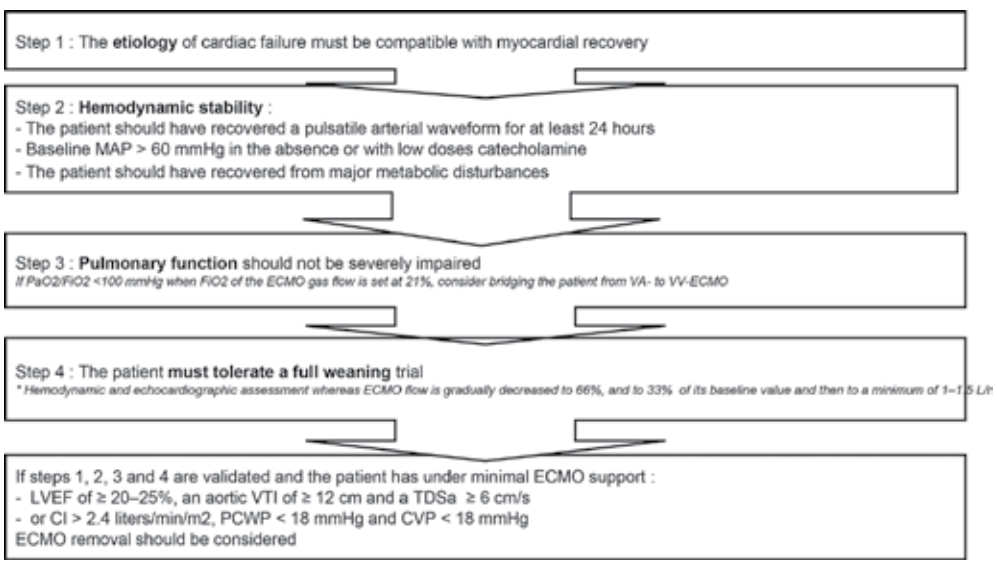

Figure 2. Recommendations for successful weaning from VA ECMO. MAP, mean arterial pressure; VTI, velocity-time integration; LVEF, left ventricular ejection fraction, TDS, tissue Doppler systolic velocity; RV, right ventricle, CI, cardiac index, PCWP, pulmonary capillary wedge pressure, CVP, central venous pressure.

First, some conditions should be gathered.

Hepatic function should first recover.

Patients with end-stage cardiac disease cannot be taken off ECMO. Indeed, the etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Examples include acute myocarditis, acute myocardial infarction, post-cardiotomy, drug intoxication, and septic cardiomyopathy. The PaO_2/FiO_2 ratio should be more than 200.

Volume overload must be managed and doses of inotropic agents should be limited to a minimum.

The patient should be considered hemodynamically stable.

We advocate the use of transthoracic echocardiography over a transesophageal approach. Weaning trials are essential. The ECMO flow should be decreased progressively to a minimum of 1–1.5 L/min for at least 15 min.

The echographic evaluation has to take into account variables assessing LV systolic function (LVEF and lateral mitral annulus peak systolic velocity), LV flow (aortic velocity-time integral), and right ventricular diameters.

A hemodynamic assessment should be carried out to verify the absence of both volume overload and high capillary pressures.

Volume loading can be used to achieve appropriate preload and inotropic support to assess the RV during the weaning trial.

ECMO removal should be considered if the patient does not have end-stage cardiac disease, tolerates the full weaning trial, and has a LVEF of ≥20–25%, an aortic velocity-time integral of ≥12 cm and a lateral mitral annulus peak systolic velocity of ≥6 cm/s under minimal ECMO support.

15. Conclusion

Weaning from VA ECMO remains a difficult decision because it unfortunately does not signify survival for the patient. We proposed a strategy to optimize the weaning process. It is especially important that the ECMO is not removed while the patient is still recovering from the condition that necessitated the use of VA ECMO implantation. Damaged organs need to recover before attempting weaning and the patient should be considered hemodynamically stable. The etiology of cardio-circulatory dysfunction must be compatible with myocardial recovery. Then, weaning trials and echocardiographic and hemodynamic assessments during these tests are indispensable to assess the behavior of the ventricles and to determine whether the ECMO can be removed.

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Section 5

Specific Complications

Chapter 16

Neurologic Issues in Patients Receiving Extracorporeal Membrane Oxygenation Support

Susana M. Bowling, Joao Gomes and
Michael S. Firstenberg

Additional information is available at the end of the chapter

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a well-established therapy for patients experiencing acute severe cardiac and/or respiratory failure. Unfortunately, despite noteworthy improvements in patient selection, technology, and multidisciplinary team management, significant complications are still common. The most dramatic and potentially severe complications are neurologic. However, the incidence of neurologic complications (i.e. embolic stroke, intracerebral hemorrhage, seizures, and anoxic injuries) has not been completely defined. Unfortunately, brain death and neurologic injuries are significant causes of morbidity and mortality for patients requiring an ECMO support. Critical to the management of patients requiring ECMO is a broader understanding of neurologic monitoring along with the clinical assessment and management of neurologic events. It is important to evaluate and potentially intervene early in the event of a neurologic problem to minimize its clinical significance. Hopefully, with a better understanding of the pathophysiology, diagnostic and therapeutic tools, and prevention strategies, the true incidence of neurologic complications can be understood and minimized.

Keywords: ECMO, stroke, neurologic, complications, seizures, brain

1. Introduction

Extracorporeal membrane Oxygenation (ECMO) provides cardiopulmonary support to patients with acute severe refractory cardiac and respiratory failure. In veno-veno (VV) support, blood is drained from the venous system, oxygenated, cleared of carbon dioxide,

and then pumped back into the central venous system (i.e. into the right atrium or cavoatrial junction), is typically used for isolated pulmonary failure. For patients with cardiac failure or combined cardiopulmonary failure, venoarterial (VA) support is typically used. Unlike VV support, in VA support, blood is returned back into the arterial system – often as close to the coronary arteries and/or cerebral arterial system as possible. The specifics, including indications, contraindications, techniques, and outcomes are discussed in other chapters of this text. However, as we will discuss in this chapter, the nuances of arterial vs. venous inflow might potentially affect the management, complications, and outcomes, particularly the risks of cerebral complications of these critically ill and high-risk patients.

Since the initial applications in 1960–70, pediatric patients, neonates, and infants with congenital heart defects or respiratory distress syndrome seem to have been the main recipients of this technique. Better equipment and an exponential increase in the body of knowledge regarding its use have resulted in a dramatic increase in its utilization in the pediatric population. However, more significantly, there has been a tremendous increase in the adult population for both cardiac and respiratory support [1]. ECMO use in adults covers the spectrum of problems ranging from adults who survive cardiopulmonary resuscitation and post-myocardial infarction-associated cardiogenic and septic shock. ECMO is being commonly used for treatment of acute respiratory failure caused by a variety of problems [2–4]. The role of ECMO during the H1N1 pandemic in 2009 is noteworthy, where the use of ECMO resulted in a survival-to-discharge rate of >50–60%; it has been accepted worldwide as an appropriate rescue therapy for these critically ill patients [5]. There is also a growing experience with the use of ECMO as a bridge to heart and/or lung transplantation in highly selected patients in whom end-organ recovery does not occur or is not expected. Conversely, in the world of acute neurocritical care, ECMO has been thought to be of limited use due to the concomitant need for anticoagulation. However, some case reports have successfully utilized this technique in patients who suffered neurogenic pulmonary edema either In the setting of aneurismal subarachnoid hemorrhage (SAH) preceding surgery or traumatic brain injury (TBI), thereby opening the door to speculation regarding the possible future use in these patient populations [6, 7].

Survival rates for patients undergoing ECMO varies dramatically. Results are often a function of the initial primary pathological insult combined with associated comorbidities. As of 2012, the Extracorporeal Life Support Organization (ELSO)—an international organization dedicated to the study of ECMO (including the voluntary collection/reporting of clinical outcomes)—reported survival rate of 50–60% for adult patients with respiratory failure and 39% for cardiac failure patients [8]. However, survival rates in single-center registries have varied from 15% to 59% [4, 9, 10] with some reporting >80% 30-day survival rates [11]. As we will discuss in this chapter, it is also becoming evident that mortality, morbidity, hospital length of stay, patient care cost, and patient discharge to long-term care (LTAC) facilities appear to be closely related to the development of neurological complications. This is particularly true for those who develop intracerebral hemorrhage (ICH), or ischemic stroke (IS), both of which are considered the most frequent complications and had been found in up to nine of 10 brain studies at autopsy for patients who die after ECMO therapy [1, 9, 11]. The incidence of

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neurological complications per se vary in the literature and range from 10 to 50% with some investigators speculating as many as 90% of patients treated with ECMO sustain some form of therapy-associated neurologic injury [1, 9, 11]. This huge disparity is a consequence of the lack of structural algorithms for the neurological evaluation of these patients. Most of the outcome data have been obtained from retrospective reviews and are based on clinical exams, imaging, pathology review, or a combination of several diagnostic assessments. Clinically significant events versus imaging or pathological events with no clinical or neurological consequence have also been poorly defined in these case series.

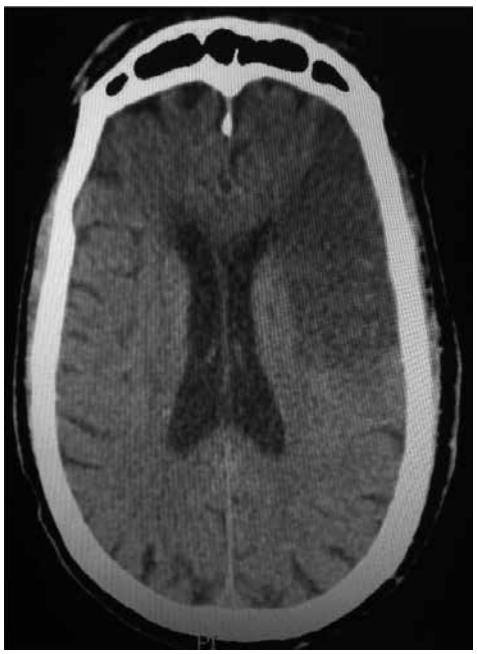

Figure 1. CT scan of a 24-year-old female patient with profound hypoxemia and septic shock. Neurologic evaluation was limited by hemodynamic instability and need for pharmacologic paralysis. Once stabilized on ECMO, imaging demonstrated a large hemispheric stroke of unknown etiology. Despite successful weaning from ECMO and recovery of end-organ function, she remained in coma and family withdrew support.

Regarding the spectrum of neurological complications, embolic ischemic strokes, ischemic watershed infarctions, ICH, SAH, seizures, brain death, and diffuse cerebral edema are the most prevalent, followed by unexplained prolonged coma and hypoxic ischemic encephalopathy. Delirium, severe neuropathy, hearing loss, and vocal cord paralysis are also to be included here; some of these may not be directly related to ECMO, but these are secondary to the need for prolonged intubation, mechanical ventilation, possible tracheostomy, and prolonged ICU stays in these extremely ill and complex patients. Acute disseminated encephalomyelitis has also been reported, but its mechanism remains unclear [9].

Adding to the complexity in the determination of true ECMO-associated complications, patients undergoing ECMO may develop neurological complications prior to the initiation of

ECMO, during, or after decannulation. Patients first receive ECMO in emergent circumstances where neurological examinations are rarely performed. Most patients are paralyzed, sedated, and even undergoing mild to moderate hypothermia during the first 24–72 h giving limited value to the bedside clinical examination [10]. Often critical care teams and neurologists are left with the use of laboratory, electrophysiology, and imaging testing as the only tools for detection of acute complications and determination of outcomes [12]. Unfortunately, sometimes definitive imaging and clinical evaluations cannot be determined until the patient is successfully stabilized (**Figure 1**) or weaned from the ECMO support (**Figure 2**).

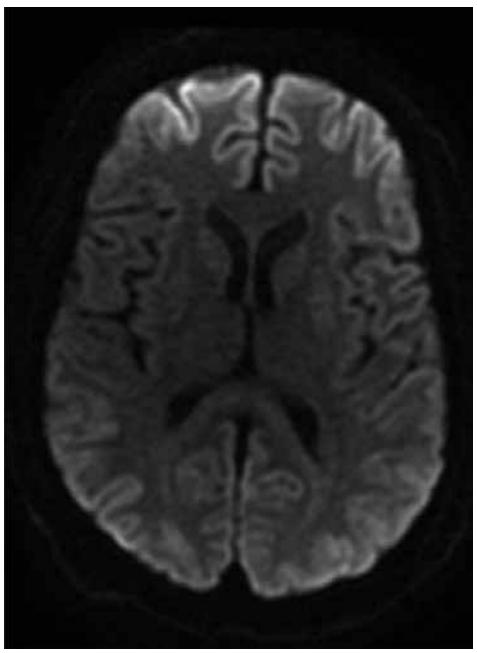

Figure 2. MRI of a 43-year-old patient who sustained an acute respiratory arrest secondary to severe respiratory failure from seasonable influenza. He was transferred immediately to an ECMO center and required 14 days of veno-veno ECMO support. Despite successful weaning from ECMO with good end-organ function, he remained in a coma. Post-ECMO MRI demonstrated an extensive diffusion defect consistent with severe anoxic brain injury/ischemia. Due to these findings and concerns for a poor long-term neurolo The family decided toly withdraw support.

A basic understanding of the physiology of cerebral blood flow (CBF), metabolism, and the management of complications, particularly in the context of long-term extracorporeal support, will be the focus of this chapter as it is critical to understanding the relationships between extracorporeal support and cerebral protection.

2. Principles of cerebral metabolism and blood flow

Under normal conditions, about 15–20% of cardiac output is devoted solely to the brain. This equates to an average perfusion of 50–55 ml/100 g brain tissue/min, with the more metabol-

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ically active areas (i.e., gray matter) receiving higher cerebral blood flow (CBF: 75 ml/100 g brain tissue/min), whereas the white matter exhibits a much lower CBF (i.e. 45 ml/100 g brain tissue/min) [13].

Regulation of CBF in the human brain is exceedingly complex, and although not fully understood, three main regulatory paradigms have been identified thus far, namely *cerebral autoregulation*, *flow-metabolism coupling*, and *neurogenic regulation.* The first mechanism refers to the ability of cerebral arterioles to maintain a constant CBF within a wide range of cerebral perfusion pressures, while a functional hyperemia or coupling between cerebral metabolism in a given area and a matched increase in regional CBF is a well-documented phenomenon. Lastly, the prominent role of *neurovascular units* comprising extensive arborizations of perivascular nerves, endothelial cells, and astrocytes has been increasingly recognized in recent years [14].

Moderate decreases in CBF down to about 30 ml/100 g brain tissue/min are usually well tolerated and do not typically lead to neuronal dysfunction. However, alterations in electrophysiological recordings become apparent once flow drops below 25 ml/100 g brain tissue/min and completely disappear with CBF of ≤12–15 ml/100 g brain tissue/min [15]. The early recognition of hypoperfused but not yet irreversibly injured brain (i.e. penumbra) constitutes one of the main rationales for multimodal brain monitoring of patients undergoing ECMO.

During ECMO support, a number of investigations have shown a significant decrease in cerebral blood flow, with mean flow velocities on transcranial Doppler sonography about half of those predicted for age and gender and a flow pattern characterized by decreased systolic upstroke, lack of dichrotic notch, and continuous diastolic flow [16]. This consistent decrement in CBF with near normalization following decannulation has been ascribed to metabolism-flow coupling secondary to decreased cerebral metabolic rate (i.e. due to the use of sedative agents), cerebral venous congestion secondary to jugular vein ligation (in pediatric and neonatal cases), and left ventricular dysfunction, particularly in patients with venoarterial ECMO [17].

Interestingly, patients who develop intracerebral hemorrhage as a complication of ECMO seem to experience reactive hyperemia with resultant increases in CBF an average of 2–6 days prior to clinical recognition of the acute neurologic injury, likely due to uncoupling of the flow-metabolism regulatory mechanism. In such patients, recent ischemic injury and the use of anticoagulants likely contribute to the elevated risk of cerebral hemorrhage [18].

2.1. Causes of neurological complications during ECMO

As previously mentioned, some of the neurological complications detected during ECMO may be the consequence of the insult that led to the need for ECMO to begin with. The extent of this pre-ECMO injury is impossible to predict prospectively in most cases. These patients are either hypoxic or hypotensive before ECMO and represent a wide range of circumstances, from cardiac arrest to severe respiratory failure and sepsis, thereby making it impossible to

identify common denominators as predictors of outcome in the front end. Data suggest that pre-ECMO lactic acidosis levels >10 mmol/L are associated with poor outcomes as well as the presence of hyperpyrexia, hyperglycemia, and metabolic acidosis. Other potential contributors to the overall injury to the central nervous system prior and during ECMO that may be considered as independent predictors of poor outcome include high ventilatory pressures, disseminated septic embolism, and air embolism.

In children, the ECMO cannulation approach represents a significant risk by altering blood flow after ligation of the internal jugular vein and common carotid arteries. In adults with extensive aortic atherosclerotic disease, arterial cannulation might result in retrograde disruption of debris from the high pressure and flow and result in diffuse microvascular embolic events. Cases of retrograde aortic (and carotid) dissection have also been discussed as the potential causes of acute catastrophic injuries during cannulation and therapy. Other similar procedures that require vascular access complications may includ currently reported causes of embolic neurologic system to oxygenate, development of pump head thrombus, and intracardiac thrombus are among the currently reported causes of embolic neurologic [18, 19].

All patients undergoing ECMO should be systemically anticoagulated. Exposure of blood to non-biological surfaces leads to a chain of biological reactions, increased inflammatory response, and increase in acute-phase reactants. This results in hypercoagulability and potential thrombotic events. This may occur acutely within 24–48 h after initiation of the circuit and can lead to ischemic complications including stroke. Embolic areas that become ischemic are subsequently prone to associated hemorrhagic transformation and intra-cranial bleeding complication. Similarly, these biological reactions, which can increase the bleeding risk via thrombocytopenia, impaired platelet function, and consumption of clotting factors as well as fibrinolysis associated with the therapeutic anticoagulation, increase dramatically the risk for hemorrhagic complications, among which ICH is the most feared [20].

Different considerations for neurologic risk are based upon VA versus VV cannulation. This is particularly true in neonates where VV ECMO has a significantly lower risk for neurologic complications when comparing with VA ECMO [11]. However, the same findings have not been consistently replicated in adult population. It is important to recognize that neurologic complications increase the risk of a poor outcome, but such events are not inherently futile [21]. In the absence of a specific diagnosis of brain death, clinically significant neurologic events are often used for justification to withdraw support on patients requiring ECMO. In one study of 87 patients treated with ECMO (for all indications), 65 experienced a neurologic event. Of these 66, 25 survived to discharge, 25 had support withdrawn, and 16 died. The distinction between the 16 patients who were listed as having “died” versus the 25 who had “support withdrawn” and presumed to have died remained unclear [11]. Given the potential implications and link between neurologic events and clinical outcomes, without a doubt, a better understanding, definitions, and management protocols are necessary.

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3. Specific complications

3.1. Intracranial hemorrhage (ICH)

ICH is most frequently reported in neonates due to easy detection using transcranial Doppler (TCD), with the incidence varying between 26% and 52% and also the cerebellum being the most common location at this age. Independent of the use of ECMO, the overall mortality from ICH is 60–70% [2, 22, 23]. This contrasts dramatically with lower incidence reported in adult population, with 2–19% patients developing ICH. The range in incidence varies depending on the variability in the use of computed tomography (CT) scanning for diagnosis or postmortem pathology data [10, 11, 20]. Conversely, the most common location in adult patients is supratentorial [11]. The existence of proven independent risk factors for ICH is limited at this time. While the duration of ECMO support and site of cannulation did not seem to affect the rates of ICH in adults, a correlation has been noted between female gender, thrombocytopenia, acute renal failure (Cr > 2.6 or the need for dialysis). Being female with thrombocytopenia (<50.000) is the most important predictor. In the case of infants, prematurity, venous cannulation, carotid artery ligation, sepsis, and acidosis carried an increased risk [20]. In adults, outcomes after ICH while on ECMO are felt to be catastrophic with mortality as high as 92.3% [24], but successful outcomes are not uncommon [25] (**Figure 3**).

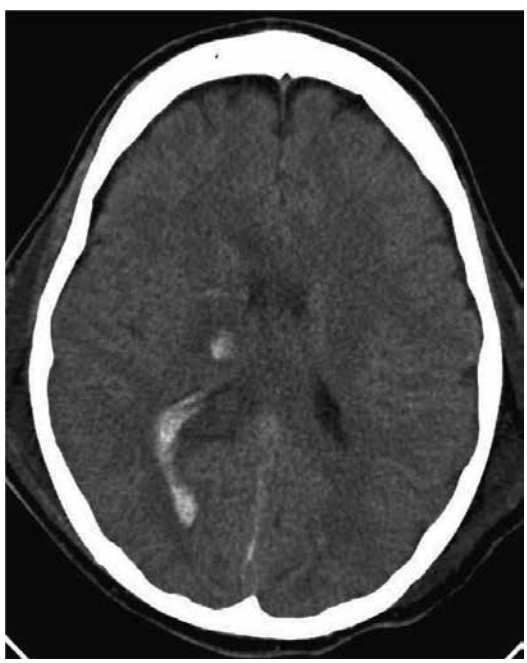

Figure 3. CT scan of a 25-year-old male patient who sustained a motor vehicle accident. He presented with hypothermia and refractory hypoxemia from severe pulmonary contusions. Despite intraventricular hemorrhage, he was supported on veno-veno ECMO for 4 days, 2 days without the use of systemic heparin. He was successfully weaned from ECMO, extubated, and discharged to a rehabilitation facility 21 days postinjury (see text for reference).

3.2. Stroke

Ischemic strokes are among the most common complications in patients on ECMO; however, the true incidence is not known. Data currently available do not differentiate among the mechanism of stroke, characteristics of the infarctions (for example, large vessel occlusions versus microembolization) or the timing of the infarction with regard to outcomes. Events caused by hypoperfusion that may have occurred during CPR leading to watershed infarctions are thought to have completely different presentations, mechanisms, and outcomes as cardioembolic events in patients with CHF, septic embolization, thrombosis caused by hypercoagulability; however, these are lump together at the time of discussing incidence and outcomes. It is therefore impossible to generalize the prediction of the prognosis of ischemic strokes in patients with ECMO, which should be considered in a case-to-case bases, rather than assuming that the presence of ischemic stroke equals poor prognosis.

Limited information exists regarding the true incidence of stroke as mentioned before. The work by Omar HR et al. [26] is worth mentioning, wherein a retrospective review of all ECMO patients at the Tampa General Hospital from 2004 to 2014 has been reviewed for detection of incidence of radiologically proven ischemic stroke. Detecting a 5.8 % of incidence, however in the report, they recognize the limitation of the study based on the lack of systematic studies with the possibility of a falsely low incidence due to underreported events. In this report, the presence of high lactic acid of >10 mmol/L prior to ECMO appeared related to an increased incidence of stroke. Literature review has associated stroke with an increased morbidity of up to 14% [11]. However, unfortunately, most of the adult studies tend to combine mortality for both ischemic and hemorrhagic cases. No stroke correlation has been proven with the duration of ECMO treatment; however, the association with high levels of lactic acid suggests that systemic post-anoxic events is more common than ischemic strokes caused by cardiac embolization. While cannula embolization or air or atherothrombotic embolisms as mechanism are far more common with venoarterial therapies in which abnormal or high pressure (and often retrograde) flows in the arterial system might predispose to this complication. Unless air is iatrogenically introduced into the system, post-oxygenator, the intrinsic filtering of modern oxygenators has virtually eliminated the risk of ECMO circuit-induced embolic complication [27]. Nevertheless, there is clearly much to learn in this specific area of neurologic complications [21].

3.3. Seizures

Post-anoxic encephalopathy, stroke, and ICH are all associated with an increased risk for development of seizures. Therefore, it is not surprising that ECMO patients also have an increased risk. Fever, metabolic changes, and medications all contribute to this risk. Their presentation may vary from post-anoxic myoclonus, focal, generalized seizures to subclinical seizures. Any indication of abnormal motor function, especially while under heavy sedation, or concern should prompt a formal evaluation. Unrecognized seizure activity, if left untreated, can result in catastrophic neuronal ischemia/anoxic injury. Formal recommendations for the systematic use of electroencephalography in this patients do not exist, thereby resulting in a potentially under reported incidence and therefore poor understanding of the role that this

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entity plays in the overall outcome. Continuous EEG recording could assist with the detection of not only seizure activity but also focal suppression of the background that could indirectly herald the presence of a structural abnormality.

4. General brain edema/brain death

The presence of generalized brain edema is clinically heralded by either persistent coma or physical examination findings suggestive of brain death. Systemic conditions resulting in severe hypoxia or hypotension will result in a global decrease in cerebral blood flow or cerebral oxygenation, which if sustained and above what the cerebral autoregulation or metabolic coupling can compensate for, the result can be general brain edema neuronal cell death Many of these patients are diagnosed with general brain edema within 3 days of cannulation for ECMO [11]. This would suggest that is the brain insult suffered during the condition that led to the need for ECMO what cause the injury and subsequent edema. Brain death occurred in 7–21% of the ECMO patients treated in academic centers [28–30].

In one recent series, 295 adult patients treated with ECMO, 21% of patients where given a diagnosis of brain death [24]. Unfortunately, given the retrospective nature of this voluntary registry data, no specific criteria were given to validate the method for making the diagnosis.

Brain death is a formal diagnosis for which there can be little margin of error in assessment. Once these diagnostic criteria are met, the diagnosis is established, which thereby provides both medical and legal grounds for terminating any and all care. Prolongation of therapies after the establishment of brain death is unethical and potentially illegal with grounds for litigation. Because many of the physiologic criteria and responses to bedside testing used for the assessment of cerebral and brainstem function can be influenced by the physiologic benefits of ECMO, the diagnosis of brain death while on ECMO can be challenging. In addition, while several authors have advocated criteria for determining brain death in a patient supported by ECMO, formal guidelines to assist in the making of such a critical, life-ending, diagnosis are lacking. This topic will be further discussed below.

4.1. Neurological monitoring during ECMO

The role of the ongoing neurological assessment while patients are on ECMO support is of particular importance in this patient population due to the high incidence of neurological complications [1, 11, 31, 32]. Findings from neurological monitoring either physical exam, laboratory, electrophysiological, or neuroimaging data have a high probability to result in a change in care plan or goals of care that may definitely lead to change in outcomes and potentially prevent further deterioration. There is no consensus regarding minimal recommended neurological assessment ether prior, during, or after ECMO. Nevertheless, to the extent possible, all patients on ECMO – even when heavily sedated and pharmacologically paralyzed – require very close and frequent neurologic assessment consistent with routine ICU clinical monitoring. Given the high risk and incidence for adverse neurologic complications, as discussed, any and all neurologic changes in patients undergoing ECMO therapy require

early and aggressive evaluation and management. Limited data exist regarding the predictive value of the different monitoring modalities and in particular physical examination prior and during treatment on ECMO outcomes.

4.2. Physical exam

As itor response to noxious stimulation. Most of this could be continued during ECMO support, limited only by sedation and paralysis, in which case, only pupillary studies may be followed. The latest can be done using an automatic computerized measure to avoid examiner variability (**Figure 4**). As with any critical care patient, we suggest the establishment of sedation vacation protocols that would facilitate clinical examination whenever possible. Identification of changes in physical exam findings has been followed traditionally by a need in cranial imaging.

Figure 4. The NPi-200 Pupillometer (Neuroptics Inc, Irvine CA, USA, http://www.neuroptics.com) uses quantitative infrared technology that objectively and accurately measures and trends the pupillary size and reactivity in critically ill patients. Eliminating inaccuracies caused by interpreter reliability. Measurement of NPi, (Neurologic pupillary index), maximal diameter at rest and maximal constriction as well as calculating % change and latency time between initiation of stimulation and onset of constriction. MCV, (maximum constriction velocities, mm/sec) is also calculated in each eye.

4.3. Imaging

Choices for imaging techniques are also limited during ECMO. While in infants, transcranial Doppler (TCD) provides extraordinary bedside imaging data prior to the closure of the fontanels; in adults, cranial computed tomography (CT) is preferred and TCD is limited to assessment of cerebral blood flow dynamics, detection of increase in ICP, and detection of microembolism [33]. Due to the ferrous properties of the ECMO pump and circuit, magnetic resonance imaging while on ECMO is obviously contraindicated.

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4.4. Cranial computed tomography (CT)

Transportation of these patients outside of the ICU is not only technically and physically difficult but also potentially dangerous [34]. For the most part, presumably, only a few patients undergo CT during actual ECMO and most are tested after decannulation. Up to 95 % of the complications found in infants and 85 % in pediatric and adult patients are found in the first 3–4 days on ECMO support, undelaying the need of imaging technique protocols during ECMO [9, 18]. The availability of portable CT scans is of particular use in the ECMO centers. With wider availability of portable CT scanning or easier transport of patient due to more compact ECMO circuit design, the hope is that closer monitoring or more frequent imaging might improve the overall understanding of ECMO therapies on clinical neurologic events and outcomes. Clearly, more comprehensive, and potentially prospective data and studies, are required in this area.

In a study by Marika K et al., 37% of patients who underwent cranial CT scanning during ECMO were found to have either ICH, IS, or generalized brain edema. Imaging findings were not always associated with clinical findings proving underreporting of neurological complications based on clinical exam alone, but the results of CT had a significant impact in clinical management, change in goals of care, and surgical indications [9, 11].

5. Electrophysiological monitoring

5.1. Somatosensory-evoked potentials (SSEPs)

Evoked potentials are electrical signals generated by the nervous system in response to sensory stimuli. In SSEPs, an electrical stimulus is applied to the median nerve at the wrist, the common peroneal nerve at the knee, or the posterior tibial nerve at the ankle, while electrodes are placed along the neuraxis measure latency and amplitude. The median nerve is the most commonly stimulated site and scalp electrodes overlying the contralateral somatosensory cortex record the so-called N20 component of the evoked potential.

The cortical generators of the N20 component are located in the territory of the middle cerebral artery and various studies have correlated decreased N20 amplitude (by >50%) with cerebral hypoperfusion in this vascular distribution [35, 36]. Furthermore, the absence of SSEPs in the setting of cardiac arrest and global cerebral ischemia strongly correlates with poor neurologic outcome, while its presence is not sensitive enough to predict a favorable one [37].

In patients undergoing ECMO, SSEP responses can be asymmetric between right and left hemispheres in up to 15% of cases [38]. Abnormalities (or absence) of the N20 component following median nerve stimulation seem to have a prognostic value for poor neurologic outcome, similar to other instances of global cerebral ischemia [39]. Future studies are warranted to further refine its role in ECMO patients.

5.2. Electroencephalography (EEG)

In major medical centers, frequent or even continuous EEG monitoring of patients with devastating neurologic injuries is becoming commonplace, and patients undergoing ECMO support should not be an exception to this rule. Akin to cardiac telemetry, this form of monitoring ("neurotelemetry") can assist in the identification and early treatment of reversible conditions, which could then lead to improved neurologic outcomes in this patient population. With this in mind, EEG monitoring can serve three main purposes: early identification of cerebral ischemia, recognition of seizure activity, and assisting with prognostication. While a review of the complexities of EEG testing and interpretation are beyond the scope of this chapter, an understanding of the basics – particularly as applied to ECMO patients – is important to clinical management (**Figure 5a** and **b**).

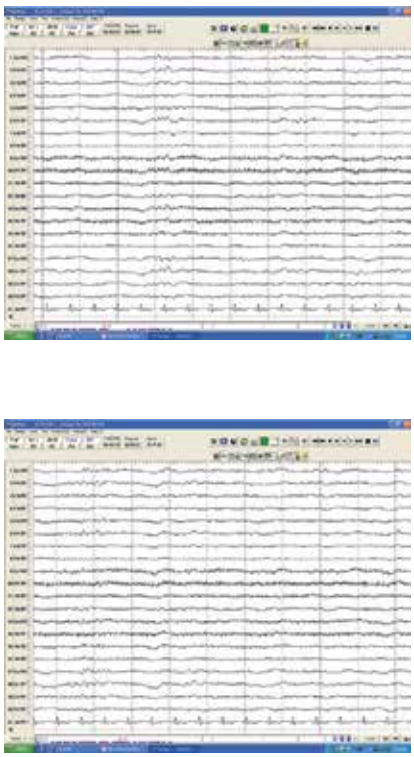

Figure 5. (a) Initial EEG in a 40-year-old, status post cardiopulmonary arrest and initiation of ECMO therapy for acute respiratory failure. CPR had been conducted on and off for over 60 min, at home, during transport to hospital and then during salvage cardiac catheterization. A 16-channel digital EEG recording 1 h after arrival to the ICU demonstrating low amplitude and severe suppression of the background rhythms with superimposed drug effect. No evidence of asymmetry or paroxysmal discharges. (b) Follow-up EEG (approximately 1 week later). A 16-channel digital EEG recording of the same patient with clinical examination concerning persistent coma off sedation and after discontinuation of ECMO. EEG demonstrates generalized suppression, which however has improved in amplitudes. No paroxysmal or asymmetric patterns were detected, despite concern for an asymmetric tone of limbs in the clinical exam. Patient recovered consciousness 48 h, following this EEG and was discharged 2 weeks later with no neurological deficits.

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Following decreased CBF and ensuing cerebral ischemia, EEG changes progress from the loss of faster frequencies (i.e. beta and alpha) to slowing, first with excess theta and, as ischemia worsens, with excess delta waves. Finally, suppression of all frequencies usually indicates neuronal cell death and infarction. Periodic lateralized epileptiform discharges (PLEDs), stimulus-induced periodic rhythmic or ictal discharges (SIRPIDs), unilateral attenuations, and asymmetric triphasic waves can all be seen in patients with cerebral ischemia and aid in early recognition and prevention of irreversible injury [40].

The relatively high risk of both ischemic and hemorrhagic stroke during ECMO support leading to irreversible brain injury can in turn elevate the risk of clinical as well as non-convulsive seizures (as mentioned above). The incidence of clinical seizures during ECMO ranges from 2 to 10%, with somewhat higher rates in younger children [41]. However, the rates of subclinical seizures have been reported to be as high as 17%, including 11% with non-convulsive status epilepticus [42]. Furthermore, the occurrence of seizures seems to be associated with neurodevelopmental disorders in neonates as well as an increased risk of death and worse functional outcomes [43]. Continuous EEG monitoring can help with early identification of ictal patterns and guidance of pharmacologic treatment.

While more studies are still required, the presence of EEG background abnormalities and certain electrographic patterns can aid in the prediction of neurologic outcome after ECMO support. In one study, the presence of an unexplained burst suppression pattern was associated with an increased risk of death or severe disability [44], while low voltage or isoelectric EEG patterns are usually correlated with poor outcomes after global cerebral ischemia [45].

6. Laboratory studies as predictors of neuronal injury and clinical outcome

6.1. Biomarkers as predictors of neuronal injury and clinical outcome

Given that neuromonitoring modalities during ECMO vary widely among institutions and their reported use is limited to small studies, the introduction of plasma biomarkers has emerged as a monitoring tool to aid in outcome prediction for patients on ECMO. An ideal biomarker would have high sensitivity for detection of both ischemic and hemorrhagic injury, provide real-time information, and allow detection of injury at the cellular level that precedes cellular death. While such an ideal marker is not available yet, a number of plasma proteins have been studied to date.

In general, these biomarkers can be divided into three groups, those that reflect glial injury (glial fibrillary acidic protein [GFAP] and S100b), those indicative of neuronal injury (neuron-specific enolase [NSE], intercellular adhesion molecule-5 [ICAM-5], and brain-derived neurotrophic factor [BDNF]), and those suggestive of increased neuroinflammation (ICAM-5 and monocyte chemoattractant protein 1/chemokine (C-C motif) ligand 2 [MCP-1/CCL-2]) [43]. For instance, elevated plasma levels of GFAP in patients with ECMO were associated with a higher risk of brain injury and death (odds ratio of 11.5 and 13.6, respectively) [44]. Similarly, S100B may serve as an early indicator of cerebral complications, in particular intracerebral hemorrhage [46].

In a more recent investigation, a combination of six different biomarkers measured daily for the duration of ECMO demonstrated that GFAP, MCP-1/CCL-2, NSE, and S100b were all significantly higher in patients with unfavorable outcomes and that peak concentrations of GFAP, NSE, S100b, and MCP-1/CCL-2 were higher in non-survivors [47]. Even after adjusting for potentially confounding variables, GFAP and NSE remained significantly associated with unfavorable outcome and NSE associated with increased mortality. Lastly, elevated concentrations of GFAP and ICAM-5 predicted abnormal neuroimaging in this cohort. Taken together, while validation in larger studies is still required, these results suggest that the biomarkers mentioned above could serve as indicators for obtaining further investigations (i.e. neuroimaging) and for initiation of neuroprotective therapies.

7. Brain death examination

The America Academy of Neurology (AAN) has outlined criteria for the determination of brain death [48]. Given the high reported mortality rates—and in particular, brain death—in patients treated with ECMO, a thorough understanding of the definition and determinations of brain death is critical. Despite the importance of the assessment of brain death, objective protocols for patients on ECMO are clearly lacking.

A key component to the determination of brain death in the ECMO patient is the bedside clinical exam—ideally performed by a neurologist or clinician specifically skilled, or credentialed, in the assessment of brain function in ICU patients. The first step is to evaluate for coma. Coma is defined by the lack of all responsiveness, including eye opening or movement (spontaneous or provoked) and motor function in response to painful stimuli (not including spinal reflects). The potentially reversible causes of coma must be excluded (**Table 1**):

Acid-base abnormalities
Electrolyte abnormalities
Endocrine complications
Presence of central nervous system depressants (neuromuscular blockade, suppressive drugs/medications
Hypothermia
Hypotension
Hypovolemia

Table 1. Potentially reversible causes of coma.

Other components to the clinical exam must include assessment of brainstem reflects and cranial nerve testing. Any evidence of brainstem function, or an incomplete assessment, is, by definition, inconsistent with a diagnosis of brain death (**Table 2**).

Continuous electroencephalographic (EEG) testing can be helpful when positive, but external electromagnetic energy sources, including the pump and ECMO circuitry, can make conclusive interpretation of results difficult. Cerebral angiography or nuclear scanning may document the absence of cerebral blow flow, but such testing in patients on ECMO can be difficult

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as transporting the patient and all of the mechanical equipment (ventilator, ECMO system, etc.) to remote areas of the hospital for testing can be dangerous and sometimes logistically impossible (i.e. will all of the equipment, the patient, and necessary clinical staff fit in a transport elevator?).

Prerequisites
Exclude the presence of central nervous system depressant drugs, neuromuscular blocking agents.
Rule out severe electrolyte, acid-base, or endocrine disturbance
Achieve normal core temperature
Achieve normal blood pressure (systolic blood pressure >100 mmHg)
Clinical evaluation of a coma
Absence of eye opening or movement to noxious stimuli
Absence of motor response other than spinally mediated reflexes to noxious stimuli
Absence of brainstem reflexes
Absence of pupillary response to a bright light in both eyes
Absence of ocular movement using oculocephalic and oculovestibular testing
Absence of corneal testing
Absence of facial muscle movement to noxious stimuli
Absence of pharyngeal and tracheal reflexes
Apnea test absence of breathing drive to carbon dioxide challenge
Ancillary tests
Electroencephalography, cerebral angiography, nuclear scan, transcranial Doppler, cerebral tomography angiography, and magnetic resonance imaging/angiogram

Table 2. Brain death criteria.

Formal apnea testing is the key procedure used in the establishment of brain death. The principle behind the test is that the absence of an appropriate respiratory drive, as manifested by an increased in $PaCO_2$ following a CO_2 challenge, is indicative of a potentially irreversible brain-stem injury and, therefore, when positive, supportive of the diagnosis of brain death. Specific criteria must be met prior to attempting an apnea test. In the absence of a history of comorbidities that might predispose to abnormalities in, or blunted responses to, CO_2 retention (e.g. COPD, sleep apnea, and/or morbid obesity), such testing can be diagnostic. Proper conduct of the test involves insuring an adequate blood pressure, preoxygenation with 100% oxygen for at least 10 min with a goal $PaO_2 > 200$ mmHg, normo-capnia with a ventilatory rate of 10 breaths/min, and a reduction of positive end-expiratory pressure to ~ 5 mmHg. If the patient remains hemodynamically stable and blood saturation remains >95%, then a baseline, pretest, arterial blood gas is obtained. The patient is then disconnected from the ventilator, but given a source of oxygen. A continuous source of oxygen, such as a T-piece or cannula placed directly into the trachea, is mandatory to prevent acute hypoxemia and therefore in validating the test. Continuous monitoring of the patient, looking for any evidence of respiratory function, gasping, or chest rise is required. Any signs of initiating a breath during the test should prompt discontinuation of the test and rule out a diagnosis of "brain death". Hypotension or desatu-

ration mandate test termination. After 8 min of observation, a repeat blood gas is obtained. If the PCO_2 level is >60 mmHg or 20 mmHg above the baseline, then the test is considered positive and diagnostic of brain death. Longer periods of apnea (10–15 min), provided the patient remains hemodynamically stable, can be used when the initial blood gas results or clinical findings are inconclusive. Unfortunately, patients who require ECMO support often have physiologic conditions that might further challenge apnea testing. For patients being supported on veno-arterial ECMO, pulsatile flow and blood pressures might be too low as mandated by the AAN prior to attempting an apnea test. As discussed above, a systolic blood pressure >100 mmHg is a prerequisite for apnea testing – a threshold that might be very difficult to accomplish in patients on VA-ECMO with non-pulsatile flow in the absence of significant doses of vasoactive agents. In such circumstances, some experts have advocated using mean arterial pressure of 75-80 mmHg as an appropriate surrogate [49].

To compensate for the confounding influence of the inherent ability of the ECMO circuit to not only provide hemodynamic stability, but more importantly, to maintain adequate oxygenation and normal PCO2 levels, some investigators have proposed modifications of ECMO flows and gas exchange during apnea testing. However, such experiences are limited to a small series of patients. For example, Reddy and colleagues from the Mayo Clinic advocating preoxygenation with 100% oxygen using the ECMO circuit. An initial blood gas is obtained and the ECMO sweep flow was then reduced to 0.5 liters/min to minimize CO_2 removal while providing some degree of continuous oxygen support. It has been advocated that at minimal sweep levels, supplemental oxygen (i.e. given directly to the trachea or airways) is not necessary. With an adequate flow (75–80% of cardiac output) and oxygen through the ECMO, significant decreases in PO_2 and hypoxemia should not occur [47]. Patients were disconnected from the ventilator and after 8 min of observation (for clinical evidence of a respiratory drive), a repeat blood gas was obtained. In two patients, a rise in $PaCO_2$ over 60 mmHg or greater than 20 mmHg above baseline was reported, which confirmed brain death [50]. This group of investigators also reported a series of three critically ill patients on ECMO support, each of who experienced catastrophic neurologic complications consistent clinically with brain death. However, in each of these patients, apnea testing could not be safely performed due to the absence of a defined protocol and hemodynamic instability. Nevertheless, they advocated the use of apnea testing using the protocol they described in their initial patients to assist in the timely diagnosis of brain death in appropriate patients. The benefits of a timely and definitive diagnosis include increased potential for organ donation, decreased resource utilization in futile cases, and most importantly definitive information for the family [51]. Such testing can be difficult because decreasing the sweep gas too much may theoretically result in a significant hypoxemia – and mandate cessation of the test – before a significant increase in $PaCO_2$ can occur to yield a definitive result [52].

Because apnea testing is dependent on intrinsic brainstem response to initiate a breath in the setting of increasing levels of carbon dioxide, it has been suggested that in patients treated with ECMO the addition of exogenous CO2 could safely and more efficiently facilitate this test. A significant concern for apnea testing is the ability to safely provide an oxygen source during testing. Oxygen depravation, particularly in an already compromised and potentially

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brain injured patient, may worsen an anoxic injury. While ECMO is used to eliminate CO_2 (while supplementing oxygen), in theory, ECMO can be used to increase $PaCO_2$ levels. Pirat and colleagues describe the addition of a CO_2 source to the ECMO circuit gas blender and the flow was initiated at 0.5 liters/min and titrated to an end titer of CO_2 of 60 mmHg. The PaO_2 level was then confirmed with blood gas after a period of clinical observation. They suggested that the addition of carbon dioxide was safer by minimizing hypoxemia and hemodynamic instability that might come with the removal of ventilatory (or gas sweep/flow) support [53]. Clearly, while such an approach sounds intriguing and physiologically possible, confirmatory studies are necessary prior to wider use.

8. Conclusions

Without a doubt, ECMO has proven to be a valuable therapy for patients with severe acute respiratory and/or cardiac failure. Early initiation of the therapy, prior to the development of irreversible end-organ function, has been shown to improve outcomes in critically ill patients. Unfortunately, despite improved technologies, earlier and more aggressive therapy and a better understanding of the complex pathophysiology and human-extracorporeal circuit interface, complications are still common. Neurologic complications, either as a function of preECMO comorbidities, presenting illnesses, or as a consequence of the intricacies of either veno-veno or veno-arterial support are unfortunately not uncommon. Such complications can manifest in a variety of anoxic, embolic, hemorrhagic, metabolic, or functional ways and are often a source of significant morbidity and mortality. Early and aggressive monitoring, diagnostic testing, optimization of cerebral perfusion, and oxygenation might not prevent complications, but might limit their impact by allowing for optimization of neuroprotective interventions. In addition, earlier testing might also provide better prognostic implications of therapy and allow for optimal resource utilization, including patient selection for ECMO. As many patients experience neurologic complications, even in the absence of definitive and comprehensive testing, a more thorough understanding of the problem will allow for better management tools and therapies. Hopefully, this review not only illustrates the complex scope of this problem but provides the foundation for further explorations into how to better protect the brain while on extracorporeal membrane oxygenation support.

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Chapter 17

Extracorporeal Membrane Oxygenation and Continuous Renal Replacement Therapy

Bijin Thajudeen, Sepehr Daheshpour and Babitha Bijin

Additional information is available at the end of the chapter

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a supportive therapy, which provides cardiopulmonary and end-organ support in critically ill patients when other measures fail. These patients receive large amounts of fluid for volume resuscitation, blood products and caloric intake, which results in fluid overload and which in turn is associated with impairment of oxygen transport and increased incidence of multiple organ failure especially heart, lungs and brain. It is common to see a decrease in urine output during ECMO that may be associated with acute renal failure. The acute renal failure is a manifestation of multiple organ system failure due to acute decompensated heart failure, sepsis, hemolysis, use of vasopressors/inotropes, nephrotoxic medications, and activation of complement system during ECMO support. It is associated with poor prognosis and higher mortality in ECMO patients. Continuous renal replacement therapy (CRRT) in patients on ECMO provides an efficient and potentially beneficial method of fluid overload and acute kidney injury management. In addition, recent data suggest that the use of CRRT may remove inflammatory cytokine released as a result of circulation of blood across synthetic surfaces during ECMO. The two most common methods to provide CRRT are through the use of an inline hemofilter or through a traditional CRRT device connected to the extracorporeal circuit. The primary objective of this chapter is to discuss current state and role of renal replacement therapy in patients on ECMO and address the controversies and challenges about its application.

Keywords: CRRT, ECMO, mortality, technical consideration, complications

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a modality of treatment used in the intensive care unit (ICU) to improve gas exchange in patients with life-threatening respiratory failure and when conventional therapeutic methods fail to sustain sufficient oxygenation and/or the removal of carbon dioxide. Renal replacement therapy (RRT) is added to the ECMO for the treatment of acid-base as well as electrolyte imbalance and fluid overload. This chapter is trying to discuss the current state and role of renal replacement therapy in patients on ECMO and address the controversies and challenges about its application.

2. Continuous renal replacement therapy

Continuous renal replacement therapy (CRRT) is the mode of therapy adopted in patients with hemodynamic instability in whom intermittent hemodialysis cannot control volume or metabolic derangements. The concept of CRRT was introduced in 1980 and was used mainly for management of critically ill patients with acute kidney injury (AKI). The better hemodynamic tolerance seen in CRRT is due to slower solute clearance and removal of fluid per unit of time. CRRT works on the principle of convection and diffusion. In regular hemodialysis, diffusion is the modality of solute movement and ultrafiltration is added to the process for the purpose of fluid removal. One of the major disadvantages of conventional hemodialysis is that it is done only for limited amount of time, and hence it is difficult to achieve adequate fluid removal in patients who have hemodynamic instability. Moreover, critically ill patients receive large amounts of fluid and in the presence of reduced renal function keeping the fluid balance is a challenge. Hence, CRRT treatment is appropriate for patients with hemodynamic instability, fluid overload, catabolism, or sepsis with acute kidney injury (AKI) [1].

The usual CRRT circuit involves a double lumen catheter, tubing to carry blood from patient's body through the catheter to the CRRT machine, CRRT machine and return tubing which sends the blood back to the patient's body. There are three different modes of doing CRRT: continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). CVVHD works on the principle of diffusion and hence it is inefficient in terms of removal of large molecular weight substances. On the other hand, CVVH works on the principle of convection, which is the movement of water along with electrolytes, and CVVHDF employs both diffusion and convection. Convection is dependent on the pressure and pore size of the membrane. Perfusion pressure generated by a peristaltic pump drives the ultrafiltration of plasma across a biosynthetic hemofiltration membrane. In this process, a high ultrafiltration rate is required to achieve convective clearance and hence replacement fluid must be added to the extracorporeal circuit to restore fluid volume and electrolytes [1].

The solution bags used for doing CRRT contains glucose and electrolytes (including sodium, potassium, calcium, and magnesium) in concentrations that are in the physiologic range. The dose of CRRT is decided based on effluent dose. It is defined as the flow of effluent in ml/kg/

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hr. Based on clinical studies, the recommended effluent dose is 20–25 ml/kg/hr. But at the same time, solute clearance will be affected by clotting and protein deposition on the hemofilter membrane. Anticoagulants are also added to the circuit for the sake of keeping the filter patent for a longer period and usual anticoagulants used include citrate and heparin. The usual blood flow rates on CRRT circuit range 150–250 cc/min.

Although CVVHDF is preferred over CVVH in most institutions, there is no one modality, which is shown to be superior over the other. There might be a theoretical advantage for CVVH and CVVHD in terms of removing larger molecules like cytokines in septic patients. But at the same time, relevant clinical studies have not shown any benefit in terms of improvement in plasma concentration of cytokines or outcome.

3. Technical aspects of combining ECMO and CRRT

There are a number of ways CRRT can be initiated in a patient undergoing treatment with ECMO. The most common technique is using separate vascular access and circuit for CRRT and ECMO. This technique ensures that both systems do not interfere with each other's hemodynamics. One of the disadvantages with this connection is the introduction of a large cannula while the patient is on anticoagulation which increases the risk of bleeding complications at the time of insertion. Additionally in some cases, multiple vascular access sites might be required for doing ECMO which will limit the number of access sites available for establishing CRRT circuit.

Another method is by introducing the CRRT machine or a hemofilter into the ECMO circuit otherwise called as inline technique. Here blood for the CRRT circuit is accessed from and returned to ECMO circuit. Inlet to the CRRT circuit can be before or after the oxygenator or centrifugal pump. Similarly, venous return from CRRT circuit is connected to ECMO circuit before or after the oxygenator or centrifugal pump. In ECMO circuits, using roller pump, a similar setting can be established. Inline hemofilter is used in conditions where the goal is only to remove the fluid and not solutes. The different inline ECMO/CRRT/hemofilter connections are depicted in **Figures 1–5**. Advantages of incorporating the CRRT circuit into the ECMO circuit include (1) cost effectiveness, (2) easy to set up the circuit, (3) use of low blood volume, (4) ease of operability, (5) less resource intensive, (6) avoid additional access placement and ensuing complications especially in the background of anticoagulation use, and (7) the oxygenator in the ECMO circuit can work as an air bubble and blood clot trap for both the ECMO and CRRT circuit (provided both inlet and outlet lines are connected to the ECMO circuit before the oxygenator or to the oxygenator). One of the major disadvantages of incorporating the CRRT circuit into the ECMO line is the interference of blood flow in the CRRT as well as the ECMO circuit. If the CRRT machine's venous (outlet) line is connected to the ECMO circuit before the centrifuge pump, purified blood from the CRRT returns into the negative pressure part of the ECMO circuit. This generates low return pressure alarm in the CRRT machine which may subsequently shut down the machine. The connection of arterial line post pump can trigger too high pressure on the arterial access side of the CRRT generating alarms inside the CRRT machine. Conversely, connections with arterial line pre-pump and

venous line post-pump can trigger low-pressure arterial (access) alarms and high-pressure return (venous) alarms in the CRRT circuit, respectively. These can interfere with pressure monitoring within the CRRT filter reducing the lifespan of the filter. Moreover, the drastic difference in flow and pressure will increase shear stress, activate the clotting cascade and release noxious cytokines. This, in turn, can predispose to the potential life-threatening hemolysis, disseminated intravascular coagulation and enhanced systemic inflammation. The hemolysis through the medium of hemoglobinuria can precipitate renal injury [2, 3].

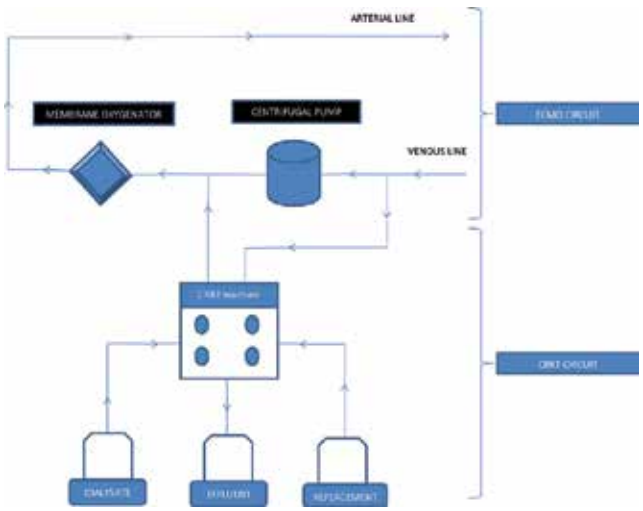

Figure 1. ECMO-CRRT connection with inlet of the CRRT circuit connected to the inlet line of ECMO circuit precentrifugal pump and outlet of the CRRT circuit to the ECMO circuit postcentrifugal pump.

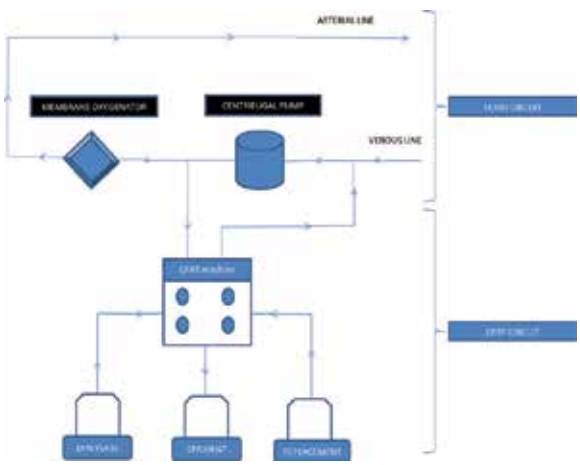

Figure 2. ECMO-CRRT connection with inlet of the CRRT circuit connected to ECMO circuit postcentrifugal pump and outlet of the CRRT circuit to the ECMO circuit precentrifugal pump.

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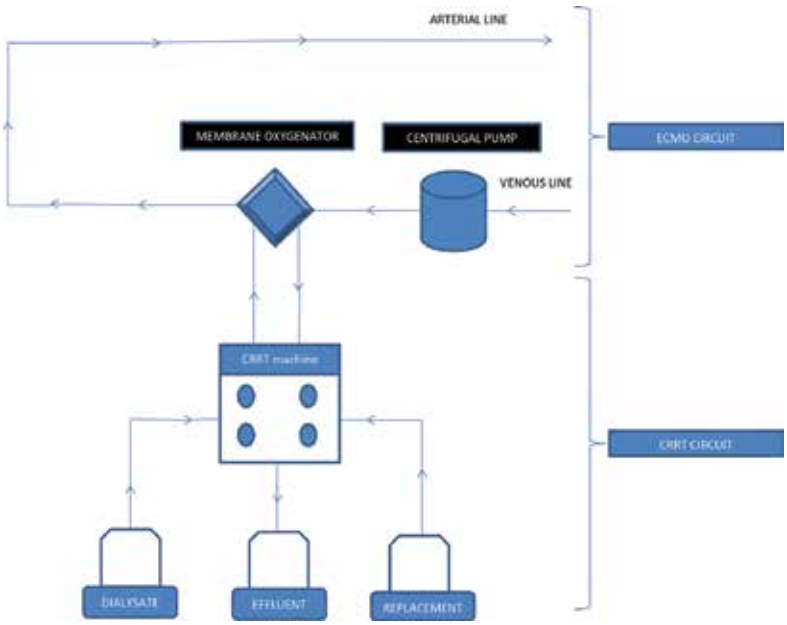

Figure 3. ECMO-CRRT connection with inlet and outlet of the CRRT circuit connected to ECMO oxygenator.

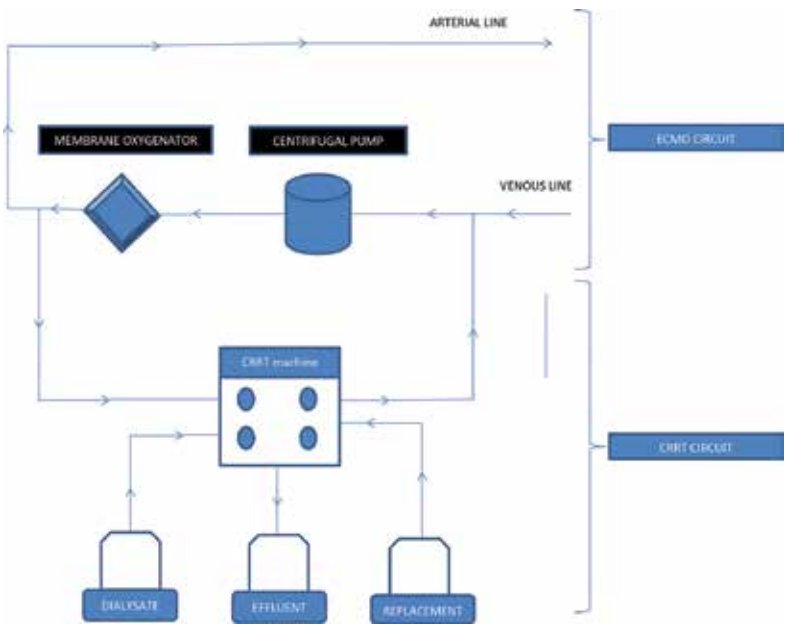

Figure 4. ECMO-CRRT connection with inlet of the CRRT circuit connected to ECMO circuit postoxygenator and outlet of the CRRT circuit to the ECMO circuit precentrifugal pump.

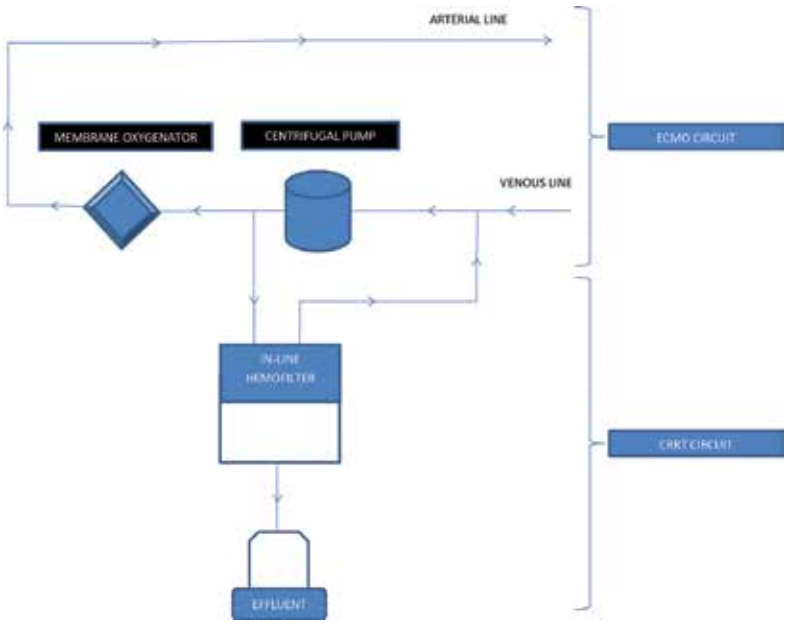

Figure 5. ECMO-hemofilter connection in an ECMO machine with centrifugal pump. The inlet of the hemofilter circuit is connected to ECMO circuit postcentrifugal pump and the outlet of the hemofilter circuit is connected to the ECMO circuit precentrifugal pump.

The flow of blood from and into the ECMO circuit can interfere with blood flow in the ECMO circuit. The support for a patient with severe hypoxemia often requires high blood flow with a pump speed of above 3000 rpm and the flow of blood into CRRT circuit may generate very low pressure particularly when the inflow to the ECMO circuit is limited. This may have clinical consequences in patients with severe hypoxemia where even small fluctuations in the ECMO flow can lead to significant drop in the arterial blood oxygenation [2, 3].

4. Indications and benefits of combined ECMO-CRRT treatment

Classic indications for initiation of renal replacement therapy in patients on ECMO include uremia, acidosis, electrolyte abnormalities, and fluid overload. The most frequently reported indications were fluid overload (43%), prevention of fluid overload (16%), AKI (35%), electrolyte disturbances (4%), and other (2%). Combined use of ECMO and CRRT has many benefits. ECMO by itself is an effective means of providing cardiorespiratory support for these patients. Similarly, provision of ECMO support may prevent the myocardial damage that can be caused by inotropic agents or hypoxia and promote hasty recovery of myocardial function. Both these factors can improve oxygenation and perfusion of organs including the kidneys which in turn may promote early recovery of renal failure. Correction of hypoxia using the ECMO machine can result in the reduction of lactic acidosis. The addition of CRRT (with bicarbonate-based solutions) efficiently manages severe lactic acidosis avoiding fluid overload

and hypocalcemia in hemodynamically unstable patients. Hence combining ECMO with CRRT might result in rapid reversal of the metabolic sequelae of lactic acidosis [4–6].

Another major advantage of combining CRRT with ECMO is the establishment of favorable volume status. Improvement in fluid overload or improving fluid balance has been found to be associated with improved lung function, faster recovery of left ventricular function, better diastolic compliance, better contractility and less myocardial edema and time to weaning off ECMO and ventilator support. In addition to the above-mentioned advantages, initiation of renal replacement therapy (RRT) also allows for the administration of adequate nutrition, medications, and blood products, while avoiding further fluid accumulation. It can correct azotemia, electrolyte imbalance and decrease levels of inflammatory cytokines as well as systemic inflammatory response syndrome induced by ECMO. The latter might be beneficial in terms of decreasing ECMO-induced renal injury [4–6].

5. Timing of initiation of CRRT in ECMO patients

The timing of initiation of CRRT on ECMO is not well defined. Clinical studies have shown a beneficial role of early initiation of CRRT and better outcomes in patients on ECMO. The benefits of early initiation of CRRT in these studies were mostly related to maintenance of fluid balance. Excessive fluid has been found to be associated with prolonged ECMO duration, mechanical ventilation, longer length of stay in the ICU, and mortality. CRRT is an important tool for managing fluid overload in these patients since it enables goal-directed maintenance of fluid balance. Hence, early initiation of CRRT before the onset of fluid overload should be considered in patients on ECMO. Blijdorp et al. observed that initiating preemptive CRRT during ECMO in neonatal patients improved outcomes by decreasing time on ECMO due to improved fluid management [6, 7]. It has also been shown that odds ratio for death was higher when CRRT was started later and longer it was performed.

6. Complications of ECMO and CRRT

Complications of CRRT are related to placement of vascular access, cardiac arrhythmias, electrolyte disturbances, nutrient losses, hypothermia, and bleeding complications from anticoagulation. Common vascular access-related complications include arterial puncture, hematoma, hemothorax, pneumothorax, formation of arteriovenous fistulas, aneurysms, thrombus formation, pericardial tamponade, and retroperitoneal hemorrhage. Electrolyte imbalances commonly encountered include hypokalemia and hypophosphatemia, which may lead to complications such as hemolysis and rhabdomyolysis. In unstable patients with multiple organ failures and fluid overload, although ECMO alone can improve hemodynamic stability by increasing cardiac output via an ECMO pump (in venoarterial ECMO) and improved myocardial oxygenation, the presence of fluid overload can nullify these advantages. Hence, maintenance of fluid balance is very essential in the treatment of critically ill patients

supported with ECMO and CRRT. Experimental and observational data have shown that ECMO itself can have hemodynamic consequences and can interfere with the accurate assessment of volume status. Traditional markers of volume assessment like CVP can be unreliable in these patients. Larsson et al. in his experiments in swine model showed that venoarterial ECMO can decrease systemic venous pressure while maintaining systemic perfusion leading to diminution of central venous pressure measurement [8]. Additionally, volume assessment can be made difficult by the myocardial dysfunction secondary to use of ECMO. Numerous mechanisms have been proposed for the pathogenesis of this phenomenon including low ionized calcium at the onset of cardiac bypass, effect of reactive oxygen species, toxic substances related to the ECMO circuit, various cytokines involved in inflammation during ECMO on the myocardium, retrograde nonpulsatile blood flow, particularly, in the background of underlying left ventricular dysfunction, coronary hypoxia due to higher oxyhemoglobin saturation in the lower extremities compared to upper body (exclusively seen with use of femoral arterial catheter placement in a VA ECMO configuration), and increase in left ventricular afterload. ECMO can additionally result in cardiac stunning as reported by Martin et al. [9]. Pyles et al. [10] in their experiment on Dorset lambs found that initiation of ECMO is associated with decreased hemodynamic and echocardiographic measures of LV function despite accounting for changes in afterload.

The incidence of AKI in patients on ECMO is estimated to be up to 70%. AKI with the need for renal replacement therapy (RRT) occurs in 50% of patients on ECMO and it is one of the most frequent additional organ failures in this patient population. ECMO initiation by itself can lead to acute kidney injury; the mechanisms include ischemia/reperfusion injury from rapid hemodynamic fluctuation in renal blood flow secondary to adjustments in vasopressors or inotropes, pigment nephropathy due to hemoglobinuria resulting from hemolysis secondary to exposure of blood to artificial surfaces, nonpulsatile retrograde renal perfusion, activation of complement system, and accumulation of cytokines. Development of renal failure is a reflection of progression to multisystem organ failure. Moreover, it can predispose to the accumulation of fluid and subsequent volume overload worsening heart and lung disease.

7. Renal recovery and combined ECMO-CRRT

Renal recovery outcome data are limited in patients who have received ECMO and CRRT. Paden et al. [11] in his study of 154 patients on ECMO and CRRT showed that renal recovery was seen in 96% of the patients who survived. Similarly, Meyer et al. [12] in a series of neonatal and pediatric survivors renal recovery was seen in 14/15 (93%) patients. In the study by Thajudeen et al., the renal recovery was found in all patients who survived. In his study, a key observation was that all those patients who had renal recovery were on VA ECMO and they hypothesized that the increased oxygen supply to renal vessels due to its close proximity to heart in the cases of VA ECMO might have played a role in the renal recovery [13]. All these studies show a favorable renal outcome in patients who survive.

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8. Mortality in patients on combined ECMO and CRRT

Clinical studies have shown the association between ECMO, CRRT, and high mortality. In a retrospective study of 200 patients who underwent ECMO 60% (120/200) required renal replacement therapy (RRT) for AKI and the survival of patients requiring RRT was only 17%. Wu et al. [14] made a similar observation where the need for RRT was found to be an independent risk factor for mortality. Although survival in ECMO patients has improved tremendously over the years, the addition of CRRT portends a worse prognosis eliminating this advantage. Severity of illness has been suggested as a cause of high mortality in these patients. It is also speculated that in the presence of multiple organ dysfunction syndromes (MODS), the presence of AKI itself rather than the requirement for CRRT is the independent risk factor for mortality in critically ill patients undergoing ECMO.

There are data supporting an association between delayed start of CRRT and mortality. Kielstein et al. [15] observed that the 90-day survival of patients on ECMO needing CRRT was only 17%; however, at the same time they found that the cohort of patients who had delayed the start of CRRT had higher mortality. Randomized controlled studies comparing early vs. late initiation of CRRT before and after the occurrence of the fluid overload in patients on ECMO would be needed to further address this issue.

9. Antibiotic dosing in CRRT and ECMO

While ECMO and CRRT are important modes of therapy that can sustain life, little is known about the independent effects of ECMO and CRRT on antibiotic pharmacokinetics. Clear data on the dosing of medications are lacking at this point. Patients on extracorporeal circuit usually will have increased volume of distribution and variable clearance. Clinical studies have shown significant alterations in the pharmacokinetics which can result in suboptimal dosing of medications (both under- and overdosing). Inadequate or underdoing of antibiotics can lead to inadequate treatment of sepsis and subsequent increase in morbidity and mortality. Similarly, too high dosing can lead to systemic toxicity. This is significant in these patients who already have high infection-related mortality. Guidelines for dosing of medications should take into consideration the mode of RRT, dose of RRT delivered, blood flow rate, filter material, and surface area of the filter [16–18].

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Section 6

Theory and Development

Chapter 18

Practical and Theoretical Considerations for ECMO System Development

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Additional information is available at the end of the chapter

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a well-established therapy for the temporary substitution for the heart and/or lungs in patients with acute cardiac or pulmonary failure. Recently, the development of portable systems has allowed for implementation of therapy outside of the intensive care units. ECMO can even be initiated in out-of-hospital situations to allow for patient stabilization and subsequent transfer to an appropriate hospital. This chapter will focus on the authors' development of a perfusion system based on a new double chamber pump. This unique design will, in theory, allow for a more complete and effective circulatory support to allow for myocardial and pulmonary recovery. The evolution from bench-top to animal testing will be described. The theoretical issues—including the advantages and disadvantages of roller and centrifugal pump designs—will also be discussed.

Keywords: blood pump, pulsatile flow, resuscitation, circulatory support

1. Introduction

The use of extracorporeal membrane oxygenation (ECMO), as a therapy for acute cardiopulmonary failure, as a form of "substitute" for the full circulation has undergone extensive development over the years. ECMO is a method of temporary replacement for cardiac and/or pulmonary function in cases of failure to wean from cardiopulmonary bypass after open-heart surgery, or cardiac arrest, or acute respiratory failure. As a result, ECMO has the ability

to provide a broad spectrum of support options for patients with severe combined heart–lung, or isolated cardiac or pulmonary diseases. The therapy is based on the temporary replacement of native vital organs (heart and lungs) with artificial analogs (blood pumps and oxygenators) in the clinical scenarios of a critical impairment or temporary absence of their functions [1, 2].

Historic milestones of ECMO development track closely the rapid development of other similar medical technologies over the past 50 years—specifically, the development of a number of clinically useful portable extracorporeal biocompatible blood pumps and membrane oxygenators. As with other developing medical technologies, the initial applications clinically tended to be in extremely high-risk or near-futile cases in which the chances of meaningful survival, even with technical success, was rare. Therefore, as with new methods for external blood circulation (extracorporeal support), membrane oxygenation was used in cases of dying patients and the outcomes, predictably, were poor [3]. Consequently, successful cases were uncommon. Hence, prior to the creation of modern membrane oxygenators, ECMO was rarely used. In subsequent years, the indications for the use of oxygenators widened and ECMO used became more common in children after cardiac surgery and in newborns with severe respiratory distress.

Regarding the terminology, according to the nomenclature of Extracorporeal Life Support Organization (ELSO-1989) a modern term—extracorporeal life support (ECLS) is often used instead of the term extracorporeal membrane oxygenation (ECMO). It is believed that ECLS simultaneously involves the use of other methods of circulatory support—ventricular assist device (VAD) as well as extracorporeal circulation (ECC) circuits [4].

In recent years, despite considerable expense, there is a trend toward a significant increased used of ECLS clinically. Annually published ELSO registry data from the 36,000 patients worldwide treated with ECLS as of 2008, more than 26,000 (72%) survived. Among the patients requiring extracorporeal cardio-pulmonary resuscitation (ECPR) 26% survived.

By 2012, nearly 51,000 patients had been treated with ECLS. Thirteen thousand patients were treated with ECLS for the purpose of circulatory support during the cardiac arrest or cardiogenic shock. Accordingly, in cases of ECPR, a 40% survival rate was observed in newborns, 49% in children, and 39% in adult patients [5, 6].

2. Types of pumps for extracorporeal perfusion

Depending on the clinical application, ECLS support differs in the manner in which the patient is connected to the artificial system, the configuration of bypass circuit, the character of pulse wave, and whether "arterial" or "venous" blood enters into the machine. The components of technical devices themselves also vary considerable as well. In order to understand the essence of the ECLS therapy, it is necessary to consider the configuration of partial (or in some cases full) blood bypass using an artificial pump and the integrated blood oxygenator [7, 8].

Thus, for the treatment of acutely and potentially reversible respiratory, cardiac, or combined failure, refractory to standard therapy, the usage of veno-venous (VV) or veno-arterial (VA),

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ECMO is indicated. While VV ECMO is used in cases of severe respiratory failure, VA ECMO is mainly used with severe heart failure. The differences between them lie in the blood bypass configuration and how the system is "connected" to the patient.

In cases of veno-venous support:

- The blood intake is drained out from the inferior vena cava through a cannula, typically, inserted into the femoral vein. As for the pumping, it is returned into the right atrium by a separate cannula, inserted through the right internal jugular vein or the contralateral femoral vein;
- With a dual-lumen cannula, inserted through the right internal jugular vein (often requiring ultrasound or fluoroscopic guidance), intake of the blood may be performed from the right atrium, pumped it through the second inflow of the catheter with flow directed across the tricuspid valve into the right ventricle.

In cases of veno-arterial support:

- The blood intake is carried out from the right atrium by means of cannula inserted through the right internal jugular vein or either femoral vein, and actively pumping into the arterial system via either the right common carotid artery (in neonates), the axillary artery, or by direct cannulation of the ascending aorta;
- Alternatively, peripheral arterial return can be provided via the femoral artery.

Each of the described methods has its own indications, advantages, and disadvantages. But, in general, veno-venous bypass is used in case of respiratory insufficiency while veno-arterial can be used for either respiratory or cardiac insufficiency [9, 10].

For cardiac arrest and cardiogenic shock developing in the hospital or in an out-of-hospital situation, the complete setup of machine is similar. The system can be assembled as a mobile, portable ECLS system is used for the ECPR [11]. Teams experienced with emergency cardiopulmonary resuscitation are required to successfully use these devices. The purpose of using ECLS during cardiac arrest (ECPR), first of all, is the restoration of blood circulation in the patient. In these instances, artificial pump replace the ejecting function of the heart. In extreme conditions, when surgical venous and arterial cut-downs cannot be performed, percutaneous cannulation of large peripheral vessels (in most cases cannulation of the femoral artery and vein) can be performed. Such configurations of ECLS implementation (veno-arterial), require, by definition, a membrane oxygenator with heat exchanger, in addition to the main blood pumping components [12–15].

When connecting an artificial perfusion system to a living body, an interdependent biotechnical system is created. In other words, complex of biological to mechanical (bio-object) system is created for the purpose of the functional support (temporary or permanent replacement of the function) of vital organs. To understand the processes taking place within this complex system, it is necessary to consider all the parameters of the operation of the artificial components of the system, their technical characteristics affecting the bio-object and disad-

vantages, causing certain morphological and functional changes within the extra and intracorporeal system [10, 11].

Advanced extracorporeal life support (ECLS) systems consist of three main components: the pumping unit, the unit for gas exchange and blood flow temperature support, and the monitoring unit. Each of them, individually, has evolved through a long path of development and formation, with each becoming specific components of the perfusion system. This applies to blood pumps as well, which are key parts of the perfusion system.

From a technical point of view, all the pumping equipment designed for pumping liquids are divided into two main classes: dynamic (so-called continuous current) and volumetric (so-called shifting volume). In dynamic pumps, liquid entered into them and then get ejected in a continuous fashion. The driving force in them becomes inertia. For volumetric pumps—pumping process is based on the alternate filling in with liquid of the operating chamber and ejecting the liquid. For dynamic pumps, there is a characteristics double conversion of energy. On the first stage, mechanical energy is converted into kinetic energy, and on the second stage, the kinetic energy is converted then into potential energy. As for volumetric pumps—liquid is transferred, under pressure at its surface, with periodic changes in the pump chamber volume, which is alternately intercommunicating with the inlet and outlet of the pump. There is only a single energy conversion. It means that mechanical energy is directly converted into potential energy. Both classes of pumps are divided into main subgroups (**Tables 1** and **2**).

	VV ECMO	**VA ECMO**
Advantages	• The ability to avoid arterial cannulation • The ability to use a single cannula • Provides direct pulmonary oxygenation • Improves coronary oxygenation • Reduces the risk of neurological disorders • May improve cardiac output	• Provides cardiopulmonary support • Reduces preload right ventricle (RV) and left ventricle (LV) • No risk of blood recirculation • Better oxygen delivery
Disadvantages	• Adequate oxygenation may be not achieved • There is no direct support for the heart • High risk of recirculation	• Increases LV post-load • Reduces pulse pressure • Coronary perfusion from the left ventricle • Stunning • Certain artery cannulation • Ischemia during peripheral arterial cannulation

Table 1. Comparison of the advantages and disadvantages according to the configuration.

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The basic requirements for blood pumps were generally formulated at the beginning of the second half of the twentieth century. Therefore, at various stages of development of the extracorporeal circulation systems industry, pumps were developed and used.

Dynamic	Volumetric
• Centrifugal	• Piston drive
• Axial	• Membrane
• Vortex	• Screw
• Auger	• Peristaltic
• Jet	• Air driven (pneumatic)

Table 2. Classification of pumping equipment for pumping over fluids.

These pumps belonged to most of the above-mentioned sub-groups with various names assigned to each design (roller, finger, rotor, rotating in a liquid, centrifugal, axial, etc.). Over time, the requirements and details were continually refined and depended on the type of perfusion system as well as their particular purpose.

Hence, we believe that a modern extracorporeal blood pump should have:

- Maximum biocompatibility (biochemical and hemocompatibility);
- Maximum atraumaticity (not to injure the plasma and formed elements—that is, blood cells);
- The ability to pump up to 10 l/min of blood;
- Minimum of dilution (to have a minimum amount of filling blood chambers);
- Discharging (outlet) mode, continuous, as well as pulse (controlled pulse flow, from the predetermined, an internal asynchronous rhythm as well as from ECG or pressure curve—cardio-synchronized counter pulsation);
- Compact and transportable (with minimum size and weight) control system and power supply (battery powered for several hours of continuous use).

Based on these requirements, today, the most commonly used ECLS systems are equipped with either a volumetric peristaltic (shifting volume, for convenience are referred to as roller) pumps, or with dynamic centrifugal pumps [16–18].

2.1. The peristaltic (roller) pumps

According to the latest classification of blood pumps, proposed at the 94th Annual Congress of the American Association of Thoracic Surgery (Toronto 2014), peristaltic (roller) pumps should be attributed functionally to extracorporeal blood pumps as for mono- or biventricular support; for mechanical short-term circulatory support [up to 4 h on the recommendations of US Food and Drug Authority (U.S. FDA)], as a bridge for the heart recovery.

The operating principle of such a pump is based on the fact that the rollers pinch the tube with a fluid and push the liquid forward while moving along the tube. Usually, it consists of a flexible tube, several (usually two or three) rollers, and the surface (track) against which the rollers compress the tube. There are some designs without a bearing surface as the tube is clamped down on the roller due to the tension applied to the roller.

According to the implementation of the housing roller, pumps can be monobloc (Cased pump) and modular (Close-coupled pump). For the monobloc pumps, the drive, the reducer (gear), and control elements are all within a single unitary case housing. In a modular pump, the modules are also connected to each other, but there is no housing. Capacity of the roller pump depends on the rotational speed of the shaft and the number of rollers. The number of rollers also determines evenness of the fluid flow.

The peristaltic pumps, in contrast to other types of pumps, are not equipped with valves or seals. When in use, the pumped blood is in contact only with the inner surface of the tube. Tubes for roller pump, the most important element of the entire pump, determine: system pressure, volume of inflow, capacity, and durability of the pump. The process of the pump service is minimal, as far as only tubes are changed. Its main hydrodynamic characteristics are as follows:

- Ability to set totally or partially occlusive;
- Positive displacement—pushes blood by "squeezing" raceway;
- Automatically calculated blood flow (stroke volume × revolutions per minute);
- Blood flow is not dependent on resistance.

These pump properties, as well as high reliability and simplicity of operation, have resulted in widespread adoption clinically. In addition, it has been successfully used in ECMO systems.

2.2. The centrifugal pump

The centrifugal pump (rotating in the direction of flow) using the same classification system as roller pumps (Toronto 2014) considers extracorporeal or paracorporeal blood pumps. Centrifugal pumps can be used for uni- or bi-ventricular bypass for mechanical circulatory support for cases that require short-term therapy (up to 9 h according to US Food and Drug Authority—U.S. FDA—recommendations) as a stage for the heart recovery.

A centrifugal pump consists of housing with a tapered shape. Positioned inside is a rigidly fixed wheel consisting of two disks with blades fixed between them. They are bent away from the radial direction in the opposite direction in which the wheel is directed to rotate. Pump connection with inlet and outlet connectors to main lines is used to direct blood flow.

The operating principle of centrifugal pumps is as follows: an impeller rotates in the case filled with fluid (i.e., blood). The result from rotation is a centrifugal force that causes flow of the fluid from the center of the wheel to the peripheral areas. This flow creates a high pressure that begins to displace fluid in the outlet pipe. Lowering the pressure in the center of the

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impeller makes fluid to enter the pump through the inlet. Thus, the work for continuous fluid supply is performed [19].

Centrifugal pumps may have a different number of impellers, the shape and number of blades, the slope and volume of the housing cone, the number of rotor rotations per minute (1000–4000 rpm), and so on. But, regardless, the operating principles of centrifugal pumps remain the same—the fluid shifts are performed by the centrifugal force caused by rotating the impeller in the fluid. This last fact is extremely important from the point of view of a blood trauma. However, technological advances and the introduction of new coating materials for the surfaces that are in direct contact with blood, significantly reduced the risk of a blood trauma. The innovation in coating surfaces has resulted in a large number of structurally modified centrifugal pumps (Roto Flow (Jostra); Sorin (Revolution); Delphin (Sarns); CentriMag (Levitronix); Capiox (Terumo); BioMedicus, BP-80 Biopump (Medtronic); Nikkiso (Nikkiso), etc) into clinical practice. In spite of such developments, the hydrodynamic characteristics of these pumps are not significantly different from each other and they generally have the following characteristics:

- Unlike roller pumps, they are totally non-occlusive
- Passive displacement—Cones or impellers create kinetic energy using centrifugal force of fluid constrained vortexing
- Revolutions per minute are proportional to resistance
- Blood flow is inversely proportional to resistance
- Priming volume 30–60 ml
- Blood flow rate 5–10 lpm
- Minimal surface area
- Low blood transit time
- No stagnant areas

Considering the above-mentioned pump characteristics, operation, and management of these pumps require specific conditions, namely

➢ They are preload and after-load dependent, that is, an increase in downstream resistance decreases forward flow delivered to the patient.
  - This has both favorable and unfavorable consequences.
  - Flow is not determined by rotational rate alone, so a flow meter must be incorporated in the arterial outflow to quantify pump flow.

➢ When the pump is connected to the patient's arterial system but is not running, blood will flow backward through the pump and out of the patient unless the arterial line is clamped.
  - This can cause reverse flow (left to right shunt), exsanguination of the patient or aspiration of air into the arterial line (e.g. from around the purse string sutures);

- Thus, whenever the centrifugal pump is not running, the arterial line MUST be clamped!

➢ Blood flow is dependent on:

- Revolutions per minute's (within limitation as increased rotational rates can result in over pressurization and cavitation);
- After-load;
- Pre-load.

Over the years, there has been a vast accumulated experience in the experimental and clinical use of these pumps in a variety of perfusion systems. Each pump has specific advantages over other types of blood pumps. However, each of them is also characterized by the specific disadvantages that are manifested in the course of their operation—especially during prolonged and long-term applications. Complications, inherent to the specifics of each pump, are associated with the peculiarities of their construction and therefore are hard to overcome.

2.3. Disadvantages and complications inherent to used pumps

The literature relating the history of the blood pump development shows a difficult, controversial path, passed by researchers from the second quarter of the last century to the present day. Trying to reproduce the work of the heart by the means of artificial analog has been initially implemented in two directions:

- The maximal work of artificial pump is according to the basic parameters of native heart operation (these systems were known for high complexity, difficult to manage, technological inaccessibility, and high prices)—hence, widespread clinical implementation has not been reached (mainly concerns pumps, shifting volume);
- The complete detachment from the morphological and physiological identity in favor of the simplicity of design, practicality, physiological adequacy, and affordability (such designs had been intensively developed and attained clinical application), while continuing to improve on all of the basic characteristics as described above.

Technical advances along with the introduction of new materials and technologies into clinical practice have led to the rapid development of industries focusing on artificial perfusion. A major area of this focus has been regarding therapies directed to advancing ECMO and ECPR. There are generalized advantages of different pump designs and perfusion benefits achieved as well as the complications and potential disadvantages related to their design. While analyzing the advantages related to the clinical application of roller and centrifugal pumps, we should note the existence of "old" deficiencies and complications, inherent in these pumps. This is interdependence of blood inflow and outflow parameters, lack of counter pulsation, potential for blood trauma, and other problems reflect the inherent limitations of all extracorporeal systems [20].

These theoretical disadvantages limit, to some extent, the effectiveness of such perfusion systems and the clinical applications in which they are being used. In situations, when the perfusion system is used for the treatment of respiratory insufficiency, the main function of

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oxygenating blood is performed by a membrane oxygenator. The blood pump then functions in an auxiliary role by serving as a means of transporting blood inside the complex biotechnological system. With veno–veno perfusion, non-pulsatile blood flow, implemented by the pump, is quite acceptable, when the oxygenation (and elimination of carbon dioxide) function of the impaired lung is replaced. A significant disadvantage of such bypass scheme is the risk of blood recirculation, which can partially reduce by modifying bypass circuit. Recirculation is where the inflow and outflow cannulas are physically close to one another and the suction of the outflow cannula actively drains the inflow. An example would be dual-lumen cannula, draining the blood from the right atrium with one lumen and with the other lumen, directed across the tricuspid valve into the right ventricle pumping the blood in which any misdirection of inflow blood is aspirated back into the drainage lumen.

The needs of the pump are greatly increased during combined cardiopulmonary insufficiency, when in addition to the needs of gas exchange replacement (i.e., lung function), the need for cardiac pumping function is also required. In such patients, the veno-arterial bypass configuration, pumping oxygenated blood directly into the aorta (or a major branch—such as the iliac, axillary, or femoral arteries) is used. This configuration allows for replacing the oxygenation function of the injured lung and simultaneously reducing the pre-load of the right heart. However, at the same time, due to the necessity of continuous shifting of the blood volume into the aorta, the after-load of the left ventricle myocardium is increased. This is an important downside of the VA support, particularly evident in patients with left ventricular myocardial dysfunction. The solution was found while using intra-aortic balloon pump (IABP) using counter pulsation in the thoracic aorta and reducing post-load of the left heart.

2.4. Extracorporeal cardio-pulmonary resuscitation (ECPR)

Since the beginning of the twentieth century, ECLS has been intensively for circulatory support in the cases of cardiogenic shock or cardiac arrest. ECLS can be applied in a variety of clinical settings—such as in out-of-hospital conditions. In cases within the hospital setting, determination the indications for use, implanting the ECLS system, and managing its operation is provided by qualified hospital staff. In out-of-hospital conditions, these activities are performed by specially trained teams of medical and technical personnel, emergently called to the scene of a witnessed cardiopulmonary arrest [21–23]. In cases where conventional cardiopulmonary resuscitation (CPR) is ineffective, an essential component of success is the speed and quality of the initiation ECLS machine and restoring systemic circulation. This more aggressive approach to extracorporeal cardio-pulmonary resuscitation (ECPR) has no other alternatives. According to recent literature, this approach is considered to be the most effective, as is quite justified from etiological and pathogenic points of view. This is confirmed by encouraging outcome data, accordingly, successful ECPR cases exceeds 60% on average, while same outcomes of the standard CPR varies—often within the range of 15% [6, 24].

The bypass configuration during ECPR is veno-arterial, but there can be used different cannulation sites. In order to connect the perfusion system, options include the femoral vessels (arterial and/or vein), jugular vein and carotid artery (inflow connection) or a combination thereof (mixed connection). Moreover, the careful selection of the cannula to ensure adequate,

smooth, and even flow of blood to the pump from the venous bed and then pumping, according to the predefined hemodynamic requirements to a particular arterial tissue bed is essential. Modern venous cannula and technique of great vessel cannulation allow for delivery of up to 70% of the circulating blood volume (CBV) through the common jugular vein from the right atrium. At the drainage location of the end of venous cannula (when it is located not in the right atrium, but in the lumen of a vein), the prevention of the suction of the venous walls should be considered, which is achieved by controlling the value "pressure gradient," in addition to using special cannulas to avoid such "suction events." Depending on specific ECPR method, in most cases for returning blood (particularly in terms of out-of-hospital conditions), the femoral artery is used. In the case of veno-arterial ECMO oxygenated blood is pumped into the aorta in a retrograde manner. Therefore, depending on position of the end of the cannula, oxygenated blood is mainly returned to the distal part of a patient's body, and the brain and ventricular myocardium are still in more unfavorable perfusion condition. In such cases, we speak of uneven redistribution of oxygenated blood at the level of the aorta and its branches, called the "Harlequin Effect." Thus, in theory, the optimal location for the location of the end of the cannula should be considered as the ascending aorta or arch.

Depending on the specific ECPR approach, important is the providing the appropriate system for safe, quick, and easy to initiate therapy. Requirements for the system include portability, mobility, flexibility, minimum weight, a complete set components, and ease of management. Obviously, affordability is also important. The basic unit of this system, of course, remains the blood pump. Modern devices in most cases are equipped with centrifugal pumps. The relatively small size, a small amount of filling, reliable control, and monitoring of the entire system all increase the chances of clinical success and a good outcome. However, considering the fact that centrifugal pumps rotate in the flow and belong to a class of dynamic pumps, they are capable of producing only a continuous, steady stream of flow. Therefore, realizing 70% of the blood flow, it can be effective even in cases of asystole. However, in cases of successful ECPR and restoration of cardiac activity, operation of the pump in continuous mode can increase the after-load of left ventricular myocardium hence limiting adequate cardiac recovery, worsening ischemia (or other pressure and/or volume overload variables). It is necessary to take into account the nature and localization of the pathological process (zone of ischemia) caused by the cardiogenic shock, especially if it covers the area of the heart and the left atrial septum. In such cases, the overall outcome of ECPR may be worsened and impact patient outcomes. Regardless, during the period of therapy in the case of ECPR, the phases of therapy can be divided into two periods—each requiring maintenance of different blood inflow and pumping options:

- I—The period before the restoration cardiac activity
- II—The period after the restoration of cardiac activity

In period I of extracorporeal resuscitation, the recovery of hemocirculation using continuous blood flow in the cardiovascular system is far preferable to blood flow, implemented by external heart massage (providing not more than 5% of cerebral blood flow). Artificial perfusion with oxygenated blood, in which the desired temperature mode, the acid-base

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balance (ABB) and drug saturation can be easily maintained, is able to provide adequate tissue and organ blood flow. In case of a high-end location of the aortic cannula, the adequate coronary perfusion is also possible. Such perfusion is able to support the required electrical activity of the myocardium and the restoration of sinus rhythm, sometimes even without defibrillation.

In period II of ECPR, after the restoration of cardiac activity, the pump must carry out support for the systemic circulation. The goal should be maximum unloading of the myocardium for the gradual, smooth and simultaneous recovery of the myocardium, weakened by "disaster". In other words, the perfusion mode should ensure that pumping of a certain volume of blood from the right atrium to the aorta not to impede the emptying of the natural ventricular. Left ventricular ejection must continue—as because stagnation of blood in the cavity can result, even in the setting of adequate anticoagulation, clotting of blood which when ejected can be fatal. Therefore, unloading of the myocardium of both ventricles in terms of volume and pressure must be considered as the best option. Such perfusion therapies, for example, are characteristic for the pulsating types of left ventricular assist devices (LVADs) with the pumps serving to shift the volume. A pump operating in counter pulsation mode, taking up a blood from the right atrium, will unload right heart in terms of volume. By pumping this volume back into the aorta, it also bypasses the left heart, also unloading it in terms of volume, while at the same time contributing to additional after-load reduction of the right heart. Finally, if the volume of blood is pumped into the aorta during diastole (provided the aortic valve is closed), there will be additional after-load reduction of the left ventricle—and much like the function of an IABP, coronary perfusion with oxygenated blood will also increase [25–28].

2.4.1. Pulse wave properties at extracorporeal circulation

Probably, the largest and longest standing debates between the experts about the advantages and disadvantages of the blood flow are the nature of extra-corporeal blood flow/wave properties. Specifically, it is the comparison of non-pulsatile, continuous flow with a pulsatile flow synchronized with the cardiac cycle of native heart flow. The main argument supporting non-pulsatile flow is the significant decrease of the pulsatile flow from the aorta and its major branches to the thin peripheral arteries—arterioles, and then the eventual elimination, or "smoothing out" of the pulse wave as it reaches the capillaries. According to this logic, if the transcapillary flow in normal physiological conditions has a continuous, non-pulsatile nature, then in case of artificial continuous flow (i.e., ECMO), cell and accordingly tissue blood flow should not be affected. On the other hand, supporters of pulsatile flow, in case of the artificial perfusion, insist on the need of maintaining the pulsatile wave, especially in the central part of the cardiovascular system. Numerous investigations suggest that besides the large arteries, arterioles, particularly those in kidneys, contain baroreceptors. In addition, the baroreceptors of the aortic arch trigger neural and humoral reactions that impact the regulation of circulating blood volume and arterial blood pressure by increasing sympathetic tone and activating the renin–angiotensin system and vasopressin release. The large main arteries provided with baroreceptors instantly and quite sensitively react to the slightest pressure changes within this system and participate in the redistribution of blood volume, depending on the needs of the

body. In the process of blood flow redistribution, little to no function is performed by the arterioles, which are called "taps" of the vascular system or "resistance vessels." About 50–60% of the total resistance to blood flow is contributed to by these vessels. Arterioles determine the systemic blood flow at the regional and microcirculatory level. Total vascular resistance at different parts of the body contribute to the systemic diastolic blood pressure, changes it a certain level as the result of common neurogenic and humoral changes of the tone of these vessels. Differently directed changes of the tone of different regional arterioles provide volumetric blood flow redistribution between regions—this complex feedback mechanism controls the microcirculation. The cardiovascular system (especially the large, main arterial vessels), which are evolutionary adapted to such neuro-humoral regulation, if not receiving the normal physiologic (or even pathophysiologic) baro-excitation, results in the adverse operating conditions. Thus, in a continuous flow, they react adversely to the non-physiological artificial perfusion. This results in repeatedly described situations of inadequate peripherial circulation, secondary impairment of the microcirculation, impairment of organ blood flow, the accumulation of toxic metabolites, and buffer shifts with homeostasis dysfunction. However, clinicians over the years have learned to correct these shifts timely, both by means of medications and fluid (crystalloid and colloid) as well as the use of technical devices (i.e., dialysis and renal replacement therapies). But, despite all attempts and various degrees at correction of these biochemical abnormalities, the damages continue to exist as they are believed to be related to the non-physiological flow of artificial perfusion [29–31].

In cases of ECLS, carried out during cardiac arrest or cardiogenic shock, there are additional reasons to employ synchronized pulsatile flow. Specifically, the need of reduce both pre- and after-load in the weakened ventricular myocardium. To do this, blood, taken by the pump from the right atrium, should be returned, provided with the required kinetic energy, to the aorta during diastole (after closing aortic valve—critical to preventing LV distention). None of the above-discussed structures of the pumps, which are commonly used clinically are able to carry out such a specific counter pulsation. Therefore, we can conclude that despite certain clinical successes of the different ECLS methods, the technology is far from perfect and there is a critical need for improvement of blood pumps. Given this, the goal of the researchers is the creation of universal extracorporeal pump is understandable. The structure of such pump, regardless of the nature of the blood flow, should allow for the desired pumping of flow both in non-pulsatile mode as well as in a controlled counter pulsatile mode [32].

2.5. Description of blood pump with own design

Since 2000, our team has been developing paracorporeal blood pumps for perfusion in ECLS systems. Currently, many of our pump designs are protected by national patents. These pumps, which are handmade, are tested in systems of cardiopulmonary bypass, ECMO systems, portable systems to be used for ECPR and in retrofit systems for the perfusion of isolated organs and organ systems "in situ."

After the bench testing, the systems are tested in various experimental models on animals. In addition to blood pumps, the complete circuit of these systems generally includes the parts and accessories for single-use perfusion sets for cardiopulmonary bypass: oxygenator with

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heat exchanger, the arterial filter, a set of flexible connecting tubes from PVC or silicone, various fittings, taps, etc. The blood pump itself belongs to the class of volume shifting pumps. With regard to the sub-group, it is a hybrid between membrane and pneumatic pumps. It is equipped with two chambers, connecting tubes (lines) for blood and air, external electronic clamps of the tube-lines, the pulsator, and a control system.

In the design of the pump, in order to separate the functions of filling and ejection, we have chosen a two-chamber circuit in which both chambers perform the opposite function at the same time. At the time, when in one of the chambers experiences blood inflow through the inlet branch conduit and it is filled, the blood from other chamber is ejected through the outlet branch conduit and the chamber is emptied. This allows controlling parameters of inlet and outlet separately. This is in contrast to similar parameters in roller or centrifugal pumps and is a significant distinguishing feature of this pump.

The second distinctive feature is the absence of any parts, moving in the flow, hence minimizing affecting blood cells and traumatizing them. So, compressed air (pressure) was chosen for pumping in the capacity of the substance imparting kinetic energy to the blood.

In the pump, running on a pneumodrive (actuator), compressed air, or a vacuum is applied to the rigid chamber from the branch pipes of the compressor with the receivers of positive and negative pressure (**Figures 1–3**). Each of the branch pipes is provided with an electrically operated stop-cock, consisting of external electronic clamps (EEC) on the tubing lines. Thus, each rigid clamp has four holes with branch pipes provided with the EEC. Accordingly, both chambers together have eight such branch pipes. In the filling cycle (diastole) of one of the chambers, two of them are open and two are closed. At this time, in the other chamber, there is a pump cycle, and again, two EEC are open and two are closed. Consequently, in each phase of the pump operation, four of the eight EECs are open, and four are closed.

1 Casing of the first chamber.

1a Bag of the first chamber.

2 Casing of the second chamber.

2a Bag of the second chamber.

3 The blood inlet branch-pipe of the first chamber.

4 The blood inlet branch-pipe of the second chamber.

5 The blood outlet branch-pipe of the first chamber.

6 The blood outlet branch-pipe for second chamber.

7 The common outlet tubing-line of the pump.

8 The common inlet tubing-line of the pump.

9 Sensors of filling and emptying the bags.

10 EEC of the blood inlet branch-pipe of the first chamber.

11 EEC of the blood inlet branch-pipe of the second chamber.

12 EEC of the blood outlet branch-pipe of the first chamber.

13 EEC of the blood outlet branch-pipe of the second chamber.

14, 15 Vacuum line EECs of the chambers.

16, 17 Pneumatic pressure line EECs.

18 Compressor of the positive and negative pressure.

19 Pressure receiver.

20 Vacuum receiver.

21, 22 Pneumatic pressure lines.

23, 24 Vacuum lines.

25 Pulsator.

26 Control system.

Figure 1. Variety of pumps developed with our design.

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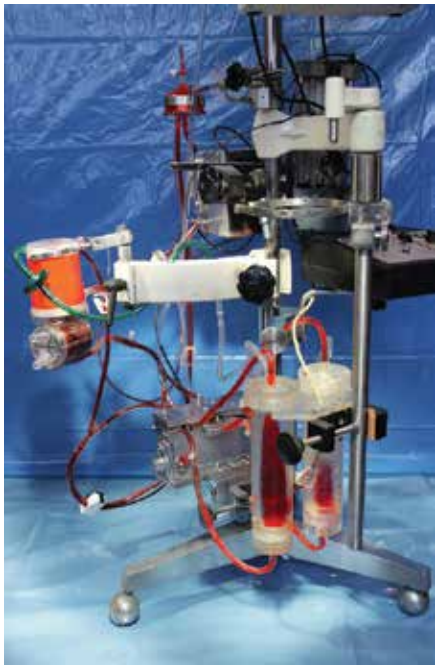

Figure 2. The external view of the pump.

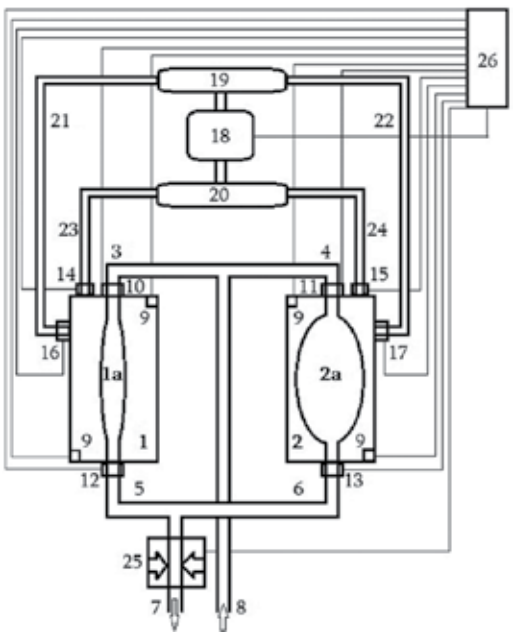

Figure 3. Scheme of the two-chamber pump.

In order to keep the components separate (i.e., blood from the air), the principle of a saccular chamber "Bag in Can" was chosen. This consists of an outer housing—"Can", which is a cylindrically shaped casing and is made of a transparent rigid material that can withstand pressures up to 3 atm (303.9 kPa). The inner, elliptically shaped, chamber—"bag", it is a thin-walled, elastic, biologically compatible (polyurethane) blood bag. Inlet and outlet conduits of the blood chamber are located at the poles of ellipsoidal bag and are mounted in the branch pipes of the rigid housing. Blood enters directly, via the inlet branch-pipe, directly into the blood chamber from the one end. After passing through the bag, it is pumped out through the outlet-branch pipe of the rigid housing, located at its opposite end.

Another feature of the pump is that each of the blood chambers filling (storage) and emptying (systole—pumping) functions is integrated. Thus, the filling (diastole) process, as well as emptying, is multi-cyclic. This means that filling (or discharging) chamber can store blood volume, equal to a few cardiac outputs. Accordingly, this increases the amount pump can store as a whole. This feature becomes evident when the pump is in a pulsatile mode. This mode of operation allows, depending on the specific requirements of the clinical situation, the blood to be stored in the blood pump for a certain number of native heart cycles with an arbitrary frequency of pulse cycles of the pump. In addition, it is possible to change the volume and pressure of each pump ejection and arbitrarily. In other words, the pump construction maintains one of the most important characteristics of myocardium—the ability to adapt to the amount of blood inflowing in accordance with the Starling law (in terms of volume and pressure changes).

Each chamber is equipped with electronic sensors for filling and emptying the blood storage "bags" (i.e., bladders). With these sensors, it is possible to set the desired maximum and minimum blood bag filling volume in each chamber. When blood volume exceeds the set value, the sensors are instantly activated and the give impulse to the control system that switches the chambers and changes their function—from filling to ejection.

Both chambers are functionally integrated into a single pump and reservoir unit, acting both —as a blood accumulator (reservoir) and a hydraulic pump. Thus, only changing the chambers of a certain size to the chambers of another leads to creation of the pump with different capacity and identical hydrodynamic characteristics to those, described above. Inlet branching conduits of both chambers are interconnected with a free end connected to the inflow (venous) bloodline of the patient. The outlet branch conduit of the chambers is also interconnected—with a free end serving as the outflow back to the patient.

Finally, one of the most important parts of the pump is pulsator. It is located at the connection between outlet tubing of the pump and the oxygenator. The principle of pulsator function is very simple—external clamping of the silicone tubing-line. However, management of this pulsator allows achieving the desired effects of adequate circulatory support, namely

- Carry out pulsation mode in cases of native heart asystole;
- Change the clamping frequency—pump pulsation frequency;
- Change the duration of clamping—the time of "diastole" of the pump;

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- Change the duration of time between clamping—the time of "systole";
- Synchronize pulsation of the pump in accordance with an electrocardiogram or pulse wave in cases even minimal cardiac activity;
- Change the timing ratio of "systole" and "diastole" of the pump in the counter pulsation mode to match the native cardiac cycle.

Although, in terms of universality of the pump, it should be noted that it has the ability to perform not only the pulsatile flow, which attempts to match physiologically arterial flow, but also non-pulsatile flow—a characteristic of the venous bed. It is this feature, which we realized in a number of experiments in the settle of liver transplantation that demonstrated adequate protection of the recipient patient in the anhepatic phase.

By choosing appropriate pump chamber sizes (i.e., volume), it can be adapted to both—perfusion applications (chamber volume up to 1000 ml) for large experimental animals (calves, donkeys—some weighing up to 100 kg), as well as medium-sized experimental animals (dogs, sheep, pigs—weighing 45 kg). We have successfully tested circuits for small experimental animals (rabbit, rat—weighing less than 3 kg) with the chamber volume up to 50 and 20 ml.

2.5.1. Description of the pump operation

The priming volume of the pump chambers may vary depending on the type and size of the experimental animal and the planned experimental model. For example, in the model ECPR on the sheep (up to 40 kg), we used blood pump with the chamber volume up to 200 ml. The total volume of priming of the entire system with the oxygenator and arterial filter was 750 ml.

I phase

In the first chamber, after the activation of the blood level sensor, the EEC closes the inlet branch-pipe for blood—a vacuum line then opens the tubing conduit for pressure and blood release. The pumping begins. Simultaneously, by a signal from the level sensor in the second chamber, the EEC closes the outlet branch-pipe for blood—the pneumatic pressure tubing conduit then opens the inlet branch-pipe for the blood and the vacuum line. Thus, the second chamber begins filling.

II phase

When blood reaches a certain volume level, the sensor switches the position of tubing conduit of the EECs. Thus, the chambers change their functions instantly: Empty changes to filling, and filling starts pumping. By changing the position of the volume level sensor in the circuit, filling level of blood chambers and therefore, the filling level of the pump system may be changed.

Since the chambers function cyclically, all their work can be divided into two opposite phases: the filling phase and the emptying phase (**Figures 4** and **5**). The compressor (#18) is switched

on after priming the blood circuit pump. The receivers (#19, #20) provide excess pressure and vacuum relief valves. Thus, in phase I in the casing of the chamber (#1), the air is supplied from the control system by the EEC (through line #21), under pressure from the receiver (#19). In this chamber under the action of an impulse from the control system, the branch conduits (#10 and #14) are closed and branch conduits (#12 and #16) are opened. Thus, the chamber (#1a) begins to pump blood through the outlet branch conduit (#12) and the outlet tubing-line (#5) to the common output line (#7). The pulsator (#25) is located on this tubing line, and it is also controlled from the general control panel. At the same time, automatically, by remote control impulses in the chamber (#2), the branch conduits (#13 and #17) are closed and the other branch pipes (#11 and #15) are opened. In the chamber casing, the vacuum is supplied through the line (#24) from the receiver (#20). The blood chamber (#2a) begins to fill with blood from the common inflow tubing-line (#8). After reaching a certain filling or emptying blood level, level sensors (#9) are switching over all and EECs of the branch conduits are changed to the opposite position and the chambers then change (reverse) functions and phase II begins.

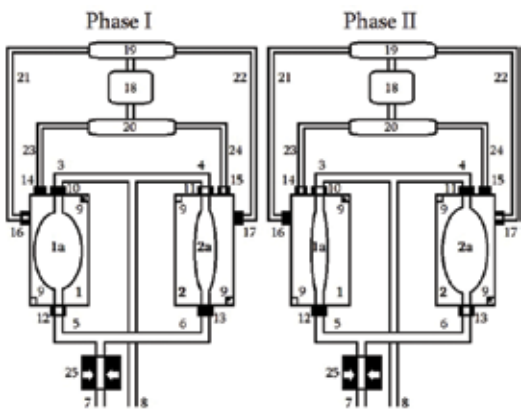

Figure 4. Phases of the pump operation.

Figure 5. Process of the experiment on animal.

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Kind of pump Specifications	Rotary (roller) pump	Centrifugal pump	Our pump on the pneumatic actuator
Design features and capabilities (resources)			
Manufacturer (Brand)	CAPIOX (Terumo)	LIFEBRIDGE (Sorin), CARDIOHELP (Maquet)	Prototype
The volume of the blood chamber (SV—stroke volume)	Variable SV for different-sized patients	Filling volume up to ≈ 50 ml	Filling volume up to ≈ 150–300 ml
Managing the power component	Electric drive	Electric drive	Pneumatic actuator
Use	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation, preferable for long-term extracorporeal support	As a system of cardiopulmonary bypass during cardiopulmonary resuscitation, as well as in preservation of organs in situ
Maximum capacity	Up to 10 l/min	Up to 8 l/min	Up to 10 l/min
Realizable value of the system pressure	60/40 mm.Hg	60/40 mm.Hg	120/80 mm.Hg
Advantages			
Duration of conducted safe perfusion	Limitation in time several (3–4) hours	Possible long-term perfusion	Possible long-term perfusion
Discharge flow characteristics	Excessive positive or negative pressure	Provides positive and negative pressure (poor)	Provides positive and negative pressure (as close as possible to the created native myocardium)
Specifications filling flow	–	–	Adaptation to the venous return
Opportunities	It provides systemic circulation	Higher bypass for right or left ventricles	Maximum bypass the right or left ventricle
The nature of the pulse wave	The possibility of a weak pulsation	The possibility of a weak pulsation	The ability to flow as a non-pulsed and clear counterpulsation
Disadvantages			
Possibility of reverse flow along arterial line	No blood return	Potentially exists	Potentially exists
Embolism	Potentially massive air embolism	Protection against massive air embolism	Protection against massive air embolism
Damage to the blood cells	Hemolysis	Slight hemolysis	No hemolysis

Kind of pump Specifications	Rotary (roller) pump	Centrifugal pump	Our pump on the pneumatic actuator
The possibility of damage to blood contact details	The destruction of tubes	The destruction of rotor blades	–
Additional requirements	Tubing-line occlusion control is required	–	An additional compressor with vacuum supply control is required
Additional accessories	The volume of ejected blood is automatically calculated	The flowmeter is required	The flowmeter is required
Possibility of circuit disruption from excessive line pressure buildup	Possible of circuit disruption and termination and termination	No possibility	No possibility
Cost	Low	High	Low

Table 3. Comparison of blood pumps used commonly and pump developed by us.

Prototype pumps are made by hand. Bench testing has shown that the main hydrodynamic parameters and efficiency, safety, and reliability are similar to clinically used, commercially available, pumps (**Table 3**).

During bench testing, a dual-chamber pump with a chamber volume of 350 ml was placed at the same level as a volume of liquid, attempting to match clinical flow. Perfusion was carried out in two different modes of blood flow—non-pulsatile and pulsatile. Blood flow was measured in the output tubing-line of pump.

In the non-pulsatile flow mode:

- Pressure in the receiver #20: 1.5 atm;
- Vacuum in the receiver #19:0.7 atm;
- Flow through lines #21, #22: up to 6 1/min;
- Flow through lines #23, #24:1 to 4 1/min;
- Total flow in the line #7: upto 10 1/min.

In the pulsatile flow mode:

- Pressure in the receiver #20: 1.5 atm
- Vacuum in the receiver #19: 0.7 atm
- Flow through lines #21, #22:8 1/min
- Flow through lines #23, #24: upto 2 1/min
- Total flow in the line #7 (after pulsator):10 1/min

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2.5.2. Experimental studies on animals

The pump was tested in several acute experiments on the animal models in the various perfusion setting:

- Heart–lung bypass (HLB) machine
- ECLS system for ECPR
- Perfusion preservation of isolated donor organs and complexes of organs "in situ"

The dual-chamber pump passed a long-standing test as a heart–lung bypass machine in 68 different experiments on dogs and sheep. In these experiments, the main pump circuit was connected via a standard configuration in cases of an open-chest model, simulating various cardiac surgery scenarios. The pump provided adequate heart–lung bypass for 2–6 h, both with the non-pulsatile and pulsatile flow without difficulty. Hemodynamic parameters were maintained within physiological limits, and therefore, the main parameters of physiology of animals during extra-corporeal perfusion did not require significant correction.

In the ECLS configuration, which was designed for ECPR on sheep, the pump was tested in 14 experimental models of cardiac arrest. A portable, mobile version of the pump and the entire perfusion system complete set with autonomous energy supply was used in these experiments. The effects of extra-corporeal perfusion in a number of experiments on models, within 10 min of cardiac arrest, confirmed the following:

- Successful recovery of the cardiac contraction (in case of non-pulsatile and pulsatile mode);
- Stable rehabilitation of cardiac activity with prolonged perfusion (in a synchronized mode counter pulsation).

In addition, in some experiments on rabbits, the pumps have been tested using a portable system for extra-corporeal isolated preservation of donor organs and organ complexes "in situ." The standard conserving solutions, as well as whole blood at various temperatures, were used as preservatives.

3. Conclusions

In the design of the dual-chamber pump, with saccular chambers modelling the concept of a "Bag in Can," there are incorporated a full range of opportunities for achieving the desired range of physiologic perfusion parameters similar to that of a healthy native heart. The dual-chamber design, with inter-changing chamber functions, allows for separate control of the different parameters for the filling and emptying functions, thus allowing for optimization of blow independently. In other words, the design allows the pump to be filled with a smooth, non-pulsatile flow, while simultaneously ejecting with physiologic pulsatile flow. The pump design provide minimal trauma of the blood cells due to lack of internal valves and, most importantly, the absence of the rotating parts in the path of flow. Changing only the chamber unit with a different size "bag," while leaving other components of the unit unchanged allows

for a full range of volumetric hemo-circulatory pump characteristics. In other words, the pump can be easily adapted for extra-corporeal perfusion experimental on animals of different sizes. Consequently, in a clinical setting, it can be used, with only minor changes, for infants, children, and as well as for adults. The pump can perform non-pulsatile blood flow—characteristic for the venous bed while also providing pulsatile flow—characteristic of flow in the aorta and large arteries. Moreover, it can be easily switched from pulsatile flow to non-pulsatile perfusion, depending on the specific necessities, at any time. Finally, counter pulsation during pump operation during ECPR allows continuous unloading of the work of the heart, hence contributing to the actual recovery of the weakened and injured myocardium. Prolonged and stable rehabilitation of cardiac activity in a synchronized counter–pulsation mode can also be accomplished.

In addition, in experiments on rabbits, the pumps have been successfully tested using a portable system for isolated perfusion and preservation of donor organs and organ complexes "in situ."

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Extracorporeal membrane oxygenation (ECMO), despite a long and troubled history, is very rapidly evolving into a therapy that can be safely and effectively applied across the world in patients experiencing acute cardiac and/or pulmonary failure. As experiences grow, there is a better understanding of nuances of the importance of teamwork, therapy guidelines and protocols, patient selection, and understanding the functional aspects of pump-circuit technology as it interfaces with human biology. The challenges in managing these very sick and complex patients cannot be understated. The goal of this text is to provide a framework for the development and successful growth of a program. Authors from Centers of Excellence Worldwide have shared their experiences in the full spectrum in dealing with this evolving field.

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