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REVIEW ARTICLE

Extracorporeal life support during lung transplantation

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Abstract

Lung transplantation surgeries are performed without extracorporeal life support (ECLS) by using an off-pump technique; however, in cases of hypoxemia or hemodynamic instability, intraoperative ECLS may be required. Cardiopulmonary bypass (CPB) has traditionally been the standard practice for ECLS but has been associated with an increased risk of bleeding in the perioperative period, increased transfusion requirements, prolonged postoperative intubation, and possibly primary graft dysfunction. More recently, because of the flexibility of using extracorporeal membrane oxygenation (ECMO) in bridging to transplantation and during postoperative recovery, its use has increased. CPB and ECMO each has advantages and disadvantages; however, because comparisons of CPB and ECMO have been limited to small retrospective observational and single-institution studies, more research is required to determine the superiority of one modality. In this review, we critically examine the pros and cons of performing lung transplantation surgery off-pump or by using the ECLS modalities of ECMO and CPB support during lung transplantation surgery.

Keywords Lung transplantation · ECMO · Cardiopulmonary bypass · Extracorporeal life support

Introduction

Lung transplantation is performed with or without the use of extracorporeal life support (ECLS). When ECLS is not used, the contralateral lung provides the oxygenation and ventilation needed to conduct the operation. The most common types of ECLS are cardiopulmonary bypass (CPB) and extracorporeal membrane oxygenation (ECMO). The decision to use ECLS depends on the surgeon's preference and the degree of support that the patient requires. Lung transplant surgeons must be prepared for unanticipated intraoperative hemodynamic instability or intolerance of single-lung ventilation, which both require urgent ECLS. Recently, there has been a trend towards the use of ECMO as a perioperative bridge because of its versatility in critically ill lung transplant recipients. Here, we review which patients benefit from planned ECLS and the pros and cons of CPB support versus ECMO.

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Off-pump lung transplantation

Many lung transplantations can be performed without ECLS, a concept referred to as "off-pump" lung transplantation (OPLTx). Diamond et al. [1] of the Lung Transplant Outcomes Group determined that only 37% of lung transplantations were performed with CPB. For all lung transplantation cases, especially those that are OPLTx, careful anesthetic considerations are required. Standard protocol should include the use of a left-sided double lumen endotracheal tube, placement of pulmonary artery pressure (PAP) monitoring catheters, monitoring of central venous pressure, and an intraoperative transesophageal echocardiogram (TEE) [2]. Ventilatory considerations should aim to maintain normocapnia and avoid hypoxia while employing lung protective ventilation strategies [3]. Approaches to reduce hyperinflation of the lungs include methods that result in lower tidal volumes, a lower respiratory rate, longer flow rates, maximized expiratory time, and intermittent disconnection of the circuit [2, 3]. To reduce

hypoxia during one-lung ventilation, continuous positive airway pressure (CPAP) can be applied to the nonventilated lung, which can reduce intrapulmonary shunting; however, this often creates technical difficulties in completing the pneumonectomy and recipient implantation. In this case, intrapulmonary shunting is prevented by early control and clamping of the pulmonary artery. In addition, positive end-expiratory pressure (PEEP) to the ventilated lung helps reduce atelectasis. The disadvantages of PEEP include decreased venous return, impaired hypoxic pulmonary vasoconstriction, and increased pulmonary vascular resistance—all of which can increase right ventricular dysfunction and unwanted shunting. However, this is often unavoidable, and a PEEP of at least 5 mmHg is standard.

A TEE is useful for monitoring right ventricular heart function, air, and pulmonary venous anastomoses after transplantation. It also helps to determine whether the right ventricle will tolerate clamping of the pulmonary artery, which increases right ventricular afterload. Other adjuncts to complete OPLTx include the use of inhaled nitric oxide (iNO), which selectively lowers pulmonary vascular resistance without affecting systemic blood pressure. However, the use of iNO remains controversial because it is expensive, and no randomized trials have shown that its use improves outcomes. In a small randomized trial of 30 lung transplant recipients, the PaO2/FiO2 (P/F) ratio was no different between patients who did or did not receive iNO [4]. If the patient remains hemodynamically stable with clamping of the pulmonary artery and can tolerate gas exchange on single-lung ventilation, then OPLTx can be completed. At our center, we prefer the intraoperative use of iNO, which, in our experience, increases the likelihood of remaining off-pump. Alternatively, we sometimes use inhaled epoprostenol, which is less expensive than iNO and reduces pulmonary vascular resistance, but it does not appear to have as beneficial of an effect on oxygenation as iNO. However, further study is needed to directly compare these two modalities.

Patient selection for ECLS

Consideration of using ECLS requires a preoperative discussion with the operating team including the surgeons, anesthesiologists, and perfusionists. Although most lung transplantations can be performed without ECLS, resources must be available should hemodynamic or ventilatory conditions change course intraoperatively. Patients who should be automatically be considered for ECLS include those with pulmonary hypertension (mean PAP >25 mmHg) and those requiring concomitant cardiac surgery procedures.

Patients with pulmonary hypertension are at risk of right ventricular dysfunction and failure from increased pulmonary vascular resistance and right ventricular afterload during clamping of the pulmonary artery during transplantation. In these cases, ECLS will offload the demands of the right ventricle. Flows should be maintained at 2 to 4 L/min, cardiac output should remain pulsatile, and the systolic PAP should be <30 mmHg [5].

Intraoperative indications to utilize ECLS are based on hemodynamic and ventilatory criteria. Patients who are unable to tolerate clamping of the pulmonary artery or single-lung ventilation will likely require ECLS. Parameters that guide the decision to initiate ECLS include persistent hypoxemia due to an intractable shunt with an SpO_2 of <90%, despite clamping the ipsilateral pulmonary artery; respiratory acidosis with a pH <7.20, in spite of optimal settings for respiratory support; and hemodynamic issues with increases in mean PAP and decreases in cardiac output with a mixed venous O_2 of <55%, despite proper use of inotropic or vasoactive agents [5]. A TEE is also useful for evaluating right ventricular function, dilation, and early signs that ECLS will be necessary with a test clamping of the pulmonary artery [3].

Lastly, ECLS may be instituted for technical reasons, such as visualization for the atrial cuff anastomosis. Intermittent manipulation of the heart may lead to intermittent hypotensive episodes, and ECLS support will ease the exposure by maintaining hemodynamics. With CPB, better venous drainage allows an "emptier" heart for better visualization. Also, there may be times when an open pulmonary artery or atrial cuff anastomosis is technically required, which would necessitate CPB. In our experience, we consider the need for intraoperative support at the time of the initial clinic visit once hemodynamic and imaging data are available. Our decision is often reinforced in the operating room on the basis of the hemodynamic response to a 5-min test clamp of the pulmonary artery (Table 1).

Conversion from OPLTx to ECLS

Conversion from OPLTx to ECLS occurs in less than 20% of lung transplant surgeries [6, 7]. To further delineate patient factors that predict conversion from OPLTx to ECLS, Hinske and colleagues [6] retrospectively evaluated a cohort of 170 consecutive lung transplantations. No single lung transplantations required ECLS at their institution and were not included in the study. Interestingly, Hinske et al. [6] found that women required ECLS more often than did men (46.8% vs. 26.8%). Preoperative mean PAP and milrinone administration after induction were the two most significant predictors for conversion to unplanned ECLS, with the threshold mean PAP starting at approximately 35 mmHg. Furthermore, patients who necessitated intraoperative conversion to ECLS had higher lung allocation scores than patients who did not (51.5 vs. 42.3), suggesting an increased need for ECLS in patients with a lung allocation score ≥ 50 [6].

Table 1 Patient criteria for consideration of ECLS

Common preoperative indications for ECLS	Intraoperative indications for ECLS	Surgical indications for ECLS
Pulmonary hypertension (mean PAP >25 mmHg)	Hemodynamic instability with clamping of the pulmonary artery • Increasing mean PAP • Right ventricular straining or dysfunction • Decreasing cardiac output and hypotension	Visualization for atrial cuff anastomosis
Need for concurrent cardiac procedures (excluding off-pump procedures)	Intolerance of single-lung ventilation • Persistent hypoxemia • Hypercarbia • Respiratory acidosis <7.20	Need for open (without clamp) pulmonary artery and atrial cuff anastomoses (CPB only)

ECLS extracorporeal life support, *PAP* pulmonary artery pressure, *CPB* cardiopulmonary bypass

To evaluate whether conversion to an unplanned ECLS strategy is associated with worse outcomes, Mohite and colleagues [7] compared results among patients who underwent OPLTx, ECLS with the use of CPB, or unplanned conversion at six designated lung transplant centers in the UK. The conversion group had significantly more patients with preoperative ventilator support and a primary diagnosis of pulmonary hypertension or pulmonary fibrosis than did the other two groups. The conversion group also had significantly poorer P/F ratios at 0 to 72 h postoperatively than did the OPLTx cohort. However, when the conversion group was propensity matched with the planned CPB group, no significant difference was observed in ventilator support time, primary graft dysfunction (PGD), intensive care unit stay, or hospital length of stay. Compared with patients who were on-pump, patients in the OPLTx group had improved P/F ratios at 24 h, reduced ventilator support time, and decreased intensive care unit and hospital lengths of stay. Given that the conversion and planned CPB groups had comparable early postoperative outcomes, the authors concluded that it was reasonable to attempt an off-pump strategy with conversion to ECLS in high-risk patients, if necessary [7].

At our institution, patients who undergo single right-sided lung transplantation are more likely to remain off-pump than are those who undergo single left-sided lung transplantation. A left posterolateral approach may reduce the need to manipulate the heart and facilitate the use of the OPLTx technique. We have a low threshold for initiating ECLS support because of its ability to improve the safety of the operation when needed. We prefer to have a well-thought-out plan for cannulation and thresholds for the initiation of ECLS before the start of the procedure. It is important to note that, although central cannulation is straightforward during a clamshell exposure, it is more challenging in isolated thoracotomies. In anticipation of this, the surgeon should have femoral venous sheaths with wires in place, exposure to the aorta through the thoracotomy, or a femoral arterial line if there is any chance of needing to convert. This will limit the difficulty involved in an emergent conversion.

CPB in lung transplantation

CPB has traditionally been the standard mode of intraoperative support when ECLS is required for lung transplantation. CPB stabilizes patient hemodynamics during transplantation and maintains oxygenation while allowing for protective ventilation strategies or minimal ventilation of the reperfusing allograft. Some centers have advocated the use of CPB because it allows for the slow initiation of pulmonary reperfusion and low oxygen concentrations during initial ventilation [8]. One benefit of using CPB during lung transplantation is improved volume control and drainage of the heart. In addition, with CPB, the atrium and pulmonary artery can be opened, if necessary, and cardiotomy suction can be used in cases of significant bleeding. CPB also facilitates the performance of a double lung transplant through a sternotomy, which, from a healing standpoint, may be a better incision than a clamshell thoracotomy. The Ochsner Clinic lung transplantation group [9] compared their experience with CPB to that with OPLTx and showed improved early outcomes, technical benefits, and no difference in the 3-year survival rate with the use of CPB. A potential disadvantage of CPB is that it requires systemic heparinization, which has been associated with increased bleeding and blood transfusion requirements [10–16]. CPB has also been associated with increased systemic inflammation [10] and postoperative allograft dysfunction [1, 10, 12, 16, 17].

CPB and allograft function

In one of the earliest studies to examine the effects of CPB on postoperative allograft function, Aeba et al. [10] at the University of Pittsburgh Medical Center reviewed the effects of CPB on the newly transplanted lung allograft during the early reperfusion period, with a focus on prolonged intubation (defined as >7 days) and histologic evidence of diffuse alveolar damage. Their definition for diffuse alveolar damage was based on the following criteria in postoperative biopsy specimens

(obtained by using flexible bronchoscopy or open thoracotomy 3 weeks after transplantation): (1) diffuse alveolar edema with a widened interstitium; (2) vacuoluation, hobnail change, or sloughing of endothelium; (3) massive alveolar hemorrhage; (4) hyaline membranes coating alveolar septa; (5) diffuse fibrin microthrombi; and (6) parenchymal and vascular necrosis. Of the 100 lung transplant recipients that they evaluated, including 13 heart-lung transplant recipients, 55 required CPB. More patients in the CPB cohort (29/55 patients) than in the OPLTx cohort (8/45) required prolonged intubation ($p = 0.0003$). For patients in whom histology was obtained, more patients in the CPB cohort (11/23 patients) than in the OPLTx cohort (3/16) showed diffuse alveolar damage ($p = 0.036$). With respect to secondary outcomes, pulmonary graft injury identified on a chest radiograph was more severe, and gas exchange calculated as a mean PaO_2/PAO_2 ratio was worse in the CPB cohort than in the OPLTx cohort. In terms of allograft function and patient survival, the OPLTx group had significantly better outcomes than did the CPB group [10].

Post-perfusion lung syndrome, defined as severe pulmonary edema and dysfunction after CPB, was seen more commonly before improvements were made in CPB design and circuits. However, lung injury after CPB continues to occur due to the activation of systemic inflammatory pathways. Contact between blood elements and artificial surfaces of the circuit activates neutrophils and proinflammatory mediators such as interleukin (IL)-6, the complement pathway (C3, C5a), platelet-activating factor, and leukotriene B4. These inflammatory mediators in turn activate proteolytic enzymes and oxygen-free radicals that enter the systemic circulation and sequester in the lung parenchyma, mediating damage locally through cellular and tissue injury. This proinflammatory state also increases alveolar-endothelial permeability, thereby increasing pulmonary edema [18].

The increase in proinflammatory markers and pulmonary edema can increase the risk of allograft dysfunction after lung transplantation. In an effort to improve research on allograft dysfunction, in 2005 and in an update in 2016, the International Society for Heart and Lung Transplantation (ISHLT) defined PGD grading on the basis of the P/F ratio and the presence of radiographic infiltrates seen on a chest radiograph that are consistent with pulmonary edema. Accordingly, there are four grades of severity, with grade 3 being the most severe (P/F ratio < 200 and radiographic infiltrates present) [19]. The Lung Transplant Outcomes Group [1] determined that the use of CPB was one of the clinical risk factors of PGD after lung transplantation (OR 2.4; 95% CI 2.2–5.3, $p < 0.0001$). In a systematic review and meta-analysis that examined recipient risk factors for the development of PGD, a 2.29-fold increased risk of PGD was observed for patients requiring CPB (OR 2.29, 95% CI 1.43–3.65, $p = 0.0005$); however, statistical heterogeneity was observed among the studies [17].

As mentioned above, one of the greatest disadvantages of CPB is the need for systemic anticoagulation, which can increase intraoperative bleeding and perioperative coagulopathy. Aeba et al. [10] showed a significant difference in transfusion requirements between patients who underwent lung transplantation with CPB or OPLTx. The CPB cohort was given significantly more transfusions of packed red blood cells (PRBC), fresh frozen plasma (FFP), platelets (PLT), and cryoprecipitate than was the OPLTx cohort. Compared with ECMO, which we will discuss below, CPB has been associated with increased transfusion requirements [13, 14].

In a meta-analysis by Liu et al. [17], increased transfusions of PRBC and FFP were found to be associated with the development of PGD; no statistical heterogeneity was observed among these studies. Ong et al. [20] evaluated the effect of transfusion requirements in patients undergoing bilateral lung transplantation while receiving CPB support and found that the median transfusion requirement within the first 24 h was 3 units of PRBC, 2 units FFP, and 1 pack PLT. Patients whose main cause of death was PGD received significantly more PLT transfusions.

The association between PGD and CPB remains uncertain. No large randomized studies have been reported to date, and most studies are small, single-institution retrospective series. Furthermore, in many cases, there is significant heterogeneity in data among the studies. However, it is clear that the need for systemic anticoagulation and the risk of coagulopathy and increased transfusion should be carefully balanced with technical indications. CPB should be utilized when clinically indicated and according to the comfort level of the surgeon and the preference of the center. It is important to note that CPB is the only ECLS modality specifically approved by the US Food and Drug Administration to assist with procedures on the heart and lungs. The main reasons for this are that CPB can recirculate blood and filter air that enters the venous system. Other ECLS modalities such as ECMO are not designed for this. However, ECMO is becoming increasingly utilized during lung transplantations because of its flexibility in the perioperative support of critically ill lung transplant patients and because of reports that its performance is superior to that of CPB in terms of lung allograft function and hemostasis.

The trend towards using ECMO

Given the increased utilization of ECMO as a bridge to transplantation and as a rescue therapy in the postoperative period, several studies have examined its utilization in the veno-arterial configuration during lung transplantation. ECMO allows for a small, closed circuit and does not expose the patient to a reservoir, thereby limiting the proinflammatory cascade and reducing anticoagulation requirements. Without a reservoir, ECMO is more reliant on patient volume and is unable to

fully drain, which may limit visualization during dissection and compromise hemodynamics. Furthermore, air cannot be introduced into the closed ECMO circuit.

Ko et al. [14] described their conversion to using ECMO instead of CPB and found that its use was beneficial in continuing support for single-lung transplant recipients with pulmonary hypertension in the postoperative period (duration 27.9 ± 24.6 h, median 18 h). Furthermore, they found that ECMO did not increase transfusion requirements. A group at Hannover Medical School [13] reported their transition from CPB to ECMO in 92 consecutive patients (CPB, $n = 46$; ECMO (since February 2010), $n = 46$). The indications for ECLS were not different between these groups of patients and included the following: pulmonary hypertension as the indication for lung transplantation, ECMO as a bridge to transplantation, suprasystemic systolic pulmonary pressures associated with primary lung disease, the need for a concomitant cardiac surgery procedure, and unplanned conversions. The unplanned conversion category included the decision to use ECLS intraoperatively because of hemodynamic or respiratory instability that ensued after test clamping of the pulmonary artery at the beginning of the procedure. Compared with the ECMO group, the CPB group required increased PRBC transfusion with a median of 10 units. In the evaluation of postoperative complications, in-hospital mortality was increased in the CPB group (OR 4.9, 95% CI 1.2–20, $p = 0.026$). Furthermore, using ECMO instead of CPB was associated with lower rates of morbidity and mortality, and lung transplantation with CPB support represented an independent risk factor for in-hospital mortality in multivariate analysis [13].

In contrast, Bittner et al. [21] found in their study that patients who received ECMO support during lung transplantation required significantly more transfusions during the first 72 h after implantation than did those supported with CPB. In multivariate analysis, transfusion of 8 or more units of PRBC during ECMO support was associated with an increased mortality rate and a reduced 1-year survival rate. The authors concluded that CPB achieved better hemodynamic stability than did ECMO, improved flow rates, and did not depend as heavily on fluid supplementation. Similarly, the group at the University of Pittsburgh Medical Center [11], who described ECMO as their first choice of ECLS for lung transplantation, reported that patients who received ECMO support required intraoperative transfusion of more units of PRBC (7.7 units) than did patients in whom CPB was utilized (5.9 units). However, no difference in overall transfusion requirements was observed in PRBC, FFP, or PLT transfusions at 72 h. There were no differences in 30-day, 6-month, or 1-year mortality rates between the ECMO and CPB cohorts. Furthermore, the causes of early or late mortality did not differ between the ECMO and CPB cohorts, and there were no differences in overall survival. In terms of short-term postoperative outcomes, more patients in the CPB cohort than in the ECMO cohort required reintubation and temporary tracheostomy. The CPB cohort also showed a trend towards longer mechanical ventilation time than did the ECMO group. Lastly, patients in the CPB cohort had a higher rate of renal failure requiring renal replacement therapy (22.1%) than did patients in the ECMO cohort (8.2%) [11].

The lung transplantation group at the Columbia University [12] compared outcomes between patients who received ECMO support or CPB support during lung transplantation and found that the transfusion requirements were higher in the CPB group than in the ECMO group, even though the estimated amount of intraoperative blood loss was comparable between groups. Cryoprecipitate, FFP, and PLT were transfused much more frequently in the CPB cohort than in the ECMO cohort. In the perioperative period, the CPB cohort showed a trend towards increased transfusion requirements, but the difference between groups was not statistically significant. Importantly, more patients in the CPB cohort had significant events of postoperative bleeding (defined as needing reoperation for bleeding or transfusion of ≥6 units of PRBC), and more reoperations occurred in the CPB group than in the ECMO group. Using the ISHLT grading for PGD, the authors showed that the CPB group was more likely to have any grade of PGD at both 24 and 72 h than was the ECMO group. No differences were observed in 30-day and 1-year survival rates [12].

The lung transplantation group at the University of Toronto [15] reported their preference for OPLTx and ECMO over CPB for lung transplantation. Their procedure typically involves inserting the first allograft in a bilateral sequential transplant off-pump and initiating ECLS only if hemodynamic instability or inadequate gas exchange ensues while attempting to support the patient on the newly implanted allograft. The exception would be patients being transplanted for primary pulmonary hypertension. In their experience, the authors reported less intraoperative transfusion of PRBC, FFP, and PLT in the ECMO group than in the CPB group, which continued into the initial 72 h after reperfusion. More patients in the CPB support cohort than in the ECMO cohort required reoperations for bleeding. They found that the ECMO group was quicker to extubate (3 vs. 7.5 days), had shorter intensive care stays, and had shorter hospital lengths of stay [15].

To clarify the differences between CPB and ECMO support for lung transplantation, Hoechter and colleagues [22] performed a meta-analysis that included six papers that excluded ECMO use as a bridge to transplantation and combined organ transplantations. The authors reported an overall trend towards less intraoperative transfusion requirements in patients supported with ECMO than in patients supported with CPB, but the difference did not reach statistical significance. Compared with the CPB group, the ECMO group also showed a 0.46-fold reduction in PRBC, a 0.65-fold reduction in FFP, and 1.72-fold reduction in PLT transfusion requirements. Furthermore, the ECMO group required a significantly shorter

duration of mechanical ventilatory support and intensive care unit length of stay than did the CPB group. All outcomes were affected by statistical heterogeneity among the studies. Gender had a significant effect, as did the year ECMO was initiated at the institution, which in turn had an effect on the transfusion requirement. The studies with predominantly male patients and with an earlier time frame seemed to favor CPB support. However, the findings of this meta-analysis did not show a clear advantage of ECMO over CPB support during lung transplantation [22]. In another meta-analysis, Magouliotis and colleagues [16] included papers that examined ECMO as a bridge to transplantation and combined organ procedures in their comparison of ECLS modalities. They showed that ECMO was preferred in cases of pulmonary hypertension and respiratory and hemodynamic instability, whereas CPB support was preferred in cases of increased intraoperative bleeding and combined cardiac surgery procedures. Furthermore, they found that intraoperative transfusion requirements were significantly greater in the CPB group with regard to PRBC, FFP, and PLT transfusions. Postoperative bleeding was significantly higher in patients supported with CPB than in patients supported with ECMO. Compared with the ECMO cohort, the CPB cohort had prolonged mechanical ventilation, an increased need for tracheostomy, and an increased length of intensive care unit stay. PGD was greater when CPB support was used (OR 2.01, 95% CI 1.27–3.19, $p = 0.003$). CPB support also increased the frequency of renal failure requiring hemodialysis. No significant differences were observed between groups in 30-day, 3-month, or 1-year mortality rates [16].

In recent years, there has been a trend towards the utilization of ECMO support during lung transplantation. ECMO is used preoperatively as a bridge in critically ill patients, and there is the additional ease of continuing ECLS support in the intensive care unit during the postoperative period should ECMO be deemed necessary. At some institutions, planned intraoperative use of ECMO has been associated with decreased transfusion requirements [12, 13, 15, 16], decreased risk of PGD [12, 16], decreased intubation time [11, 15, 16, 22], and decreased hospital length of stay [15, 16]. Intraoperative ECMO support has also been associated with increased survival rates when compared with CPB [13]; however, these claims continue to be debated.

At our institution, we recognized a need to reduce bleeding and graft dysfunction while maintaining consistent hemodynamic support throughout the procedure. Although ECMO seemed to be the logical solution to this, concerns for the possible need to convert to CPB because of air or bleeding led us to begin with a modified CPB circuit. This modified circuit bypasses the volume reservoir to provide a closed ECMO-like circuit. If there were any issues requiring conversion, the heparin dose could be increased, and the clamps on the volume reservoir removed. This allowed easy and rapid conversion if needed. However, over time, we migrated towards using a simple closed ECMO circuit with the minimum tubing required, usually with the Quadrox® oxygenator and Rotaflow® pump. To date, we have not had a single case in which bleeding or air was a concern. We hypothesize that these smaller circuits further improve allograft function while allowing a smooth, hemodynamically stable operative experience. We favor the use of a femoral venous cannula, which is inserted percutaneously with ultrasound guidance and is removed at the end of the surgery with a deep reinforcement suture and pressure. We rarely perform surgical cut-down.

ECLS and protection during reperfusion

The current ISHLT Consensus Guidelines for the prevention of PGD state that most operations can be performed without intraoperative ECLS and to utilize OPLTx when feasible [23]. Yet, several studies have demonstrated techniques that allow for slow pulmonary reperfusion of the allograft, which may protect the newly implanted lungs. Taka and colleagues [8] describe their use of CPB with extended criteria donor lungs to maintain slow reperfusion and protect these more susceptible allografts. They preferred to use CPB with every bilateral lung transplantation. To protect against reperfusion injury of the allograft, the mean PAP was strictly maintained at 10 to 15 mmHg by reducing or increasing the CPB and the pulmonary artery flow, and the ventilator was set at 21% FiO_2. Both lungs were implanted before allowing reperfusion. In their experience, no significant difference was observed in the P/F ratios between standard criteria and extended criteria lungs during the first 72 h when using this strategy. Furthermore, early outcomes of patients who received extended criteria lungs were comparable to those of patients who received standard criteria donor allografts in terms of postoperative mechanical ventilator support times, necessity for postoperative ECMO support, and intensive care and hospital lengths of stay. The authors reported having better control of reperfusion, which they attributed to improved control of CPB flows when compared with ECMO [8]. The lung transplantation team at the Medical University of Vienna [24] described their technique of controlled reperfusion when utilizing ECMO support. While the implanted allograft received retrograde and antegrade flushing, they temporarily reduced the ECMO flows to 1 L/min. Then, throughout the second allograft implantation, they meticulously adjusted the ECMO flow to maintain a systolic PAP <25 mmHg with pulsatile flow and maintain an end-tidal CO_2. After bilateral sequential implantation, the ECMO support was gradually reduced, and the cannulas were clamped. They connected the circuit to itself to self-circulate in case it was needed for postoperative support. The vast majority of patients in this study (80%) showed no evidence of PGD (grade 0) at time point 0 (6–8 h after reperfusion). Only 7.5% ($n = 12$) of patients had PGD grade

3 at time point 0. At 72 h, 76.7% of patients were extubated and on a nasal cannula, and 1.3% ($n = 2$) patients had grade 3 PGD. The authors of this study advocated for the use of a veno-arterial ECMO support strategy, given the protective lung ventilation strategies that can be implemented when performing the contralateral pneumonectomy and implantation. They also concluded that reducing the ECMO flow to 40% of the cardiac output prolonged the controlled reperfusion of the graft, improved allograft function, and stabilized hemodynamics throughout the entire transplantation [24].

ECLS registry and future research

Currently, the available information regarding the use and outcomes of ECLS in patients during lung transplantation is primarily from single-institution, retrospective observational studies. With this deficiency in mind, our institution is developing a protocol for a registry that will be the largest multicenter prospectively maintained database for the practice of intraoperative ECLS strategies and outcomes. Although a randomized control study would be the gold standard for identifying the preferred method of intraoperative ECLS, it would be extraordinarily difficult to organize, given the established practices of institutions across the world and the insufficient equipoise to randomize. Centers that are currently enrolled in the international multicenter registry on ECLS and lung transplantation include Baylor–St. Luke's Medical Center (Houston, TX), Duke University (Durham, NC), Hannover Medical School (Hannover, Germany), Massachusetts General Hospital (Boston, MA), St. Joseph's Hospital (Phoenix, AZ), Temple University (Philadelphia, PA), University of Florida (Gainesville, FL), University of Leuven (Leuven, Belgium), University of Minnesota (Minneapolis, MN), University of Pittsburgh Medical Center (Pittsburgh, PA), and University of South Florida (Tampa, FL). Our primary end points include PGD and survival after transplantation. We anticipate that the registry will clarify the significance of intraoperative practices on lung transplant outcomes.

Conclusions

At this time, there is no standard regarding ECLS during lung transplantation. The most current ISHLT Consensus Guidelines recommend utilizing OPLTx when feasible. Clinical indications for ECLS include patients with pulmonary hypertension, those that become unstable during transplantation, and those who are unable to tolerate single-lung ventilation. Among the methods of ECLS, there has been a recent trend towards veno-arterial ECMO because of the ease of perioperative bridging of support. Also, CPB may cause a greater inflammatory response than ECMO, with activation of cytokines, leukocytes, and the complement cascades, leading to adverse short-term outcomes such as prolonged ventilatory support, need for tracheostomy, renal failure, need for hemodialysis, increased bleeding, need for increased transfusion requirements, and longer intensive care and hospital lengths of stay. The debate continues as to whether CPB contributes to PGD; while some studies suggest worse survival and allograft function with CPB, these studies are small and limited to single institutions. Proponents of either CPB or ECMO demonstrate useful reasons of when and how to utilize intraoperative ECLS. At this point in time, until large multicenter registries shed light on these questions, surgeons should choose the clinically indicated support type that they are most comfortable with.

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