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Advances in Extracorporeal Membrane Oxygenation in the Setting of Lung Transplantation

Michael Mazzei, Suresh Keshavamurthy and Yoshiya Toyoda

Abstract

Lung transplantation has become an increasingly important modality for the treatment of severe lung disease. From its inception, the procedure has been refined so that it now represents the standard of care for end stage respiratory failure. The widespread adoption of this treatment option, however, has brought into sharp relief the current organ donor shortage. In tandem with the explosion in lung transplant procedures, a number of support modalities have seen an expanded role. Perhaps one of the most versatile tools in the armamentarium of the pulmonary transplant surgeon is extracorporeal membrane oxygenation (ECMO). This powerful tool is being increasingly implemented in all stages of lung transplantation—from supporting the failing native organ as a bridging tool to transplantation, to stabilizing the patient intra-operatively during the transplant procedure, to rescuing the patient with severe primary graft dysfunction immediately post-transplant. A number of advanced techniques for the application of ECMO in order to optimize the pulmonary transplant procedure are gaining traction—and with ECMO's expanded role in lung transplantation, so also has come a new set of technical and ethical challenges that must also be overcome.

Keywords: ECMO, veno-veno, veno-arterial, bridge to transplantation

1. Introduction

Lung transplantation has become an increasingly important modality for the treatment of severe lung disease. From its inception in 1985, the procedure has been refined so that it now represents the standard of care for end stage respiratory failure. As the efficacy of this treatment has been proven, we have seen the frequency of lung transplantation undergo an exponential rise. In 1993, for example, the International Society for Heart and Lung Transplantation (ISHLT) reports that a total of 1055 lung transplant procedures was performed. A decade later in 2003, that number had nearly doubled to 1934 and in 2013, the number of lung transplant procedures per year rose to 3892 [1]. In the same vein, a study in 2018 analyzing national trends of extracorporeal membrane oxygenation use in the National Inpatient Sample identified an over 360% increase in admissions for ECMO support from 2008 to 2014, among which mortality decreased among total admissions from over 60% down to 43% despite a trend toward an increased risk profile [2]. The widespread adoption of this treatment option, however, has brought into sharp relief the current organ donor

shortage; there is currently a yearly potential lung transplant recipient mortality of up to 16% while awaiting organs to become available [3].

In tandem with the explosion in lung transplant procedures, a number of support modalities have seen an expanded role. Perhaps one of the most versatile tools in the armamentarium of the pulmonary transplant surgeon is extracorporeal membrane oxygenation (ECMO). This powerful tool is being increasingly implemented in all stages of lung transplantation—from supporting the failing native organ as a bridging tool to transplantation, to stabilizing the patient intraoperatively during the transplant procedure, to rescuing the patient with severe primary graft dysfunction immediately post-transplant. A number of advanced techniques for the application of ECMO in order to optimize the pulmonary transplant procedure are gaining traction—and with ECMO's expanded role in lung transplantation, so to have come a new set of technical and ethical challenges that must also be overcome.

The goal of this chapter is to discuss some of the recent advances in the application of ECMO in the setting of lung transplantation. We discuss the application of ECMO in the preoperative, perioperative, and postoperative period, and focus in particular on advances such as the use of awake ECMO and various cannulation strategies. We also briefly discuss some of the ethical issues surrounding ECMO for lung transplantation, including cost, quality of life, and the application of ECMO to marginal recipients.

2. VV- and VA-ECMO in lung transplantation

In the setting of lung transplantation, ECMO may be utilized in either a venovenous (VV) or a veno-arterial (VA) configuration. The VV-ECMO modality is used strictly for respiratory support; this review will explore the current frontiers of usage in the setting of either pre-operative bridge to transplant, as well as for bridging to graft recovery the subset of patients who develop severe post-transplant primary graft dysfunction (PGD). Alternatively, VA-ECMO may be utilized in the subset of patients with either pulmonary arterial hypertension requiring both cardiac and pulmonary support in the preoperative period, recently transplanted patients exhibiting hemodynamic instability, or in the intra-operative period for cardiopulmonary support [4].

Cannulation strategies for VA- and VV-ECMO are listed here. VV-ECMO is typically achieved via outflow and inflow cannulas in the femoral and internal jugular veins, with the tip of the drainage cannula placed to the level of the inferior vena cava-right atria junction and the tip of the return cannula at the right atrium. Alternatively, VV-ECMO may be achieved via a femoral-femoral cannulation strategy, with the tip of the drainage cannula in inferior vena cava and the tip of the outflow cannula is in the right atrium. Alternatively, a one-site cannulation strategy makes use of a dual lumen Avalon cannula (Avalon Elite, Maquet, Rastatt, Germany) percutaneously placed in the either internal jugular vein or in the subclavian vein [5].

VA-ECMO cannulation may be achieved using either a peripheral or central cannulation strategy. In a peripheral cannulation strategy, the femoral vein and artery are cannulated in a percutaneous fashion, with the tip of the arterial cannula placed in the common iliac artery. Alternatively, the arterial inflow cannula can be placed into the right subclavian artery. Because these peripheral strategies may in some cases only transmit arterial blood flow as far as the aortic arch (where blood oxygenated from the patient's native lungs and transmitted by the patient's heart) this may have the effect of poorly perfusing the heart and lungs (known as the Harlequin Syndrome). In this case, central cannulation of VA-ECMO is an option,

with the venous cannula placed directly in the right atrium and the arterial cannula placed in the ascending aorta through a median sternotomy incision [4].

A number of hybrid options also exist for selected scenarios; these include Venovenous-arterial ECMO (VVA-ECMO) where an additional venous cannula is inserted to offload the left ventricle, typically into the right internal jugular vein. This may also describe the conversion of venovenous (VV) ECMO to additionally supply cardiac support by the insertion of an arterial cannula. Other triple-catheter strategies include the insertion of a distal perfusion cannula to the cannulated lower extremity in peripheral VA-ECMO in order to decrease limb ischemia. This armamentarium provides the surgeon with a number of different techniques for providing either isolated pulmonary or cardiopulmonary support in the transplant patient.

3. ECMO in the preoperative period

3.1 ECMO as a bridge to lung transplantation

The first successful use of ECMO in the preoperative period prior to lung transplant may be traced back to 1975, when ECMO was described as being initiated to correct a profound hypercapnia in a 19-year-old boy prior to transplantation. While the patient was successfully removed from the oxygenator and weaned from mechanical ventilation, he ultimately died on the eighteenth postoperative day due to a bronchial dehiscence [6]. For the next 20 years, this modality was occasionally described in the literature in case studies; however, it was associated with dismal outcomes and as a result did not gain widespread use.

In the past decade, however, there have been a number of advances in both the technology surrounding ECMO, and the management of the patient on ECMO, such that institutions are increasingly turning back to preoperative ECMO as an acceptable or even preferred modality for bridging patients with end stage respiratory disease to lung transplantation. This shift in management was preempted by a number of forces. First, the institution of the lung allocation score in 2005 allowed for more efficacious allocation of donor organs to those patients most emergently in need of a transplant rather than just the length of time on the waiting list. This meant that patients receiving continuous mechanical ventilation were listed with scores. ECMO was found to serve as a useful tool to stabilize ventilator-dependent patients approaching transplantation. Additionally, multicenter trials in the non-transplant population began to demonstrate the effectiveness of ECMO in ameliorating severe adult respiratory distress syndrome [7]. With the significant improvement in ECMO technologies, an increasing number retrospective and prospective studies have been conducted that show promising outcomes related to the use of ECMO as a bridging strategy [5, 8–17].

Some of those studies are reported here. Much of the initial research consisted of single-center retrospective studies. One of the first studies to demonstrate the efficacy of this therapy reported 17 bridged patients with a 78% 1-year survival after transplant, among whom allograft function did not differ between patients who did and did not receive ECMO bridging support [8]. A 2012 institutional study of 11 patients demonstrated shorter durations of mechanical support, and shorter post-transplant ICU and hospital stay in patients bridged with ECMO; a 1-year survival rate of over 85% after ECMO compared to 50% in patients with traditional mechanical ventilation was highlighted [15]. In 2013, a retrospective review of the medical records of 39 French patients bridged to lung transplantation on ECMO highlighted successful bridging to transplant in over 80% of the population,

perioperative survival of 75%, and successful discharge from the hospital in 50%. While 2-year survival was largely a function of the underlying disease state, outcomes were largely similar between the ECMO and non-ECMO use groups, supporting the use of ECMO as a bridge to lung in order to preserve a medium-term survival benefit in the critically ill [14].

A large single-institution study retrospectively reviewed 715 consecutive lung transplants performed between the start of LAS implementation in May of 2005 until September 2011, of which 3.4% were performed on patients with attempted pre transplant ECMO. While patients in the pre-transplant ECMO group had significantly higher lung allocation scores, and median hospital stay was nearly double that for the ECMO group compared to the control group there was no difference in survival, with an overall 2-year survival approaching 75% in both cohorts [16]. A 2017 retrospective single-institution study looking particularly at cardiac outcomes in the population bridged to lung transplantation on ECMO identified a successful bridging rate of 60%, with a 1-year survival of over 90%. This study in particular noted right ventricular systolic dysfunction and worsening volume overload to be associated with unsuccessful bridging, but otherwise identified adequate outcomes [18].

In order to overcome some of the weaknesses of small retrospective cohorts, the question of ECMO's efficacy as a bridging strategy to transplant has been additionally queried of large national databases. A 2015 study of the United Network for Organ Sharing (UNOS) database highlighted 119 patients who were bridged to transplantation using extracorporeal membrane oxygenation compared to 12,339 patients who were not. The study period was divided into four 3-year intervals, and this demonstrated both an increasing number of patients bridged per year with ECMO and progressively increasing survival with each period, as did the number of patients bridged using extracorporeal membrane oxygenation. This highlights that short-term survival with the use of extracorporeal membrane oxygenation as a bridge to lung transplantation continues to significantly improve as it is more widely adopted [19].

The use of bridge-to-transplant with ECMO has also been trialed in small cohorts consisting of patient subsets at increased risk due to the presence of comorbidities. For example, this therapy has been demonstrated as effective in patients with cystic fibrosis; the authors of a 2012 case series of this population demonstrate good perioperative outcomes and describe the early initiation of ECMO soon after development of acute respiratory failure requiring mechanical ventilation as an important part of the treatment algorithm for these patients due to their high risk of ventilator-acquired complications [20]. Furthermore, in the subset of patients with advanced interstitial lung disease and secondary pulmonary hypertension, medical management remains complex and mechanical ventilator support are associated with poor outcomes. Small retrospective reviews, however, suggest that this subset had at least a comparable survival when requiring an extracorporeal membrane oxygenation bridge to that of other high acuity patients placed on extracorporeal membrane oxygenation as a bridge to lung transplantation [21]. Taken in sum, these studies suggest that extracorporeal membrane oxygenation is a feasible tool for use as a bridge to lung transplantation.

3.2 Awake and ambulatory ECMO

One benefit of ECMO compared to normal mechanical ventilation is that extracorporeal membrane oxygenation allows for adequate oxygenation to occur in patients who are awake, spontaneously breathing, and liberated from the ventilator. This could potentially represent a novel bridging strategy in that the complications

associated with prolonged mechanical ventilation, such as ventilator-acquired pneumonia, are avoided. For example, a 2012 retrospective, single-center analysis of consecutive potential lung transplant patients receiving awake ECMO support compared with a historical control group receiving conventional mechanical ventilation demonstrated a 6-month survival after lung transplantation at 80% in the awake ECMO group versus 50% in the mechanical ventilation group. They also had shorter postoperative recovery periods [10].

In addition to avoiding mechanical ventilation complications, freedom from the vent also allows for novel rehabilitation efforts, such as ambulation and physical therapy while on ECMO, which could potentially help to stave off deconditioning while awaiting transplantation in the unit. Subjects on awake ECMO usually received a combination of passive and active physiotherapy; emerging research in the field affords preliminary evidence supporting the safety of early mobilization and ambulation in patients on awake ECMO support [22]. For example, a retrospective observational study in which ECMO patients were managed with early aggressive physical therapy, ambulation, and spontaneous breathing led to 30-day, 1-year, and 3-year survival outcomes after transplant of 92, 85, and 80%, respectively [11]. A second retrospective study compared five pre-transplant ECMO patients receiving active rehabilitation and ambulation to patients who were bridged with ECMO but did not receive pre-transplant rehabilitation. A third study of 72 patients receiving ECMO as a bridge to lung transplantation of which daily participation in physical therapy was achieved in 50 patients demonstrated favorable survival in patients receiving ECMO as a bridge to lung transplantation, particularly good outcomes in patients receiving physical therapy and maintaining avoidance of mechanical ventilation, and high rates of successful ambulation and therapy in the overall ECMO group [9]. Pre-transplant physical therapy was associated with shorter mean post-transplant mechanical ventilation, intensive care stay, and overall hospital days [23]. In general, preservation of pre-transplant ambulatory status has been found to improve outcomes in patients bridged to lung transplantation with ECMO [24]. These encouraging findings support the concept that ambulatory ECMO allows for preservation of vitality while critically ill candidates await donor organs, which may improve outcomes.

Efforts to ambulate patients on ECMO bridging to lung transplant have been aided by the implementation of single-site, dual-lumen cannulation via an Avalon catheter. In conventional VV-ECMO, the outflow and inflow cannulas are placed percutaneously using the Seldinger technique, most commonly in the femoral and internal jugular veins. Alternatively, a one-site cannulation strategy makes use of a dual lumen Avalon cannula (Avalon Elite, Maquet, Rastatt, Germany) percutaneously placed in the either internal jugular vein or in the subclavian vein, under direct imaging such as fluoroscopy or transesophageal echocardiogram. This approach avoids use of the femoral site, which aids in mobilization and may limit the risk of recirculation and groin infectious complications [5]. Downsides include the need for precise placement and orientation of the catheter, requiring fluoroscopic guidance; femoral-femoral or femoral-jugular cannulation is much more expeditious, and suited to emergency situations. The Avalon catheter is also significantly more expensive than more conventional cannulation strategies [4]. Ultimately, however, the complication rate of this approach is comparable to traditional two-site ECMO in most studies [25], and many centers are now routinely using single-site ECMO as a first-line cannulation strategy.

Awake ECMO has been shown to be particularly effective for those patients at elevated risk of deconditioning. For example, the subset of patients requiring lung re-transplantation is a particularly challenging transplantation cohort because of the critical illness often associated with graft failure, as well as the higher

likelihood of deconditioning after transplant failure. In a 2014 study looking specifically at this group, re-transplant patients bridged on awake, ambulatory ECMO support demonstrated a mortality of 0% compared to 39% in the group requiring mechanical ventilation. The study concludes that awake ECMO bridging for re-transplantation provides comparable results to elective re-transplantation [26]. Larger retrospective studies have also made use of clinical databases such as the United Network for Organ Sharing database. In 2016, a study of all adult patients undergoing isolated lung transplantation in the last decade were identified based on their need for preoperative support: no support versus ECMO, invasive mechanical ventilation, or both, while 1-year survival was decreased in all patients requiring any type of support, mid-term survival was comparable between patients on ECMO alone and those not requiring support, but significantly worse with patients requiring mechanical ventilation with or without ECMO. This highlights the fact that those patients supported via ECMO with spontaneous breathing demonstrate improved survival compared with mechanical ventilation [27].

3.3 CO₂ removal in the bridge-to-transplant population

In patients awaiting lung transplantation, adequate gas exchange may not be sufficiently achieved by ventilation alone if acute respiratory decompensation arises. This may result in a life-threatening hypercapnia. ECMO may serve an additional purpose in patients bridging to lung transplantation as an adjunct for CO₂ removal (ECCO₂-R). For some patients, increased CO₂ clearance may spare them the need for mechanical ventilation [28]. A 2016 study of 20 patients (15 invasively ventilated and five noninvasively ventilated patients) demonstrated effective correction of hypercapnia and acidosis within the first 12 hours of therapy. Nineteen patients were successfully transplanted, and hospital and 1-year survival was 75 and 72%, respectively. This highlights ECCO₂-R as a feasible rescue therapy that can be associated with high transplantation and survival rates [29].

3.4 Prolonged bridging with ECMO

Outcomes in the unique subset of patient requiring the prolonged use of ECMO prior to lung transplantation have in recent years become the subject of study. For example, in a 2016 review of 974 patients who required prolonged (>14 days) ECMO in the Extracorporeal Life Support Organization international multi-institutional registry, 46% of these patients did not sustain native lung recovery; among these, 40 patients (4.1%) underwent lung transplant with a 50% post-operative in-hospital mortality [30]. While 14 days appears to be the consensus after which ECMO is considered to be prolonged, the upper bounds for the length of time for which ECMO can be continued as a bridging method continue to be tested. For example, a recent case report describes a patient remaining on ECMO for as long as 403 days while waiting for a lung transplant. This required changing the membrane oxygenator 23 times and the cannula 10 times; This therapy was ultimately terminated due to a loss of access for cannula insertion. The authors conclude that it is at least technically feasible to maintain patients awaiting lung transplantation on ECMO for extended periods of time, albeit maintaining for than 1-year may be difficult [31]. While case reports have described successful transplantation after many months on ECMO support, ultimately the outcomes remain dismal in this cohort; for example, as late as 2016 there were no recorded cases of pediatric long-term post-transplant survival after more than 52 days on ECMO support [32].

3.5 Selected issues in bridge-to-transplant

3.5.1 Cost-effectiveness

With the increasing utilization of ECMO in the lung transplant population, the question of utility is growing in importance. Recent studies have examined the cost associated with the use of extracorporeal membrane oxygenation in the setting of lung transplantation. A 2017 study using the Nationwide Inpatient Sample evaluated hospital charges of patients undergoing lung transplant who required ECMO during their hospital course; represented 4.2% of the patients undergoing lung transplantation overall. Median charges for lung transplant recipients who required ECMO were \$780,391.50 versus \$324,279.80 for non-ECMO recipients; the characteristics particularly associated with exorbitant hospital costs included black recipient race, pulmonary hypertension, and Medicare enrollees [33]. Studies have shown a disproportionately high amount of extracorporeal membrane oxygenation use in the Northeast compared to other parts of the country; this is highlighted as a regional disparity [2].

The economic impact of ambulatory versus either non-ambulatory ECMO strategies or mechanical ventilation as a bridge to lung transplantation is also of interest. In a retrospective 2016 study at a single center, subjects who were rehabilitated while supported with ECMO before lung transplantation were compared with those who were not rehabilitated during ECMO. When hospital cost data for the month before transplantation through 12 months after initial post-transplant hospital discharge were compared, subjects supported with ambulatory ECMO had a 22% (greater than \$60,000) reduction in total hospital cost, 73% (greater than \$100,000) reduction in post-transplant ICU costs, and 11% (greater than \$30,000) reduction in total costs compared with non-ambulatory ECMO subjects [34].

3.5.2 Quality of life

With the increasing use of extracorporeal membrane oxygenation as a bridge to lung transplantation, the impact of preoperative ECMO on quality of life and depressive symptoms has been additionally targeted as an area of study. This question stems from the possibility that, due to complications after ECMO coupled with critical illness in the period up to transplantation may have adverse effects of quality of life in patients after transplantation. This does not appear to be the case; a 2018 single-institution prospective cohort study found that lung transplantation provides substantial quality of life improvements following lung transplantation, and these were generally similar among patients on pre-operative ECMO compared to those patients brought in for transplantation from the outpatient setting [35]. A second study in 2017 examining quality of life in ECMO-bridge lung transplant recipients demonstrated that outcomes after successful transplantation after ECMO are comparable with the general population undergoing lung transplantation in terms of quality of life, lung function, performance tests, and mortality [36].

3.5.3 Quality of the data

The increasing need for multi-institutional analysis of ECMO usage has had the effect of highlighting the dramatic differences in the implementation of ECMO at various programs. A survey of all US lung transplant centers in showed that two-thirds of responding centers used of ECMO as a bridge to transplant. Among these, a patient age greater than 65 was a cutoff in nearly half of centers, but otherwise many centers had no official age cutoff. Additionally, there was little consensus on

the upper bounds for an acceptable duration of pre-transplant ECMO therapy, and this varied from as little as 10 days to a policy in which ECMO support duration was not bounded. Overall, the institutional criteria for ECMO initiation, age limits, and duration of support are widely disparate across centers [37].

A systematic review in 2014 highlighted the inconsistencies in design between these studies; while 82 potential studies of ECMO bridging were identified at the time, the vast majorities were excluded and the broad heterogeneity among the studies precluded any wider meta-analysis. In this analysis, the preoperative mortality rate of patients on ECMO ranged from 10–50%. It was ultimately concluded that ECMO support as a bridge could potentially provide reasonable perioperative and 1-year survival outcomes, but no broader statement could be made owing to a general paucity of high-quality data and significant heterogeneity among studies [38].

While these largely retrospective studies are compelling, it is acknowledged that retrospective studies are not the ideal candidates for definitively proving the efficacy of ECMO compared to mechanical ventilation, which has in tandem with ECMO evolved in the past decade to include more advanced strategies of protective lung ventilation. While the challenges of randomizing patients to different therapies in end-stage respiratory failure are apparent, at this point significant equipoise now exists to justify the randomized comparison of ECMO with standard ventilator therapy as a bridging strategy [39].

4. ECMO in the peri- and postoperative period

4.1 ECMO versus cardiopulmonary bypass

While partial or full cardiopulmonary support was initially a necessary aspect of lung transplantation, this has become less of a requirement with improvements in ventilation and operative technique. However, for those cases where cardiopulmonary support remains a necessity (such as failure of single lung ventilation, or right heart failure), VA ECMO is playing an increasing role as an alternative to traditional cardiopulmonary bypass. Cardiopulmonary bypass is at least theoretically responsible for the development of pulmonary injury and has been implicated in adult respiratory distress syndrome [40]. Pulmonary injury during cardiopulmonary bypass has been the subject of a significant amount of research over the past 30 years. At this time, it is theorized that lung damage occurs as the result of an inflammatory cascade triggered by a combination of surgical trauma, the interface of blood products with the extracorporeal circuit, and lung reperfusion injury; this triggers the generation of oxygen free radicals that are in turn sequestered within the lung and lead to pulmonary injury [41, 42].

Other issues related to cardiopulmonary bypass include a need for high-dose heparinization, which can lead to intra- and postoperative bleeding complications, and high blood turnover with a high volume of blood necessary to load the circuit. Cardiopulmonary bypass also requires central cannulation that can preclude other interventions in the operative field such as coronary artery bypass grafting. These issues have led providers to seek alternate supportive options. On its face, ECMO has a number of perceived benefits over cardiopulmonary bypass. With this in mind, there have been a number of studies comparing the efficacy of ECMO to cardiopulmonary bypass in the lung transplant setting [43–50].

The first studies of VA ECMO as a replacement therapy were not initially associated with good outcomes. For example, in 2007 a single institute retrospective study, ECMO was found to have a trend toward increased 90-day mortality rate, a higher incidence of severe graft ischemia/reperfusion injury, and a significantly

reduced 1-year survival compared to cardiopulmonary bypass [45]. However, with increasing experience in using ECMO, results have been more promising. A 2012 retrospective study of outcomes of patients treated using ECMO versus cardiopulmonary bypass demonstrated a higher transfusion requirement in the cardiopulmonary bypass group, as well as a significantly higher incidence of in-hospital mortality, the need for hemodialysis, and new postoperative ECMO support. In this study transplantation with cardiopulmonary bypass was identified as an independent risk factor for in-hospital mortality [51].

In a 2014 study comparing differences in 47 lung transplant patient outcomes with intraoperative ECMO versus cardiopulmonary bypass, the ECMO group was required fewer transfusions and had less bleeding, fewer reoperations, and less primary graft dysfunction with no 30-day or 1-year survival differences [44]. Similarly, in a 2014 comparison of 271 consecutive patients who underwent lung transplant using either cardiopulmonary bypass or ECMO, there were differences in 30-day or 6-month mortality, and less postoperative complications among the ECMO group [43]. A number of more recent studies similarly comparing VA ECMO to cardiopulmonary bypass have confirmed the finding of a lower perioperative blood product transfusion requirement and lower 90-day mortality among the extracorporeal membrane oxygenation cohorts [48, 49, 52, 53].

Recently, a meta-analysis of the existing evidence to support ECMO versus cardiopulmonary bypass showed beneficial trends of ECMO regarding blood transfusions, duration of ventilator support and intensive care unit length of stay, 3-month and 1-year mortality; these findings, however, were not statistically significant. At this time, while it appears that ECMO is at least non-inferior to cardiopulmonary bypass in the setting of lung transplantation, the superiority of ECMO remains to be determined and will likely require larger multi-center randomized trials [47].

Outcomes compared between patients requiring intraoperative ECMO versus those not requiring any support are less conclusive; in a 2018 study of 53 patients, while patients who underwent ECMO received more intraoperative transfusions, outside of the immediate postoperative period there were no differences in in-hospital and 6-month complications with similar survival between the two groups [50]. In contrast, however, a 2017 single institution study demonstrated 5-year survival to be 52.8% in intraoperative ECMO recipients versus 70.5% in those not requiring ECMO, with multivariate analysis identifying intraoperative ECMO support as significant risk factors for overall survival [46].

4.2 Postoperative ECMO for primary graft dysfunction

Early primary graft dysfunction, defined as lung injury causing decreased oxygenation during the first 3 days after lung transplant, is a devastating albeit fairly uncommon occurrence. ECMO is a useful adjunct for supporting the patient with primary graft dysfunction, either to recovery or as a bridge to redo transplantation.

One-year survival is compromised in patients with severe primary graft dysfunction compared to those without; in addition to the underlying causal factors contributing to dysfunction in the first place, this is often worsened by the high airway pressures and inspired oxygen concentration necessary to adequately oxygenate the patient via mechanical ventilation. ECMO may be desirable for its ability to avoid these risk factors. In a single-institution study of patients with primary graft dysfunction, successful weaning from ECMO was achieved in 96% of patients, with substantially improved long-term outcomes including a 5-year survival of nearly 50%. While allograft function in the ECMO group was worse than in transplant recipients not requiring ECMO, the benefits of ECMO in pulmonary support in the immediate postoperative period is clear [54]. Furthermore,

these trends toward better outcomes after primary graft dysfunction appear to be improving due to ECMO support; in a large database study of the highest-risk transplant patients, patients demonstrate improving outcomes, particularly at high-volume centers [55]. In a review of the UNOS database, the use of post-operative ECMO support for primary graft dysfunction was still associated with a 6-month survival of over 60%, and while the subset of ECMO recipients also requiring dialysis had a only a 25% 6-month survival, if dialysis was not needed survival was over 85% [56].

Unfortunately, while early postoperative ECMO in the setting of primary graft dysfunction is associated with reasonable outcomes, the late implementation of ECMO postoperatively (after 7 days) does not appear to have the same good outcomes. In a 2011 study of late ECMO support in lung transplant patients with infection or graft failure, none of the individuals who received late ECMO support survived to hospital discharge, due to the propagation of uncontrolled infection or organ failure that preempted ECMO support. This suggests that while ECMO can provide early support while awaiting graft recovery, it does not represent a means of reversing complications existing prior to initiation of ECMO [57].

4.3 Routine ECMO prolongation

With increasing comfort with ECMO as postoperative support, the indications for extending its use have continued to expand. In some institutions, for example, intraoperative extracorporeal membrane oxygenation has been adopted for all unstable lung transplantations. Protocols have been proposed in which ECMO is prophylactically extended into the postoperative period based on graft quality and the preoperative presence of pulmonary hypertension. A recent single-institution analysis of this prophylactic protocol identified patients receiving ECMO as having improved survival compared to non-ECMO patients despite higher levels of medical complexity. Prophylactic ECMO prolongation is being increasingly recognized as a safe option for the routine postoperative support of patients with either marginal graft function or underlying pulmonary hypertension [12].

In the same vein, research has been conducted to identify those patients at increased risk of ECMO weaning failure after lung transplantation, in order to identify those patients who might benefit from continued extracorporeal support. Identified risk factors including older donors, longer periods of donor mechanical ventilation, donor PaO₂ prior to organ procurement and longer operative time [58]. In these patients, prophylactic ECMO support postoperatively may be recommended.

4.4 Ex-vivo lung perfusion using ECMO

Ex vivo lung perfusion is another exciting breakthrough for the reconditioning of poor quality grafts as high risk of postoperative primary graft dysfunction. In this setup, retrieved donor lungs are perfused in an ex vivo circuit. This provides an opportunity for transplant surgeons to reassess graft function before transplantation, providing a more accurate window into the likelihood of success in transplantation with high-risk donor lungs. The use of an ex vivo circuit allows time for toxic waste products and inflammatory cytokines to be filtered out, for more optimal recruitment of collapsed lung areas, and for the fluid-overloaded lung tissue to be dehydrated by the perfusate high oncotic pressure [59]. In a 2015 study, lung transplant recipients who received lungs reconditioned in an ex vivo manner demonstrated significantly shorter hospital stay and trends toward shorter length of mechanical ventilation [48, 49].

5. Conclusions

Ultimately, recent advances in ECMO have led it to become a critical tool in the armamentarium of the transplant surgeon, in both the preoperative period as a bridging strategy, as a tool for cardiopulmonary support during the operation, and for the rescue of potentially dysfunctional grafts postoperatively. The use of ECMO in lung transplantation has been need-driven in an incredibly complex and medically challenging complication; innovative thinking by basic scientists and transplant surgeons has led to remarkable improvements in patient outcomes. Continued advances in ECMO technologies, deeper experience with the implementation of ECMO in complicated clinical situations, and further high-quality research will help determine the areas where ECMO can help provide a benefit to lung transplant recipients.

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