Extracorporeal membrane oxygenation in the pre and post lung transplant period

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Abstract: Evolution in technology has resulted in rapid increase in utilization of extracorporeal membrane oxygenation (ECMO) as a bridge to recovery and/or transplantation. Although there is limited evidence for the use of ECMO, recent improvements in ECMO technology, personnel training, ambulatory practices on ECMO and lung protective strategies have resulted in improved outcomes in patients bridged to lung transplantation. This review provides an insight into the current outcomes and best practices for utilization of ECMO in the pre- and post-lung transplantation period.

Keywords: Lung transplantation; extracorporeal life support; bridge to transplant; extracorporeal membrane oxygenation

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Introduction

Extracorporeal Life Support (ECLS) also known as Extracorporeal Membrane Oxygenation (ECMO) is a life support technology device that performs gas-exchange external to the body by providing cardio-respiratory support for patients with severe respiratory and/or cardiac failure (1). Current evidence supporting use of ECMO in adult patients remains limited. Early randomized trials examining ECMO in the 1970's failed to show a survival advantage for ECMO with high rates of complications in the ECMO arm (2,3). Subsequent single-center experiences showed no survival benefit (4). However, a recent multicenter, randomized trial investigating the use ECMO for acute respiratory distress syndrome (ARDS) (CESAR) found that referral to centers with ECMO expertise was associated with significant improvement in survival in ARDS compared to previous studies (5). Several retrospective case series and studies since the CESAR trial have reported survival benefits of ECMO in patients with severe ARDS secondary to influenza (6-14).

Despite limited evidence, there has been an increased use of ECMO to support patients with cardio-respiratory failure (15). Proponents of this advanced life support technology believe that its increased utilization and better outcomes are due to improvements in ECMO technology, personnel training, ambulatory practices on ECMO and lung protective ventilation strategies. Another important but controversial aspect of ECMO today is its use as a means to bridge patients to lung transplantation. This evolving practice involves a select few transplant centers who also have experience with ECLS technology. Patients requiring ECMO are more severely ill and thus have a higher lung allocation score (LAS), which is advantageous for lung transplant listing (16). Initial studies after the inception of LAS scoring noted that one-year outcomes in patients with higher LAS (17) and patients bridged with ECMO were lower (18,19). However, more recent studies analyzing the UNOS database have showed that outcomes in ECMO patient's post-lung transplant may be similar to non-ECMO patients, especially in centers with higher transplant volumes and experience (20,21).

The focus of this article is to provide a concise review of the best practices for utilization of ECMO in the pre- and post-lung transplantation period.

ECMO in the pre-transplant period

Current trends in utilization and outcomes

Regional differences in organ availability, institutional preferences related to the use and management of ECMO, surgeon-specific preferences regarding organ selection and operative technique may have profound effects on the outcomes of ECMO as a bridge to lung transplantation.

According to cumulative global data from the Extracorporeal Life Support Organization (ELSO) from 2016, approximately 10,601 adult patients have been treated with ECLS for respiratory failure since 1990 with a survival to discharge rate of 58% (22). On querying the ELSO database [1990–2016], 1,066 lung transplant recipients and/or patients on the transplant waitlist were supported with ECLS in the pre-, peri or post-operative period with an overall ECLS survival to hospital discharge of 65% (22). The overall utilization of ECLS as a bridge to lung transplant remains miniscule as compared to the total rates of lung transplantation. The United Organ Sharing Network (UNOS), data registry (SRTR data files) reports that, of the total 21,927 patients with lungs transplanted in the United States from 2000–2014, 414 adults have been bridged using ECLS technology (www.UNOS.org). It has been shown that the volume of lung transplantation may determine post-transplant outcomes. Weiss *et al*. reported a 2% increase in mortality with every percentage decrease in lung transplant center volume in the United States (23). Similar results were seen in patients bridged to transplant using ECLS. Of the 65 centers performing lung transplantation in the United States, only 26 centres utilized ECLS as a bridge to lung transplantation (24). Of these 26 centers, 12 performed one or less transplant using ECLS, while 14 performed >1 lung transplant using ECLS as a bridge (24). Two recent studies examining the UNOS registry showed that the overall one-year survival of patients bridged to lung transplant using ECLS in centers with greater volumes and ECLS experience were significantly higher than those with lower volumes/experience (20,24). Likewise, several single-center studies have reported one-year survivals similar to non-ECMO bridged patients (25-29). These results suggest a trend towards improving short to medium term post-transplant outcomes in ECMO bridged patients, especially at higher volume and more experienced ECLS centers.

LAS score and organ availability

In 2005, UNOS introduced the LAS scoring system, which resulted in improvement in the organ allocation system for lungs, reduced waitlist mortality and time to transplant (16,30). Listed patients with more severe disease requiring higher fraction of inhaled oxygen on respiratory support devices such as mechanical ventilation and/or ECMO (Fio2 on ECMO is usually 100%) receive a higher LAS score (16). Consequently, these patients have a higher priority in receiving organ offers and may have shorter times to transplant. However, several other factors may influence wait times for transplant for patients on ECMO support. It has been noted that local allocation of donor organs to candidates with lower LAS scores over regional candidates with higher LAS may occur (31), thus potentially increasing the wait times on ECMO support. Additionally, surgeon-specific preferences regarding organ selection, complications on ECMO such as bleeding or vascular compromise, poor nutritional status and/or deconditioning leading to temporary waitlist inactivation or human leukocyte antigen (HLA) sensitization due to transfusions may prolong wait times/duration on ECMO. The mean reported duration on ECMO as a bridge to lung transplant is 13–25 days (25). Several case studies have reported that longer ECMO duration may be feasible (32-35). Our center has successfully performed lung transplant on a patient supported with ECMO for 370 days (unpublished data-in review). Thus, it seems that despite the challenges, long-term ECMO support as a bridge to lung transplantation may be feasible.

Candidate selection

Inappropriate patient selection and delayed deployment of ECMO technology have been significant predictors of poor patient outcomes (19,25). Unfortunately, there are no universally accepted guidelines available, and individual institutional practices dominate the decisions to bridge a

Table 1 Considerations for selection of candidates as ECMO bridge to lung transplant

Already listed patients	Comments
Whether acute worsening of previous ESLD or new problem?	To assess recoverability if any
Whether all other options for support have been evaluated?	Mechanical ventilation, high flow nasal cannula, inhaled nitric oxide
Assess physical rehabilitation potential	Muscle wasting and poor rehabilitation potential on ECMO portends to poorer outcomes
Whether any contraindications to anticoagulation?	Relative contraindication though some centers are performing no anticoagulation
Assess nutritional status?	Malnutrition associated with worse outcomes
Is there multi-organ failure?	Relative contraindication unless multi-organ transplant an option
Whether any new multi-drug resistant infection?	Difficult to treat infections may portend to poor outcomes
High panel reactive antibodies?	Longer wait-times for organs despite higher LAS, may affect outcome of bridging
If unlisted patient, then whether any contraindication to lung transplant?	Unlisted patients usually have to be good candidates for lung transplant evaluation based on their pre-event condition

ESLD, End stage lung disease; ECMO, extracorporeal membrane oxygenation.

patient on ECMO. Initial experience in the use of ECMO in pulmonary transplantation was primarily for post-operative primary graft dysfunction or acute rejection episodes (36-38). Generally, it is agreed that ECMO be deployed in the pre-transplant phase in patients who are already listed and suffer an acute decompensation of their existing lung disease.

Additionally, these patients should have a good nutritional status, moderate functional status and/or the perceived ability to rehabilitate while on ECMO support (19,27). Early consideration of ECMO in the management algorithm of these decompensating patients appears to result in more favorable outcomes. *Table 1* details some considerations for selection of candidates as a bridge to lung transplantation. Several centers have reported use of ECMO as a bridge to transplantation in acute respiratory failure patients who previously did not have a lung disorder (25,32). In our experience, it is possible to perform expedited transplant workup especially in younger patients supported with ECMO and bridge them to transplantation.

ECMO cannulation strategies

Several aspects have to be considered to choose the optimal ECMO cannulation strategy for bridging patients to pulmonary transplantation. The objective of any cannulation strategy is not only to provide respiratory and/or cardiac support but also to facilitate early ambulation and minimize undue complications, while reducing common complications that occur with mechanical ventilation. In addition, the average wait times to receive organs on ECMO may also determine the choice of cannulation. Centers with shorter wait times may choose peripheral veno-venous (VV) or veno-arterial (VA) configuration versus a double lumen internal jugular cannula (DLC) or a central VA ECMO approach.

In cases of isolated respiratory failure, a VV configuration using a dual-lumen catheter (DLC) is preferred to facilitate ambulation (25,29,39). Although several centers are still utilizing conventional internal jugular-femoral or femoro-femoral VV configurations, more experienced centers now prefer DLC due to lesser rates of recirculation and opportunities to ambulation/rehabilitation with the DLC (40-43). In patients with a predominantly hypercapnic respiratory failure, lower ECMO flow rates may be as effective and hence a small caliber DLC or peripheral venous cannula can be utilized (44,45). However, patients with pre-existing significant primary/secondary pulmonary hypertension and/or right ventricular failure may potentially have worsening of their RV dysfunction with a VV configuration alone due to the increased venous return. In these circumstances, an atrial septostomy with VV (46,47) (either DLC or peripheral VV), peripheral VA or a central VA approach (48-50) (*Table 2*) may be considered. Based on individual patient requirements for additional ECMO blood flow or cardiac support, a mixed configuration with additional cannulation on the venous or arterial side can be performed. More recently, our group has utilized a

Table 2 ECMO cannulation strategies

ECMO configuration	Comments
Veno-venous	
Femoro-femoral	Easier cannulation, non-ambulatory, need to have faster organ availability
IJ-femoral	Easier cannulation Less rehabilitation potential, May work
Right IJ double lumen cannula (DLC)	Ambulatory ECMO/Rehabilitation potential, More difficult cannulation technique
DLC with atrial septostomy	May be able to support patients with significant pulmonary hypertension, technically challenging
Directional double lumen catheter (Protek Duo™)	Support patients with significant pulmonary hypertension, technically challenging, risk of damaging pulmonary artery, higher ECMO flows not achievable (3.5–4 L)
Veno-arterial	
Femoral artery-femoral vein	Easy procedure, Non-ambulatory, differential hypoxemia, LV overload, risk lower limb ischemia
Femoral artery- Internal Jugular (IJ) vein	Easy procedure , Non-ambulatory, differential hypoxemia, LV overload , risk for lower limb ischemia
Subclavian/axillary artery-IJ vein	Potential for ambulation, risk for upper extremity ischemia, technically challenging
Central VA	Potential sternotomy required, potential for RV bypass to decompress right heart, surgical site infections, scarring of sternotomy site if prolonged support , Ambulation potential
PA-LA	
RA-Aorta	
Systemic veins-inominate artery	

PA, pulmonary artery; LA, left atrium; LV, left ventricle; RA, right atrium.

directional catheter (double lumen VV cannula directed to pulmonary artery- Protek Duo™) approach successfully in patients with significant pulmonary hypertension (51). This approach can potentially reduce the need for further invasive procedures such as atrial septostomy or sternotomy for central cannulation in patients with pulmonary hypertension requiring ECMO support.

Management of pre-transplant patient on ECMO

Ventilator & sedation management

One of the primary objectives of ECMO support is to minimize the intensity and/or dependence on mechanical ventilation. After ECMO initiation, an effort should be made to reduce intensity of mechanical ventilation by reduction of PEEP and/or set Fio2 on the ventilator. Although, significant improvement in lung function cannot be expected in patients who are bridged to lung transplant on ECMO, lung protective ventilation strategies (tidal volume (6 cc/kg), plateau pressures <30 mmHg) should be adhered to minimize barotrauma and volutrauma related complications (52). In several cases, awake and cooperative patients who can tolerate weaning off mechanical ventilation can be safely extubated on ECMO support (53,54). In patients with ongoing ventilator need, an early tracheostomy should be preferred especially in those with increased secretions and/or intensive sedation requirements.

In our experience, an early tracheostomy facilitates sedative weaning and early ambulation. Attempts should be made to wean off sedation as tolerated. Although, sedation management is unique to each center, we prefer to avoid benzodiazepines and high dose narcotics.

Anticoagulation and blood transfusion management

Systemic anticoagulation remains an important component in ECMO management to maintain a thrombus-free circuit. Clots can develop in the oxygenator membrane and can prevent optimal gas exchange but rarely result in embolization to the systemic circulation. The goal of anticoagulation is to balance therapeutic doses to prevent circuit thrombus with minimization of bleeding complications. Unfortunately, bleeding remains a major complication of ECMO support with a cumulative incidence of up to 43% (22). Apart from the anticoagulation several other factors including the circuit related factors such as increased inlet and outlet pressures and kinks (leading to mechanical trauma to blood components), surgical procedures, and infections contribute to the risk of bleeding on ECMO (55). Minor bleeding episodes such as oozing from cannula or tracheostomy sites can be efficiently managed with compression dressings and/or instillation of subcutaneous vasoconstrictors. However, significant or catastrophic bleeding in the GI tract, central nervous system and the lungs have to be managed with cessation or sometimes reversal of anticoagulation. Unfractionated heparin is the most utilized anticoagulant for systemic anticoagulation on ECMO due to its shorter half-life and availability of a reversal agent in case of catastrophic bleeds. However, other agents such as bivalirudin and argatroban have also been used for anticoagulation on ECMO (56-58). Anticoagulation is usually tailored based on presence of clots in the circuit, coagulopathy and bleeding while on ECMO (59). Several groups have also reported reduced or no systemic anticoagulation use especially on VV ECMO support successfully (60,61). In our experience, if necessitated, it may be feasible to restrict anticoagulation in VV configuration in specific cases, but particular care should be taken to rule out presence of atrial/ventricular septal defects to prevent systemic embolism. In addition, careful circuit/oxygenator monitoring and use of heparin-bonded circuits with minimal adaptors/connections may be helpful in preventing excessive clot formation (62). In patients on a VA configuration, systemic anticoagulation should be maintained as tolerated due to risk of systemic embolism (63).

In the current era, sensitive assays are available to monitor anticoagulation status. The choice of anticoagulation monitoring tests is usually based on institutional practices. Activated clotting time (ACT), activated partial thromboplastin time (APTT), anti-factor Xa levels and thromboelastography (TEG) have all been utilized to measure level of anticoagulation on ECMO. Despite some limitations, recent studies describe the accuracy and ease of anti-factor Xa assays to monitor unfractionated heparin on ECMO (64,65). Additionally, TEG monitoring has also shown to be helpful in anticoagulation management on ECMO (66). Given the myriad of hematological changes occurring on ECMO due to both anticoagulation and ECMO circuit factors, it seems plausible that a protocol involving measurement of heparin activity with anti-factor Xa and overall clot reaction with TEG may be beneficial. At out institution, we utilize TEG monitoring and keep a reaction(R) time of 2.5–3 times normal (67). ELSO guidelines provide details about possible anticoagulation strategies (www.ELSO.org).

Another important aspect of ECMO management is the transfusion of blood products for bleeding complications and/or volume support. Traditionally, a hemoglobin level of 9–10 g/dL was suggested for optimal oxygenation and maintenance of circuit flow on ECMO (68). However, in pre-transplant patients, frequent blood product transfusion can lead to allo-sensitization which is associated with elevated panel reactive antibody (PRA) titers and production of donor related antibodies to blood products (69,70) that can potentially reduce donor allograft and recipient survival. Additionally, there is risk for transfusion associated reactions and complications from intravascular volume overload (71). Recent reports suggest that a more conservative transfusion strategy may lower transfusion requirements and bleeding complications, with comparable survival and organ recovery to a more liberal transfusion practice (72). During ECMO circuit changes due to any reason, auto transfusion of the patient's blood in the circuit tubing can be performed using a cell-salvage device (Haemonetics™) to reduce the need for allo-transfusion (73). We suggest that blood product transfusion practices should be tailored to hemodynamic and oxygenation needs and a more conservative transfusion strategy should be followed to reduce allo-sensitization.

Ambulation on ECMO

Increased pre-transplant frailty is a risk factor for worse post lung transplant outcomes (74,75). Critically ill patients on prolonged mechanical ventilation and/or ECMO support are prone to developing significant neuro-muscular weakness (76,77). Several studies have demonstrated that physical rehabilitation in patients on ECMO support is safe and can potentially improve post-transplant recovery and outcomes (25,29,39,78,79). Ambulation can be safely achieved in patients cannulated via a DLC in a VV configuration or subclavian/central VA configuration (48,80-82). In patients with configurations requiring femoral cannulation, ambulation may result in cannula dislodgement and be potentially harmful (83). A multidisciplinary team comprising of a physician, nursing staff, perfusion, respiratory and physical therapists facilitates safe and effective physical rehabilitation on ECMO. At our center, patients bridged on ECMO ambulate several times a day as tolerated. Bedside upper and lower extremity strength training exercises are also performed regularly. In addition, in some cases, we have utilized activities such as video games on Wii (Nintendo™) to promote physical rehabilitation in our younger patients bridged on ECMO. Patients with prolonged ECMO support are also prone to severe mental health issues including major depression and post-traumatic stress disorder (37,84-86). Previous studies have shown that physical rehabilitation improves the mental health in several disease states (87). It is possible that it may help those supported with ECMO as well. In our experience, physical rehabilitation, and other recreational activities such as music therapy and creative art help patients cope with the daily stressors during ECMO support.

Perioperative management

Management of ECMO in the peri-operative period is largely based on individual surgeon preference. Several groups have reported continued utilization of ECMO support intra-operatively with reduced need for anticoagulation/blood transfusions, reduction in neurological and vascular complications (88-90). Others prefer to convert to a conventional cardiopulmonary bypass support intra-operatively. Continued post-operative ECMO in patients transplanted for pulmonary hypertension has been advocated by some to control reperfusion and provide non-aggressive ventilation after transplant (91). Additionally, ECMO support has been utilized for management of primary graft dysfunction after lung transplantation (36,37).

ECLS during organ procurement

There has been recent interest in providing extracorporeal membrane support to marginal/higher risk donor organs during organ harvesting (92). The use of this technology called the *ex vivo* lung perfusion (EVLP) allows transplantation of marginal/high-risk donor lungs that are physiologically stable during *ex vivo* perfusion. Recent reports have shown that post-operative outcomes in organs supported with EVLP technology is similar to those obtained with conventionally selected lungs (92-94).

Another application of ECLS technology in organ procurement is harvesting of lungs after donor cardiac death (DCD). This technology involves deployment of VA ECMO support in donors after cardiac death to continue organ perfusion and harvesting. Outcomes of DCD lung have been shown to be similar to conventionally harvested organs (95-97). Sometimes EVLP support is utilized after DCD organ harvesting and may result in improved outcomes (98). The overall long-term impact of EVLP and DCD organ donation in lung transplantation is not fully understood, and further research is needed to establish a clear role for these technologies in organ transplantation.

Conclusions

Despite limited data to support its use, there has been a recent increase in utilization of ECMO as a bridge to lung transplantation. ECMO as a bridge to transplantation is not suited for all patients. Careful patient selection should be performed to optimize resource utilization and provide the best opportunity for transplantation.

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Footnote

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