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Extracorporeal Membrane Oxygenation (ECMO) for Long-Term Support: Recent Advances

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Abstract

Considerable progress has been made in component technology, circuitry, and clinical practice related to extracorporeal membrane oxygenation (ECMO). These advances allow prolonged support with fewer complications when compared to the past eras. Long-term support cases were frequently reported with indications including respiratory failure, cardiac failure, bridge to transplantation, extracorporeal cardiopulmonary resuscitation (ECPR), and even ambulatory extracorporeal membrane oxygenation (ECMO) support. The common complications associated with ECMO, including thrombosis, hemorrhage, nosocomial infection, neurological injury, vessel injury, multiple organ failure and mechanical failure, and the disease process of patients remain limiting factors. In spite of the complications, ECMO remains the only possible option in treatments for patients requiring long-term respiratory or cardiopulmonary support. In this chapter, the recent advances in long-term ECMO support are reviewed. Clinical etiology of patients placed on long-term ECMO support, the various circuit configurations, clinical and technical issues, management aspects, and clinical outcomes are discussed.

Keywords: extracorporeal membrane oxygenation (ECMO), long-term ECMO, critical care medicine, respiratory failure, cardiopulmonary failure, cardiac failure, blood oxygenator, blood pump

1. Introduction

In its earliest application, extracorporeal membrane oxygenation (ECMO) was used as a rescue therapy in support of patients with acute circulatory or respiratory failure. The first reported use of ECMO was to support a 24-year-old trauma patient suffering from acute

respiratory failure, where venoarterial ECMO provided 75 h of life-sustaining support in 1972 [1]. Despite initial barriers to widespread adoption, by the 1990s, a growing body of literature demonstrated a clinical benefit to ECMO in certain patients. Advances in ECMO technology, critical care, rehabilitation, and comorbidity management have resulted in increased adoption of ECMO, with ever-increasing duration of ECMO runs. In 2003, there were 1606 patients supported with ECMO [2], with this number increasing to 2895 by 2011 [3] and more than 6600 cases in 2015 [4]. Although the mean duration of ECMO support is approximately 1 week, reports of over 7 months exist in the literature. Long-term ECMO, defined as 3 weeks or longer of ECMO support, has become increasingly prevalent, with many centers reporting success in long-term support.

In general, the initial indications for long-term ECMO support are the same as short-term ECMO support, and it is the patient’s recovery which dictates the duration of use. **Table 1** lists respiratory indications for ECMO support, with diagnosis, average run duration, and percent survival stratified by age group. Despite the ability of ECMO to treat both respiratory and circulatory conditions, it is the patients with severe respiratory failure who are most commonly supported on long-term ECMO. In contrast, patients with cardiogenic shock are typically transitioned to ventricular assist device (VAD) therapy or heart transplant prior to 3 weeks of ECMO support. The most prevalent respiratory indications for long-term ECMO include bacterial and viral pneumonia, acute respiratory distress syndrome (ARDS), and acute respiratory failure in the adult and pediatric populations. In the neonatal patient

Age group	Diagnosis	Average run duration (h)	% survival
Neonatal	Congenital diaphragmatic hernia	257	51
	Persistent pulmonary hypertension of newborn	155	77
	Sepsis	144	72
	Respiratory distress syndrome of newborn	136	84
	Meconium aspiration syndrome	133	94
Pediatric	Viral pneumonia	317	66
	Bacterial pneumonia	283	60
	Aspiration pneumonia	242	69
	Acute respiratory failure, non-ARDS	226	52
Adult	Viral pneumonia	325	65
	ARDS, non-post-op/trauma	313	54
	Acute respiratory failure, non-ARDS	275	55
	Bacterial pneumonia	261	61
	ARDS, postop/trauma	256	57

Table 1. Average ECMO run duration and % survival by age group and diagnosis, 2016 data [4].

population, meconium aspiration syndrome, persistent pulmonary hypertension of the newborn, congenital diaphragmatic hernia, sepsis, and respiratory distress syndromes are more prevalent.

2. Indications and outcomes

The decision to support a patient with ECMO is based on the severity of cardiopulmonary dysfunction, the response to conventional therapy, as well as patient and family preferences for the aggressiveness of treatment. The duration of ECMO use, in contrast, is dependent on patient recovery and the patient's ability to transition to alternative therapies. Indeed, patient and family preferences for the duration of aggressive critical care must be considered, and honest explanations of ECMO outcomes must be provided.

Unfortunately, the data necessary to predict patient outcomes on long-term ECMO support remain limited. Instead, case series and case reports guide much of the decision-making, and key examples are described later.

2.1. Respiratory failure

Respiratory failure remains the condition most commonly supported with long-term ECMO, with ARDS the inciting respiratory insult in many cases. When supporting a patient with severe respiratory failure with ECMO, clinicians must consider strategies for decannulation, which currently include patient recovery and lung transplantation. Despite increased acceptance of ECMO as a long-term therapy, it is currently unable to support patients outside of the intensive care unit (ICU), and does not allow for patients to return to activities of daily living. The ideal scenario for these patients is a full recovery, and there are increasing reports of patients recovering from long-term ECMO support for severe respiratory failure. The longest reported ECMO run with recovery is in a 26-year-old drowning victim, who was supported for 117 days on ECMO [5].

In patients unlikely to recover their native pulmonary function, or in patients with progressive underlying respiratory failure, ECMO may be utilized as a bridge to lung transplantation. The longest reported successful bridge to transplant required ECMO support of 155 days [6]. In these cases, ECMO provides the needed gas-exchange function, allowing for reduced reliance on mechanical ventilation. The principle advantage of this strategy lies in the ability to liberate patients from mechanical ventilation, allowing some patients to talk, eat, and ambulate, which serve to prevent pre-transplant deconditioning. There are two patient populations who receive ECMO as a bridge to lung transplantation: patients with chronic respiratory failure who are listed for transplantation prior to ECMO initiation and those patients without history of respiratory failure, who are only listed for transplantation after ECMO therapy has begun.

In the setting of acute respiratory decompensation, it is unlikely for a patient's transplant candidacy to improve beyond their baseline—instead, the role of ECMO in these patients is

to prevent their deconditioning and to avoid transplant-precluding complications. As such, the contemporary management of patients with respiratory failure exceeding the abilities of conventional support measures involves ECMO support followed by urgent lung transplantation, as the prolonged ECMO use continuously exposes patients to the risk of complication.

Acute respiratory decompensation occurs not infrequently in patients who are listed for lung transplantation. For these patients, the use of ECMO provides necessary gas-exchange function in the setting of inadequate native lung function. The use of ECMO in these patients has been widely reported, and the algorithms guiding this management strategy are maturing. One single-center experience reports the use of ECMO as a bridge to lung transplant over a 9-year period, in which the median duration of ECMO use was 12 days (interquartile range—IQR 6.25 to 18.75) [7]. In the series of 72 patients, 56% of patients were successfully bridged to transplant, with 38% surviving for up to 2 years. Notably, the patients were free from mechanical ventilation for a mean time of 10.2 days (SD 18.8 days), and 69% of patients were ambulatory while on ECMO. A similar experience was reported on 31 patients who were bridged to lung transplantation using ECMO over a 5-year period at two institutions [8]. They report ambulation while on ECMO in 18 patients, liberation from the ventilator in 3 patients, and a median duration of ECMO use of 11 days (IQR 3.5–17). Five patients were on ECMO for over 21 days, with one patient requiring 53 days of support. Of note, 7 of the 31 patients were not listed for transplantation prior to ECMO cannulation.

The decision to support patients with acute or acute-on-chronic respiratory failure with ECMO is a challenging one, and no single guideline exists to aid in decision-making. Even so, multiple high-volume pulmonary transplant and ECMO centers have published their experience with ECMO as a bridge to transplant. A typical decision tree is shown in **Figure 1** (adapted from Biscotti et al. [7] and Hoopes et al. [8]). Note that the clinical management decisions are highly center specific, and these treatment algorithms must be adapted to appropriately fit the clinical setting.

Continuous advancement in the technology of ECMO as well as improvements in critical care and rehabilitation have improved the outcomes of all ECMO patients, including those requiring long-term support. A study describing the course of 127 patients placed on ECMO for respiratory failure between 2006 and 2010 found an overall survival to decannulation of 64%. In the stratified analysis, they found that 59, 31, and 52% of patients survived after being placed on ECMO for 10 days or less, 11–20 days, or more than 21 days, respectively. They found no statistically significant difference in survival between the 45 patients who were supported on ECMO for 10 days or less, and the 10 patients who were supported long term ($p = 0.39$) [9]. Similarly, a study of 55 patients placed on ECMO for severe ARDS demonstrated no significant difference in hospital or 30-day mortality, with 27% of patients supported for 3 or more weeks expiring versus 43% of patients supported less than 3 weeks [10]. These data, albeit limited, provide evidence for cautious optimism in the care of patients with severe respiratory failure.

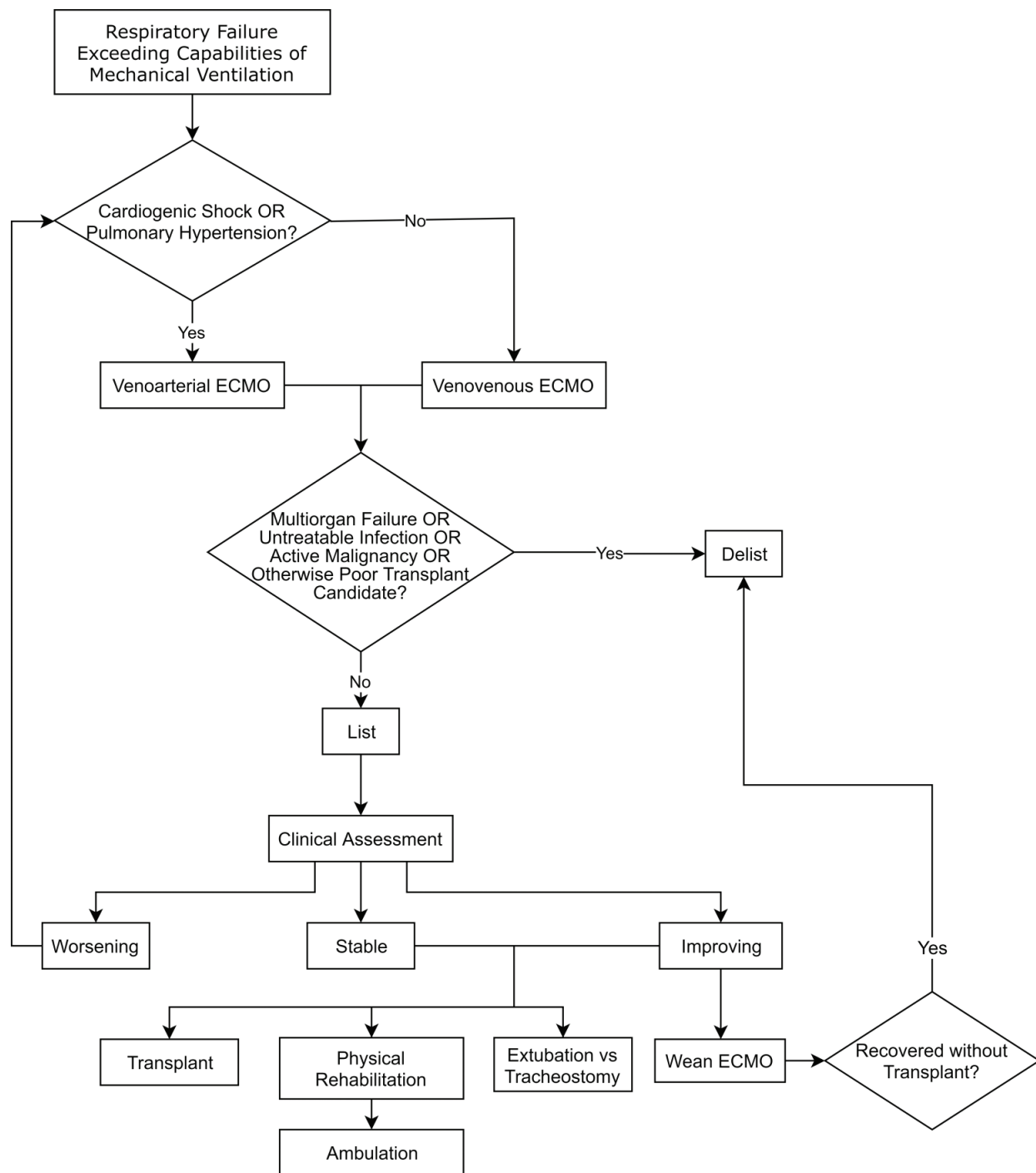


Figure 1. General treatment algorithm for ECMO as a bridge to lung transplant. Note that implementation details are highly dependent on clinical setting.

2.2. Circulatory collapse

The use of long-term ECMO for the treatment of cardiogenic shock is less common than for respiratory failure, as many are transitioned to VAD therapy before their tenure on ECMO

would be considered long term (21 days). Reports of patients being supported on venoarterial ECMO for prolonged durations do exist in the literature, however. In one study, a patient unable to wean from cardiopulmonary bypass following re-do sternotomy and aortic valve replacement was supported with venoarterial ECMO for 33 days postoperatively before being successfully weaned and decannulated [11]. Unfortunately, this patient ultimately suffered a cerebrovascular accident and died in a high-dependency unit. In a cohort of 98 patients receiving ECMO for refractory cardiogenic shock, Rousse et al. reported a median duration of ECMO use of 8 days, with the maximum duration of 81 days [12]. This cohort suffered 50% mortality, with 30% of patients recovering to normal cardiac function, 13% of patients receiving a heart transplant, and 7% of patients transitioned to VAD therapy.

The decision to provide long-term ECMO support for these patients is largely dependent on their presumed recovery path, and it is the patients who are poor candidates for VAD support who are typically supported on venoarterial ECMO in the long term. These patients must be aggressively medically optimized, as the goal of the ECMO therapy is in recovery of native cardiac function prior to decannulation. Indeed, some patients will not recover native cardiac function, will never become transplant candidates, and are unsuitable for VAD as a destination therapy. Management of these patients is a significant challenge both medically and ethically, and the family must frequently be updated in the plan of care.

3. ECMO circuit configuration

3.1. Cannulation strategies

Initial cannulation strategies for long-term ECMO are identical to short-term ECMO support, with the goal of achieving adequate blood flow to support gas-exchange requirements, while minimizing recirculation between the cannulae. For patients with isolated respiratory failure, venovenous cannulation is possible. If hemodynamic support is required, or if there is significant pulmonary hypertension, venoarterial ECMO may be necessary. For the expeditious initiation of ECMO, percutaneous cannulation of femoral and jugular vessels is preferred, as it allows for initiation of ECMO at the bedside in a rapid manner.

As the patient's tenure on ECMO becomes prolonged, however, cannulation must not only provide appropriate cardiopulmonary support but must also provide long-term stability and allow for rehabilitation with possible ambulation. In general, long-term femoral cannulation is not preferred due to infectious risk as well as relative limit to mobility associated with access to the femoral vessels.

For isolated respiratory support, early transition to a double-lumen internal jugular cannula (Avalon Elite®), placed under echocardiographic or fluoroscopic guidance, has proven to be beneficial in many centers. Since the double-lumen internal jugular cannula allows for full mobility of the lower extremities, these patients are able to ambulate and undergo physical therapy with the goal of limiting deconditioning. This double-lumen cannula does impose a restriction to flow, however, and careful patient selection is required.

For patients with cardiogenic shock or pulmonary hypertension, the cannulation options are more limited. In principle, the cannulae must provide venous drainage as well as return of oxygenated blood to the arterial system with adequate return pressure to provide end-organ perfusion. In the acute cannulation of patients with cardiopulmonary collapse, the common femoral artery is the preferred vessel for arterial cannulation in adults. Of note, the presence of the arterial cannula in the common femoral artery can compromise distal limb perfusion, and insertion of a distal perfusion catheter is often required. Unfortunately, the groin access required for cannulation of the common femoral artery limits mobility and may be deleterious to rehabilitation.

Although there is no commonly accepted cannulation site for long-term venoarterial access, one reported technique is cannulation of subclavian vessels [13]. This technique is reported to provide adequate flows and improved ambulation options. Technically, this cannulation method requires a small infraclavicular incision, anastomosis of a synthetic arterial graft with the subclavian artery in an end-to-side fashion, and direct insertion of the cannula into the arterial graft. Naturally, decannulation from this arrangement requires a surgical procedure with either explant or close ligation of the arterial graft.

In cases where there is right heart dysfunction or severe pulmonary hypertension, venoarterial ECMO through femoral vein and femoral artery is the traditional means of decompressing the right ventricle. In patients with a congenital atrial septal defect, a less invasive technique can be employed, in which a dual-lumen cannula is placed under fluoroscopic or echocardiographic guidance [14]. This goal of this configuration is to direct the oxygenated blood returned from the ECMO circuit through the atrial septal defect and into the left atrium, thus reducing the blood delivered through the right ventricle. This configuration promotes ambulation, as the dual-lumen venovenous cannula is inserted through the internal jugular vein. Both animal and human studies have shown success with creation of an atrial septostomy in conjunction with venovenous ECMO for the treatment of pulmonary hypertension [15]. If this technique cannot provide adequate right ventricular unloading, central cannulation is required, with two primary configurations.

The first central cannulation technique involves venous drainage from the right atrium and return of oxygenated blood into the pulmonary artery. Technically, this is accomplished through a median sternotomy or thoracotomy, with insertion of the venous drainage cannula into the right atrial appendage, and a synthetic arterial graft is anastomosed to the main pulmonary artery in an end-to-side fashion. The arterial cannula is inserted into this graft. In the patient with pulmonary hypertension, this configuration requires that the ECMO circuit pumps against this high-resistance pulmonary vasculature. This is rarely an issue, however, as even the vasculature of severe pulmonary hypertension has a lower driving pressure than systemic arterial pressure, and modern ECMO circuits have little difficulty driving blood through the systemic circulation. One major advantage of this configuration is that it places the arterial return in the main pulmonary artery, benefiting from the systemic-embolus protection afforded by the pulmonary vasculature. Additionally, cannulae can be tunneled out of the subcutaneous tissues and skin without access to upper or lower limbs, promoting mobility.

Central cannulation between the right atrium and left atrium can also be a strategy to mitigate pulmonary hypertension or right heart dysfunction [16]. In this case, venous blood is drained from the right atrial appendage, passed through the ECMO circuit for gas exchange, and oxygenated blood is returned to the left atrium. Again, cannulae for this technique can be tunneled allowing for mobility. Unfortunately, the invasiveness of the thoracotomy or median sternotomy is required, and there is no “pulmonary filter” to mitigate the consequences of ECMO circuit embolism, with a theoretical increase in the risk of stroke.

In a long-term ECMO patient, physicians may need to transition between cannulation sites, due to changes to patient’s support needs, desire to promote mobility, as well as cannulation site complications such as infection, hemorrhage, or inadequate distal perfusion. Continuous reevaluation of the appropriateness of cannulation must be performed, as a highly mobile patient on venovenous ECMO will likely fare better than a bedbound patient supported by a venoarterial configuration. Additionally, long-term ECMO patients may suffer unusual cannulation site and hardware complications. The securing sutures of cannula must be frequently examined, as they may pull from the skin or break during long-term support. Additionally, cannulae are subject to prolonged periods of fatigue, which may lead to early failure. In this author’s experience

Drainage	Return	Cannulation	Mobility	Decannulation	Embolization Site	Comments
Femoral vein	Jugular vein	Rapid, bedside	Low	Bedside	Pulmonary	
Jugular vein	Jugular vein	Rapid, bedside	High	Bedside	Pulmonary	
Jugular vein	Jugular vein with atrial septostomy	Lengthy, OR	High	Bedside	Systemic	Requires fluoroscopy or transesophageal echocardiography for positioning
Femoral vein	Femoral artery	Rapid, bedside	Low	Bedside vs. OR	Systemic	Possible limb ischemia, Consider distal perfusion catheter
Subclavian vein	Subclavian or axillary artery	Lengthy, OR	High	OR	Systemic	Possible limb ischemia, vascular complications
Right atrium	Pulmonary artery	Lengthy, OR	High	OR	Pulmonary	Requires chest exploration for bleeding
Right atrium	Left atrium	Lengthy, OR	High	OR	Systemic	Requires chest exploration for bleeding
Right atrium	Aorta	Lengthy, OR	High	OR	Systemic	Requires chest exploration for bleeding

Table 2. Possible cannulation sites.

with long-term cannulation in an ovine model, evidence of impending cannula failure has been detected (and repaired) on multiple occasions (unpublished data) (Table 2).

3.2. Circuit maintenance and component exchange

Due to the prolonged duration of component use in patients on long-term ECMO, component failure is a realistic possibility. Catastrophic failures, such as component rupture and hemorrhage, are managed through emergent circuit exchange. As such, a primed backup circuit should be available for emergent exchange at all times.

More gradual failures can occur in both the pump and the oxygenator, requiring exchange of these components. For the pump, failure can occur due to thrombus formation (typically on the impeller or bearing) causing decreased pump performance and increased hemolysis. This can be detected by trending pump rotational speed, blood flows, and plasma-free hemoglobin (PFH). A PFH level of approximately 10 mg/dL is generally acceptable, with a level over 50 mg/dL suggestive of excess hemolysis [18]. Rapid changes in PFH are perhaps more informative than the absolute value, and any rapid increase in PFH should be investigated. Of note, it is critical that blood samples be obtained gently while measuring PFH, as hemolysis can occur during sample acquisition causing an erroneously high reading.

Oxygenator failure can occur as a result of several conditions. The most acute failure is rupture of the fiber bundle, allowing sweep gas to enter the blood path and placing the patient at risk for an air embolism. Slow decline in oxygenator performance can occur due to protein deposition on the membrane, condensation buildup inside the gas passage, or the development of thrombus within the oxygenator. Condensation buildup can be prevented by periodically increasing the sweep gas to a high flow rate (10 LPM) for several seconds to blow the condensate into the exhaust. Care must be taken not to reduce the patient's CO₂ by maintaining this high sweep for a prolonged period. A flashlight can be used to examine the oxygenator (and tubing) for thrombus. Any thrombus visible on the oxygenator outlet side is impetus for oxygenator exchange, as this thrombus is at risk of embolization. Any other thrombus greater than 5 mm or enlarging may also warrant component or circuit exchange [17]. Finally, oxygenator performance may slowly decline as a result of protein deposition on the membrane. There is no reliable test to identify this as the cause of poor oxygenator performance, thus any oxygenator that cannot generate an exhaust oxyhemoglobin saturation of at least 95% is a candidate for exchange [18].

4. Complications

The use of ECMO for long-term support can lead to any number of complications. Although a multitude of complications can occur during long-term ECMO support, the typical complications are related either to cannulation, anticoagulation, concomitant organ failure, or infection. A meta-analysis by Cheng et al. reports complication rates on 1866 adult patients receiving ECMO as rescue therapy for the treatment of cardiogenic shock [18]. The rates of complications from this analysis are as follows: lower extremity ischemia—16.9%, lower extremity fasciotomy or compartment syndrome—10.3%, lower extremity amputation—4.7%, stroke—5.9%, neurologic complication—13.3%, acute kidney injury—55.6%, kidney injury

requiring renal replacement therapy—46.0%, major bleeding—40.8%, re-thoracotomy for bleeding or tamponade—41.9%, and significant infection—30.4%. These complications are discussed below.

4.1. Vascular complications

Vascular trauma secondary to cannulation is highly dependent on the selected cannulation strategy. Complications such as perforation of major vessels and arterial dissection are serious issues that can lead to extensive local bleeding, retroperitoneal hematoma formation, and limb ischemia. Perforation of the right atrium is relatively rare, while perforation or dissection of the femoral vessels, subclavian vein, or carotid artery is the more common form of vascular trauma [19, 20].

Compartment syndrome of the cannulated limb can occur in a subset of patients. Secondary complications of compartment syndrome include, but are not limited to, limb ischemia, neurologic deficits, or amputation of the affected limb. The first line of treatment for compartment syndrome is an urgent fasciotomy of the affected limb to release the elevated pressure and restore tissue perfusion [18, 19, 21]. Often, it is the detection of compartment syndrome that is challenging, especially if the patient is intubated and sedated, as they cannot report the altered sensation. As such, it is prudent to document distal perfusion after cannulation with a pulse exam (and Doppler if necessary) and to reexamine at frequent intervals (every few hours by nursing). Laboratory signs such as an elevated lactate, creatine phosphokinase, or myoglobin may be suggestive of compartment syndrome, and further investigation may be necessary. Of note, measurement of compartment pressures often provides little clinical guidance.

Limb ischemia can occur in the absence of compartment syndrome and is a frequent complication of ECMO therapy. The presence of a cannula within an artery (especially with percutaneous femoral artery cannulation) may lead to inadequate distal perfusion. This inadequate perfusion is exacerbated by hemodynamic instability, the need for vasopressors, thromboembolism, compression of the femoral artery and vein, or vascular trauma during cannulation. This risk is mitigated by the usage of a distal perfusion cannula, which is a standard practice at many high-volume ECMO centers [20].

4.2. Hemorrhage

Despite widespread use of antithrombotic surface coatings on ECMO equipment, it remains standard of care that patients on ECMO are on therapeutic anticoagulation. In the majority of patients, unfractionated heparin is used to mitigate the risk of thrombotic events, with the subsequent increased risk of both minor and major bleeding events. The 2014 Extracorporeal Life Support Organization (ELSO) guidelines on anticoagulation therapy provide definitions of both major and minor bleeding events. Major bleeding events are defined as a drop in hemoglobin by at least 2 g/dL within 24 hours, loss of 20 mL/kg of blood within 24 hours, the requirement of at least one 10 mL/kg packed red blood cells (PRBC) transfusion within 24 hours, or the need for reoperation or re-cannulation secondary to bleeding [22]. Blood loss

in ECMO patients may present as bleeding at cannulation sites (or at the sites of other vascular access), or may present as a retroperitoneal hematoma, mediastinal hemorrhage (especially in post-operative patients), cardiac tamponade, pulmonary hemorrhage, gastrointestinal (GI) bleeds, intracranial hemorrhage, epistaxis, and hematuria, among others [18].

Minor bleeding is defined by ELSO as a loss of less than 20 mL/kg/day of blood or a requirement of 10 mL/kg or less of PRBC transfusion per day. The most significant concern of minor bleeding events is progression to a major bleeding event, and thus these harbingers must be investigated. Any major bleeding event while on ECMO therapy is known to greatly increase patient mortality [22].

4.3. Thrombosis

Thrombosis is a common occurrence and a concern for patients on prolonged ECMO therapy. Exposure of the patient's blood to foreign substances, non-physiological shear stress, endothelial injury, immobility, alteration of normal blood flows, and critical illness increases the risk of a thrombotic event. In order to mitigate this risk, most modern ECMO circuits are lined with antithrombotic surface coatings that reduce the risk of thrombosis. While cannulated, patients are typically anticoagulated with unfractionated heparin, although there is the risk of developing heparin-induced thrombocytopenia. For these patients, or other patients with a contraindication to unfractionated heparin, direct thrombin inhibitors or factor XIIa inhibitors should be used. Naturally, these options carry a risk of hemorrhagic complication, may be more difficult to titrate, and may pose difficulty in the reversal of anticoagulation if necessary for hemorrhage or procedures [22].

The development of thrombus not only occurs within the patient's native vasculature, but thrombus can develop throughout the ECMO circuit. Oxygenators, connectors, and stopcocks are needed for thrombus formation, due to disrupted local blood flow patterns, non-physiologic shear stresses, and foreign surfaces. Thrombus developed within the ECMO circuit can embolize, and cerebrovascular event such as ischemic stroke and limb ischemia secondary to thromboembolism are of major concern [19].

4.4. Cerebrovascular events

Cerebrovascular events, while on prolonged ECMO therapy can be devastating, leading to increased mortality, permanent neurological deficits, and, in bridge-to-transplant patients, loss of transplant candidacy. Any sudden change to neurologic function in the ECMO patient warrants further workup, including full neurological examination and imaging. If applicable, sedation should be weaned to facilitate accurate neurological examination. Cerebrovascular events can be broadly categorized into hemorrhagic or ischemic stroke. The prolonged exposure to therapeutic anticoagulation places these patients at an increased risk of hemorrhagic stroke [19]. As discussed, hemorrhagic stroke is classified as a major bleeding event, and immediate management is necessary.

Despite therapeutic anticoagulation, patients are also at risk for ischemic stroke, as a result of thromboembolism. As discussed in the section on thrombosis, prolonged ECMO therapy

creates disturbances to blood flow, presence of a foreign body, endothelial injury, chronic illness, and non-physiologic shear stress—all of which increase the risk of thromboembolism. For patients on venoarterial ECMO, or in patients with an atrial septal defect or pulmonary arteriovenous malformation, thrombus from the ECMO circuit can travel to the systemic circulation and potentially embolize in the cerebral vasculature.

Cerebral ischemia can also occur without embolus. In patients on venoarterial ECMO with blood return in the femoral artery, it is possible for the great vessels to receive poorly oxygenated blood from the dysfunctional lungs, while the remainder of the body is perfused by well-oxygenated blood from the ECMO circuit. This phenomenon, known as Harlequin syndrome, can lead to chronic cerebral hypoxia [23]. Like other cerebrovascular events, this condition warrants immediate investigation and remedy. There are multiple solutions to this inadequate mixing, ranging from repositioning of the arterial return cannula within the femoral artery, conversion to veno-venoarterial ECMO (which delivers oxygenated blood to the right atrium as well as the arterial circulation), central cannulation of the aorta, or operative cannulation of the subclavian vessels.

4.5. Acute kidney injury

Acute kidney injury (AKI) secondary to ECMO therapy is a relatively common occurrence and is associated with a fourfold increase in mortality when it progresses to chronic kidney disease or end-stage renal failure. The development of AKI is common in critical illness and the underlying disease process necessitating ECMO initiation places the patient at risk for AKI. Additionally, ECMO itself can exacerbate the progression of AKI, due to potential changes to renal perfusion, chronic inflammation resulting in renal injury, changes to endocrine homeostasis, as well as the risk of exposure to nephrotoxic substances during a period of prolonged critical care [24].

4.6. Infection

Patients on long-term ECMO therapy are at significant risk of infectious complications. The combined presence of critical illness, chronic blood-contacting medical devices, and an ICU stay greatly increase the likelihood of infection. Patients on long-term ECMO who develop a systemic infection have an increased mortality rate, possibility for loss of transplant candidacy, and increased complexity of care. Many patients decompensate to a level requiring ECMO as a result of an infectious process, with pneumonia a common presenting condition. Due to the presence of indwelling cannulae, bloodstream infection is a major concern in caring for the ECMO patient. For the long-term ECMO patient, prolonged exposure to nosocomial pathogens is of particular concern, as these pathogens are likely to exhibit multidrug resistance. Cannula site infections may also occur, which require re-cannulation at a distant site, as well as debridement and drainage of the infected cannulation site. Infection at a cannulation site places patients at risk for vascular complications, such as hemorrhage, hematoma, arteriovenous fistula formation, or development of an aneurysm or pseudoaneurysm. Treatment of the infected ECMO patient can be a particular challenge, and consultation with Infectious Disease specialists is often required. The gas exchange requirements of the ECMO circuit result in the development of a large surface area, which results in a large foreign attachment site for bacteria.

Development of biofilms and reduced antimicrobial penetration within the ECMO circuit are factors which contribute to difficult treatment of these patients [18, 19, 25, 26].

5. Rehabilitation

Like all patients with organ failure, patients requiring ECMO therapy for cardiac or respiratory failure are critically ill and are subject to ICU-related complications, deconditioning, and muscle wasting. In the earliest applications of ECMO, patients were highly sedated and immobilized. With technological developments and advancements in ECMO patient management, the once sedated ECMO patient has now been awakened and extubated. In the population of patients with respiratory failure, the awake ECMO technique showed promising results, with improved survival over sedated ECMO patients and mechanically ventilated patients. Currently, patients on ECMO frequently receive physical therapy, with ambulatory physical therapy the goal for many patients.

Physical therapy in the ECMO patient begins with stationary strengthening and mobility exercises, performed supine while in their ICU bed. These typically consist of core strengthening, limb raises, and stretching. The patient is then progressed to exercises while sitting on their bed, with strengthening of their core and limbs, as well as sitting balance as a goal. When tolerating this, the patient can be transitioned to a chair to be out of bed for a period of each day. With assistance, the patient on ECMO can stand and then ambulate [27].

Patients who cannot ambulate due to either preexisting mobility deficits or incompatible cannulation sites can exercise using a stationary bicycle or an upper body hand bike. In general, access of the femoral vessels limits the ability of patients to ambulate while on ECMO, and for the long-term ECMO patient, transition to other cannulation sites may be necessary. Notably, femoral cannulation is not an absolute contraindication to ambulation, and many centers ambulate patients on ECMO despite venous and arterial access to the femoral vessels.

The approach to ambulatory physical therapy begins with patient preparation, with many centers electing to free the femoral vessels from cannulation as a first step. With adequate ECMO oxygenation, patients may then be extubated if possible; if patients are not candidates for extubation, placement of a tracheostomy can facilitate secretion management, weaning from the ventilator, and weaning of sedation. Following these preparatory procedures, the patient is ready to begin active physical therapy, culminating in ambulation. This is a resource-intensive task, requiring physicians, nurses, perfusionists, respiratory therapists, physical therapists, and assistants. Particular attention must be paid to cannula management, as cannula dislodgement has significant adverse consequences [28].

6. Ethical considerations

Since the earliest use of ECMO for short-term life support, the technology has produced ethical dilemmas. The earliest ECMO systems exposed patients to significant risk of morbidity

and mortality, and it was not until maturation of the technology and critical care that ECMO could clearly demonstrate benefit to patients. The decision to cannulate a patient and initiate ECMO therapy is viewed as the pinnacle of aggressive modern critical care, and early identification of a decannulation strategy can pose an ethical concern. This is particularly important for patients who are unlikely to recover and will not be a candidate for transplantation. For the patient supported on ECMO for a prolonged duration, the principle ethical concern arises when determining that continuation of ECMO therapy is futile, and this section explores the concept. Indeed, the ethical dilemmas surrounding ECMO may have contributed to the use of ECMO for long-term treatment, as disagreements between the patient's family and treatment teams can result in prolonged duration of ECMO therapy.

A reported case of a 44-year-old patient who received 37 days of venovenous ECMO for severe *Klebsiella pneumonia* offers an insight into the ethical conundrum facing patients, their family, and the medical team. The case reports that the patient was not a candidate for lung transplant and was treated with long-term venovenous ECMO due to severe respiratory failure. With radiographic signs of irreversible lung damage, the treatment team recommended discontinuation of ECMO. The patient's family would not accept this outcome, however, and despite support from the hospital ethics board to withdraw care, threats of medicolegal action challenged the transition to comfort care. Ultimately, the patient died on day 88 of ECMO after deteriorating with septic shock. This case highlights important guidelines to be established to prevent ethical disagreements with patients and family members. Specifically, the authors suggest that ECMO centers specify (1) guidelines for patient selection, (2) consent process, (3) family engagement and education, (4) protocols for circuit configuration and concomitant care, (5) duration of ECMO therapy, (6) futility, (7) managing impasse, and (8) Quality Assurance [29]. The authors specify that the consent process should include indications for ECMO withdrawal in case of futility and further indicate that venoarterial ECMO of greater than 3 weeks or venovenous ECMO for greater than 3 months should be considered as unusual circumstances.

The management of ECMO therapy in patients without a decannulation strategy is further complicated when the patient is awake and an active participant in their care. A case report by Moon et al. presented a 53-year-old patient on venovenous ECMO for acute respiratory failure [30]. After 4 weeks of ECMO treatment, recovery of native lung function appeared unlikely, and a lung transplant was suggested to the patient. The patient refused transplantation due to cost and unspecified personal concerns, however. After discussion with the center's ethics committee, a written do not resuscitate (DNR) was obtained and the plan to forgo further oxygenator changes was agreed upon. After 95 days of ECMO therapy, however, the patient showed signs of radiographic improvement, and he was successfully weaned off ECMO care after 104 days. Due to the novelty of prolonged ECMO therapy, it remains a challenge for physicians to fully define the futility of treatment, as it is unclear which patients will recover on prolonged ECMO treatment.

In 2013, a physician survey was conducted to examine the nature of authoritative decision-making during venoarterial ECMO care [31]. The purpose of the study was to assess physician attitudes toward the doctor-patient engagement in ECMO therapy versus a medical professional dominated form of decision-making. This survey of 179 physicians concluded that the majority of physicians with experience in administration of venoarterial ECMO are in favor of physicians having authority for decision-making. The majority of the physicians surveyed also

felt that authority in decision-making should extend to termination of venoarterial ECMO therapy against the wishes of the patient's surrogate. They credited this finding to the perceived complexity of the technology and the inability to properly inform and educate the patient and patient surrogates. Without suitable patient and patient surrogate understanding of the complex treatment plan, proper joint decision-making in ECMO therapy may be difficult to achieve.

The ethical dilemmas surrounding long-term ECMO therapy highlight the importance of maintaining good rapport with both the patient and their family. The technology surrounding ECMO is complex, and it is important for the physicians to have honest conversations with patients and their families to ensure that the benefits, risks, and limitations of ECMO therapy are well understood. One can envision a future where technological and therapeutic advancements obviate the need for careful navigation of ethical issues, but at present, the onus is on the physician to bridge the gap between patient preferences and realistic outcomes.

7. Future directions

If current trends are indicative of the future, ECMO will continue to be used for long-term respiratory and circulatory support, with the duration of support continuing to increase. Currently, animal studies in ECMO are focusing on high-mobility devices, with the current designs being compact, paracorporeal, and portable. The immediate goal of these devices is to allow the patients to freely ambulate with minimal assistance, with the long-term goal of allowing patients to leave the ICU, and possibly leave the hospital.

Advances in control systems may allow for the development of adaptive ECMO systems, which can automatically modify the blood and sweep gas flows to match the metabolic demands of patients. These devices aim to allow for increased mobility, greater device efficiency (and smaller size), and improved safety. Currently, such devices are in benchtop or animal studies, without incorporation into clinical practice. In one study of six adult pigs placed on venovenous ECMO, a control system was able to maintain automated blood and sweep gas flows over a 6-hour period [32]. Other such reports exist in the literature, and ECMO is ripe for application of advancements in biomedical engineering.

One further area of investigation is the use of novel surface coatings to reduce the need for anticoagulation and improve the biocompatibility of the ECMO circuit. Development in this area will reduce the risk of hemorrhagic and thromboembolic complications associated with ECMO and may prove to reduce immune cell activation and infectious complications as well.

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