CONSENSUS STATEMENT

ISHLT CONSENSUS STATEMENT ON THE PERIOPERATIVE USE OF ECLS IN LUNG TRANSPLANTATION: PART II: INTRAOPERATIVE CONSIDERATIONS

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The use of extracorporeal life support (ECLS) throughout the perioperative phase of lung transplantation requires nuanced planning and execution by an integrated team of multidisciplinary experts. To date, no multidisciplinary consensus document has examined the perioperative considerations of how to best manage these patients. To address this challenge, this perioperative utilization of ECLS in lung transplantation consensus statement was approved for development by the International Society for Heart and Lung Transplantation Standards and Guidelines Committee. International experts across multiple disciplines, including cardiothoracic surgery, anesthesiology, critical care, pediatric pulmonology, adult pulmonology, pharmacy,

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https://doi.org/10.1016/j.healun.2024.08.027

psychology, physical therapy, nursing, and perfusion, were selected based on expertise and divided into subgroups examining the preoperative, intraoperative, and postoperative periods. Following a comprehensive literature review, each subgroup developed recommendations to examine via a structured Delphi methodology. Following 2 rounds of Delphi consensus, a total of 39 recommendations regarding intraoperative considerations for ECLS in lung transplantation met consensus criteria. These recommendations focus on the planning, implementation, management, and monitoring of ECLS throughout the entire intraoperative period.
J Heart Lung Transplant xxxx;xxx:xxx–xxx

KEYWORDS:
ECMO; ECLS; lung transplant; multidisciplinary; end-stage lung disease

While the first use of cardiopulmonary bypass (CPB) in lung transplantation is unknown, extracorporeal membrane oxygenation (ECMO) was first used as a bridge to lung transplantation in 1977.[1] Despite this early adoption of ECMO, CPB remained the primary modality for intraoperative extracorporeal life support (ECLS) in lung transplantation into the early 21st century.[1] The data regarding intraoperative ECLS utilization are mixed, with most recommendations resulting from single-center retrospective studies. A recent consensus statement from the American Association of Thoracic Surgery (AATS) provided guidance regarding intraoperative use, but the sample population of experts was from a single specialty.[2]

This perioperative utilization of ECLS in lung transplantation consensus statement was approved for development by the International Society for Heart and Lung Transplantation (ISHLT) Standards and Guidelines Committee. International experts across multiple disciplines, including cardiothoracic surgery, anesthesiology, critical care, pediatric pulmonology, adult pulmonology, pharmacy, psychology, physical therapy, nursing, and perfusion, were selected based on expertise with a balance of geographical, gender, and career-grade diversity. After selection, the writing group was separated into preoperative, intraoperative, and postoperative subgroups. Following a comprehensive literature review, each subgroup developed recommendations to examine via a structured Delphi methodology as described in the Part I manuscript of this consensus. Following 2 rounds of Delphi consensus, a total of 39 recommendations regarding intraoperative considerations for ECLS in lung transplantation met consensus criteria. These recommendations focus on the planning, implementation, management, and monitoring of ECLS throughout the entire intraoperative spectrum. The class and levels of evidence standards (Table 1) were utilized to grade the respective recommendations (Appendix 1), although many recommendations are based solely on expert opinion due to a lack of available data.

While there have been recent guidelines discussing mechanical circulatory support within cardiothoracic transplantation,[3] the purpose of this consensus is to provide guidance to multidisciplinary teams (MDTs) as they provide perioperative care for lung transplantation recipients. The intraoperative consensus focuses on presurgical planning for intraoperative implementation, intraoperative management, and considerations for future research and technological development for ECLS in lung transplantation.

1. PRESURGICAL PLANNING

Presurgical planning for intraoperative utilization of ECLS should be part of a continuum of care for lung transplantation recipients. The foundation of this planning is an MDT discussion, which should primarily focus on surgical, anesthetic, and perfusion considerations. However, these presurgical planning discussions should also consider postoperative considerations, as these patients may have prolonged ECLS beyond the operating room.

1.1. MDT discussion

The current practice of lung transplantation continuously pushes the medical boundaries of this treatment but faces increasing challenges. The increasingly complex recipient with multiple and severe comorbidities, together with frequent utilization of extended criteria and suboptimal donor allografts,[4] represents substantial risks for not only primary graft dysfunction (PGD) development but also systemic organ dysfunction, severe postoperative complications, and overall outcomes.[5]

Table 1 Class of Recommendation and Levels of Evidence

Class I Evidence and/or general agreement that a given treatment, procedure, or technique is beneficial, useful, and effective as applied to patients, clinicians, or researchers
Class II Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment, procedure, or technique*Class IIa* Weight of evidence/opinion is in favor of usefulness/efficacy*Class IIb* Usefulness/efficacy is less well established by evidence/opinion
Class III Evidence or general agreement that the treatment, procedure, or technique is not useful or effective and, in some cases, may be harmful
Level of evidence A Data derived from multiple, high-quality randomized clinical trials, meta-analyses of high-quality randomized controlled trials (RCTs), or one or more RCTs corroborated by high-quality registry studies
Level of evidence B Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCTs, or large nonrandomized studies *B1* Data derived from a single or multiple moderate-quality randomized clinical trial(s), meta-analyses of moderate-quality RCT *B2* Data derived from one or more high-quality nonrandomized, observational, or registry studies
Level of evidence C Consensus of expert opinion *C1* Expert opinion supported by small, observational studies, retrospective studies, meta-analyses of such studies, or physiologic/mechanistic studies *C2* Expert opinion alone or with group communications/questionnaires

Over the last decade, models of clinical care have transitioned due to worldwide paradigm shifts in the traditional doctor/patient relationship characterized by single physician and specialty management toward a shared decision, with patient-oriented care models that derive strategic guidance from MDT evaluation, planning, and management. The multidisciplinary approach was defined to appropriately utilize knowledge, skills, and best practice from multiple disciplines to explore problems outside of normal boundaries and to achieve solutions based on a new understanding of these problems across specialty boundaries.[6]

This broader paradigm change aligns with the history of lung transplantation, which indicates that improvement in outcomes was characterized by MDT coordination. While traditionally, surgeons and pulmonologists represented the core members of this collaboration, anesthesiologists and intensive care physicians are increasingly taking part in the transplant MDT to contribute to listing decisions, risk stratification, and developing appropriate perioperative management plans for the patient's transplant journey due to the significant impact of perioperative events on overall outcomes.[7,8] Such expansion is not solely in the purview of physician specialties, and the formulation of a patient-centered management, plan as well as clear communication between the various MDT stakeholders, is essential to mitigate medical, organizational, surgical, and anesthetic risk factors.[9] Utilizing these formally structured teams and interdisciplinary relationships, the MDT should determine ECLS utilization based on a broad variety of recipients factors, while allowing for dynamic discussions to occur that evaluate real-time recipient status changes in the context of previous ECLS planning.

This strategy provides the opportunity for open discussion of ECLS by the MDT stakeholders, focusing on the type and approach of ECLS to be used intraoperatively, if any at all. Each ECLS option comes with its own advantages and disadvantages; however, lately there is an emerging trend in literature and clinical practice suggesting that ECMO is the preferred ECLS modality for intraoperative support as compared to CPB. A key reason for this trend may be the increasing use and improving outcomes of ECMO bridging to transplantation in lung transplantation recipients.[10] Another reason may be the literature reporting morbidity outcomes of ECMO versus other forms of intraoperative ECLS in lung transplantation. When considering the application of ECMO, some advocate for its use in all recipients due to the ability to control flow during reperfusion of the graft, provide hemodynamic stability, and promote a lung protective ventilation strategy.[11] Under a guideline of routine application of intraoperative ECMO to all patients within a single center, very low percentages of PGD were reported combined with a 2-year survival of 86%.[12] In a study by Diamond et al,[13] the use of CPB was identified as an independent risk factor for severe PGD. In a meta analysis of 785 patients, ECMO provided a favorable, yet

nonstatistically significant, trend of superiority to CPB in areas of PGD or other morbidities.[14] Finally, a recent multicenter trial reported that the odds of developing PGD grade 3 were higher when utilizing CPB as opposed to ECMO intraoperatively.[15]

Recommendations:

1. Increased recipient, donor, and surgical complexity within the practice of lung transplantation necessitates multidisciplinary perioperative transplant management, including the provision of a spectrum of surgical, anesthesia, and intensive care management. Strength of Agreement: 100%. (CoR: I LoE: C2)
2. An MDT discussion at the time of listing can be helpful to balance risk-to-benefit for proceeding to transplantation with or without intraoperative ECLS based on recipient co-morbidities such as etiology of end-stage lung disease (ESLD), co-morbidities, and ongoing clinical status. The decision taken at listing should be re-evaluated if the patient's condition deteriorates. Strength of Agreement: 96%. (CoR: I LoE: C2)
3. An emerging trend in literature and clinical practice amongst international lung transplant centers suggests that ECMO is the preferred ECLS modality for intraoperative support as compared to CPB. Strength of Agreement: 86%. (CoR: I LoE: B2)

1.2. Criteria for selection of ECLS versus no ECLS

Reported outcomes for patients bridged using ECMO to lung transplantation are improving, especially at high-volume centers, and thus the presence of preoperative venovenous (VV) ECMO or venoarterial (VA) ECMO has become increasingly common.[10,16,17] Considering those patients already on ECMO as a bridge to transplantation, there should be further studies on how to manage these patients. Modality of ECMO is often tied the patients underlying ESLD as patients with respiratory insufficiency without any hemodynamic component are likely to be bridge on VV ECMO while patients with hemodynamic instability often require VA ECMO, and there is general support that patients who are bridged preoperatively should have support continued intraoperatively.[18] Hashimoto et al[19] found no comparable differences between VA ECMO and VV ECMO following bridging with VV ECMO, except for a statistically insignificant difference for an increased need for transfusion following a switch to VA ECMO. While blood transfusions have been linked elsewhere to a higher risk of PGD with increased mortality,[13] other benefits outlined in Hashimoto et al's[19] work regarding the main conclusion of considering a low threshold to conversion between ECMO types are reached by finding comparable results between the 2.

There are no clear criteria for the elective use of ECMO or any ECLS at all during lung transplantation, and as such, individualized risks and benefits often dictate local practice. The proponents of the utilization of ECLS often emphasize the hemodynamic instability that may ensue without ECLS support.[20] Pulmonary concerns related to the increased inspired fraction of oxygen required at reperfusion, which has been proposed as a risk factor for PGD development,[13] also lead teams to consider ECLS as an adjunct to promote a lung-protective ventilatory strategy. On the other hand, the proponents of no utilization of ECLS emphasize the risks of cannulation, heparinization, and the effects of nonphysiological shear stress and artificial surfaces.[20,21]

Localized practices engrain center expertise, which may provide a bias for the training and experience of individual transplantation teams. Opinions are divided, with some who report that there can be similar postoperative outcomes between planned no ECLS cases which required emergency conversion to ECLS and elective ECLS.[22] Some studies have shown that no ECLS provides a superior outcome to either ECMO or CPB[15]; other studies have shown superiority of ECMO as the chosen form of ECLS as compared to no support at all.[11] Longer-term studies comparing ECMO to no ECLS have found no significant difference in 5-year survival or chronic lung allograft dysfunction between the 2 groups.[23]

Beyond center practice patterns and individual team experiences, recipient characteristics also need to be considered when forming criteria for ECLS versus no ECLS. These characteristics may include cardiopulmonary comorbidities related to the underlying ESLD or even the ESLD itself,[24] as studies have reported that the use of CPB led to increased transfusion[25] and independently predicted mortality in pediatric and adult cystic fibrosis patients.[26] Other recipient characteristics reported in the literature that promote the selection of elective ECLS include the following: moderate or greater pulmonary hypertension, significant right ventricular anatomical abnormality or physiological dysfunction, baseline hypoxemia/hypercarbia with resultant suspected inability to tolerate single-lung ventilation, cardiac index < 2 liter/min, and preoperative bridging with ECLS.[8,20,27-29] The intersection of pulmonary hypertension and right ventricular dysfunction, which may be aggravated by

intraoperative pulmonary arterial clamping during explantation, may also lead to severe impairment of left ventricular function.[8] As such, patients with these concomitant cardiopulmonary comorbidities may benefit from utilization of ECLS to avoid hemodynamic instability.[30] Hinske et al[31] explored a scoring system to predict the need to convert from no intraoperative support to VA ECMO, finding that all patients with a mean pulmonary arterial pressure (mPAP) ≥35 mm Hg and a lung allocation score >50 required intraoperative conversion to VA ECMO. Salman et al[30] suggested that an mPAP exceeding 50 mm Hg and pulmonary vascular resistance exceeding 9.4 wood units were risk factors for the need for intraoperative ECLS.

Utilization of most ECLS requires heparinization with resultant secondary impairment of hemostasis. Recipients with widespread adhesions due to underlying ESLD or previous thoracic surgery are at an increased risk for blood loss, transfusion, and reoperation due to bleeding. These patients might, therefore, benefit from procedures without ECLS or with ECLS in the form of ECMO rather than CPB. This suggestion is supported by the data from Ius et al[23,32] who showed that recipients transplanted using CPB had a greater need for blood products, postoperative ECMO prolongation, and overall poorer outcomes. Concomitant cardiac procedures require some type of mechanical support, with the type being determined by the required operation and/or surgeon preference. If possible, catheter-based procedures and treatment options of cardiac pathology should be evaluated at listing by the MDT to optimize ECLS requirements during lung transplantation.[8] The surgical approach to sternotomy results in a smaller surgical field and therefore also often necessitates mechanical support to avoid hemodynamic instability.[29] Although not a recipient characteristic per se, ECLS should be considered in lung transplantation when there is a perceived need for careful reperfusion of the first implanted lung or lobe.[2]

Intraoperative ECLS in nonbridged patients is almost always placed postinduction of general anesthesia. The induction of recipients undergoing lung transplantation is one of the most critical phases of the intraoperative period due to acute changes within the cardiopulmonary unit. Despite adequate preoxygenation, rapid desaturation occurs due to a low respiratory reserve. Hypoxia and concomitant hypercarbia lead to acute increases in pulmonary vascular resistance, precipitating right ventricular failure and cardiovascular collapse.[33] The introduction of positive pressure ventilation leads to decreased cardiac venous return as well as increased pulmonary vascular resistance, with these effects compounded by the suppression of the sympathetic nervous system by anesthetic induction medications that can produce myocardial depression with reduced systemic vascular resistance.[34,35]

Preinduction initiation of ECLS should be considered in those patients who are at a high risk of hemodynamic collapse who present with a history of severe pulmonary hypertension, right ventricular dysfunction, or recent signs of increasing right ventricular failure, including peripheral edema, dyspnea, orthopnea, and ongoing hypotension. An international survey of anesthesiologist practices noted a rate of 8.7% of preinduction ECMO in such high-risk recipients.[36] Patients at high risk of respiratory collapse, such as those who may require high intrathoracic positive pressure to ventilate or present with anticipated difficult intubation with intolerance to long periods of apnea, should also be considered for preinduction ECLS. While awaiting further literature supporting utilization of elective ECLS or no ECLS tailored to recipient ESLD and co-morbidities, center expertise and expertise of the specific intraoperative team may form a predominant base for the decision regarding utilization and timing of ECLS support versus none at all.

Recommendations:

1. When preoperative VV or VA ECMO is used for bridge to transplantation, it should continue during the intraoperative setting. VV ECMO can be maintained or switched to a VA ECMO depending on the intraoperative need for hemodynamic support. Strength of Agreement: 78%. *(CoR: IIa LoE: C1)*
2. Criteria for utilization of ECLS as intraoperative support versus no ECLS support include center expertise, recipient characteristics, and intraoperative team selection. Strength of Agreement: 100%. *(CoR: I LoE: C2)*
3. Recipient characteristics that should be included in the evaluation for selection of ECLS versus no ECLS utilization include risk of bleeding, previous thoracic surgery, right ventricular dysfunction, pulmonary hypertension, concomitant cardiac procedures, extrapulmonary organ dysfunction, and severity of pulmonary dysfunction. Strength of Agreement: 100%. *(CoR: I LoE: C1)*
4. Intraoperative VA ECMO is preferred over VV ECMO for cardiopulmonary support during lung transplantation, regardless of the etiology of recipient lung disease. Strength of Agreement: 100% *(CoR: I LoE: B2)*
5. Preinduction initiation of ECLS should be considered in patients with severe cardiopulmonary failure, resulting in a high risk of hemodynamic collapse with the induction of anesthesia. Strength of Agreement: 100% *(CoR: I LoE: C2)*

2. INTRAOPERATIVE MANAGEMENT

While successful intraoperative utilization of ECLS begins with a thorough MDT presurgical planning, it is completed with a comprehensive strategy of intraoperative management. Due to the varied complexity of recipient, donor, and surgical factors, intraoperative management plans should consider a full spectrum of possibilities ranging from planned to unplanned deployment of ECLS. Despite these variables, intraoperative management of ECLS should be as tailored as possible to the recipient ESLD, intraoperative team experience, and the dynamic surgical environment. This section will focus primarily on surgical, anesthetic, and perfusion management from the induction of anesthesia to patient arrival in the intensive care unit.

2.1. Criteria for unplanned ECLS

Unplanned need for intraoperative ECLS has been quoted as high at 51% of unsupported lung transplants, but the true prevalence is unknown.[31] Emergent general surgical procedures are noted to be associated with increased morbidity and mortality as compared to elective,[37] but there are few data examining the impact of unplanned ECLS in patients with cardiothoracic disease. In patients undergoing transfemoral valvular replacement, mortality has been reported to be significantly higher in patients who received unplanned ECLS.[38] Patients with cardiopulmonary instability during lung transplantation are at risk for acute kidney injury,[39-41] with a relative risk for acute kidney injury of 1.942 ($p = 0.006$) in patients with systolic blood pressure < 90 mm Hg, cardiac index of < 2.2 liter/min/m,[2] or vasopressor requirement to maintain systolic blood pressure of 90 mm Hg or greater.[41] Given these potential risks, criteria for intraoperative unplanned ECLS should be formulated and discussed in the presurgical planning phase.

When lung transplantation is planned without ECLS, there are several scenarios that warrant an urgent implementation of ECLS. Preexisting right ventricular dysfunction may contribute to the risk of hemodynamic instability, but other dynamic intraoperative events may result in abrupt hypotension. Sometimes, patients cannot tolerate single-lung ventilation, such as in severe pulmonary fibrosis. However, a more common finding is hemodynamic instability during pulmonary arterial (PA) clamping or dynamic mechanical compression of the heart. The routine use of transesophageal echocardiography (TEE) and PA catheter to monitor right ventricular function and PA pressures throughout the duration of the case is recommended, with particular care to be noted during the various surgical phases of the case.[8] During the dissection phase of the right side of the chest, central dissection of the pulmonary veins or the PA sometimes requires partial compression of the superior vena cava. This reduced inflow can be counteracted with the utilization of vasopressors, inotropes, or by optimizing the intracardiac preload. During the dissection phase on the left side, exposure of the left hilar structures may result in decreased right ventricular contractility and hemodynamic impairment. The utilization of a retraction suture on the pericardium and left diaphragm can help improve exposure and decrease hemodynamic stress. After respective dissection phases, clamping of the PA is sometimes poorly tolerated. One technique recommended is the use of probe clamping or temporary occlusion of the PA to assess right ventricular strain or dilatation. In such cases where a high risk of right ventricular failure with PA clamping is anticipated, planned ECMO may be beneficial due to prolonged controlled reperfusion and low ventilator effort.[11,12,42]

If the hemodynamic conditions during these various phases do not respond to medical optimization, then rapid deployment of ECLS is necessary. As several studies have shown inferior outcomes in patients supported with CPB as compared to patients supported by ECMO, central VA ECMO is considered the standard of care for rescue intraoperative ECLS.[2,14,43] A detailed algorithm for when and how to implement VA ECMO in the setting of hemodynamic impairment has been suggested by the Hannover group.[44] They note in their retrospective study of 595 lung transplant recipients that unplanned ECMO was mainly necessary in patients with idiopathic pulmonary fibrosis (65%), and the majority of patients (61%) had a substantial PA hypertension with a median of 41 mm Hg (Interquartile range: 30-61).

Unplanned ECLS might benefit from a central rather than peripheral cannulation as central cannulation ensures a comparatively higher blood flow due to vessel diameter capacity allowing for larger inflow and outflow cannulas. Central cannulation also avoids peripheral ECLS-related issues such as blood flow insufficiency and limb ischemia.[45] In addition, the peripheral VA ECMO configuration delivers oxygenated blood to the coronary arteries and brain via retrograde flow of the aortic arch. If left ventricular function is intact, the retrograde flow might compete with the ventricular ejection fraction. As a result, the coronary arteries and brain might be perfused

with deoxygenated blood from the failing lung.[46] The central approach to cannulation is via the right atrium and ascending aorta and may be used for either VA ECMO or CPB.

Recommendations:

1. The right ventricular function and PA pressures, evaluated using TEE and Swan-Ganz catheter, should be assessed after the pulmonary artery clamping, unclamping, and reperfusion of the lungs. The right ventricular function and PA pressure are essential in making the decision to initiate ECLS. Strength of Agreement: 75% (CoR: I LoE: B2)
2. Severe right ventricular dysfunction, refractory to medical optimization, should result in the implementation of ECLS for intraoperative support. Strength of Agreement: 100%. (CoR: I LoE: B2)
3. Severe hemodynamic instability due to mechanical compression, despite optimal fluid management and support by vasoactive medication, requires the implementation of ECLS. Strength of Agreement: 76%. (CoR: I LoE: C2)
4. Central cannulation is the preferred approach for unplanned ECLS. Strength of Agreement: 78% (CoR: IIa LoE: C2)

2.2. Selection of ECMO versus CPB

Historically, double lung transplantation was performed with a bilateral en-bloc procedure with tracheal anastomosis that required CPB.[47] With the development of bilateral sequential lung transplantation with bibronchial anastomosis, the procedure became technically feasible without any circulatory support. However, off-pump lung transplantation is not possible in every case, and patients with ESLD, such as primary pulmonary hypertension, secondary pulmonary hypertension due to interstitial lung disease, or right ventricular dysfunction, are often unable to tolerate the cardiopulmonary instability that arises from their preexisting disease or intraoperative course.

VA ECMO is the preferred primary choice for intraoperative ECLS as compared to CPB due to its superior risk profile and improved outcomes. Evidence supporting this statement was historically found within single-center, retrospective trials that showed lung transplantation performed on CPB comes at the cost of a higher rate of postoperative complications. A first comparison between the outcomes of lung transplantation on ECMO and CPB was published in 2007.[48] This initial experience was followed by a series of single-center studies from around the world.[32,49-51] Most of these series have shown that CPB was associated with an increased blood turnover, higher need for packed red blood cells and coagulation factors, increased risk of PGD, higher rates of postoperative renal failure, longer intensive care unit stays, and longer hospital stays. However, Magouliotis et al[14] published a meta analysis of 7 studies showing that VA ECMO showed a lower rate of PGD and morbidity as related to nonpulmonary end-organ dysfunction and hospital length of stay compared to CPB. To date, 2 meta analyses are available that both highlighted the increased risk of postoperative complications in lung transplantation using CPB.[43] Subsequent to this time, these findings have been confirmed in a variety of high-quality studies, including retrospective, single-center, and multicenter trials.

Chan et al[52] published a propensity-matched analysis of a large retrospective single-center cohort comparing VA ECMO and CPB for intraoperative support, showing VA ECMO resulted in decreased PGD grade 3, decreased end-organ dysfunction, and length of mechanical ventilation. Loor et al[15] published a multicenter study which examined the impact of mode of intraoperative ECLS on PGD after lung transplantation, utilizing data from 8 centers within the United States and Europe. Although this study was limited in design due to heterogenous ECMO approaches, the authors noted that the risk of developing postoperative PGD grade 3 was higher in the CPB versus ECMO group (Odds Ratio [OR] 1.89, 95% Confidence Interval [CI] 1.05-3.41; $p = 0.033$). The recently published AATS Expert Consensus Statement on the use of ECLS in lung transplantation recommended VA ECMO as the preferred form of intraoperative ECLS support over CPB.[2]

A common theme reported in the literature is discussion regarding the lack of prospective data comparing VA ECMO and CPB in lung transplantation. A key recent manuscript provides some supporting evidence behind the theory put forth by the prospective study of Hoetzenecker et al[12] that described superior outcomes in VA ECMO due to attenuation of the ischemic-reperfusion injury. Calabrese et al[53] published a pilot study showing evidence of decreased cellular signs of ischemic-reperfusion injury in recipients who underwent VA ECMO support intraoperatively versus no support. While these data are limited in applicability to the comparison between VA ECMO and CPB, they may inform future studies examining this topic. These studies should be designed in a

prospective multidisciplinary fashion, examining outcomes of mortality, morbidity, and cellular markers of ischemic reperfusion injury.

Based on a superior risk and outcome profile, VA ECMO is the mode of choice for intraoperative support in standard lung transplantation, but there are some scenarios where CPB still plays a role including need for surgical exposure, hemodynamic instability refractory to medical treatment, or concomitant cardiac procedures.[54] The primary scenario is lung transplantation with concomitant cardiac procedures. This is a rare situation, and based on the most recent ISHLT guidelines for selection of lung transplant candidates, requires a rigorous evaluation of the risks and benefits.[55] Several high-volume lung transplant centers have shown that a concomitant cardiac repair is feasible and associated with acceptable short- and long-term outcomes.[56] There are limited data to guide the determination of superiority between a combination open-repair at the time of transplantation versus a delayed hybrid of percutaneous repair of cardiac pathology, such as a coronary stent, transfemoral valve intervention, or interatrial septal defect closure. However, delayed percutaneous repair for atrial septal defects has been shown feasible even in complex PA hypertension patients.[57] A hybrid VA ECMO-CPB circuit has been described[58] that allows for intraoperative VA ECMO with the possibility to immediately convert to CPB if needed, and the utilization of this circuit has been described for lung transplantation with concomitant cardiac surgical repair in coronavirus disease 2019 (COVID-19) patients.[9] With evidence being limited to single-center retrospective case series, it remains unclear whether a 2-staged approach (endovascular repair/stent and lung transplantation on ECMO) is superior to a single-staged approach (lung transplantation and concomitant repair on CPB). If a single-stage approach is favored by the transplant center, teams should consider lung transplantation to be performed on VA ECMO with conversion to CPB for the concomitant procedure with a hybrid VA ECMO-CPB circuit.

Recommendations:

1. VA ECMO is the preferred primary choice for intraoperative support in standard lung transplantations as compared to CPB. Strength of Agreement: 79% (CoR: I LoE: B2)
2. Inclusion of postoperative complication risks should be considered when choosing the mode of ECLS, and data show that CPB has been associated with a higher rate of postoperative complications compared to VA ECMO. Strength of Agreement: 77% (CoR: I LoE: B2)
3. In cases where a concomitant cardiac procedure such as coronary artery bypass grafting, valve repair, or atrial septal defect closure is needed, CPB should be used as intraoperative support. Strength of Agreement: 90% (CoR: I LoE: C1)

2.3. ECLS cannulation approach

Although VV ECMO can offer intraoperative oxygenation and decarboxylation, it does not provide any role in supporting the recipient's hemodynamic status. Hence, VV ECMO should be switched to VA ECMO regardless of the choice of cannulation site in bridged patients experiencing refractory hemodynamic compromise. The timing of ECMO conversion and arterial cannulation has not been studied yet; however, there are some data in favor of an early switch. First, it has been demonstrated that prophylactic ECMO achieved better results in high-risk patients as compared to on-demand ECMO for PGD grade 3.[11] Second, VV ECMO has no impact on lung reperfusion injury, whereas VA ECMO offers the possibility of controlled reperfusion conditions by its impact on transpulmonary flow modulation.[12,19] For this reason, as well as the potential for prevention of graft dysfunction, a switch to VA ECMO should be considered as early as possible in case of hemodynamic compromise. In fact, lung transplant teams consider prophylactic switches at the beginning of the lung transplantation procedures to achieve these goals.[12,19]

Intraoperative central ECMO cannulation allows for the use of larger cannulas, improved venous drainage, and avoids the vascular complications associated with groin approach including infection, thrombosis, lymphatic leaks, and pain.[45] In addition, weaning central ECMO at the end of transplantation limits exposure to mediastinal bleeding and chest infections. If the recipient is unable to be weaned from central ECMO at the end of the procedure or if ECMO prolongation is planned, then peripheral cannulation should be initiated as it facilitates postprocedural ambulation, chest closure, avoids the morbidity associated with central cannulation, and does not require sedation to maintain.

Vascular morbidity from deep vein thrombosis and limb ischemia related to venous and arterial peripheral cannulation should not be underestimated and may be the source of serious intraoperative complications.[45,59] Incidence of deep vein thrombosis after peripheral ECMO remains unknown, as vascular ultrasound artifacts due to the ECMO cannulae alter the reliability of diagnostic imaging. In addition, arterial complications such as lower

limb ischemia can occur in up to 17% of patients, as described in a national registry study of ECMO in cardiogenic shock patients.[60] While the studied population may not be the same as the lung transplantation recipients, limb ischemia is a concern in numerous ESLD patients due to the size of the femoral vessels. Bronchial circulation recovers after the first few weeks of transplantation, making the lungs a single-circulation organ thereafter.[61,62] Any pulmonary embolism occurring during this period of time may result in pulmonary infarction that can become subsequently infected.[63] Such thrombotic complications preferentially occur during prolonged ECMO, and differences in rates of pulmonary embolism between central and peripheral cannulation may disappear for short-term intraoperative use, but sufficient data are lacking. However, in the case of peripheral cannulation for intraoperative support for transplantation, vigilance is required to avoid vascular injury at the cannulation site by the MDT during the postoperative period. Use of arterial closure devices may increase risk of arterial dissection or thrombosis, and their use still necessitates MDT surveillance of peripheral cannulation sites.[64] Ultimately, randomized prospective data are lacking to drive the clinical decision of optimal cannulation approach, and the choice should depend on perioperative ECLS strategy tailored to the patient's individual needs.

Recommendations:

1. In case of intraoperative hemodynamic compromise refractory to medical optimization, a VV ECMO cannulation, which was used to bridge patients to their transplantation, should be switched to a VA ECMO. Strength of Agreement: 100% (CoR: I LoE: B2)
2. Central cannulation is preferred for short-term intraoperative support, whereas peripheral cannulation is preferred for postoperative continuation of ECMO. Strength of Agreement: 78% (CoR: I LoE: C2)
3. Inclusion of postoperative complication risks should be considered when choosing the intraoperative cannulation strategy of ECLS, and data show that central cannulation avoids peripheral vascular venous and arterial thrombotic complications. Strength of Agreement: 95% (CoR: I LoE: C1)

2.4. ECLS flow and coagulation management

Pulmonary allografts are submitted to cold ischemia after their procurement with subsequent reperfusion when transplantation occurs. Cold ischemia is obtained by storing the grafts at 4°C to 8°C[65] and is considered mandatory to reduce cellular metabolic rate and enzymatic activity of the grafts.[66] Following graft reperfusion, ischemia-reperfusion injury (IRI) might develop, which could lead to PGD.[66] The IRI mechanism of PGD is through the generation of reactive oxygen species, activation of a proinflammatory cascade, vascular dysfunction, pulmonary edema, and impaired gas exchange.[67]

If cardiopulmonary support is needed, VA ECMO is considered the mode of choice, and the management thereof should be focused on attenuating PGD in the recipient. Blood and gas flow management of VA ECMO requires detailed knowledge of the physiology of lung transplantation as well as close cooperation between the MDT of surgeons, anesthesiologists, and perfusionists. Blood flow should be set at 40% to 50% of cardiac output,[11] supporting bypassing a significant reperfusion volume from the pulmonary circulation. After the implantation of the first lung and during the pneumonectomy/implantation phase of the second side, blood flow must be monitored and readjusted if necessary. Reperfusion pressures of the first lung should remain low; however, a minimum of graft reperfusion must be maintained.[68] No quantitative values have been reported, but the qualitative presence of pulsatile flow over the PA catheter must be maintained at all times.[11] If the VA ECMO blood flow is too high, the pulsatility will be lost with the risk of in-situ thrombosis of the graft. If the blood flow is too low, controlled reperfusion of the graft fails with subsequent increased risk for pulmonary edema and PGD.[68-70]

Gas flow and fraction of inspired oxygen (FiO_2) should be adjusted throughout the surgery according to the arterial blood gas (ABG) to diminish IRI at the time of reperfusion. Hypoxia should be avoided, and sweep gas flow should be adjusted, aiming for normoxia (PaO_2 60-100 mm Hg).[71] In 2013, Diamond et al[13] showed that elevated FiO_2 was associated with the development of PGD. A subsequent multicenter cohort study confirmed that an elevated value of FiO_2 at the time of reperfusion was an independent risk factor of PGD at 48 or 72 hours post-lung transplantation as compared to a FiO_2 value lower than 0.4.[72] In addition to maintaining normoxia, rigorous monitoring of $PaCO_2$ is also mandatory through regular intraoperative ABG draws, with a goal of 35 to 45 mm Hg to maintain appropriate cerebral oxygenation and perfusion.[28]

Perioperative blood transfusion is commonly required in lung transplantation[72] and associated with severe PGD, thus increasing risk of morbidity and mortality in the lung transplant population.[18,73-79] It has also been

observed that platelet transfusion is associated with the release of inflammatory mediators, leading to an increased amount of chronic rejection, donor-specific antibodies, and all-cause mortality. The infectious risk that platelet transfusion brings may also contribute to the above-mentioned associated outcomes.[76]

Transfusion protocols have been shown to decrease blood product administration during cardiothoracic surgery, and adherence to tailored algorithms has been advocated for in the literature by several international societies.[80-82] It has been proposed that lung transplant centers establish intraoperative transfusion protocols to minimize the utilization of exogenous blood products.[72,76] A randomized controlled trial by Durila et al[83] was able to a show a decrease in perioperative consumption of PRBC and coagulation factors when utilizing a point-of-care rotational thromboelastometry-guided transfusion protocol in lung transplantation. No one algorithm may be recommended over another given the lack of comparative protocol outcomes data, as well as limited access worldwide to point-of-care testing. As such, we recommend an algorithm created by an MDT of anesthesiologists, intensivists, pathologists, perfusionists, and surgeons that incorporates both point-of-care and traditional laboratory-based algorithms to guide teams based on the best available data and locally available resources.

Other factors to routinely consider when addressing intraoperative transfusion management include temperature, pH, ionized calcium level, cell salvage, and consideration of antifibrinolytic use.[80] Fibrinolysis, which occurs following clot formation, is an important part of a normal coagulation system but can lead to significant coagulation dysfunction if overstimulated.[84] Antifibrinolytic therapy for transfusion mitigation in noncardiac surgery has gained favor over the last several years, with efficacy and safety reported in a wide variety of clinical scenarios, including trauma, postpartum hemorrhage, and orthopedic surgery.[85-87] However, for lung transplantation without mechanical support, direct evidence for antifibrinolytic therapy is absent. There is evidence that the fibrinolytic system is involved in acute lung injury.[88,89] Other studies reveal that solid organ transplant is a risk factor for thromboembolic events, which lead to decreased survival in lung transplant recipients as well as increase rates of pulmonary infarction rate for lung transplant recipients with pulmonary emboli secondary to absence of bronchial circulation.[90,91] Given the above factors, the risk versus benefit of empiric antifibrinolytic administration in lung transplant recipients cannot be determined.

The utilization of ECLS requires an anticoagulation strategy that is aimed at attenuating the impact of the prothrombotic state brought about by blood/air and blood/circuit interface. One of the purported benefits of VA ECMO as compared to CPB is the need for relatively decreased anticoagulation, with growing evidence that safety in a lower anticoagulation approach may be related to advances in oxygenators and coated circuits. A meta analysis by Lv et al[92] showed decreased bleeding without complications in patients receiving low or no anticoagulation while on ECMO, although the analysis was heterogenous for VV or VA ECMO approach. Several publications have reported success with low systemic anticoagulation during VA ECMO, with one case report specific to use in lung transplantation.[93-95] Raman et al[94] examined outcomes in VA ECMO patients with standard anticoagulation in the control group versus a single 5,000-unit heparin bolus while maintaining a minimum flow of 2.5 to 3.0 liter/min. The standard group had a higher incidence of bleeding complications as compared to the low anticoagulation group, with oxygenator change requirements in 2 of the low anticoagulation group after 30 days of ECMO.[94] While the data for supporting a reduced anticoagulation strategy remain relatively sparse, the available evidence is compelling enough that a reduced anticoagulation strategy was recently endorsed by a single discipline consensus statement from the AATS as an acceptable approach for lung transplantation recipients who are at increased risk of bleeding.[2]

Recommendations:

1. In double lung transplantation, VA ECMO flow needs to be adjusted during the implantation of the second lung. A low but pulsatile flow in the pulmonary artery is necessary to avoid no-flow phases through the first implanted graft. Strength of Agreement: 89% (CoR: I LoE: B2)
2. Gas flow and FiO_2 need to be continuously adjusted according to the recipient's arterial blood gas analysis. Strength of Agreement: 84% (CoR: I LoE: C2)
3. A transfusion algorithm should be used to decrease transfusion during lung transplantation. Strength of Agreement: 81% (CoR: I LoE: B1)
4. There is not enough evidence available to make a determination regarding the efficacy or safety of prophylactic antifibrinolytics use during lung transplantation without mechanical support, and its use should be determined by individualized risks and benefits. Strength of Agreement: 90% (CoR: I LoE: C2)
5. It is reasonable to consider a low-dose heparin protocol for VA ECMO during transplantation if adequate flows can be maintained. Strength of Agreement: 80% (CoR: I LoE: C1)

2.5. Anesthetic management

A recent ISHLT consensus statement discussed the perioperative anesthetic and critical care management throughout the entire spectrum of lung transplantation care.[8] However, unique challenges of recipient etiology of ESLD present diverse and significant cardiopulmonary anesthetic management challenges when ECLS is utilized for lung transplantation.[24] The cardiac anesthetic challenges arise when determining the timing of ECLS deployment, balance of native cardiac output and ECLS output when VA ECMO is used, and intraoperative separation from ECLS support. Pulmonary anesthetic challenges arise when crafting an ideal lung protective ventilatory strategy of native lungs tailored to ESLD, as well as management of newly implanted grafts at reperfusion.[7]

Cardiac anesthetic management is challenging at different phases of intraoperative ECLS care with the focus of anesthetic management being the maintenance of the following independent determinants of native cardiac output: heart rate, heart rhythm, preload, afterload, and contractility. These challenges are primarily seen in VA ECMO, as VV ECMO does not impact cardiac hemodynamics, and CPB management is routine during bypass regardless of presenting ESLD. However, phases leading up to ECLS deployment do require special attention to recipient ESLD.

Real-time hemodynamic monitoring is paramount in lung transplantation, and some ESLDs may present challenges when placing invasive hemodynamic monitoring, such as cystic fibrosis or systemic sclerosis, due to small vessel caliber.[24,96] Immediately postinduction, the introduction of positive pressure ventilation can impact right ventricular preload through decreased venous return as well as right ventricular afterload through increases in pulmonary vascular resistance.[34] These impacts are most dramatically seen in patients with right ventricular dysfunction, most commonly seen in primary pulmonary hypertension or restrictive lung disease with secondary pulmonary hypertension as the presenting ESLD.[24] Patients presenting with chronic right ventricular hypertrophy due to chronic pulmonary hypertension are at risk of dynamic right ventricular outflow obstruction,[97] which presents particular challenges in maintaining adequate native cardiac output when utilizing VA ECMO. Given the diversion of cardiac preload from the native cardiac output to VA ECMO flow, the heart is relatively underfilled as compared to normal loading conditions.[98] Manipulation of the heart during all phases of the lung transplantation may lead to arrythmias, and these are particularly common in patients presenting with right ventricular failure or supported with inotropic medications.[99]

Increasing amounts of intraoperative fluid administration have been shown to increase PGD in an off-ECLS or CPB model.[100] However, the controlled reperfusion of VA ECMO limits cardiac output directed at newly implanted grafts, and the optimization of the systemic preload may allow for anesthetic management of intraoperative VA ECMO that results in the ability to maintain systemic organ perfusion, controlled reperfusion, and overall hemodynamic stability.[11,98] Intraoperative VA ECMO volume management is routinely determined by clinical end-points such as minimum mean arterial pressures of 60 to 65 mm Hg and urinary output. Additionally, high negative pressures in the inflow cannula secondary to the collapse of the surrounding vein can result in vibrations or "chatter" within the ECLS circuit. This often occurs secondary to intravascular hypovolemia and can be corrected by the administration of fluids or decreasing the ECLS circuit flow. The balance of all determinants of native cardiac output with ECLS flow is evidenced by the qualitative pulsatility in the PA and systemic arterial waveforms.[98,101] Decreased pulsatility in these waveforms suggests decreased biventricular contractility, diminished systemic preload, or excessively high ECMO flows.[98] However, when ECMO flows are maintained in constant fashion, the most likely cause of the gradual decrease in pulsatility is systemic preload.

Pulmonary anesthetic management during ECLS is determined pre-explantation by the recipient ESLD.[102] Regardless of presenting ESLD, patients with an insufficient pulmonary reserve may require initial placement of a single-lumen endotracheal tube with exchange to a double-lumen tube performed on intraoperative ECLS support. Patients with end-stage obstructive versus restrictive disease require different ventilatory strategies based on inspiratory/expiratory time ratios, peak inspiratory pressures, and avoidance of alveolar overinflation.[8,24] Postimplantation, the foundation of a lung protective ventilatory strategy is ensuring limited mechanical trauma and the use of a low FiO_2.[7] The administration of a high FiO_2 concentration during allograft inflation and reperfusion has been demonstrated to be a risk factor for the development of PGD in multiple studies.[13,103] When utilizing ECLS, whether CPB, VV, or VA ECMO, inflation and reperfusion of the graft should occur with the lowest possible FiO2, with an optimum concentration of 21% to be used.[12,104]

The intraoperative analgesic strategy has been shown to impact patient outcomes, and the advantages of regional analgesia in patients undergoing lung transplantation have been well documented.[8,105,106] By reducing the amounts of systemic opioids and providing superior pain control, the use of regional analgesia has been demonstrated to reduce the length of mechanical ventilation, intensive care unit length of stay, and perioperative respiratory complications.[105] Multiple studies have demonstrated the safety and efficacy of thoracic epidural

analgesia, including the ability to allow for early extubation, resulting in reduced extravascular lung water, lower mPAPs, reduced vasopressor requirements, and higher arterial to inspired oxygen ratios.[105-109] Thoracic epidural analgesia may present an increased risk of bleeding complications in anticoagulated patients, leading to the use of newer regional analgesic techniques such as paravertebral, erector spinae, and serratus anterior blocks.[7] In the cardiothoracic and lung transplant literature, the incidence of epidural hematoma is rare,[106,110] suggesting that a recipient who meets the American Society of Regional Anesthesia guidelines should be considered for a pre-ECLS regional analgesia adjunct for their intraoperative management.

Recommendations:

1. Anesthetic management of patients undergoing lung transplantation with ECLS should be tailored to cardiopulmonary comorbidities of the underlying etiology of ESLD. Strength of Agreement: 83%. (CoR: I LoE: C1)
2. In the setting of constant ECMO flow, volume resuscitation should be directed toward maintaining pulsatility in the systemic and PA waveforms during intraoperative ECLS for lung transplantation. Strength of Agreement: 83%. (CoR: I LoE: B2)
3. Regardless of ECLS approach, the lowest possible FiO_2 should be used upon reinflation and reperfusion of donor graft to minimize PGD. Strength of Agreement: 86% (CoR: I LoE: B2)
4. Pre-ECLS utilization of regional anesthesia is not contraindicated but should be approached cautiously in the setting of utilization of anticoagulation. Strength of Agreement: 78% (CoR: I LoE: C1)

2.6. Intraoperative monitoring guidance management

Diverse monitoring is vital to ensure appropriate intraoperative management of ECLS in lung transplantation. Standard American Society of Anesthesiologists monitoring, invasive hemodynamic monitoring, and TEE are required for any form of intraoperative ECLS.[98] While selected monitors are considered universally applicable to ECLS, VA ECMO monitoring has specific principles of management to ensure systemic perfusion, controlled reperfusion, and hemodynamic stability in the setting of parallel native and mechanical cardiac outputs.

Achieving systemic perfusion through the maintenance of adequate volume, ECMO flows, and native cardiac output is a delicate balance facilitated by appropriate monitoring and MDT communication intraoperatively. Monitoring strategy should include routine laboratory draws of lactate and ABG to assess adequacy of systemic perfusion.[111] Indices of nonpulmonary end-organ function, such as renal or neurological monitoring, may also provide information regarding overall systemic perfusion. Intraoperative urine output, which should be maintained at > 0.5 cm^3/kg/hour, provides a surrogate monitor for overall renal function during lung transplantation on ECLS.[101] The use of near-infrared spectroscopy monitoring intraoperatively during ECLS may also provide monitoring for overall systemic perfusion, as it has been shown to detect cerebral and limb ischemia when applied within an ECMO model.[112]

Given the parallel management of native cardiac output with VA ECMO output, central venous pressure does not provide meaningful hemodynamic data to assess preload or guide intraoperative fluid management.[113] Likewise, the traditional role of intraoperative echocardiography as gold standard in evaluation of systemic preload is absent due to balance of flows.[114] Thus, maintaining the requisite preload to achieve systemic perfusion and controlled reperfusion needs to be assessed through a plurality of qualitative and semiquantitative monitors.[98] The qualitative pulsatility seen in PA and systemic arterial waveforms may provide monitoring guidance,[12] as does pulse pressure within these waveforms.[115] End-tidal carbon dioxide ($ETCO_2$) on waveform capnography is associated with cardiac output and transpulmonary flow on ECLS.[115] As such, maintaining fixed mechanical ventilation during dissection, explantation, and implantation allows for $ETCO_2$ monitoring that functions as a semiquantitative measure of systemic preload when assessed during a fixed ECLS flow.[98] Literature suggests varied targeted $ETCO_2$ values, ranging from 14 to > 20 mm Hg during intraoperative VA ECMO support as a threshold for adequate cardiac output.[115]

Recent practice guidelines recommend TEE as an integral part of the intraoperative monitoring and management of lung transplantation recipients.[8] TEE provides instant intraoperative diagnosis of hemodynamic instability, ventricular dysfunction, intracardiac preload, interatrial shunts, and pulmonary vascular anastomoses.[116] Before initiating intraoperative ECLS, a baseline exam should be performed to examine the form and function of the heart, as well as to guide the placement of ECLS wires and cannulas.[117] Due to the diversion of native cardiac output to the ECMO circuit, intraoperative TEE is unable to quantitatively assess systemic preload, although complete obliteration of the left ventricular cavity at end-systole is likely indicative of hypovolemia requiring further resuscitation.[118] TEE evaluation performed before separation from CPB or VA ECMO and optimization of preload can lead to inaccurate assessments

and measurements of pulmonary vasculature. Once separated from ECLS, baseline pulmonary venous and PA waveforms should be compared to postimplantation imaging for the evaluation of vascular stenosis or vascular obstruction. Recommendations for hemodynamic and anatomical values associated with pulmonary vasculature patency have been reported in the literature, and accurate intraoperative monitoring of these anastomoses is vital to avoid morbidity and mortality associated with inadequate vascular diameters or elevated velocities.[119,120]

Recommendations:

1. Constant assessment of diverse monitors, including echocardiography, urine output, and $ETCO_2$, is required to direct volume management during VA ECMO. Strength of Agreement: 90%. (CoR: I LoE: B2)
2. $ETCO_2$ should be utilized as a qualitative and semiquantitative indicator of transpulmonary flow during intraoperative VA ECMO. Strength of Agreement: 90% (CoR: I LoE: B2)
3. TEE should be considered a standard monitor in all lung transplantations, and performing a comprehensive TEE exam is recommended. Strength of Agreement: 96% (CoR: I LoE: C1)
4. When utilizing ECLS support, standard TEE assessment of intracardiac preload may be limited due to offloading of cardiac output and should be used in the context of other monitors. Strength of Agreement: 95% (CoR: I LoE: C2)
5. When utilizing TEE during ECLS, pulmonary vascular anastomoses should be evaluated for size and velocity when the patient is separated from ECLS support due to potential perturbations in measurements on ECLS. Strength of Agreement: 89% (CoR: I LoE: C2)

2.7. Criteria for weaning ECLS

The use of ECLS has the advantage of not suffering from the hemodynamic consequences of pulmonary artery clamping as well as having fewer respiratory consequences compared to 1-lung ventilation during lung transplantation. However, the employment of ECLS involves an increased risk to patients if done by a nonexperienced or nontrained team. Thus, ECLS within a lung transplant program requires a multidisciplinary approach with a fully trained team, which is ideally experienced in both mechanical circulatory support and transplantation. The institution should implement ECLS within its program using established societal guidelines along with local input from cardiothoracic transplant anesthetists, surgeons, and perfusionists. The MDT should consider strategies for volume management, inotropic support, and ventilation optimization during ECLS weaning. The maintenance of continuity during the weaning requires an MDT strategy, and this has proven to increase the proportion of patients who are able to maintain cardiopulmonary stability throughout the weaning process while also increasing the success rate of weaning.[121]

Before weaning off ECLS, the patient should be optimized with respect to cardiopulmonary function to facilitate a stable weaning process. The ability to wean off ECLS takes multiple factors into account, including the hemodynamics, respiratory function, and echocardiographic findings. The weaning process consists of reducing the amount of ECLS support while closely monitoring the patient's hemodynamics and echocardiographic measurements. The reduction in ECLS support leads to changes in the loading conditions of the right and left ventricles of the heart, which includes an increase in the preload and a decrease in the systemic afterload. A stable cardiac output without signs of biventricular function is required for successful weaning, especially while weaning off CPB or VA ECMO support. Weaning off ECLS also requires optimization of the ventilation, with a strategy that primarily focuses on oxygenation capacity and intrinsic ability to remove carbon dioxide. The strategy should consider striving toward lung-protective ventilation principles with physiological tidal volumes, avoidance of high inspiratory plateau pressures, and the use of low driving pressures with low positive end-expiratory pressure. If the weaning trial is unsuccessful in maintaining pulmonary and circulatory stability, the weaning should be postponed.[11,12,121,122]

In patients on intraoperative VA ECMO, the ECMO system can be either weaned successfully at the end of the procedure or prolonged into the early postoperative period. The latter option, which was previously a last-rest treatment for patients with a failing graft, is now emerging as a possible pre-emptive option to prevent severe damage to the graft or allow for remodeling of the cardiac system in particular recipient ESLDs.[11] As the recent ISHLT guidelines on acute MCS note, there is significant variability amongst centers in weaning strategies.[123] Our recommendation is that VA ECMO should be weaned by reducing the blood flow, as opposed to VV ECMO, where weaning through a reduction of sweep gas flow is recommended. A slow reduction of ECMO flow with constant monitoring of saturation, PA pressure, and systemic arterial pressure should proceed until an ECMO flow of 1 liter is set. Before the ECMO tubes are clamped, it is recommended to wait 1 to 5 minutes with the ECMO blood

flow at this minimal level. If the patient cannot maintain gas exchange, has ongoing hemodynamic instability despite optimization, or has a primary diagnosis of PA hypertension, prolongation of ECMO by switching to a peripheral cannulation is recommended. This strategy of low threshold for ECMO prolongation in patients with questionable initial graft function has been shown to have a beneficial effect by several groups.[11,122,124]

Prolongation of ECMO can be either VV or VA ECMO, with no direct evidence of the superiority of 1 modality or the other in for postoperative lung transplantation. Therefore, prolongation is a clinical decision based on recipient need, with isolated respiratory dysfunction often leading to VV ECMO and cardiopulmonary dysfunction leading to VA ECMO. VA ECMO, however, does have the benefits of providing hemodynamic stability and reduction in transpulmonary blood flow as compared to VV ECMO, which only facilitates a lung protective strategy. The criteria for ECMO prolongation include high ventilator effort or hemodynamic considerations such as ongoing right ventricular dysfunction or elevated PA pressures. Of note, a recent study recommended that MDT examine the decision to prolong at dynamic time points throughout the operation, particularly after implantation when the chest is open followed by another evaluation at time of chest closure.[12]

Recommendations:

1. Institutional, multidisciplinary guidelines for weaning ECLS need to be developed before the utilization of ECLS within a lung transplant program. Strength of Agreement: 85%. (CoR: I LoE: C2)
2. Cardiopulmonary optimization, including fluid management, inotropic support, and ventilation, should be optimized before MCS weaning. Strength of Agreement: 92% (CoR: I LoE: B2)
3. Blood flow should be reduced to 1 liter for 1 to 5 minutes before ending intraoperative ECMO to evaluate graft function. Strength of Agreement: 75% (CoR: I LoE: C1)
4. High ventilator effort for gas exchange and decreased graft compliance should result in prolongation of ECMO postoperatively, with severe right ventricular dysfunction refractory to medical optimization resulting in prolongation of VA ECMO postoperatively. Strength of Agreement: 90% (CoR: I LoE: C1)

3. INTRAOPERATIVE ECLS OUTCOMES AND PERSPECTIVES FOR FURTHER RESEARCH

Advancing the science and art of lung transplantation is achieved through collaborative efforts from diverse groups across the global community. This section of the consensus looks toward the future, with expert consensus on selected topics that are recommended to be studied by the broader scientific community.

3.1. Multicenter research and future technological focus

In 2020, there were an estimated 4,600 lung transplants performed worldwide.[125] With such a relatively small number of transplants performed each year for a variety of indications, large multicenter studies are needed to gather sufficient data per indication to determine the optimal strategy for each specific patient population. Currently, the literature recommends ECLS in a variety of ESLDs and patient co-morbidities,[126] but the recommendations are mainly based on single-center retrospective data. The recommendations put forth in this consensus statement, while based on these data and expert opinion, should be examined in multicenter studies that can capture more data to evaluate the outcome of patients in differing etiologies and co-morbidities. These multicenter studies also need to determine optimal circuit configuration, heparinization strategy, ECLS reperfusion flow during weaning, ECLS impact on antibiotic or immunosuppressant regimens, and ideal protective lung ventilation strategies during ECLS tailored to recipient ESLD. A composite outcome, based not merely on mortality but on morbidities, including PGD, end-organ function, and intensive care length of stay, is recommended to be studied within the context of evaluating an ideal intraoperative ECLS strategy.

Expansion of the ISHLT Registry to include intraoperative ECLS variables is another strategy to improve our collective understanding of how to best use ECLS in lung transplantation. Although the ISHLT complies with a comprehensive lung transplantation registry, it is limited in its collection of intraoperative variables, as it focuses on donor and recipient characteristics, outcomes, and survival.[8,55,127] Expansion of the registry to include intraoperative characteristics of ECLS can examine the impact of prophylactic versus rescue ECLS, the influence of intraoperative anesthetic management on ECLS versus non-ECLS strategies, and criteria for postoperative

ECLS prolongation. Anesthetic-specific variables, including volume resuscitation, echocardiography, analgesic strategy, regional analgesia, time to extubation, and anesthetic maintenance strategy, should also be considered for inclusion within the ISHLT Registry. Variable design should be integrated throughout the entire perioperative process to allow for examination across the preoperative, intraoperative, and postoperative epochs.

A limitation in studying optimal circuit design using multicenter or registry data is the variability in technology across centers, regions, and countries. However, recent advances in ECMO technology aim to reduce bleeding and inhibit the immune response and transfusion requirements. As such, these ongoing developments need to be scientifically evaluated to establish their value within the intraoperative course of lung transplantation. Bleeding is reduced by the use of cannula and circuit tubing coated with a nonthrombogenic substances that reduce clot formation, reduce or eliminate the need for systemic anticoagulation, decrease coagulation factor consumption, and inhibit the immune response.[128,129] Improvements in oxygenator technology with the use of polymethyl pentene polymers permit gas permeability, lower resistance to flow, and inhibit plasma leakage.[130] Other advantages of newer oxygenators include reduced inflammatory response, platelet deposition, and red blood cell shearing. The integration of these circuits and oxygenators into ECLS holds the promise to further improve heparinization strategies, which continues to be a key area of examination for intraoperative management.[131]

Recommendations:

1. Larger multicenter studies need to be performed to determine whether all or only specific patient populations benefit from elective ECMO. Strength of Agreement: 96%. (CoR: I LoE: C2)
2. The ISHLT Lung Transplant Registry should be expanded to include a comprehensive perioperative dataset to study the impact of intraoperative ECLS support and its interaction with recipient, donor, and procedural factors on patient outcomes. Strength of Agreement: 88% (CoR: I LoE: C2)
3. Ongoing developments of ECMO technological need to be scientifically evaluated to fully establish this impact on coagulation and systemic inflammatory response syndrome. Specifically, the feasibility of low/zero heparin ECMO should be investigated to reduce intraoperative blood loss. Strength of Agreement: 92% (CoR: I LoE: C2)

4. CONCLUSION

The intraoperative management of lung transplantation patients has significantly changed since the first lung transplantation was performed by James Hardy in 1963. Over time, the evolution of management has progressed through the efforts of multiple medical disciplines, often driven more by expert opinion than rigorous data. The multidisciplinary nature of this consensus statement adds significant weight to the expert opinion achieved, but it is our hope that these statements form the foundation of future scientific investigations of these diverse topics within the intraoperative utilization of ECLS in lung transplantation.

ACKNOWLEDGMENTS

The authors would like to thank Megan Barrett, Programs Manager at the ISHLT, Matthew D. Bacchetta (Department of Thoracic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee), Suresh Keshavamurthy (Department of Cardiothoracic Surgery, University of Kentucky, Lexington, Kentucky), for their tireless support of the process from inception to completion.

APPENDIX 1: SUMMARY OF RECOMMENDATIONS

Presurgical planning

MDT discussion

Increased recipient, donor, and surgical complexity within the practice of lung transplantation necessitates multidisciplinary perioperative transplant management, including the provision of a spectrum of surgical, anesthesia, and intensive care management. Strength of Agreement: 100%. (CoR: I LoE: C2).

An MDT discussion at the time of listing can be helpful to balance risk-to-benefit for proceeding to transplantation with or without intraoperative ECLS based on recipient co-morbidities such as etiology of end-stage lung disease, co-morbidities, and ongoing clinical status. The decision taken at listing should be re-evaluated if the patient's condition deteriorates. Strength of Agreement: 96%. (CoR: I LoE: C2).

An emerging trend in literature and clinical practice among international lung transplant centers suggests that ECMO is the preferred ECLS modality for intraoperative support as compared to CPB. Strength of Agreement: 86%. (CoR: I LoE: B2).

Criteria for selection of ECLS versus no ECLS

When preoperative VV or VA ECMO is used for bridge to transplantation, it should continue during the intraoperative setting. VV ECMO can be maintained or switched to a VA ECMO depending on the intraoperative need for hemodynamic support. Strength of Agreement: 78%. (CoR: IIa LoE: C1).

Criteria for utilization of ECLS as intraoperative support versus no ECLS support include center expertise, recipient characteristics, and intraoperative team selection. Strength of Agreement: 100%. (CoR: I LoE: C2).

Recipient characteristics that should be included in the evaluation for selection of ECLS versus no ECLS utilization include risk of bleeding, previous thoracic surgery, right ventricular dysfunction, pulmonary hypertension, concomitant cardiac procedures, extrapulmonary organ dysfunction, and severity of pulmonary dysfunction. Strength of Agreement: 100%. (CoR: I LoE: C1).

Intraoperative VA ECMO is preferred over VV ECMO for cardiopulmonary support during lung transplantation, regardless of etiology of recipient lung disease. Strength of Agreement: 100% (CoR: I LoE: B2).

Preinduction initiation of ECLS should be considered in patients with severe cardiopulmonary failure, resulting in high risk of hemodynamic collapse with the induction of anesthesia. Strength of Agreement: 100% (CoR: I LoE: C2).

Intraoperative management

Criteria for unplanned ECLS

The right ventricular function and pulmonary arterial pressures, evaluated using TEE and Swan-Ganz catheter, should be assessed after the pulmonary artery clamping, unclamping, and reperfusion of the lungs. The right ventricular function and pulmonary arterial pressure are essential in making the decision to initiate ECLS. Strength of Agreement: 75% (CoR: I LoE: B2).

Severe right ventricular dysfunction, refractory to medical optimization, should result in the implementation of ECLS for intraoperative support. Strength of Agreement: 100%. (CoR: I LoE: B2).

Severe hemodynamic instability due to mechanical compression, despite optimal fluid management and support by vasoactive medication, requires the implementation of ECLS. Strength of Agreement: 76%. (CoR: I LoE: C2).

Central cannulation is the preferred approach for unplanned ECLS. Strength of Agreement: 78% (CoR: IIa LoE: C2).

Selection of ECMO versus CPB

VA ECMO is the preferred primary choice for intraoperative support in standard lung transplantations as compared to CPB. Strength of Agreement: 79% (CoR: I LoE: B2).

The inclusion of postoperative complication risks should be considered when choosing the mode of ECLS, and data show that CPB has been associated with a higher rate of postoperative complications compared to VA ECMO. Strength of Agreement: 77% (CoR: I LoE: B2).

In cases where a concomitant cardiac procedure such as coronary artery bypass grafting, valve repair, or atrial septal defect closure is needed, CPB should be used as intraoperative support. Strength of Agreement: 90% (CoR: I LoE: C1).

ECLS cannulation approach

In case of intraoperative hemodynamic compromise refractory to medical optimization, a VV ECMO cannulation, which was used to bridge patients to their transplantation, should be switched to a VA ECMO. Strength of Agreement: 100% (CoR: I LoE: B2).

Central cannulation is preferred for short-term intraoperative support, whereas peripheral cannulation is preferred for postoperative continuation of ECMO. Strength of Agreement: 78% (CoR: I LoE: C2).

Inclusion of postoperative complication risks should be considered when choosing the intraoperative cannulation strategy of ECLS, and data show that central cannulation avoids peripheral vascular venous and arterial thrombotic complications. Strength of Agreement: 95% (CoR: I LoE: C1).

ECLS flow and coagulation management

In double-lung transplantation, VA ECMO flow needs to be adjusted during the implantation of the second lung. A low but pulsatile flow in the pulmonary artery is necessary to avoid no-flow phases through the first implanted graft. Strength of Agreement: 89% (CoR: I LoE: B2).

Gas flow and FiO_2 need to be continuously adjusted according to the recipient's arterial blood gas analysis. Strength of Agreement: 84% (CoR: I LoE: C2).

A transfusion algorithm should be used to decrease transfusion during lung transplantation. Strength of Agreement: 81% (CoR: I LoE: B1).

There is not enough evidence available to make a determination regarding the efficacy or safety of prophylactic antifibrinolytics use during lung transplantation without mechanical support, and its use should be determined by individualized risks and benefits. Strength of Agreement: 90% (CoR: I LoE: C2).

It is reasonable to consider a low-dose heparin protocol for VA ECMO during transplantation if adequate flows can be maintained. Strength of Agreement: 80% (CoR: I LoE: C1).

Anesthetic management

Anesthetic management of patients undergoing lung transplantation with ECLS should be tailored to cardiopulmonary comorbidities of the underlying etiology of ESLD. Strength of Agreement: 83%. (CoR: I LoE: C1).

In the setting of constant ECMO flow, volume resuscitation should be directed toward maintaining pulsatility in the systemic and pulmonary arterial waveforms during intraoperative ECLS for lung transplantation. Strength of Agreement: 83%. (CoR: I LoE: B2).

Regardless of ECLS approach, the lowest possible FiO_2 should be used upon reinflation and reperfusion of donor graft to minimize PGD. Strength of Agreement: 86% (CoR: I LoE: B2).

Pre-ECLS utilization of regional anesthesia is not contraindicated but should be approached cautiously in the setting of utilization of anticoagulation. Strength of Agreement: 78% (CoR: I LoE: C1).

Intraoperative monitoring guidance management

Constant assessment of diverse monitors, including echocardiography, urine output, and $ETCO_2$, is required to direct volume management during VA ECMO. Strength of Agreement: 90%. (CoR: I LoE: B2).

$ETCO_2$ should be utilized as a qualitative and semiquantitative indicator of transpulmonary flow during intraoperative VA ECMO. Strength of Agreement: 90% (CoR: I LoE: B2).

TEE should be considered a standard monitor in all lung transplantations, and performing a comprehensive TEE exam is recommended. Strength of Agreement: 96% (CoR: I LoE: C1).

When utilizing ECLS support, standard TEE assessment of intracardiac preload may be limited due to offloading of cardiac output and should be used in the context of other monitors. Strength of Agreement: 95% (CoR: I LoE: C2).

When utilizing TEE during ECLS, pulmonary vascular anastomoses should be evaluated for size and velocity when the patient is separated from ECLS support due to potential perturbations in measurements on ECLS. Strength of Agreement: 89% (CoR: I LoE: C2).

Criteria for weaning ECLS

Institutional, multidisciplinary guidelines for weaning ECLS need to be developed before utilization of ECLS within a lung transplant program. Strength of Agreement: 85%. (CoR: I LoE: C2).

Cardiopulmonary optimization, including fluid management, inotropic support, and ventilation, should be optimized before MCS weaning. Strength of Agreement: 92% (CoR: I LoE: B2).

Blood flow should be reduced to 1 liter for 1 to 5 minutes before ending intraoperative ECMO to evaluate graft function. Strength of Agreement: 75% (CoR: I LoE: C1).

High ventilator effort for gas exchange and decreased graft compliance should result in prolongation of ECMO postoperatively, with severe right ventricular dysfunction refractory to medical optimization resulting in prolongation of VA ECMO postoperatively. Strength of Agreement: 90% (CoR: I LoE: C1).

Intraoperative ECLS outcomes and perspectives for further research

Multicenter research and future technological focus

Larger multicenter studies need to be performed whether all or only specific patient populations benefit from elective ECMO. Strength of Agreement: 96%. (CoR: I LoE: C2).

The ISHLT Lung Transplant Registry should be expanded by a comprehensive perioperative dataset to study the impact of intraoperative ECLS support and its interaction with recipient, donor, and procedural factors on patient outcomes. Strength of Agreement: 88% (CoR: I LoE: C2).

Ongoing developments of ECMO technological need to be scientifically evaluated to fully establish this impact on coagulation and systemic inflammatory response syndrome. Specifically, the feasibility of low/zero heparin ECMO should be investigated to reduce intraoperative blood loss. Strength of Agreement: 92% (CoR: I LoE: C2).

APPENDIX 2: AUTHOR AND REVIEWER RELEVANT RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES

The ISHLT must collect financial disclosure information from all guideline authors and reviewers about their financial relationships with ACCME-defined ineligible companies **within the prior 24 months**.

An Ineligible Company is any entity whose primary business is:

- **Producing** healthcare products used by or on patients
- **Marketing** healthcare products used by or on patients
- **Re-selling** healthcare products used by or on patients
- **Distributing** healthcare products used by or on patients

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