ECMO in lung transplant: pre, intra and post-operative utilization—a narrative review

Jose P. Garcia[1,2], Cristina L. Ashworth[1], Chadi A. Hage[3]

[1]Thoracic Transplantation, Artificial Heart and Lung Programs, Indiana University Health Methodist Hospital, Indianapolis, IN, USA; [2]Department of Thoracic and Cardiovascular Surgery, Indiana University School of Medicine, IU Health Methodist Hospital, Indianapolis, IN, USA; [3]University of Pittsburgh, Pulmonary, Allergy and Critical Care Medicine, UPMC Lung Transplant Program, Pittsburgh, PA, USA

Contributions: (I) Conception and design: JP Garcia; (II) Administrative support: C Ashworth; (III) Provision of study materials or patients: C Ashworth; (IV) Collection and assembly of data: JP Garcia, C Ashworth; (V) Data analysis and interpretation: JP Garcia; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jose P. Garcia, MD. Surgical Director, Thoracic Transplantation and Artificial Heart and Lung Programs, Indiana University Health System- Methodist Hospital; Associate Professor of Clinical Surgery, Thoracic and Cardiovascular Surgery, Indiana University School of Medicine, IU Health Methodist Hospital, Professional Center 2, 1801 N Senate Boulevard, Suite 2000, Indianapolis, IN 46202, USA. Email: jgarcia9@iuhealth.org.

Objective: The goal of this chapter is to evaluate the use of extracorporeal membrane oxygenation (ECMO) in the lung transplant patient. ECMO will be evaluated pre, intra and post-operative lung transplant with discussion on cannulation, benefits and risks that can affect patient outcomes.

Background: Patients with end-stage lung disease (ESLD) unresponsive to medical therapy will succumb to their disease unless they undergo lung transplantation which remains the gold standard for treatment. Unfortunately, there are not enough donors to meet the demand of the united network for organ sharing (UNOS) waitlist. Due to donor shortage and long wait times, some patients will not survive to transplant. The introduction of the current allocation system for lungs in 2005 was aimed to improve donor organ allocation and outcomes by determining disease burden and risk factors allowing for transplantation of the sickest patients first. ECMO is a form of temporary mechanical support that removes CO_2 and oxygenates the blood and can also provide hemodynamic support if needed. ECMO technology has rapidly expanded over the last 15 years and is now being used to support patients as a bridge-to-transplant (BTT), intraoperative pulmonary and/or cardiac support and post-operative support in patients with severe graft dysfunction. Early results utilizing pre-operative ECMO support were not promising before 2010.

Methods: Systematic review of the available literature to investigate ECMO in pre, intra and post-operative lung transplant patients. A systematic review of available research articles was reviewed from 1990 to 2021 to evaluate ECMO as a bridge to transplant. Focusing on the use of ECMO preoperatively, intraoperatively, and post operatively including the risk and benefits to the patient.

Conclusions: Recent studies have shown survival outcomes in ECMO supported recipients comparable to non-ECMO recipients in appropriately selected patients, such as younger patients with single system failure. Intra-operatively, it is increasingly being used for hemodynamic support, especially in patients with fibrotic disease undergoing double lung transplantation via an anterior approach. Hybrid circuits allow for conversion from ECMO to full cardiopulmonary bypass (CPB) and back to ECMO easily. Current reports have also shown a decrease incidence of primary graft dysfunction in double lung transplants that are supported by intra-operative ECMO. With the improvements in ECMO technology and better patient management protocols, we can expect increasing use of this technology in lung transplantation.

Keywords: Extracorporeal membrane oxygenation (ECMO); end-stage lung disease (ESLD); primary graft dysfunction; bridge to lung transplant; pre-, intra- and post-operative ECMO in lung transplant

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Introduction

End-stage lung disease (ESLD) is the result of longstanding diseases such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis/usual interstitial pneumonia (IPF/UIP), cystic fibrosis (CF), alpha-1 anti-trypsin deficiency, primary pulmonary hypertension and rarely lymphangioleiomyomatosis. The only definitive treatment for ESLD is lung transplantation but unfortunately there is a short supply of donor organs that cannot meet the demand. The organ shortage prolongs the waiting time in these patients that cannot survive very long once they are listed. In the United States, lung donor allocation is determined by the lung allocation score (LAS) introduced in 2005 which aims to allocate organs to the sickest patients. The intention of using the LAS was to increase patient survival rates and the overall efficiency in lung transplant outcomes and allocation. The use of the LAS brought about changes as to how patients were brought to transplant because it prioritized transplanting patients with high LAS who are usually at increased risk for operative complications due to frailty and other medical comorbidities. These include patients who are hospitalized due to increased oxygen requirement and those on mechanical ventilation and other support systems. Extracorporeal membrane oxygenation (ECMO) is a form of temporary mechanical support that removes CO_2 and oxygenates the blood and can also provide hemodynamic support. ECMO is a resource intensive technology that can be used for respiratory and/or cardiac support in critically ill patients. ECMO technology has rapidly expanded over the last 15 years and improvements in patient management have led to the use of ECMO to support patients undergoing lung transplant (1). ECMO has been used as a bridge-to-transplant (BTT), intraoperative pulmonary and/or cardiac support and post-operative support in patients with severe graft dysfunction. Of note, although ECMO can be an effective BTT, unfortunately it does not increase LAS for those on the wait list as 100% O_2 on mechanical ventilation as being used as a proxy. We present the following article in accordance with the Narrative Review reporting checklist (available at https://ccts.amegroups.com/article/view/10.21037/ccts-21-29/rc).

Methods

A systematic review of the available literature was performed to investigate ECMO in pre, intra and post-operative lung transplant patients. Searching biomedical databases for primary research material identified literature relevant to ECMO as a bridge to transplant. Databases were searched for publications from 1990 to 2021 to evaluate ECMO as a bridge to transplant with key articles obtained primarily from PubMed, UpToDate and MEDLINE. Search terms were entered broadly and included "extracorporeal membrane oxygenation or ECMO," "ECMO as a bridge to transplant, "ECMO pre lung transplant", "intra operative ECMO," "primary graft dysfunction, " "end-stage lung disease" and "post-operative ECMO." Studies were eligible for consideration in this review if the focus of the study was on ECMO, ECMO used for pre, intra and post-operative lung transplant, ECMO as a bridge to lung transplant or any combination of the two items. A comprehensive search was made of Internet resources nationally and internationally with the Extracorporeal Life Support Organization (ELSO) website and the International ECMO Network website as the primary reference sites.

Narrative

ECMO as a pre-operative bridge

ECMO as a bridge-to-lung transplant was attempted by several institutions before 2010 but the results were not promising. A study by Mason *et al.* based on the United Network for Organ Sharing (UNOS) database examined the results of patients who were bridged to lung transplant using ECMO between 1987–2007. They found that only 51 patients out of 15,934 were bridged and their one year survival rate was only 50% (2). A subsequent study by George *et al.* included 122 lung transplants bridged with ECMO in the UNOS registry documented a one-year survival of 76% (3). It is important to note that the survival rates tended to be better in more recent transplants.

More recent studies have provided better clarification as to which patients can be successfully bridged to lung transplant with ECMO. Hayes *et al.* reported on 198 patients in the UNOS database and found that patients under 40 years of age had survival rates comparable to patients not bridged with ECMO (4). While patients supported with invasive mechanical ventilation (IMV) have shown consistent rates of survival during the period of the UNOS review noted above, ECMO bridging does appear to have a more positive trajectory with increased use. While several variables may be in play in the different outcomes reported, namely that younger patients were more likely to be placed on ECMO (5), the trend is hard to ignore. In more direct comparisons of IMV and ECMO support, another UNOS database study examined 12,000 lung transplants from 2005 to 2013 and included patients requiring ECMO support alone, ECMO and IMV, and IMV alone. One-year survival was decreased in all patients that required any support pre-transplant as opposed to those transplanted without support. However, multivariate analysis showed ECMO + IMV and IMV alone were independently associated with decreased survival compared to non-supported patients whereas ECMO alone was not significantly associated with decreased survival (6). Recent data showed that lung transplants are being performed in patients with higher degree of ESLD as evidenced by the increasing median LAS at time of transplantation. Despite this trend, the overall survival rates have not decreased in the US (7).

More patients are being bridged to transplant with ECMO and there are several reasons as to why this treatment modality is being used and why the outcomes have improved over time. As in any type of treatment attempted, patient selection is of utmost importance. Younger patients and patients with single system organ dysfunction tend to do better with the more aggressive treatments such as ECMO. The early poor patient outcomes that utilized ECMO as a bridge to transplant could be attributed to poor patient selection, but that was not the only reason. Before 2009, patients waiting for a transplant were bed ridden for days to weeks. During that time, they experienced significant deconditioning and were very difficult to rehabilitate after their transplant. Furthermore, they were at a higher risk to develop complications seen in immobilized patients such as pneumonia, bed sores and other infections. From a technological standpoint, several advances were accomplished that made managing the circuit easier and with fewer complications. The development of smaller pumps/consoles such as the CentriMag RVAS (Levitronix® Japan, 2008), the introduction of the dual lumen catheter (Avalon Laboratories® Canada, 2009) and the introduction of more durable oxygenators such as the Quadrox oxygenator (Maquet® Germany, 2010) made mobilization easier and thus significantly improving preoperative rehabilitation (8). The goal of using ECMO for ESLD is to allow for patient mobilization while they gain strength and maintain adequate nutrition. Deconditioning during the bridging period can manifest itself as critical illness myopathy (CIM) and by preventing myopathy, patients can experience a much faster recovery time (9). Active rehabilitation during ECMO has been found to lead to decreased mechanical ventilation days, shorter stays in the ICU and in the hospital after transplant (10). Recent studies have shown similar one-year survival between ECMO supported transplant patients and non-ECMO patients despite significant differences in LAS (7). In that sense, ECMO is now truly considered a bridge to successful transplantation.

Indications

Indications for using ECMO as a bridge-to transplant include rapid deterioration of respiratory function in patients who are otherwise candidates or already listed for lung transplantation, and able to actively participate in physical therapy with no active infections, or other organ dysfunction. Patients that are refractory to standard medical therapy or cannot be mobilized on maximal ventilatory support are potential candidates meeting selection criteria. It is important to point out that patients should be active on the transplant list and be otherwise ready for transplant. There are few circumstances that would allow the use of ECMO as a bridge-to-decision if the patient has not been fully evaluated for transplant such as a very young, previously healthy individual. Patients with pulmonary fibrosis that decompensate and require ECMO will have limited options. They will either be placed on the waitlist and receive the transplant or if they don't meet the criteria, comfort care will be pursued, and support will be withdrawn as a terminal wean (11).

Pre-operative ECMO configuration strategy

The three basic configurations for ECMO are veno-venous (V-V), veno-arterial (V-A), and arterio-venous (A-V) (12). These configurations provide different types of support and should be tailored to the patient needs. Patients who have isolated pulmonary pathology and absence of right ventricular or left ventricular dysfunction, V-V ECMO can provide adequate oxygenation and CO_2 removal, especially when treating non-fibrotic patients. The use of dual lumen catheters make mobilization easier and are ideal if CO_2 removal is the main goal (13). Bridging fibrotic patients can be more difficult as getting oxygenated blood from the right ventricle to the left ventricle becomes harder to achieve as time on ECMO support increases. In these patients, the lungs develop edema and become stiffer and the right ventricle begins to fail leading to decreased cardiac output and right-sided congestion. These patients will require adjustments to the ECMO circuit configuration if more time to find suitable organs is needed.

Most patients that need to be bridged have parenchymal disease that creates severe restricted gas exchange while still maintaining a normal right ventricular function. Patients without severe pulmonary hypertension usually will do well with some form of V-V ECMO. ECMO circuits that utilize dual lumen catheters are ideal for these patients because the patients are easily mobilized and gas exchange including oxygenation and CO_2 removal can be easily accomplished. As placement of dual lumen catheters require imaging guidance, these procedures are best suited for non-emergent cannulation. Strict criteria should be in place and followed prior to mobilizing the patient whatever the configuration. Patients must be able to fully participate in physical therapy, should not be on significant hemodynamic support and have good gas exchange. It is important to note that patients with standard bi-caval cannulation via the right internal jugular (IJ) vein and right femoral vein can still be ambulated safely (14). The femoral limb of the circuit should be closely guarded to prevent accidental de-cannulation. Also, the sutures holding the cannula in place should be checked prior to getting the patient upright. Fem-fem veno-veno is not ideal because of the need to cannulate both femoral veins.

Patients suffering from interstitial lung disease (ILD) and pulmonary arterial hypertension or from primary pulmonary hypertension are not suitable for V-V ECMO as this will not be enough to overcome their gas exchange and hemodynamic limitations. These patients are prone to develop severe right ventricular dysfunction on V-V ECMO, to the point where blood cannot get across to the left ventricle. The low cardiac output and right sided congestion will worsen leading to multi-system organ failure. In patients with right sided dysfunction and only mild to moderate pulmonary hypertension, one might consider the use of a dual lumen catheter, such as the Protek Duo cannula (LivaNova®, PLC, UK), which allows for right atrium (RA) to pulmonary artery (PA) ECMO flow. This configuration serves as an oxy-RVAD and has two major benefits; it provides better gas exchange as the ECMO flow is delivered to the main pulmonary artery. In addition, it allows the right ventricle to "rest" while waiting for transplant. The author has had significant success in bridging patients with right ventricular dysfunction and mild to moderate pulmonary hypertension using an oxy-RVAD, especially with patients who have ILD. Our center uses V-V or V-A ECMO routinely intraoperatively in these patients. The excellent outcomes in use of ECMO in transplant are maybe due to better hemodynamic stability during transplantation.

In some patients, the right IJ vein cannot be cannulated and alternative means for cannulation must be considered. The Avalon dual lumen catheter can be placed percutaneously from the left venous system but not the Protek Duo cannula. Alternatively, the right atrium and the PA can be cannulated directly via a hemi-sternotomy approach. This approach allows for maximum efficiency and does not prohibit either a sternotomy or clamshell approach at the time of transplant. Whatever approach is used for the RA to PA configuration, one must be careful not to overflow into the lungs as this will lead to capillary damage, pulmonary hemorrhage and worsening gas exchange.

Complications with V-V ECMO

There are several issues that can be encountered with inferior vena cava (IVC) to superior vena cava (SVC) V-V ECMO regardless of whether a dual lumen cannula or two single lumen cannulas are being used. Complications seen with V-V ECMO include cerebrovascular accident, renal failure, bleeding, and hypoxia. Cerebrovascular accidents and renal failure usually disqualify a patient from transplant. The bleeding issue is usually easier to manage as anticoagulation can be safely withheld in most of these patients until bleeding is controlled, especially after being on ECMO for several days with the associated platelet dysfunction. Correction of bleeding indices is of utmost importance and any significant bleeding should be aggressively investigated to locate and control the source (15).

Hypoxia on V-V ECMO is not uncommon and might be challenging to manage. There are five possible mechanisms for hypoxia while on V-V ECMO; circuit issues, recirculation, fluid overload, pulmonary shunting or any anatomical or physiological issue that impedes the flow out of the right ventricle (16). Circuit issues are the easiest to address as there are only two possibilities. The first factor that must be ruled out is oxygenator failure and that can be easily done by checking a post membrane arterial blood gas. If the oxygenator is not performing as it should, then an exchange is indicated and must be done cautiously and quickly if the patient is already on maximum ventilatory support. Having arterial access with a small caliber catheter might be prudent and quite helpful if the patient experiences hemodynamic instabilities secondary to hypoxia during the oxygenator exchange and conversion to emergent V-A ECMO is required. Recirculation is usually more common with a bicaval configuration where the IVC and SVC cannula tips are too close to each other creating a loop. This issue can readily be diagnosed by obtaining a CXR and examining the location of the cannula tips. Effective oxygenation requires that 2/3 of the total circulating blood volume is captured and oxygenated by the ECMO circuit. So, if the patient is markedly fluid overloaded, the circuit will not provide enough oxygenated blood to meet body demands and systemic hypoxia will occur. In situations where volume status is difficult to assess, one can up-titrate the ECMO pump speed and observe the increase in flow until chugging on the inflow limb of the circuit is noted. If one can attain high flows (e.g., over 6 L/min) without line chugging and recirculation, especially in a small or average sized patient, then it is safe to conclude that the patient is fluid overloaded.

Achieving adequate oxygenation may be more difficult in patients with significant degree of right-to-left pulmonary shunting due to high disease burden. Inhaled pulmonary vasodilators may be useful in this situation and inotropes can be useful in a failing right ventricle. Lastly, any condition that interferes with forward flow out of the right ventricle will lead to increased recirculation. One must keep a watchful eye in case the patient develops a pericardial effusion with tamponade, failing right ventricle, tricuspid or pulmonary regurgitation or pulmonary hypertension.

Most patients with pulmonary fibrosis requiring ECMO for oxygenation will remain stable for several days before hypoxia becomes an issue. In this situation, several options are possible depending on the existing ECMO configuration. If a dual lumen catheter is being used, a balloon atrial septostomy up to 2 cm can be created to allow for oxygenated blood to flow directly into the left atrium (LA). This requires significant pulmonary hypertension so that blood will flow through the path of least resistance into the LA and not through the tricuspid and out into the lungs (17). A complicating issue with this approach is that the septostomy will usually close within 5–7 days and will require a second intervention. If the septostomy is stented, then that will require closure at the time of the transplant. This approach however has the added benefit that the patient can still be mobilized. Patients with a failing right ventricle and only moderate pulmonary hypertension may benefit to conversion to a Protek Duo catheter as preciously described.

Patients that remain good transplant candidates and are hypoxic with a percutaneous veno-veno circuit should be converted to a right atrium to LA or to V-A ECMO configuration using one of the standard approaches. It can be argued that a RA to LA configuration should be the first choice in patients with severe fibrosis or pulmonary hypertension. It is preferable to use the RA to LA configuration because this approach leaves the left-sided loading conditions in a normal physiologic state and decreases the risk of left sided clot formation that can occur with V-A ECMO. Patients with severe fibrosis or primary pulmonary hypertension, V-A ECMO is a preferred option. It would be preferable to provide antegrade ECMO flow via right atrium to axillary artery although central cannulation can be used as long as the heart is contracting well or is vented. If flow is directed into the axillary artery, one must remain vigilant and monitor limb hyper-perfusion and ischemia. Femoral percutaneous cannulation can also be used but North-South syndrome will be an issue with fibrotic lungs. This too can be overcome by VAV ECMO configuration, which might limit the patient's ability to participate in physical therapy (18).

Complications with V-A ECMO

V-A ECMO can be used to provide excellent support with antegrade flow. Unfortunately, V-A ECMO is associated with significant risks as compared to V-V ECMO because the systemic circulation is involved. Higher levels of anti-coagulation are required to prevent clots and possible embolization leading to organ ischemia and possibly a cerebral vascular accident (CVA). Higher levels of anti-coagulation increase the risk of significant bleeding. Overall, 30–40% of patients on V-A ECMO will experience a bleeding complication and the most common source is the cannulation site. Also, there is an increased risk of neurological complications because of the higher degree of the required anti-coagulation and the risk of air entry into the closed circuit (19). Cannulation for V-A ECMO has a higher degree of vascular problems especially if a percutaneous approach is undertaken (17). As noted above, axillary cannulation places the upper limb at a high risk for hyper-perfusion and ischemia. Central cannulation provides the ultimate support but is associated with the morbidity of a hemi or full sternotomy. Peripheral femoral cannulation can also be used, and it does not prevent ambulation although it is not ideal.

A-V ECMO has also been used as a BTT in a small number of patients. This approach makes use of a pumpless circuit utilizing systemic arterial blood pressure to drive flow through a gas exchanger in the absence of a pump. A-V ECMO creates a parallel systemic circuit that is dependent on the function of the heart. This system only works with normal ventricular function and when the main objective is CO_2 removal, high flows cannot be achieved (19).

Intra-operative ECMO configuration strategy

Patients with advanced pulmonary disease may not tolerate single lung ventilation and will require mechanical support for gas exchange and sometimes hemodynamic support. The disease process and burden will provide insight as to whether mechanical support will be needed and what type of support is most suitable. Other factors that need to be considered include surgical approach and patient body habitus. Of the three types of support, V-V ECMO, V-A ECMO, or cardiopulmonary bypass (CPB), V-V ECMO is the least invasive but the decision of which type of support is needed is based on the totality of the factors listed above. Patients with COPD, CF, or alpha-1 deficiency are usually relatively easy to manage with single lung ventilation and V-V ECMO is usually not needed regardless of surgical approach or body habitus although most of these patients are not obese. Intraoperative circulatory support is usually required for patients with severe pulmonary fibrosis or pulmonary hypertension. Patients with pulmonary fibrosis that are approached via a full lateral thoracotomy will tolerate single lung ventilation with V-V ECMO support. The decision to use ECMO assisted support is preferably made prior to starting the transplant as the first step in the procedure. After induction, a dual lumen catheter can be placed in the right IJ vein and flows around 2.5 liters aimed at achieving 50% of the native cardiac output can be maintained throughout the procedure. In the lateral thoracotomy position, the left ventricle can be easily retracted medially to allow for exposure of the hilar structures. This minimal retraction of the heart does not usually affect hemodynamic stability unless the left ventricle is enlarged. Hilar exposure via an anterior approach is more difficult as the hilar structures are behind the heart. Patients supported intraoperatively can be decannulated at the end of the procedure or can be decannulated in the ICU. Recent data suggest that use of intra-operative ECMO can produce better outcomes as compared to transplants performed without mechanical support (20).

If patients undergo an anterior approach, then the use of V-A ECMO may be preferred because it provides both gas exchange and hemodynamic support. It is usually possible to perform the transplant on the right side without any support and then use V-A ECMO for hemodynamic support while retracting the heart to allow for visualization of the hilar structures on the left to safely perform precise anastomoses. A hybrid circuit can be utilized with a bridge that can be clamped to convert the circuit from VA to CPB and then back to ECMO if gas exchange support is still needed at the end of the procedure. This approach negates the need for an additional circuit. Secondly, a short-term circuit can be used which keeps the cost down as well. Using a hybrid circuit does not affect cannulation strategies and thus doesn't place technical limitations on the surgeon (21).

Patients requiring sequential double lung transplantations may need CPB during the surgical procedure to decrease operative time, hemodynamic instability and avoid overperfusion of the initial implanted lung. CPB can lead to a higher risk of bleeding due to large doses of heparin needed to maintain the open circuit in addition to systemic inflammatory activation increasing the risk for primary graft dysfunction (PGD) by neutrophil margination and sequestration of the pulmonary capillary bed (20). On the other hand, CPB provides hemodynamic stability and limits the risk of overperfusion and hyperinflation of the transplanted lungs (21).

There are some patients that do not tolerate V-A ECMO and will require full CPB. CPB has advantages and disadvantages (22,23). CPB, unlike V-A ECMO, requires full anti-coagulation and a higher risk of bleeding can be encountered both intra and post operatively. The advantage is that it not only makes the operation possible, but it also makes it faster as any inadvertent bleeding can be easily addressed because the blood is re-directed back into the circuit with the pump suckers (24). A major disadvantage of using an ECMO circuit is that any blood lost has to be collected, washed, and then transfused back via a peripheral IV. Patients requiring CPB can easily be converted back to V-A or V-V ECMO at the end of the procedure if further support is needed. Patients with severe pulmonary hypertension are best approached using CPB as the risk of bleeding is quite high while dissection of the enlarged PA's can be challenging (25).

Post-operative ECMO utilization

The most common cause of death post lung transplant is severe primary graft failure (PGF). PGF usually occurs within the first 3 days after transplant. Oto *et al.* reported on the use of ECMO for severe PGD after lung transplant comparing outcomes from 1990–1999 and 2000–2003 and found benefits with the improvement in technology resulted in better outcomes with PGF (26) Nguyen found that patient who developed PGD within the first 24 hours of transplantation tolerated ECMO wean and survived. On the other hand, graft dysfunction noted 7 to 16 days after transplantation carry a very poor prognosis with a 100% mortality due to irreversible lung injury rendering ECMO ineffective and therefore futile (27).

PGD can be seen intra-operatively or several hours to days post-operatively. If patients are persistently hypoxic in the OR and cannot come off mechanical support or if they develop hypoxemia off support, then ECMO must be readily initiated in the OR. The configuration chosen and the type of ECMO used is dependent on the surgical approach used. If the cannulas prohibit chest closure, the chest can be left open and the patient be brought back to the OR 24 hours later for re-configuration and chest closure. Management of the transplanted patient on ECMO is similar to other patients on ECMO with a few exceptions. The patient is maintained on low ventilatory support and the lungs are allowed to rest using lung protective ventilation. The patient's fluid status is optimized as most of these patients will develop pulmonary edema due to endothelial injury and capillary leak. Coagulopathy is aggressively addressed, and hemodynamics are maintained to achieve total tissue perfusion. The patient is subsequently weaned off ECMO over the course of 2–3 days.

Conclusions

ECMO now plays a vital role in lung transplantation in all three phases: pre-operative, intra-operative and post-operative. There are two main types of ECMO used in transplantation but they each can be configured in many ways. The ECMO configuration that is employed must take several factors into consideration such as disease process and burden, body habitus, co-morbidities and above all the condition of the patient and what is needed to stabilize patient to achieve an optimal outcome. There is now good data to suggest that appropriately selected patients can be bridged to transplant with outcomes similar to non-bridged patients. Recent studies also show that the intra-operative use of ECMO can produce outcomes that are better than the standard approach without mechanical support. Lastly, ECMO is highly effective in treating patients that experience PGD post lung transplant. ECMO will continue to play a major role in lung transplantation as we continue to refine techniques and achieve better patient management on mechanical support.

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