Extracorporeal Membrane Oxygenation Management

Techniques to Liberate from Extracorporeal Membrane Oxygenation and Manage Post–Intensive Care Unit Issues

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KEYWORDS

• Decannulation • Weaning • Complications • Rehabilitation • Palliative

KEY POINTS

- Once extracorporeal membrane oxygenation (ECMO) has been established, attention must be directed toward optimizing recovery, minimizing complications, minimizing end-organ damage, and ultimately weaning patients from ECMO support.
- Detailed understanding of the weaning process and application of validated weaning techniques can greatly improve patient outcomes.
- Post-ECMO patients often require physical, occupational, and speech therapy in addition to assistance with nutritional issues.
- Recent studies have shown that both physical and emotional domains improved with longer follow-up after ECMO.

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a life-saving technique used in circumstances when patients require pulmonary and/or cardiac support for days to weeks for recovery, bridge to decision, or transplantation.[1] Over the past several decades, ECMO has evolved to provide cardiopulmonary support to patients recovering from lung failure; heart failure; trauma; acute arrest; and pretransplantation, during transplantation, or post–cardiac transplantation or post-lung transplantation in both children and adults. More recently, ECMO has been used for temporary

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support to allow diagnostics, recovery, or determination of eligibility or availability of a suitable donor organ. Decades of publications and educational materials have addressed the management of ECMO in different settings and populations. Little has been written regarding post-ECMO management and optimal rehabilitation of the ECMO survivor. In many ways, the post-ECMO period recapitulates the entire field of critical care.

COMPLICATIONS

As ECMO continues to evolve so does its safety profile. Nevertheless, it remains an invasive therapy with requirement for extracorporeal circulation of the patient's blood volume to remove carbon dioxide and oxygenate red blood cells before returning blood to the patient's body. Caregivers must be particularly vigilant to prevent or minimize the complications that may arise while a patient is on ECMO to lessen the burdens of post-ICU care.

WEANING FROM EXTRACORPOREAL MEMBRANE OXYGENATION

Due to the complications associated with ECMO, as discussed previously, it is best to keep patients on ECMO as little time as necessary to accomplish recovery, a bridge to destination therapy, transplant, or withdrawal. Patients can potentially be on ECMO for several days to weeks to months. As the technology of ECMO has improved and complications have decreased, the risk/benefit of longer ECMO runs has improved. Recruitment maneuvers should be performed prior to the weaning trial to optimize lung function. Also, according to Extracorporeal Life Support Organization guidelines, hepatic function should have recovered prior to any attempt to wean patients from ECMO, irrespective of the findings of cardiac assessment. Once a patient demonstrates good performance with no support from the oxygenator, the cannulas may be removed, either percutaneous (with pressure) or open (with direct vascular control or repair). Either can be done at the bedside or in the operating room with the patient sedated and monitored. In an international survey that analyzed 141 responses from 283 Extracorporeal Life Support Organization–registered ECMO centers contacted across 28 countries, 90% of the centers favored weaning patients from the ECMO circuit before weaning from the ventilator.[2]

Weaning protocols at the authors' center have been streamlined to a standardized method. The principles of weaning from ECMO no matter the etiology require the following pre-weaning parameters: clear chest radiograph, afebrile, euvolemia, and resolution/treatment options (left ventricular assist device [LVAD], total artificial heart [TAH], and transplantation) of the first problem. Failure to respect the principles results in unsuccessful outcomes.

Weaning from VV support in the setting of respiratory failure alone is somewhat subjective but involves an amalgamation of the data derived from a patient's overall pulmonary performance from current ventilator parameters, including oxygen requirements, compliance, and radiologic evidence of resolution of the initial insult. The goal of weaning should be successful conversion to conventional modes of ventilatory support without the need for ECMO support.

In the circumstances of dual system failure, such as cardiac stunning secondary to a hypoxic event, successful weaning involves encompassing a combination of both approaches. Regardless of which mode of support is weaned from, the primary mandate remains that there must be resolution of the original organ system insult to allow for ongoing physiologic stability without ECMO support or an alternative capability to

take over its function. An example is transition to an LVAD from VA-ECMO in the setting of unresolved left ventricular (LV) dysfunction in the appropriate candidate.

Weaning from venovenous–extracorporeal membrane oxygenation

The methods for weaning from venovenous (VV)-ECMO differ from those for venoarterial (VA)-ECMO (Table 1). Based on the type of ECMO, multiple breathing tests are usually done prior to the discontinuation of ECMO to confirm that the heart and lungs are ready. For years, measures of respiratory mechanics served as a surrogate to determine a patients' ability to breathe on their own. These measures have included minute ventilation, vital capacity, maximum inspiratory force (also called negative inspiratory force), and respiratory rate.

VV-ECMO trials are performed by eliminating all countercurrent sweep gas through the oxygenator. Circuit flow does not need to be reduced, and extracorporeal blood flow remains constant so no additional heparin is required.[3] Systemic arterial oxygen saturation and pCO_2 should be monitored closely, and lung ventilation should be increased to ensure adequate CO_2 clearance as indicated by arterial and venous blood gas results. The authors observe patients for 4 hours to 24 hours with ventilation at nonharmful settings and the gas flow to the ECMO circuit at 0 L/min. If parameters remain stable, patients are ready to be removed from VV-ECMO.

Weaning from venoarterial–extracorporeal membrane oxygenation

Formal weaning studies must be performed to ascertain if a patient's heart is capable of circulatory support without VA-ECMO. VA-ECMO weaning trials require temporary clamping of both the drainage and infusion lines, while allowing the ECMO circuit to circulate through a bridge between the arterial and venous limbs. This prevents thrombosis of stagnant blood within the ECMO circuit. In addition, the arterial and venous lines should be flushed continuously with heparinized saline or intermittently with heparinized blood from the circuit. Once the native circulation can be sustained by the native heart, gas flow is reduced from 2.5 L/min by 0.5 L/min increments while assessing both hemodynamic and echocardiographic changes, and lung ventilation is increased. In general, VA-ECMO trials are shorter in duration than VV-ECMO trials because of the higher risk of thrombus formation. Once cardiac function is improved,

Table 1
Difference in methods for weaning from venovenous–extracorporeal membrane oxygenation differ from those for venoarterial–extracorporeal membrane oxygenation

Venovenous	Venoarterial
• Maintain ECMO flow rate	• Heparin so activated clotting time >400 to decrease risk clotting
• Re-establish patent's full ventilation	• Decrease pump flow 1 L while ventricular function assessed by TEE
• Turn off O_2 to oxygenator	• Period of low-flow ECMO before decannulation ○ Respiratory function is a concern: turn off gas flow (only at circuit flows $\leq$1.5 L/min) and assess oxygenation achieved using the ventilator exclusively. Note: in this situation, the circuit flow acts as a right-to-left shunt. If adequate oxygenation and CO_2 removal can be maintained in the presence of this shunt, it is likely that respiratory failure can be managed without ECMO.
• 6-h stability, then decannulation	• If O_2 good and CO_2 managed by ventilation, consider decannulation.

ECMO removal is scheduled; however, ECMO flow should be maintained above 2.5 L/min until decannulation. An algorithmic approach to weaning from VA-ECMO is outlined in Fig. 1.

Venoarterial Extracorporeal Membrane Oxygenation Weaning for Cardiogenic Shock

For patients who require VA-ECMO secondary to myocardial stunning from cardiogenic shock second to acute myocardial infarction, postcardiotomy failure, right ventricular (RV) failure secondary to pulmonary embolism or cardiac dysfunction, primary graft failure after cardiac transplantation, or other etiologies compromising hemodynamic stability, the anticipation is that the cardiac function will recover within a realistic time frame to allow for weaning off ECMO or as a bridge to support devices. Myocardial recovery typically occurs in the range of 7 days to 10 days. Although a majority of cases are secondary to primary LV dysfunction, the issue of interventricular dependency and secondary RV dysfunction makes information from traditional subjective trials difficult to use with standard hemodynamic monitoring. Determination of cardiac

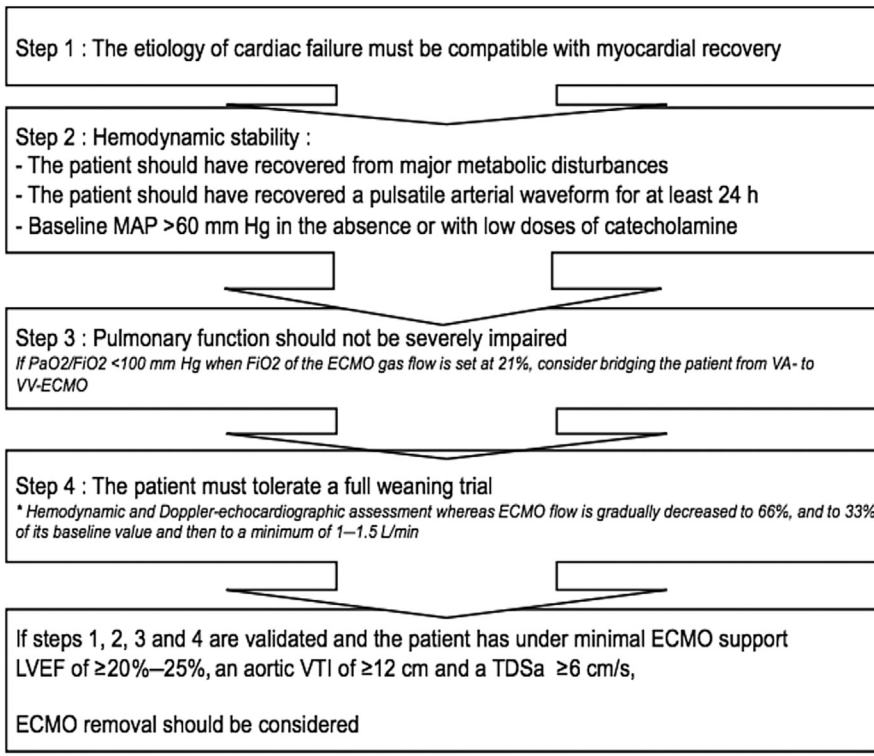

Fig. 1. Recommendations for successful weaning from VA-ECMO. CI, cardiac index; CVP, central venous pressure; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; TDS, tissue Doppler systolic velocity; VTI, velocity-time integration. (*From* Aissaoui N, Brehm C, El-Banayosy A, et al. Weaning strategy from veno-arterial extracorporeal membrane oxygenation (ECMO). In: Firsternberg MS, editor. Extracorporeal membrane oxygenation – advances in therapy. InTech Online Publishers: 2016. Available at: http://www.intechopen.com/books/extracorporeal-membrane-oxygenation-advances-in-therapy/weaning-strategy-from-veno-arterial-extracorporeal-membrane-oxygenation-ecmo.)

output using the Swan-Ganz catheter is negated by the negative pressure generated in the right atrium by the ECMO circuit; this obscures any accurate readings.[4] Real-time dynamic changes of the ventricle function during ECMO weaning would not be reflected by serial mixed venous oxygen saturation assessments, which require both the presence of a pulmonary catheter and time gaps between sampling.[5]

Failure to accurately evaluate either biventricular, or at least univentricular, recovery would carry significant potential for morbidity and mortality in any subsequent LVAD intervention. A patient assumed to have only ongoing LV dysfunction after a subjective ECMO wean failure may go on to an LVAD with a difficult and potentially fatal outcome when ongoing RV dysfunction was not recognized and the patient should have been accessed for biventricular device support or transplantation.[6] When RV failure exists in the setting of an LVAD implantation, the perioperative mortality rate increases to as high as 19% to 43%.[7] Prior to weaning the patient from ECMO, any end-organ dysfunction resulting from the pre-ECMO insult needs to be recovered to baseline.[8] Elevated lactate, significant hepatic dysfunction, and renal derangement need to be corrected. The patient needs to be afebrile and euvolemic and to demonstrate resolution of pulmonary edema on x-ray films. The fraction of inspired oxygen (FiO_2) on both the ECMO and ventilator circuits must be weaned to 50%, allowing for an acceptable upper extremity PaO_2 and saturation. The authors' institution follows an anticoagulation protocol with titration of a partial thromboplastin time (PTT) normally between 45 seconds and 55 seconds. During the weaning trial, the authors increase the PTT to 60 seconds to 70 seconds to avoid thrombotic complications while decreasing ECMO flow. The authors prefer the use of a miniaturized hemodynamic transesophageal echocardiography (hTEE) probe to access biventricular function and filling during the course of the weaning process.[9,10] The weaning process is staged to allow for progressive weaning of support while observing cardiac performance, with volume loading on reduction to half-baseline flow and finally to 1-L flow with a dobutamine drip added to demonstrate increased contractility as evidence of potential inotropic rescue if needed.

Attending ICU staff need skills to be comfortable with the use of hTEE, transthoracic echocardiogram (TTE), or transesophageal echocardiogram (TEE) and its interpretation. It is possible to follow the protocol, discussed previously, using staged bedside TTE performed by echocardiography technicians, as is the routine at many institutions. This, however, can be not only problematic from the viewpoint of availability of staff during the weaning intervals, with the weaning process taking from 4 hours to 6 hours, but also limited by the individualized body habitus of a patient, which can limit available windows for a TTE. Traditional TEE performed by a cardiologist represents an excessive commitment of resources and personnel, which is unrealistic in most hospitals. Bedside hTEE weaning has allowed the authors' center to have a positive predictive value for ventricular recovery of 100% using a standardized ECMO weaning protocol (95% CI, 73%–100%). The authors have had no major complications with the use of hTEE whereas those quoted for regular TEE are 0.2% to 0.5% per insertion. The only interval complication that has occurred has been oral-pharyngeal bleeding in a small number of patients who have required packing secondary to difficulty in passing the probe.[11–14] The weaning protocol has allowed for definitive decision making to be able to wean off ECMO, allow surgical planning to transition to an LVAD in cases of ongoing univentricular LV failure or in cases of ongoing biventricular failure transition to mechanical biventricular support or transplantation. If a patient with biventricular failure is deemed to not be a candidate for advanced mechanical support or transplantation, then appropriate preparations can be made with the family for withdrawal. The authors' weaning protocol is easily reproducible in an ICU setting and is consistently

accurate. As a result, patients can be taken to an operating room for decannulation without unexpected weaning failures intraoperatively or undergo insertion of an LVAD minimizing the potential for an unpredicted need for a RV assist device or excessive inotropic in the setting of unrecognized RV dysfunction, as discussed previously. A summary of the VA weaning protocol is outlined in Table 2.[9]

Weaning from VV-ECMO requires the resolution of the primary issues, which may require an extended amount of time. The mantra is to be patient. The principles of weaning from VV-ECMO require the following: clear chest radiograph, afebrile, euvolemia, and resolution/treatment options (LVAD, TAH, and transplantation) of the first problem. Failure to respect the principles results in unsuccessful outcomes. The FiO_2 on both the ventilation and ECMO circuit should be weaned down to 50% or lower, with sweep less than 3 to 4 before considering weaning. The maneuvers involved in the initial weaning for VV-ECMO are (1) wean down the sweep without any increase in tidal volume, which indicates if patient lung with low volumes will remove CO_2; if successful, proceed to full weaning; (2) if step 1 is unsuccessful, wean sweep and increase tidal volumes, which should allow for adequate CO_2 removal; if successful, wean off, and, if unsuccessful, stop weaning and try another day; and (3) if step 2 is successful, wean ECMO flow down progressively while returning to standard mode of mechanical ventilation without high plateau and PEEP pressures; if successful, ECMO weaning is possible and open surgical repair is suggested for decannulation. Postdecannulation systemic inflammatory response syndrome (SIRS) has been reported to occur in approximately 60% of patients and requires attention and fever work-up. The reported observed series from the authors' group

Table 2
venoarterial–extracorporeal membrane oxygenation weaning protocol using hemodynamic transesophageal echocardiography

Stages of Separation	Actions
Prewean assessment	Prerequisite: patient is euvolemic and afebrile, chest radiograph is clear, and end-organ injury is resolved. Increase heparinization for PTT goal 60–70 s. Insert hTEE probe.
Stage 1	Baseline assessment of RV and LV functions with full ECMO flow.
Stage 2	Decrease flow from full flow to half-flow in increments of 0.5 L/min and assess LV and RV functions by hTEE over at least 0.5 h after each decrease. If distention occurs, return to full flow and abort trial.
Stage 3	Volume load (10 mL/kg)/20 min, with half-flow and assess RV and LV functions by hTEE over at least 1 h.
Stage 4	Load inotrope (dobutamine and/or milrinone), decrease flow to minimum (1–1.5/min), and assess LV and RV functions at least 1 h.
Postweaning assessment	If biventricular failure persists, consideration of end-of-life discussion should begin. If LV dysfunction persists but RV function is recovered, consider LVAD insertion. If RV dysfunction persists but LV function is recovered, consider external RV assist device. If both LV and RV functions are recovered, consider ECMO decannulation. Return to full flow and discuss timing of surgical intervention.
After weaning	Return to full flow and discuss timing of surgical intervention.

demonstrated that approximately 80% of patients had fever, approximately 70% had leukocytosis, and approximately 50% had escalation of vasopressor requirement[9] (see **Table 2**).

POST–EXTRACORPOREAL MEMBRANE OXYGENATION MANAGEMENT

After weaning from ECMO, there are still many things to be addressed. Among these are (1) potential for SIRS post-decannulation; (2) post-ECMO complications, such as deep vein thrombosis, wounds, renal failure, and stroke; (3) delirium; (4) posttraumatic stress disorder (PTSD); (5) rehabilitation; and (6) end of life.

Systemic Inflammatory Response Syndrome

SIRS is a common occurrence after ECMO. The length of time a patient's blood is exposed to the nonendothelialized surface of the cannula and extracorporeal circuit during ECMO may be responsible for the widespread activation of the innate immune system[15] and bacteremia.[16] If unchecked, inflammation and organ injury follow. Similarly, long-term ventilator support may increase the chance of ventilator associated pneumonia and subsequent development of sepsis.[5]

In a recent retrospective, single-institution study of 62 patients from Thangappan and colleagues,[17] both post-ECMO SIRS phenomenon (approximately 60%) and post-decannulation infection (approximately 60%, including infection carried over during ECMO, and approximately 35% newly developed infection after ECMO decannulation) were found common. The differentiation between SIRS and infection, however, can be difficult. In the study from Thangappan and colleagues,[17] the outcomes in patients with post-ECMO infection were poor whereas 100% of patients with SIRS only survived. Patients with suspected SIRS should be treated similarly to patients with infection with broad-spectrum antibiotics until culture results are available, and perhaps as a preventive measure antibiotics should be considered for the first 24 hours post-decannulation.

Post–Extracorporeal Membrane Oxygenation Complications

A recent meta-analysis reviewed published peer-reviewed studies related to ECMO, focusing on outcomes and complications of ECMO in adult patients; 12 studies and 1763 patients were included.[18] The most common complications associated with ECMO were found to be renal failure requiring continuous venovenous hemofiltration or short-term dialysis (occurring in 52%), bacterial pneumonia (33%), any bleeding (33%), oxygenator dysfunction requiring replacement (29%), sepsis (26%), hemolysis (18%), liver dysfunction (16%), leg ischemia (10%), venous thrombosis (10%), central nervous system complications (8%), gastrointestinal bleeding (7%), aspiration pneumonia (5%), and disseminated intravascular coagulation (5%).[18] When coming off ECMO, many patients require long-term ventilation with tracheostomy, respiratory therapy, and wound care for the various ports of entry associated with ECMO. Several studies have found, however, that both physical and emotional domains improved with longer follow-up.[19–21]

Delirium

Delirium affects mortality, length of stay, cost of care, and quality of life. As the application of ECMO has expanded, more patients are treated for weeks, even months. Such prolonged periods invite increasing opportunity for ICU delirium. Conditions that are associated with ECMO contributing to delirium include drug inducement, addiction withdrawal, sepsis, electrolyte abnormalities, nutritional deficiencies, and,

in general, organ failure. Common to all ECMO is the setting for drug-induced encephalopathy. Both approaches to sedation are vulnerable. Too much sedation encourages ICU psychosis, frailty, deconditioning, deep vein thrombosis, decubitus ulcers, and other vegetative complications and increases the risk of delirium and long-term cognitive impairment.[22] Recently, enthusiasm has increased for awake and ambulatory patients on ECMO. Although many of the problems seen with over-sedation are alleviated, PTSD, discussed later, has emerged.

Several drugs are associated with anticholinergic delirium (**Table 3**).

Other common ICU medications also contribute to drug-induced delirium, including norepinephrine—α_2-agonists and opioids; serotonin—antipsychotics and antidepressants (also have anticholinergic effects); histamine—antihistamines (also have anticholinergic effects); *N*-methyl-D-aspartate (glutamate) antagonists—ketamine; and γ-aminobutyric acid modulators—barbiturates, benzodiazepines, hypnotics, inhalational anesthetics, and ethanol. Clearly, many opportunities exist to receive 1 or more of these drugs. Often, patients and families minimize the degree of alcohol dependency; therefore, alcohol withdrawal is also common in the ICU setting. Increasingly, recreational drug dependencies and withdrawal are seen. Sepsis is both a reason for ECMO and a complication of ECMO.

Electrolyte abnormalities are often seen during ECMO. Although total parenteral nutrition was previously associated with this problem, enteral nutrition with gastrointestinal motility and absorption abnormalities plus diuretic use often contribute to sodium imbalance. During respiratory failure, CO_2 retention has been associated with delirium, especially at levels seen with permissive hypercapnia. Organ failure can directly contribute to encephalopathy. Although outside the scope of this review, hepatic encephalopathy, uremic encephalopathy, and nutritional deficiencies (thiamine, vitamin B_6, and niacin) are all well-recognized causes of delirium that can confuse ECMO management.

Most importantly, delirium must be not only recognized but also prevented. Approaches that modify risk factors include limiting sedation with benzodiazepines, nonopioid analgesia, early mobilization, early liberation from ventilator, removal of catheters and restraints, correcting electrolytes, reducing noise and limiting exposure to artificial light at night (turn off TVs), normalizing sleep-wake cycles (preferably nonpharmacologically), encouraging social interaction, improving communication with patients, reorienting patients as needed, providing cognitive stimulation, and, finally, putting on their glasses and/or hearing aids.

Posttraumatic Stress Disorder

Current evidence from observational studies suggests that ECMO survivors have high rates of adverse mental health outcomes, including PTSD.[22–24] There are several factors that may cause a patient to develop PTSD after ECMO weaning. These include

Table 3
Mechanism contributing to anticholinergic delirium

Mechanism	Examples
Predominant muscarinic antagonists	Atropine, scopolamine, hyoscine, benztropine includes many plants
Muscarinic antagonists with other mixed effects	Antihistamines, tricyclic antidepressants, antipsychotics
Decrease acetylcholine release	Carbamazepine, opiates, cannabinoids, ethanol, Clonidine
Decrease acetylcholine synthesis	Thiamine deficiency

young age, mechanical ventilation, illness severity, drug administration, heterogeneous conditions, delirium, agitation, prolonged ICU stay, and memory of in-ICU experiences. Memory of distressing in-ICU experiences is the longest-term post-ICU PTSD risk factor.[25,26] Patients in the ICU are increasingly conscious during active treatment, and awake ECMO, in which patients are conscious, may represent a unique PTSD risk factor.[27] In the PRESERVE (Predicting the Safety and Effectiveness of Inferior Vena Cava Filters) study, data from 140 ECMO-treated acute respiratory distress syndrome patients admitted to 3 French ICUs (2008–2012) were analyzed, including health-related quality of life surveys. Health-related quality of life evaluation in 80% of the 6-month survivors revealed satisfactory mental health but persistent physical and emotional-related difficulties, with anxiety (34%), depression (25%), and PTSD (16%) symptoms reported.[25]

Although some patients only require ECMO for a few days or weeks, others have remained on ECMO and in the hospital for months. In these instances, a psychologist who interacts with patients and families is advised to help with the anxiety and stress of going through such a traumatic event.

Rehabilitation

Post-ECMO patients often require physical, occupational, and speech therapy in addition to assistance with nutritional issues. With the development of ambulatory ECMO, active rehabilitation and physical therapy can continue as patients heal or as they wait for transplantations even before weaning from ECMO. Patients who receive early rehabilitation have improved rates of return to independent functioning, decreased rates of delirium, and shorter durations of mechanical ventilation, ICU length of stay, and hospital length of stay.[25,28–31]

End-of-Life Issues

Weaning from ECMO does not always signify patient improvement or survival. Due to factors, such as age and comorbid conditions, ECMO is not always life-saving. There are times when a health care team has to discuss with patients and their families the fact that they simply cannot recover. Most hospitals that provide ECMO have a dedicated palliative care team, which becomes involved as soon as patients are put on ECMO and follows them throughout their hospitalization, in addition to providing support for patients' families.

SUMMARY

The recent success of ECMO is a consequence of both significant advances in technology of the components of the circuit as well as ECMO configuration that allows the use of ECMO in awake and ambulatory patients. The objectives are to improve the preoperative condition of the by enhancing physical strength and cardiovascular fitness and reducing the risk for post-transplant complications.

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