The American Association for Thoracic Surgery (AATS) 2022 Expert Consensus Document: The use of mechanical circulatory support in lung transplantation

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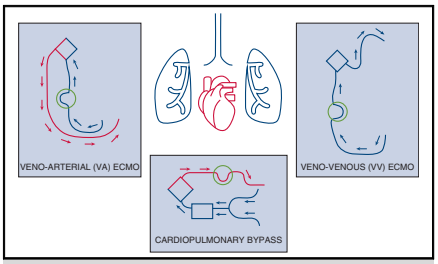
ABSTRACT

Objective: The use of mechanical circulatory support (MCS) in lung transplantation has been steadily increasing over the prior decade, with evolving strategies for incorporating support in the preoperative, intraoperative, and postoperative settings. There is significant practice variability in the use of these techniques, however, and relatively limited data to help establish institutional protocols. The objective of the AATS Clinical Practice Standards Committee (CPSC) expert panel was to review the existing literature and establish recommendations about the use of MCS before, during, and after lung transplantation.

Methods: The AATS CPSC assembled an expert panel of 16 lung transplantation physicians who developed a consensus document of recommendations. The panel was broken into subgroups focused on preoperative, intraoperative, and postoperative support, and each subgroup performed a focused literature review. These subgroups formulated recommendation statements for each subtopic, which were evaluated by the entire group. The statements were then developed via discussion among the panel and refined until consensus was achieved on each statement.

Results: The expert panel achieved consensus on 36 recommendations for how and when to use MCS in lung transplantation. These recommendations included the use of veno-venous extracorporeal membrane oxygenation (ECMO) as a bridging strategy in the preoperative setting, a preference for central veno-arterial ECMO over traditional cardiopulmonary bypass during the transplantation procedure, and the benefit of supporting selected patients with MCS postoperatively.

Conclusions: Achieving optimal results in lung transplantation requires the use of a wide range of strategies. MCS provides an important mechanism for helping these critically ill patients through the peritransplantation period. Despite the complex nature of the decision making process in the treatment of these patients, the expert panel was able to achieve consensus on 36 recommendations. These recommendations should provide guidance for professionals involved in the care of end-stage lung disease patients considered for transplantation. (J Thorac Cardiovasc Surg 2023;165:301-26)



Mechanical circulatory support plays an important role in supporting lung transplantation.

CENTRAL MESSAGE

Mechanical circulatory support is an important component of support for lung transplantation candidates and recipients in the preoperative, intraoperative, and postoperative settings.

PERSPECTIVE

Mechanical circulatory support has had an expanding role in lung transplantation and is now involved in preoperative stabilization, facilitation of the operation, and postoperative support. An expert panel identified recommendations for the use of mechanical circulatory support in these various settings.

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Abbreviations and Acronyms

AATS	= American Association for Thoracic Surgery
ARDS	= acute respiratory distress syndrome
BTR	= bridge to recovery
COR	= class of recommendation
COVID-19	= Coronavirus disease 2019
CPB	= cardiopulmonary bypass
CPSC	= Clinical Practice Standards Committee
ECCO2R	= extracorporeal CO_2 removal
ECMO	= extracorporeal membrane oxygenation
LOE	= level of evidence
MCS	= mechanical circulatory support
PGD	= primary graft dysfunction
TEE	= transesophageal echocardiography
UNOS	= United Network of Organ Sharing
VA	= venoarterial
VAV	= venovenous and venoarterial
VV	= venovenous

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Lung transplantation remains the sole therapeutic option for end-stage lung disease resulting from many etiologies. Despite the complexity of the care required for these patients, the prevalence of lung transplantation has continued to increase over the past several decades, with more than 4500 transplants recorded in the registry of the International Society for Heart and Lung Transplantation in 2016.[1] With continued efforts to refine operative technique, patient selection, and optimization of postoperative care, both short-term and long-term survival for lung transplantation has been gradually improving.[2]

Mechanical circulatory support (MCS) has been an important component of lung transplantation since the initial successful cases used cardiopulmonary bypass (CPB) as part of the operation.[3] The intraoperative use of MCS remains an important tool to facilitate a successful operation, but over time, the use of veno-venous (VV) or veno-arterial (VA) extracorporeal membrane oxygenation (ECMO) instead of full CPB has been gaining in popularity.

In addition to its use in the operating room, MCS has an increasing role in the preoperative and postoperative management of end-stage lung patients. Hill first reported the use of ECMO as a treatment for cardiopulmonary failure in 1972.[4] Outcomes in the adult population were generally dismal, and a randomized prospective trial in 1979 demonstrated no survival benefit of ECMO for patients with acute respiratory failure.[5] For the next 2 decades, use of ECMO in the adult population was sporadic and limited to a few centers; however, significant improvements in ECMO-associated technologies (specifically membrane oxygenators and centrifugal pumps), as well as a better understanding of ECMO physiology, have led to a recent resurgence in the use of this technology. This has manifested in the lung transplantation community in 2 important ways—bridging acutely ill patients to transplantation with the use of MCS and providing continued support for patients immediately postoperatively to facilitate recovery of the transplanted lung. Despite the numerous publications about the effectiveness of MCS in these settings, there are no universally accepted indications for this practice.

The objective of this expert consensus document from the AATS Clinical Practice Standards Committee is to systematically review the available literature on the use of MCS and to determine recommended use criteria for MCS in the peritransplantation period. We present 36 recommendations, broken into preoperative (Table 1), intraoperative (Table 2), and postoperative (Table 3) time periods, with the associated evidence to support those recommendations. Because of a lack of robust data, many of these recommendations are consensus opinions. The class

of recommendation (COR) and the level of evidence (LOE) on which the recommendation is based are reported according to the terminology adopted by the American College of Cardiology and American Heart Association[6] (Figure 1).

METHODS

The AATS Clinical Practice Standards Committee and Assembly of Expert Group

The Clinical Practice Standards Committee (CPSC) co-chairs and members of the committee were appointed by the AATS. The CPSC committee selected the topic of utilization of MCS in lung transplantation recipients. The co-chairs of the CPSC then assembled a writing group of published experts on lung transplantation, especially with the use of MCS, as well as individuals with experience in clinical practice guideline development, evidence-based medicine, research, systematic review preparation, or quality improvement. The writing group members were approved by the AATS. All members completed a conflict of interest disclosure (Appendix 1 and 2).

Formulation of Clinical Topics and Working Groups

After selecting the writing group, the co-chairs generated an a priori organizational structure and list of topics for the consensus statement to discuss. These topics were reviewed in a group session and revised to a final group of topics. The writing group was then split into smaller working groups covering each topic, based on areas of published expertise and individual interest.

Development of an Expert Consensus Document

The working groups performed a systematic review of the literature specific to their topic and shared their references with the group for consideration. They then generated recommendation statements about their specific topics, justified with appropriate references when available, and presented them to the group for evaluation using a modified Delphi method. The expert consensus panel was asked to evaluate each recommendation on a 5-point Likert scale (graded as 1 = strongly disagree; 2 = disagree; 3 = neither agree nor disagree; 4 = agree; 5 = strongly agree). A predetermined response rate of 80% was required for the vote to be considered complete. A predefined threshold of a minimum of 75% agreement ("agree" or "strongly agree") was required for consensus statements to be accepted.[7] If the 75% threshold was not achieved, the statement was revised after discussion with the writing group and resubmitted for voting. This cycle was repeated until there was consensus on all recommendation statements.

SECTION 1A: PREOPERATIVE PULMONARY FAILURE

Although early referral and timely transplantation represent the ideal approach to lung transplantation, a patient's disease progression often requires bridging strategies with extracorporeal pulmonary support systems. These support strategies include extracorporeal membrane oxygenation and CO_2 removal technologies to supplement or entirely replace the pulmonary function of a candidate awaiting transplantation. The principal goals of these strategies are to restore acceptable oxygenation and ventilation, avoid end-organ injury, and maintain or improve functional capacity and physical conditioning.

1. VV-ECMO is the preferred initial option for bridging strategies in patients with isolated hypoxia and/or hypercapnia in the absence of hemodynamic instability or right ventricular dysfunction (COR: 2a, LOE: C-LD [level C, limited data]).

In patients with isolated pulmonary failure, outcomes with VV-ECMO are superior to those of VA-ECMO support as an initial modality.[8-11] Although new-onset or progressive hemodynamic instability or right ventricular dysfunction can develop from worsening pulmonary vascular resistance, the need for conversion from VV-ECMO to VA-ECMO support remains low. In cases where hemodynamic support is needed, considerations for choice of conversion to a right ventricular assist device with an in-line oxygenator or full VA-ECMO support should include urgency of conversion, relative risk of pulmonary hemorrhage, expected timing of transplantation, and any anatomic limitations.

2. In patients supported with VV-ECMO as a bridge to lung transplantation, periodic evaluation of right ventricular function (by clinical assessment or otherwise) should be performed to evaluate the need for alternative support strategies (COR: 1, LOE: C-EO [level C, expert opinion]).

Late recognition of right ventricular dysfunction can be associated with significant morbidity and mortality in patients supported with VV-ECMO as a bridge to transplantation, and as such, periodic monitoring of the right ventricle should be performed. This monitoring may include assessment for hemodynamic compromise, intermittent echocardiography, and/or evaluation of right-sided hemodynamics via a pulmonary artery catheter. The mere presence of right ventricular dysfunction does not dictate the immediate need for alternative support strategies, but it should be considered an important part of the overall clinical picture of any given transplantation candidate.

3. While providing extracorporeal pulmonary support as a bridge to lung transplantation, ambulation and rehabilitation should be aggressively pursued to improve bridge success rate and post-transplantation outcomes (COR: 1, LOE: C-LD).

It is widely accepted that there is significant clinical benefit of aggressive ambulation and rehabilitation in critically ill patients. Similarly, aggressive physical therapy, including ambulation, in patients bridged to lung transplantation with ECMO is associated with improved rates of successful transplantation and post-transplantation survival and recovery.[12-15] It is important, however, to stress the need for a multidisciplinary group to be present and assist with ambulation, which can be time- and resource-intensive. Proactive efforts to avoid unnecessary complications, such as cannula migration or dislodgement, system power failure, and oxygen source depletion, are also critical

TABLE 1. Preoperative MCS for lung transplantation

Recommendations for preoperative MCS for lung transplantation	COR	LOE
1. Veno-venous ECMO is the preferred initial option for bridging strategies in patients with isolated hypoxia and/or hypercapnia in the absence of hemodynamic instability or right ventricular dysfunction.	IIa	C-LD
2. In patients supported with veno-venous ECMO as a bridge to lung transplantation, periodic evaluation of right ventricular function (by clinical assessment or otherwise) should be performed to evaluate the need for alternative support strategies.	I	C-EO
3. While undergoing extracorporeal pulmonary support as a bridge to lung transplantation, ambulation and rehabilitation should be aggressively pursued to improve bridge success rates and post-transplantation outcomes.	I	C-LD
4. Femoral venous cannulation should not be considered a contraindication to ambulation and rehabilitation in patients supported with veno-venous ECMO as a bridge to lung transplantation.	IIa	C-LD
5. While extracorporeal circulatory support is the preferred strategy for bridging to transplantation to promote physical therapy, bridging with mechanical ventilation alone can be used in highly selected cases where deconditioning can be avoided.	I	C-LD
6. In select circumstances when hypercapneic respiratory failure is the predominant issue, extracorporeal CO_2 removal can be an effective bridging strategy.	IIa	C-LD
7. VA-ECLS as bridge to lung transplantation is a valuable option in selected patients with end-stage pulmonary hypertension evolving with right ventricular failure, despite the risk of impaired short-term outcomes.	I	B-NR
8. Both femoral and subclavian arterial cannulation could be considered (based on lung oxygenation and cardiac output) for VA-ECMO bridging for lung transplantation.	I	B-NR
9. In patients with combined circulatory and respiratory failure, the use of VAV-ECMO, as opposed to VA-ECMO only, is a valuable option to prevent differential upper body hypoxia in patients with peripheral femoral artery cannulation.	IIa	C-EO
10. Selected patients with COVID-19-related ARDS supported with ECMO can be considered for transplantation in the absence of any signs of lung recovery.	IIa	C-EO
11. Patients considered for transplantation for COVID-19 ARDS should meet other standard criteria for listing and demonstrate the potential for post-transplantation rehabilitation.	I	C-EO
12. Patients with pulmonary artery hypertension should be considered for bridging with mechanical support when clinical signs of right heart failure are evident, such as need for inotropes, poor mixed venous saturation, and early signs of kidney and liver dysfunction	I	C-EO
13. In exceptional circumstances, bilateral pneumonectomies and central ECMO initiation can be considered in selected patients with uncontrolled pulmonary sepsis as a bridge to transplantation.	IIb	C-EO

considerations. Having a thoughtful and comprehensive guideline in place prior to initial attempts at ambulation may be helpful in patients supported with ECMO.[16,17]

4. Femoral venous cannulation should not be considered a contraindication to ambulation and rehabilitation in patients supported with veno-venous ECMO as a bridge to lung transplantation (COR: 2a, LOE: C-LD).

Traditional dogma has dictated the need to convert femoral venous, 2-site cannulation to upper-body, single-site cannulation before attempting ambulation and rehabilitation of patients supported with VV-ECMO. With careful planning and execution, however, full ambulation even with a femoral venous cannula site has proven safe and effective.[16,18] This strategy could preclude the need for unnecessary procedures and potential complications associated with converting support strategies solely for the indication of ambulation and rehabilitation.

5. Although extracorporeal circulatory support is the preferred strategy for bridging to transplantation to promote physical therapy, bridging with mechanical ventilation alone can be used in highly selected cases when deconditioning can be avoided (COR: 1, LOE: C-LD).

Historical efforts to bridge patients in respiratory failure to lung transplantation with mechanical ventilation have been associated with poor bridge success rates and post-transplantation outcomes.[19,20] For this reason, extracorporeal support in these patients has become the preferred bridging strategy. In highly selected patients, however, bridging with mechanical ventilation alone can be successful and should not be viewed as a contraindication to proceeding with transplantation. An important caveat is that this should only be performed in patients in whom deconditioning can be avoided. Examples include isolated hypercapnia in a young cystic fibrosis patient still able to ambulate on the ventilator and a patient with acute decompensation with normal muscle mass and functional status just prior to mechanical ventilation with an expected short wait time to transplantation.

6. In selected circumstances where hypercapnic respiratory failure is the predominant issue, extracorporeal CO2 removal (ECCO2R) can be an effective bridging strategy (COR: 2a, LOE: C-LD).

Although ECMO has gained progressive adoption and success as a bridging strategy for patients with hypoxia

MCS, Mechanical circulatory support; *COR*, class of recommendation; *LOE*, level of evidence; *ECMO*, extracorporeal membrane oxygenation; *C-LD*, level C, limited data; *C-EO*, level C, expert opinion; *VA*, veno-arterial; *VAV*, venovenous and venoarterial; *ECLS*, extracorporeal life support; *B-NR*, level B, nonrandomized; *COVID-19*, Coronavirus disease 19; *ARDS*, acute respiratory distress syndrome.

and/or hypercapnia to lung transplantation, an ECCO2R device may be appropriate and effective in highly selected cases of isolated hypercapnia.[21] The theoretical advantage over ECMO in this selected population are the need for only a single-site, relatively small-bore upper body access. Because of its lower flow rate, oxygenation support is quite limited with this modality and relatively ineffective. Continuous evaluation of progressive hypoxia should be evaluated to guide the need for and time to apply alternative bridging strategies are required (ie, ECMO). Also, although an ECCO2R strategy theoretically may be beneficial, no data currently support its use as effective or superior to full extracorporeal pulmonary support options as a bridge to lung transplantation.

SECTION 1B: PREOPERATIVE CARDIOPULMONARY SUPPORT FOR THE LUNG TRANSPLANTATION CANDIDATE

Although VV-ECMO is the first choice for support of end-stage, isolated respiratory failure in candidates being bridged to lung transplantation, end-stage lung failure caused by increased pulmonary vascular resistance may be better treated by volume-unloading the right ventricle and preserving arterial oxygenation and flow. This is best achieved by VA-ECMO treatment. Because of the need to cannulate peripheral arteries to gain access for sufficient flow, VA-ECMO has a higher complication rate than VV-ECMO. A good protocol and a dedicated team are necessary to obtain good results.

7. Veno-arterial ECMO as bridge to lung transplantation is a valuable option in selected patients with end-stage pulmonary hypertension evolving with right ventricular failure, despite the risk of impaired short-term outcomes (COR: 1, LOE: B-NR [level B, nonrandomized]).

VA-ECMO support is ideally suited for those with hemodynamic deterioration in the context of RV failure due to increasing pulmonary vascular resistance.[8-10,12,22-24] In addition, for combined ventilatory failure and right ventricular failure, support with VA-ECMO is advised.[25,26] The decision to initiate VA-ECMO support is complex and multifactorial and includes consideration of the underlying disease and the expected time on the waitlist.[22,27]

8. Both femoral and subclavian arterial cannulation could be considered (based on lung oxygenation and cardiac output) for VA-ECMO bridging for lung transplantation (COR: 1, LOE: B-NR).

In the treatment modality of VA-ECMO, various cannulation and perfusion approaches are available.[9,28,29] The best evidence for successful support exists for peripheral VA-ECMO placed in a femoral vein and artery.[8,10,12,22-25] The great advantage of this approach is that it can be performed at the bedside, promptly and safely by either an open or percutaneous technique.[30] Drawbacks include the risk of malperfusion of the leg at the cannulated side and the more limited possibilities of mobilizing the patient. Furthermore, there must be a sustained left ventricular output to prevent stasis and thrombosis in the left cardiac chambers.[31] The risk of limb ischemia is not negligible, reportedly ranging from 9% to 33%. Preventive measures, such as the use of a distal perfusion cannula or an end-to-side vascular graft, are advised.[32]

Some programs use subclavian artery cannulation either by direct cannulation or via a graft, although this technique does not prevent vascular complications.[33,34] There are limited data to recommend femoral access over subclavian access or vice versa. The use of subclavian cannulation has the potential benefit of preventing differential upper body hypoxemia because the oxygenated blood is infused into the ascending aorta. For refractory hypoxemia, or in patients with small peripheral vessels, central cannulation via a thoracotomy or mini-sternotomy is possible, although

TABLE 2. Intraoperative MCS for lung transplantation

Recommendations for intraoperative MCS for lung transplantation	COR	LOE
14. Lung transplantation for patients with a preexisting moderate/high secondary pulmonary hypertension should be performed routinely while on mechanical support.	I	B-NR
15. Planned mechanical support can be used for controlled reperfusion of the lung allograft, a factor that might reduce the risk for PGD.	IIa	C-LD
16. Frequent nonemergent use of MCS promotes standardization of technique.	I	C-EO
17. Intraoperative mechanical support is associated with acceptable intraoperative risk and should be used as indicated.	IIa	C-LD
18. The need for MCS does not exclude sternal-sparing approaches.	I	C-OE
19. Routine use of intraoperative VA-ECMO does not increase the likelihood of temporary chest closure or unplanned reexploration for bleeding.	IIa	C-LD
20. The preferred intraoperative support system for lung transplantation is VA-ECMO.	I	B-NR
21. Central cannulation is preferred over peripheral cannulation.	IIa	C-LD
22. Low or no heparin regimens are suggested for patients with significant adhesions and impaired coagulation status.	IIa	C-EO
23. For patients bridged to lung transplant with VV-ECMO, intraoperative switch to VA-ECMO is preferred.	IIa	C-EO
24. Use of CPB is recommended for lung transplantation combined with intracardiac repair.	I	B-NR

MCS, Mechanical circulatory support; *COR*, class of recommendation; *LOE*, level of evidence; *B-NR*, level B, nonrandomized; *PGD*, primary graft dysfunction; *C-LD*, level C, limited data; *C-EO*, level C, expert opinion; *VA*, veno-arterial; *ECMO*, extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass.

TABLE 3. Postoperative MCS for lung transplantation

Recommendations for postoperative MCS for lung transplantation	COR	LOE
25. When intraoperative ECMO indication is PGD, ECMO should be maintained post-transplantation until lung function recovers.	I	B-NR
26. If required, ECMO can be maintained post-transplantation regardless of cannulation approach (central or peripheral).	I	B-NR
27. Prophylactic post-transplantation ECMO maintenance may be indicated in pulmonary hypertension patients to reduce the arte of PGD and improve postoperative early outcomes.	I	B-NR
28. Bridged patients should not automatically be maintained on ECMO after lung transplantation.	IIa	C-EO
29. There are clear situations with right ventricular dysfunction (eg, high pulmonary artery pressures) when patients should not be weaned off ECMO at the end of the transplantation procedure.	I	C-EO
30. Early weaning from ECMO after transplantation may avoid complications (bleeding, infection, and vascular complications).	I	C-LD
31. Mechanical support with ECMO is recommended immediately after lung transplantation in patients with severe cardiopulmonary instability; peripheral cannulation is preferred over central cannulation.	I	B-NR
32. Early institution of ECMO is recommended in lung transplantation recipients with clinical signs of severe PGD with worsening trend in the first hours after lung transplantation to allow allograft recovery while protecting from ventilator-induced injury.	I	B-NR
33. In patients with post-transplantation PGD resulting in primarily respiratory failure (hypoxemia/hypercarbia) with otherwise stable hemodynamics and cardiac function, extracorporeal support with VV-ECMO is recommended over VA-ECMO because fewer procedure-related complications (hemorrhagic, vascular, neurologic) can be expected.	IIb	C-LD
34. Although overall mortality is higher in recipients with severe PGD requiring ECMO support compared to those without, the impact on long-term pulmonary function in survivors remains unclear.	IIb	C-LD
35. In patients on mechanical support for severe post-lung transplantation PGD with no functional improvement within the first 2 weeks, continued ECMO as a bridge to retransplantation is not recommended because of the low likelihood of a successful outcome after early retransplantation. A decision to list for urgent retransplantation can be made only after multidisciplinary consensus.	III	B-NR
36. Trans-esophageal echocardiography is recommended in all recipients with severe post-transplant PGD to exclude other causes of pulmonary graft edema and/or hypoxia, such as left ventricular dysfunction, the presence of intracardiac shunts, or anastomotic pulmonary vein stenosis or thrombosis.	IIa	C-LD

MCS, Mechanical circulatory support; *COR*, class of recommendation; *LOE*, level of evidence; *ECMO*, extracorporeal membrane oxygenation; *B-NR*, level B, non-randomized; *C-LD*, level C, limited data; *C-EO*, level C, expert opinion; *PGD*, primary graft dysfunction; *VV*, veno-venous; *VA*, veno-arterial; *ECMO*, extracorporeal membrane oxygenation; *CPB*, cardiopulmonary bypass.

this may increase the complexity of the subsequent transplantation.[29]

9. In patients with combined circulatory and respiratory failure, the use of venovenous and venoarterial (VAV)-ECMO, as opposed to VA-ECMO only, is a valuable option to prevent differential upper-body hypoxia in patients with peripheral femoral artery cannulation (COR: 2a, LOE: C-EO).

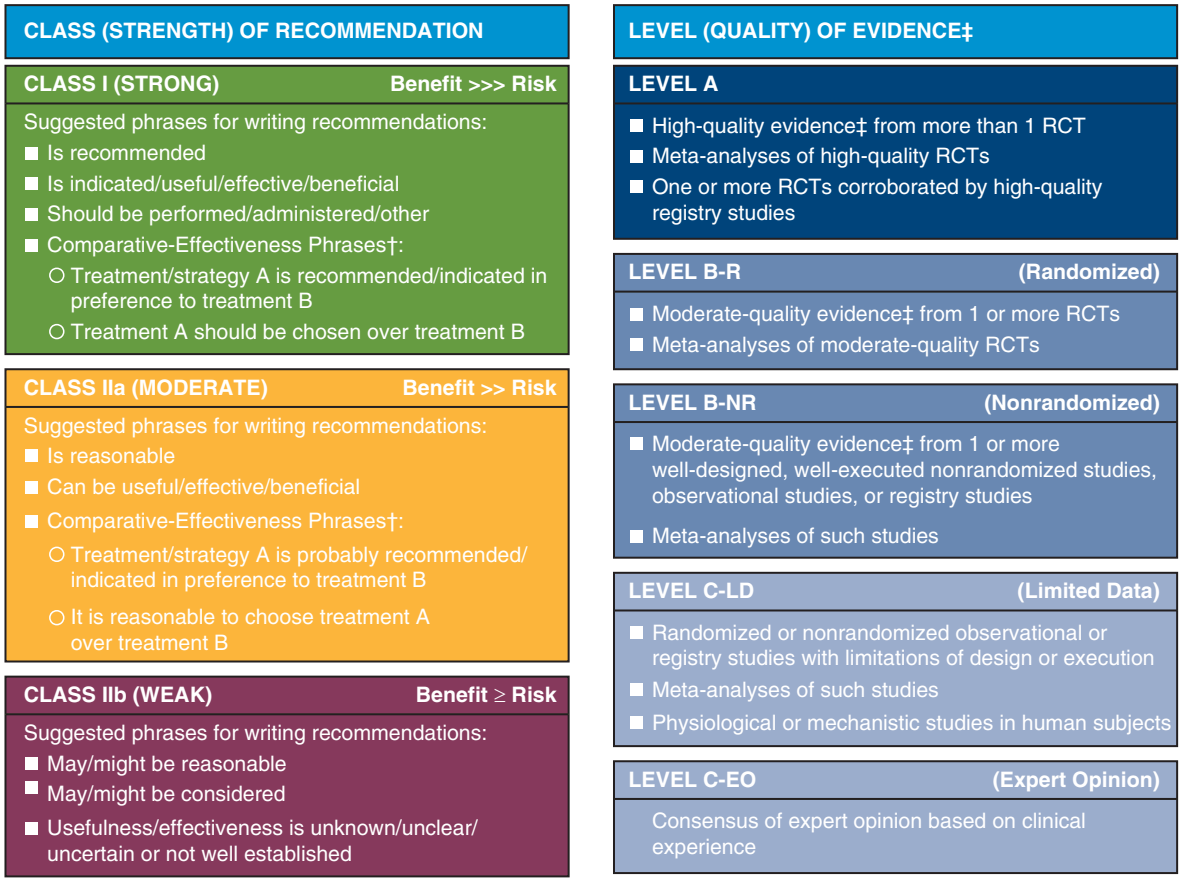
Understanding the pathophysiology of true cardiopulmonary failure in patients with end-stage lung disease is crucial to matching a patient's physiologic needs with the appropriate MCS mode.[35,36] The cannulation site also affects the expected effects of each support mode. VA-ECMO with peripheral cannulation of the femoral artery generates a retrograde flow of oxygenated blood in the descending aorta. In the context of end-stage lung disease, there often is right ventricular failure with partially preserved LV forward flow of deoxygenated blood, which increases the risk of differential upper body hypoxemia with deleterious myocardial and cerebral ischemia.[37] In these patients, pulse oximetry should be performed on the right hand, and arterial blood gases should be drawn from the right radial artery. The simplest way to overcome this phenomenon is by adding a cannula to the internal jugular vein and Y-connecting it to the outflow side of the circuit to escalate the support to VAV-ECMO. The use of a partially occluding clamp and a second flow probe are useful in preventing excessive flow to the less-resistant venous side. Adjustment of venous versus arterial flow should be based on arterial blood gases along with surrogates of right ventricular function, such as transthoracic and transesophageal echocardiography, additional end-organ dysfunction (kidney, liver, gut), central venous pressure, and central venous oxygenation.

SECTION 1C: SPECIAL CIRCUMSTANCES FOR PREOPERATIVE BRIDGING WITH MCS

Although the use of MCS is worth considering for all patients approaching lung transplantation, some special use circumstances merit additional consideration. This section addresses 3 of these circumstances: patients with Coronavirus disease 2019 (COVID-19), patients with severe pulmonary hypertension, and patients with uncontrolled pulmonary sepsis.

10. Selected patients with COVID-19–related acute respiratory distress syndrome (ARDS) supported with ECMO can be considered for transplantation in the absence of any signs of lung recovery (COR: 2a, LOE: C-EO).

ARDS is a common terminal pathway of lung injury in response to a variety of etiologies, including COVID-19.



COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic informations).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

FIGURE 1. Updated American College of Cardiology/American Heart Association table of class of recommendation (*COR*) and level of evidence (*LOE*). (Reprinted with permission.[6])

Although early deaths in patients with severe COVID-19 ARDS are related to infectious complications, those who survive the initial phase can develop fibroproliferation resulting in the inability to wean off mechanical life support. Unfortunately, no medical or pharmacologic therapies targeting fibroproliferation have been effective to date. Nevertheless, with mechanical ventilation and extracorporeal support, many patients with COVID-19 ARDS can develop sufficient lung recovery. Anecdotes of patients developing spontaneous recovery after a very prolonged duration of ECMO support also exist. The probability of weaning off ECMO, however, is significantly reduced with the duration of support, which correlates with an increased probability of death. In a consensus of multiple centers across 4 countries as well as in editorialized reports, it has been proposed that evaluation for lung transplantation can be considered after 4 to 6 weeks of initiation of ECMO because the probability of death is greatly increased at this time.[38-43]

How to accurately identify patients who would not recover spontaneously and benefit from lung transplantation remains unclear. For COVID-19–associated ARDS, the following indicators may be helpful in the medical decision making surrounding consideration for lung transplantation: (1) development of extensive pulmonary sequelae, (2) presence of lung necrosis with cavitation associated with sepsis, (3) presence of significant pulmonary hypertension, and (4) evidence of diffuse pulmonary fibrosis. Transplantation should be deferred in patients who show signs of lung recovery, as suggested by improvements in lung compliance, chest radiography, and gas exchange. Recent single-center as well as national registry US data and European multicenter study indicate that lung transplantation can achieve good outcomes, despite a complex medical course, in carefully selected patients suffering from COVID-19 ARDS who remain unable to wean from extended extracorporeal or mechanical ventilator support.[40,44,45]

Although there have been several case reports demonstrating the feasibility of lung transplantation for patients with COVID-19 ARDS, 2 recent studies have reported longer- term outcomes in single-center and national cohorts.[40,44] In the first, 102 consecutive patients, 30 with COVID-19 ARDS and 72 with non–COVID-19 lung diseases, who underwent lung transplantation at a single center between January 21, 2020, and September 30, 2021, were reported. The median lung allocation scores for the 2 groups were 85.8 and 46.7, respectively. The surgical procedure was more complex in the COVID-19 ARDS group, as evidenced by increased operative time, allograft ischemic time, use of ECMO, and blood transfusions. In addition, the COVID-19 ARDS patients experienced greater primary graft dysfunction (PGD) and increased use of hospital resources, such as length of stay. Nevertheless, these patients with COVID-19 ARDS demonstrated much more rapid improvement in performance status following transplantation. With a median post–lung transplantation follow-up of 351 days, survival was 100% (30 of 30) in the lung transplantation recipients with COVID-19 ARDS, compared to 83.3% in the non–COVID-19 lung transplantation recipients.[40]

In a concurrent analysis of the US Scientific Registry of Transplant Recipients database of 118 COVID-19 ARDS patients who underwent lung transplantation, similar to the single-center report, a high percentage (81.4%) were supported on ECMO before transplantation. Despite the critical state of these patients prior to transplantation, mortality was only 1.7% at 30 days and 3.4% at 90 days.[44]

11. Patients considered for lung transplantation for COVID-19 ARDS should meet other standard criteria for listing and demonstrate the potential for post-transplantation rehabilitation (COR: 1, LOE: C-EO).

Given the heterogeneity of COVID-19 patients, it is important to select them carefully. This is particularly important in those with COVID-19 ARDS. Bridging patients on extracorporeal support while they are awake has become an increasingly used practice in lung transplantation. Many centers consider it a prerequisite for transplantation, because patients who are bridged awake have significantly better outcomes than patients who are bridged sedated, and because it allows first-person consent and assessment for the potential for post-transplantation rehabilitation.

Ideally, COVID-19 ARDS transplantation candidates should be in stable condition with single system organ failure. Temporary kidney failure in a patient with a previous normal kidney function generally should not be considered a contraindication for lung transplantation; therefore, patients who require kidney replacement therapy during their wait time should not be immediately delisted until it is determined that the kidney injury is irrecoverable. In contrast to renal dysfunction, cholestatic liver dysfunction due to secondary sclerosing cholangitis is a dreadful complication in patients requiring prolonged MCS for ARDS and should be considered a relative contraindication for lung transplantation.[46,47]

Diffuse bleeding during MCS or septic shock are other contraindications. Whereas the COVID-19 ARDS patients who are considered for transplantation are young and their likelihood of an undetected malignancy or a significant cardiovascular comorbidity is low, older patients should be scrutinized for possible indolent coronary disease or malignancy. Finally, psychosocial history and level of financial support should be evaluated in all prospective candidates.

12. Patients with pulmonary hypertension should be considered for bridging with mechanical support when clinical signs of right heart failure are evident, such as a need for inotropes, poor mixed venous saturation, and early signs of kidney and liver dysfunction (COR: 1, LOE: C-LD).

Patients listed for lung transplantation with pulmonary hypertension developing severe right-sided heart failure require comprehensive care, including treatment of factors causing or contributing to heart failure, fluid management, and strategies to improve cardiac function. Such patients should be treated at expert centers that are capable of providing all treatment options, including MCS and lung transplantation. MCS should be initiated when the clinical course suggests that significant right heart failure is present and associated with imminent secondary organ dysfunction despite optimized medical therapy.[48]

The most common MCS approach for patients with pulmonary hypertension is VA-ECMO. VA-ECMO placed under local anesthesia via the femoral vessels is well tolerated and safe. This is often the initial approach for most patients. However, femoral-femoral VA-ECMO prevents mobilization and is associated with a risk of ischemic limb complications if support is required for several weeks. Therefore, many centers prefer the use of central VA-ECMO via cannulation of the axillary artery, innominate artery, or ascending aorta.[49,50] Some recent studies on the use of central VA ECMO via a mini-anterior right thoracotomy on the third intercostal space have reported promising results in terms of durability and patient mobilization.[49]

An alternative approach for patients with pulmonary artery hypertension includes the use of a pulmonary artery–left atrium pumpless interventional lung assist device (Novalung; Xenios). In this mode, the device is placed in parallel with pulmonary circulation. Because of its very low resistance, the device provides an excellent way to decompress the right ventricle. In a previous report, more than 80% of patients were successfully bridged with this approach.[48] More recently, right atrium/right ventricle–to–pulmonary artery dual-lumen ECMO cannulas have been used in this population.[51] As with right ventricular assist devices, however, increasing forward flow in lungs with very high vascular resistance is often not successful, and thus this approach should be reserved for patients with less severe secondary pulmonary hypertension such as in interstitial pulmonary fibrosis.

For patients with right ventricular failure and unfavorable anatomy or complicated arterial access, the combination of VV-ECMO with a single dual-lumen cannula and a balloon atrial septostomy may offer a reasonable alternative. Even though some success was obtained with atrial septostomy alone to bridge patients with pulmonary artery hypertension and right ventricular failure, the mortality associated with the procedure can be as high as 16%.[52,53] In these cases, the main cause of death was refractory hypoxemia. With this recently proposed mode of support, the rationale is to provide an oxygenated right-to-left shunt through the artificially created septostomy, unloading the right heart without causing excessive hypoxemia.[54] The limited experience with this method along with the potential premature closure of the septostomy represent barriers for widespread acceptance of this mechanical support mode as a bridge to lung transplantation.

13. In exceptional circumstances, bilateral pneumonectomies and central ECMO initiation can be considered in patients with uncontrolled pulmonary sepsis as a bridge to lung transplantation (COR: 2b, LOE: C-EO).

Patients bridged with ECMO may develop significant pulmonary sepsis, leading to secondary organ dysfunction. Especially in patients with cystic fibrosis and bronchiectasis on mechanical ventilation, secretions tend to accumulate with multiresistant microorganisms and uncontrolled sepsis develop despite broad antibiotic coverage. In 2016, Cypel and colleagues[55] performed bilateral pneumonectomies (to remove the source of sepsis) in conjunction with central VA-ECMO and PA-LA Novalung (biventricular support). A successful bilateral lung transplantation was performed 6 days later. Barac and colleagues[56] repeated this approach albeit with a slight modification (ie, substitution of a shunt between the left pulmonary artery and left pulmonary vein for a pulmonary artery catheter). Again, a successful double lung transplantation was performed 6 days after the pneumonectomies. Given the limited experience with this approach to date, it should be considered only in exceptional situations and in centers with extensive experience in mechanical support and lung transplantation.

SECTION 2A: SHOULD ROUTINE LUNG TRANSPLANTATION BE PERFORMED WITH OR WITHOUT MECHANICAL SUPPORT?

Historically, the first reported double lung transplantations were performed with mechanical support. These en bloc transplantations with a tracheal anastomosis required CPB. With the development of bilateral sequential techniques of lung transplantation and the change from sternotomy to anterolateral thoracotomies/clamshell incisions, it became possible to perform lung transplantation without mechanical support.

The use of mechanical support devices provides several advantages in routine lung transplantation. First, it provides hemodynamic stability, especially when the surgical access to the hilar structures is difficult. It facilitates lung

protective ventilation strategies with low inspired oxygen fraction and low driving pressures. It also facilitates prolonged controlled reperfusion of the newly implanted graft and minimizes right heart strain while the pulmonary artery is clamped. These advantages are somewhat diminished by certain risks, including a higher rate of intraoperative blood transfusion and activation of proinflammatory cytokines, which result in higher rates of PGD and of nonpulmonary complications (eg, kidney failure). There is evidence that most of these disadvantages are restricted to the use of CPB and are uncommonly seen with ECMO,[57-61] although PGD rates are still higher in patients who undergo transplantation with ECMO compared with patients who did not require any MCS.[62]

There currently are 2 categories of intraoperative MCS use:

1. Selective MCS. MCS is used only in selected, high-risk patients. Selective MCS use can be planned (decision before the start of operation, start of CPB/ECMO after chest opening) or unplanned (when either anatomic or physiologic parameters dictate).
2. Routine MCS. MCS is used in every lung transplantation.

Several retrospective single-center studies have identified donor- and recipient-associated factors that are more likely to require MCS. These include a diagnosis of idiopathic pulmonary arterial hypertension, moderate/severe secondary pulmonary hypertension with or without right ventricular dysfunction present at the time of transplantation, interstitial lung disease with a retracted chest cavity, planned concomitant cardiac procedures, and lobar transplantation. Intraoperative factors include an inability to tolerate single-lung ventilation, inability to tolerate clamping of the pulmonary artery, and hemodynamic instability during hilar dissection.

14. Lung transplantation for patients with preexisting moderate to high secondary pulmonary hypertension should be performed routinely on mechanical support (COR: 1, LOE: B-NR).

Most patients with end-stage lung disease develop secondary pulmonary hypertension.[63] Several studies have demonstrated that increased pulmonary artery pressure requires intraoperative MCS. Ius and colleagues[64] found significantly higher pulmonary artery pressures in patients who required intraoperative ECMO support compared with those who did not. Similar results were published by the Pittsburgh group.[65] Some authors have proposed a systolic pulmonary artery pressure cutoff of 50 mm Hg as indicating a high likelihood that a patient will not tolerate pulmonary artery clamping and will require MCS.[66]

15. Planned mechanical support can be used for controlled reperfusion of the lung allograft, a factor that might reduce the risk for PGD (COR: 2a, LOE: C-LD).

Evidence suggests that elevated early reperfusion pressures contribute to worse graft outcomes.[67] Reperfusion should be performed at low pressure because the graft should be exposed slowly to normal perfusion pressures.[68] Preclinical studies have shown that the duration of controlled reperfusion may be important: 5 minutes is insufficient,[69] and 30 minutes is superior to 15 minutes or 5 minutes.[70] Importantly, when performing a sequential bilateral lung transplantation without MCS, the first implanted graft is exposed to the full cardiac output (twice the usual blood flow), a situation that can augment ischemia-related damage and lead to the clinical picture of "first lung syndrome."[71] MCS (VA-ECMO, CPB) facilitates controlled reperfusion over a prolonged period, during which reperfusion pressure can be readily manipulated by increasing or decreasing blood flow through the device. The positive effect of controlled reperfusion on primary graft function achieved through a routine VA-ECMO strategy has been highlighted recently[72,73]; however, a prospective trial with an intention-to-treat breakdown is needed to provide a final answer to this question.

16. Frequent nonemergent use of MCS promotes standardization of technique (COR: 1, LOE: C-EO).

Minor and major cannulation-related complications are reported in up to 32% of patients receiving VA-ECMO, with a lower complication rate in central VA-ECMO compared to femoral cannulation (23% vs 36%).[74] In the same study, limb ischemia was described as the most common complication in peripheral VA-ECMO cannulation. Hemorrhage was the most typical complication in central VA cannulation, however, suggesting that surgical-technical complications are the most common type of complication in intraoperative VA-ECMO.[74] Therefore, standardization of cannulation techniques is pivotal to improving performance and avoiding unnecessary complications. In a study of peripheral VV cannulation, a learning curve requiring 100 cases was described[75]; a similar number can be assumed for central VA cannulation. Although there is no direct evidence in the literature for central VA-ECMO cannulation, the expert panel agreed that the frequent use of MCS in nonemergent, elective situations enhances learning and standardization of these techniques by the team. Routine use of central VA-ECMO was associated with a very low rate of complications in patients receiving nonemergent intraoperative VA-ECMO during lung transplantation.[73]

17. Intraoperative mechanical support is associated with acceptable intraoperative risk and should be used as indicated (COR: 2a, LOE: C-LD).

The intraoperative risk of MCS is largely related to technical vascular complications, air embolism, or the need for large-volume blood transfusion. Although more than 20% of patients in a non-transplantation population placed on central VA-ECMO for hemodynamic support develop a cannulation-related hemorrhage,[74] central cannulation for intraoperative VA-ECMO or CPB support for lung transplantation is generally associated with a very low risk of aortic dissection or major bleeding.[73] This is likely related to the short duration of circulatory support, the technical familiarity of central cannulation, and the low incidence of severe atherosclerotic aortic disease in lung transplant recipients. Up to 10% of patients undergoing femoral cannulation for VA-ECMO develop hemorrhage or limb ischemia, however.[76] Liberal use of a distal limb perfusion cannula can prevent limb ischemia.

The true incidence of air embolism during MCS for lung transplantation is unknown; however, it is a rare event. Air entrapment in the VA-ECMO circuit may occur in up to 4% of cases,[77] but it can be avoided by meticulous technique. The risk of these intraoperative complications must be weighed against the benefits of MCS, including hemodynamic stability, improved operative exposure, and controlled reperfusion. In the absence of published literature to directly inform this choice, based on retrospective series and implicit information from the general publications on MCS, the expert group agreed that intraoperative mechanical support is associated with acceptable risk and should be used when indicated.

18. The need for mechanical support does not exclude sternal sparing approaches (COR: 1, LOE: C-OE).

Bilateral lung transplantation can be performed using a clamshell incision, sternotomy, or bilateral anterolateral thoracotomy approach, which spares the sternum and reduces the risk of wound complications, including malunion and infection. Experienced centers advocate for sternal-sparing approaches and prefer the clamshell for specific indications, such as reoperation and difficult exposure.[78,79] Either central or peripheral cannulation can be performed for MCS during bilateral lung transplantation with a sternal-sparing approach[80] (Figure 2). A hybrid cannulation technique with central arterial and peripheral venous cannulation also may be considered and can provide a more unhindered operative field compared with central arterial and venous cannulation. Peripheral cannulation of the femoral vessels has been described in multiple cohort studies in which a sternal-sparing approach was used for the majority of lung transplantations.[58,81] The risk of complications, including limb ischemia, hematoma, infection, and lymphocele, exceeds 10%-15% with peripheral cannulation[76,81] and must be considered in the choice between central and peripheral cannulation.

19. Routine use of intraoperative VA-ECMO does not increase the likelihood of temporary chest closure or unplanned reexploration for bleeding (COR: 2a, LOE: C-LD).

Unsatisfactory hemostasis in the surgical field at the completion of lung transplantation may prompt a temporary chest closure and is often associated with reexploration for bleeding. Although 17% to 27% of patients undergo reoperation for hemothorax after the use of CPB for lung transplantation, the incidence of this complication is lower with the use of intraoperative VA-ECMO.[57,58] Similarly, a meta-analysis has shown that intraoperative transfusions of packed red blood cells, fresh frozen plasma, and platelets are significantly more likely during MCS with CPB than during MCS with VA-ECMO.[82]

The risk of reoperation for hemorrhage ranged from 5% to 9% in multiple recent cohort studies in which VA-ECMO was selectively used for lung transplantation[81,83-85] and is comparable to the results reported when VA-ECMO was routinely used for all operations.[72,73] In the absence of published direct comparisons of the incidence of temporary chest closure with selective or routine intraoperative VA-ECMO, extrapolation from the published risk of hemothorax indicates that any clinically meaningful differences are unlikely.

SECTION 2B: WHAT IS THE OPTIMAL SUPPORT STRATEGY IF INTRAOPERATIVE SUPPORT IS NECESSARY, AND WHAT IS THE OPTIMAL MECHANICAL SUPPORT FOR PATIENTS BRIDGED TO LUNG TRANSPLANTATION WITH ECMO?

The traditional intraoperative support system during lung transplantation has been CPB.[86] In the past decade, VA-ECMO has become more popular, and it recently replaced CPB in the majority of centers.[57-61,73] This trend is based on several specific advantages that ECMO offers, including low or no anticoagulation, a closed circulation system without suction, and lower proinflammatory potential without breaching the air–blood interface. In contrast, the use of CPB requires full anticoagulation, acts through an open suction system with the potential to introduce bacteria into the circulation, and in general, has a greater proinflammatory potential.

20. The preferred intraoperative support system for lung transplantation is VA-ECMO (COR: 1, LOE: B-NR).

Although prospective randomized studies comparing CPB with ECMO are lacking, several retrospective reports have uniformly identified better outcome parameters for

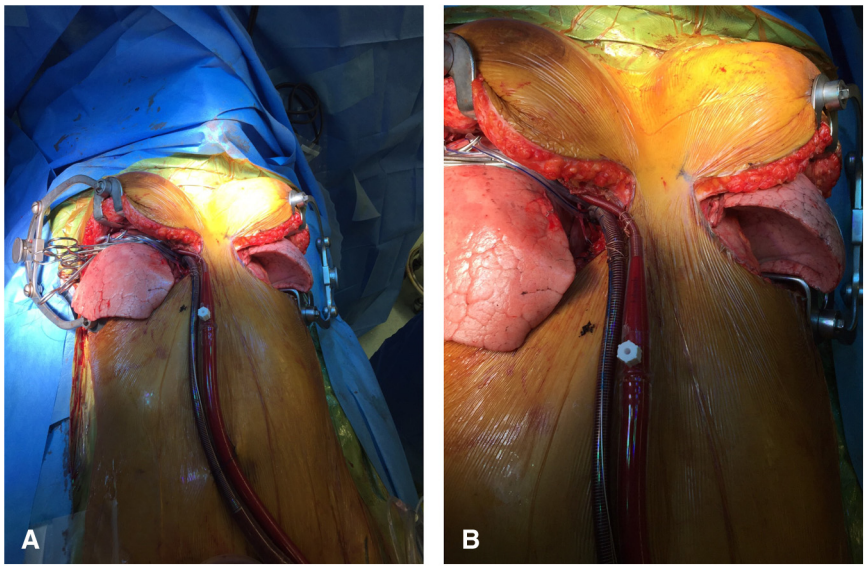


FIGURE 2. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) through right thoracotomy. A, Figure depicting the use of intraoperative mechanical support during cadaveric lobar lung transplantation in a 14-year-old girl with idiopathic pulmonary arterial hypertension performed at the University Hospitals Leuven, Belgium. Central VA-ECMO was installed at the start of the procedure with direct cannulation of the ascending aorta and right atrium through a sternal-sparing right anterior thoracotomy incision. B, Close-up picture of the cannulation site entering the chest in the fourth intercostal space next to the sternal bone.

ECMO. Ius and colleagues[59] compared 46 patients who underwent transplantation on ECMO with 46 patients who underwent transplantation on CPB and found a greater need for blood products, a higher incidence of PGD, as well as higher need for secondary ECLS implantation, all combined with overall poorer outcomes in the CPB group.

Similar inferior results for the CPB group were reported by Machuca and colleagues[57] in a matched cohort study. These findings were further confirmed by Biscotti and colleagues[61] in a retrospective study of 55 patients who underwent transplantation on CPB and 47 who did so on ECMO. In addition, Bermudez and colleagues[58] reported a greater need for reintubation, tracheostomy, and postoperative hemodialysis in 222 patients who underwent transplantation on CPB compared with 47 who did so on ECMO. Further confirmation of these findings was provided by DellÀmore and colleagues,[87] who compared 21 patients with pulmonary artery hypertension who underwent transplantation on ECMO and 17 who did so on CPB and found a higher incidence of renal impairment and greater degree of PGD in the CPB group but with lower in-hospital mortality in the ECMO group.[87] In pediatric lung transplantation, Parikh and colleagues[88] compared children supported intraoperatively on ECMO (n = 13) versus CPB (n = 22) and found that the ECMO group required fewer transfusions of fresh-frozen plasma, platelets, and red blood cells.

The sole available prospective one-arm study by Hoetzenecker and colleagues[72] looked at PGD rates at 72 hours in 159 consecutive patients who underwent transplantation on routine intraoperative VA-ECMO and reported an incidence of PGD3 of only 1.3% at 72 hours. Even though a prospective randomized trial on CPB versus ECMO is lacking, the available data suggest intraoperative VA-ECMO as the preferred intraoperative support system for lung transplantation.

Another difference between ECMO and CPB is that the latter allows for direct autotransfusion through a cardiotomy reservoir. Nevertheless, the use of intraoperative cell salvage devices along with reinfusion of the retained blood in the ECMO circuit before decannulation represent additional measures to decrease blood product use during lung transplantation.

21. Central cannulation is preferred over peripheral cannulation (COR: 2a, LOE: C-LD).

From a technical standpoint, cannulation for intraoperative ECMO can be performed centrally or peripherally. Central cannulation can provide excellent drainage of blood and cardiac decompression, whereas peripheral cannulation drainage can be more challenging in patients with low intravascular volume. Moreover, additional morbidities associated with peripheral cannulation—namely site infection, deep vein thrombosis, and limb ischemia—should not be underestimated.[80,87] For these reasons, central cannulation is preferred over peripheral.

Although significant advancements have been made in ECMO technology, certain complications remain inherent to its use. Catastrophic air embolism via the central atrial cannula is the one most feared and requires constant team

awareness. The use of an umbilical tape Rummel tourniquet around the atrial muscle at the cannulation site and bubble detector alarms are preventive measures.

22. Low or no heparin regimens are suggested for patients with significant adhesions and impaired coagulation status (COR: 2a, LOE: C-EO).

Although practice varies, most studies report a bolus of systemic unfractionated heparin ranging from 2000 to 5000 IU at cannulation, followed by maintenance of activated clotting time at 160 to 250 seconds or activated partial thromboplastin time at 1.5 to 2.0 times the control value.[11,57,58,60,61,80] Because heparin-coated tubes are used uniformly, additional systemic applications of heparin can be omitted if clinically necessary, as shown in a prospective study reported by the Vienna group.[72]

Going one step further, recent reports have described the intraoperative use of ECMO without therapeutic anticoagulation.[89,90] This is a particular advantage for patients with adhesions and impaired coagulation status, although that advantage must be balanced against the risk of catastrophic support failure if the circuit clots. Using a circuit without anticoagulation should be considered only in highly selected circumstances, with a clear recovery plan in place should the system fail.

23. For patients bridged to lung transplantation with VV-ECMO, an intraoperative switch to VA-ECMO is preferred (COR: 2a, LOE: C-EO).

A special situation arises whenever patients are bridged with VV-ECMO to lung transplantation. Whereas in such, cases VV-ECMO would guarantee sufficient intraoperative oxygenation, it has no effect on cardiac support or reperfusion injury of the first lung. VA-ECMO has the potential to reduce the cardiac output that otherwise goes through the first lung during implantation of the second lung, which provides optimal controlled reperfusion conditions. For this reason, conversion to VA-ECMO should be considered for patients who come bridged with VV-ECMO to transplantation.[72,91]

24. Use of CPB is recommended for lung transplantation combined with intracardiac repair (COR: 1, LOE: B-NR).

The only absolute exception to the use of VA-ECMO is the need for any concomitant intracardiac procedures.[92] In such a situation, CPB remains the recommended method of intraoperative support because of its additional possibility for use of a suction system with or without cardiac arrest. Another consideration is related to cases of anticipated massive blood loss. The potential benefit of CPB and the previously mentioned autotransfusion capacity must be weighed against the need for therapeutic anticoagulation and risk for coagulopathy.

SECTION 3A: WHICH PATIENTS SHOULD BE MAINTAINED ON MCS AFTER LUNG TRANSPLANTATION?

Once lung transplantation is performed under mechanical support, the question of weaning from MCS (timing and the procedure itself) is raised. Indeed, the use of ECMO during lung transplantation has changed the approach of many institutions because it facilitates the opportunity to prolong support after the surgical procedure.

Maintaining support after lung transplantation with ECMO provides several advantages during the early postoperative period. It secures immediate hemodynamic and respiratory stability. It allows progressive initiation of reverse cardiac remodeling in patients with pulmonary hypertension. It also avoids deterioration of dysfunctional implanted lungs necessitating emergent secondary ECMO for severe graft failure. On the other hand, it carries additional risks of bleeding, vascular access complications, infection, venous and/or arterial thrombosis, and pulmonary embolism because of cannulation and anticoagulation. Finally, when CPB is used during the operation, the surgeon will need to transition to a different mode of support.

There are currently 2 situations in which MCS is maintained at the end of the lung transplantation procedure:

1. The MCS weaning attempt fails because of graft dysfunction as determined by objective criteria, including hemodynamic and respiratory factors.
2. The patient is at high risk for severe PGD, and prophylactic MCS prolongation is chosen with the goal of improving the early postoperative phase.

ECMO has been proved efficient for the treatment of severe PGD.[93-98] Continuing ECMO when dysfunction occurs during the procedure has been determined to achieve good results despite the morbidity of prolonged ECMO runs. The decision for prolonged ECMO rather than weaning has been evaluated for selected patients at risk for developing early graft dysfunction.[73] These include patients with pulmonary hypertension, lobar lung transplantation, and interstitial lung disease with donor lung size discrepancy. In this population of patients, preemptive use of ECMO may achieve better survival results than on-demand emergent use.

25. When the indication for intraoperative ECMO is PGD, ECMO should be maintained post-transplantation until lung function recovers (COR: 1, LOE B-NR).

The effectiveness of ECMO in supportive care for most cases of severe PGD has been demonstrated by several retrospective, single-center studies.[93-98] Maintaining ECMO, or switching from CPB to ECMO at the end of the procedure when transplanted lungs are dysfunctional, allows progressive recovery of lung function and promotes satisfactory early survival. It also has been

shown that the earlier ECMO is instituted, the better the results.[99-103] The question of the type of ECMO (VA vs VV) remains debatable,[104] and neither technique has proven superior. VA-ECMO has the advantage of decreasing transpulmonary blood flow and supporting heart function, but it can lead to watershed phenomenon (harlequin syndrome) or graft ischemia if there is loss of pulsatility and absence of pulmonary arterial blood flow. VV-ECMO provides better oxygenation and avoids arterial access complications.[105,106]

26. If required, ECMO can be maintained post-transplantation regardless of cannulation approach (central or peripheral) (COR:1, LOE: B-NR).

Central or peripheral ECMO cannulation does not affect the ability to maintain ECMO after lung transplantation,[87,107] although the common complications associated differ with the 2 approaches. Central cannulation carries a risk of bleeding and contamination of the operative field. Peripheral cannulation carries risks of groin infection, lower limb ischemia, arterial stenosis, and venous thrombosis.[108]

27. Prophylactic post-transplantation ECMO maintenance may be indicated in patients with pulmonary hypertension to reduce the rate of PGD and improve early postoperative outcomes (COR: 1, LOE: B-NR).

Pulmonary hypertension is an independent risk factor for PGD after lung transplantation because it induces cardiac remodeling, including left heart diastolic dysfunction.[109] The first 72 hours are critical because lungs subjected to the ischemia-reperfusion process are sensitive to any elevation of left atrial pressure. Retrospective single-center studies have shown that VA-ECMO maintenance during the early phase of recovery from transplantation was associated with a decreased rate of PGD and improved early and long-term survival compared with delayed ECMO.[73,110,111] These retrospective single-center studies did not show a higher rate of bleeding complications; however, the survival benefit was balanced by vascular access complications and longer duration of mechanical ventilation and intensive care unit stay.[73] The optimal duration of ECMO support remains unknown but ranges between 3 and 8 days in the literature. There is no preference between awake and nonawake ECMO, as both modes have been used in published series. Further studies are needed to better determine when and how this "prophylactic" ECMO strategy should be applied.

28. Bridged patients should not automatically be maintained on ECMO after lung transplantation (COR: 2a, LOE: C-EO).

Bridging patients to lung transplant with pre-operative ECMO should not change the choice of maintaining ECMO at the end of the procedure. Although it is assumed that the decision of maintaining ECMO shares the same rules regardless of the need of pre-transplant ECMO, this issue has not been specifically addressed by clinical studies. Of interest, in a United Network of Organ Sharing (UNOS) registry study, pre-transplant ECMO was associated with a higher rate of post-transplant ECMO.[112] Despite this association, if graft function is good and the patient's hemodynamics are stable, ECMO should be weaned at the completion of the procedure, unless there are competing concerns.

29. There are clear situations with right ventricular dysfunction (for example, high pulmonary artery pressures) where patients should not be weaned off ECMO at the end of the transplantation (COR: 1, LOE: C-EO).

The principle of weaning ECMO at the end of transplantation for pulmonary hypertension relies on the calculation of the probability of developing severe PGD and/or early hemodynamic impairment. As stated previously, emergent on-demand use of ECMO has achieved poor early survival and should be avoided in this population of patients. The decision is based on multiple parameters, including hemodynamic parameters from a Swan-Ganz catheter, morphologic criteria from transesophageal echocardiography, and biological parameters (blood gases, lactic acid levels). The goal is to predict the reliability of the weaning for the next days. Decreased pulmonary artery pressures and adequate oxygenation have been shown to be useful parameters for determining when to wean from ECMO, with a published 98.5% rate of successful weaning.[73]

30. Early weaning from ECMO after transplantation may avoid complications (bleeding, infection, and vascular complications) (COR: 1, LOE: C-LD).

ECMO-related complications are correlated to its duration of use. Increased duration of use leads to vascular access complications, including infection and thrombosis, as well as oxygenator clotting and bleeding. The range of vascular access complications ranged between 10% and 17% according to peripheral ECMO follow-up publications.[108] There is no determined threshold, but the longer the support, the higher the rate of complication. Hence, the patient should be weaned from ECMO as quickly as feasible. Further studies are needed to balance this goal against the goal for achieving optimal left ventricular remodeling in patients with severe pulmonary hypertension.

SECTION 3B: WHAT IS THE OPTIMAL MECHANICAL SUPPORT FOR PGD AFTER LUNG TRANSPLANTATION?

It is well recognized that 1-year survival is compromised in patients with severe PGD following lung transplantation.[113] In addition to prolonged ventilatory and pharmacologic

support, ECMO as a BTR is an important adjunct to support patients with rapid onset of PGD who are not improving within the first 6 to 12 hours after lung transplantation.[94] Based on data from the UNOS Registry for 2015 and 2016, approximately 5% of all lung transplant recipients required ECMO support following transplantation.[112]

31. Mechanical support with ECMO is recommended immediately after lung transplantation in patients with severe cardiopulmonary instability. Peripheral cannulation is preferred over central cannulation (COR: 1, LOE: B-NR).

In patients with signs of severe cardiopulmonary instability on weaning from intraoperative extracorporeal life support (CPB or ECMO) at completion of the transplantation procedure, mechanical support with ECMO is recommended. Although intraoperative central ECMO via the right atrium and ascending aorta can be extended to the postoperative setting, most teams prefer to switch to peripheral cannulation to facilitate chest closure and reduce the risk of postoperative bleeding from the chest despite a greater risk of limb complications.[80,107] However, no prospective studies are available comparing outcomes after central versus peripheral ECMO in the post-transplantation period.

32. Early institution of ECMO is recommended in lung transplant recipients with clinical signs of severe PGD with a worsening trend in the first hours after lung transplantation, to allow allograft recovery while protecting from ventilator-induced injury (COR: 1, LOE: B-NR).

Although it is often considered a treatment option of last resort, several published reports describe good experiences with ECMO for PGD and early post-transplantation outcomes.[93,95,99,101-103,105,112,114] These studies indicated acceptable perioperative outcomes when ECMO was instituted in a timely fashion, whereas delayed initiation (>48 hours) has been associated with worse outcomes.[102] ECMO support allows the lungs to rest and recover protected from otherwise aggressive ventilation (peak inspiratory pressure >35 cm H_2O) and oxidative stress (fraction of inspired O_2 >60%) that can further aggravate lung injury.

Patients with PGD requiring ECMO have inferior but acceptable medium- and long-term survival compared with those no receiving ECMO.[98,104,105] Outcomes have improved over the years with advances in oxygenating technology and surgical techniques.[100]

33. In patients with post-transplantation PGD resulting in primarily respiratory failure (hypoxemia/hypercarbia) with otherwise stable hemodynamics and cardiac function, extracorporeal support with VV-ECMO is recommended over VA-ECMO because fewer procedure-related complications (hemorrhagic, vascular, neurological) can be expected (COR: 2b, LOE: C-LD).

VV-ECMO has been preferred over VA-ECMO for BTR in recipients with severe PGD, resulting in fewer late vascular complications.[108] Patients with PGD and severe hemodynamic compromise may require peripheral or central VA-ECMO, however.[80,107] Careful attention must be paid to avoid limb ischemia distal to the arterial outflow cannula, which potentially can obstruct the vessel. An antegrade leg perfusion cannula can mitigate this issue (Figure 3); however, vigilance is still required to perform regular arterial pulse checks with or without Doppler and/or oxygen saturation with pulse oximetry in the distal leg. Additionally, in patients on VA-ECMO, it is important to use partial flows to ensure flow pulsatility, which is needed to avoid stasis in the pulmonary circulation and allow for proper graft perfusion and recovery.

The group from Duke proposed using VV-ECMO in patients with PGD instead of a VA cannulation strategy because early right heart dysfunction with increased pulmonary artery pressure and pulmonary vascular resistance may recover with VV-ECMO following improved gas exchange. The controlled flow of oxygenated blood through the lungs maintained by VV-ECMO may facilitate recovery of the lung parenchyma and minimize hypoxic pulmonary vasoconstrictive response and risk of distal pulmonary

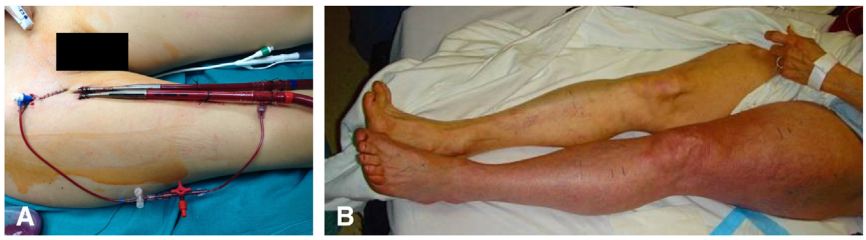


FIGURE 3. Anterograde perfusion with femoral cannulation. A, Antegrade distal limb perfusion catheter connected to the retrograde femoral arterial cannula via side Luer-Lok. B, Arterial insufficiency from retrograde femoral arterial cannula.

vasculature thrombus formation.[105] However, no prospective studies are available comparing outcomes after VV-ECMO with VA-ECMO in the post-transplantation setting.

34. Although the overall mortality is higher in lung transplant recipients with severe PGD requiring ECMO support compared to those without, the impact on long-term pulmonary function in survivors remains unclear (COR: 2b, LOE:C-LD).

Although some authors have reported on the impact of preoperative ECMO bridging to transplantation on long-term pulmonary function and graft survival,[11] the impact of postoperative ECMO BTR on allograft function has not been widely published. The Duke group reported considerably worse maximum allograft function in lung transplant recipients who required ECMO compared with those who did not (peak forced expiratory volume in 1 second, 58% in ECMO vs 83% in non-ECMO; $P < .001$).[96] Analyses of long-term outcomes from centers that have previously reported their experience with postoperative ECMO BTR are needed.

35. In patients on mechanical support for severe post-transplantation PGD with no functional improvement within the first 2 weeks, continued ECMO as a bridge to retransplantation is not recommended, given the low likelihood of a successful outcome after early retransplantation. A decision to list for urgent retransplantation can be made only on multidisciplinary consensus (COR: 3, LOE: B-NR).

Several case series on early retransplantation after initial lung transplantation have reported poor survival when the indication for the procedure is prolonged PGD compared with late retransplantation due to chronic lung allograft dysfunction or an intractable airway problem.[115-118]

The increased mortality after early retransplantation was validated previously in a retrospective analysis of the UNOS registry between May 2005 and December 2011. Of the 456 lung retransplantations identified during the study period, 64 were retransplantations performed within 90 days of the initial transplantation and the remainder were retransplantations performed after 90 days. Following a 1:1 propensity score matching, early retransplantation (within 90 days) was associated with a survival disadvantage compared with initial transplantation and late retransplantation (after 90 days). Factors conferring worse outcomes after retransplantation included intensive care unit admission, unilateral transplantation, poor functional status, and PGD as the indication for retransplantation.[119]

Listing for urgent retransplantation in cases of nonresolving PGD should always be discussed in a multidisciplinary setting. Candidates should be carefully selected in light of the ethical consideration of allocating a second lung to one individual with a decreased predicted survival while others await their first lung.

36. Transesophageal echocardiography is recommended in all recipients with severe post-transplantation PGD to exclude other causes of pulmonary graft edema and/or hypoxia, such as left ventricular dysfunction, the presence of intracardiac shunts, or anastomotic pulmonary vein stenosis or thrombosis (COR: 2a, LOE: C-LD).

Other causes of lung edema also may result in PGD, for example, left ventricular diastolic dysfunction, especially in those with pulmonary arterial hypertension with chronically underfilled left ventricle with low cardiac output caused by high pulmonary vascular resistance. Such a deconditioned left ventricle is not primed to handle "normal" preload in the early postoperative period.[109,120-123] In addition, stenosis or thrombosis of the pulmonary vein anastomosis may result in graft edema and infarction if not recognized and treated early (Figure 4).[124-126] Finally, hypoxia post-transplantation may be related to right-to-left shunting in patients with (unrecognized) intracardiac shunts, such as patent foramen ovale.[127]

Therefore, transesophageal echocardiography (TEE) is recommended in all recipients with refractory hypotension and unexplained hypoxia to exclude other causes. A comprehensive TEE exam allows detailed examination of the heart including valves, atrial septum, pulmonary veins, pulmonary arteries, and biventricular function.[128,129] TEE in the early postoperative period has become routine in many lung transplantation centers to obtain a baseline for future comparisons should problems arise in the early postoperative period.

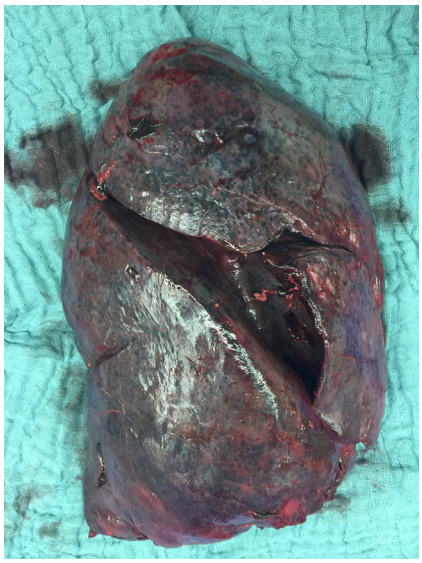


FIGURE 4. An infarcted pulmonary allograft secondary to thrombosis of the pulmonary venous anastomosis.

CONCLUSIONS

Lung transplantation is a challenging endeavor requiring a team of dedicated individuals to navigate a complex set of clinical situations. As with many aspects of medicine, insufficient data are available to provide clear answers about the optimal path for many of these situations. We convened a group of experts to systematically review the available literature on the use of MCS in lung transplantation and to determine recommended use criteria for MCS in the peritransplantation period. In this document, we present 36 recommendations along with associated evidence to support the recommendations. As the field continues to gain experience with this patient population and additional data become available for analysis, some of these recommendations may require revision. Until that time, we hope that this document will serve as a useful reference for practitioners navigating the complicated courses that lung transplantation patients can exhibit.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: http://www.aats.org/resources/1836.

Conflict of Interest Statement

The authors disclose relationships with industry and other entities in Appendix 1 and 2.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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Key Words: lung transplantation, ECMO, mechanical circulatory support, guidelines

Discussion

Presenter: Dr Matthew G. Hartwig

Dr Frank D'Ovidio (*New York, NY*). Matthew, thank you for providing the manuscript well in advance. This is a consensus document generated by a panel of world-recognized luminaries in the field. I have one potential conflicting question or comment. In an era where we are trying to switch from protocolized medicine to personalized precision medicine, should we be advocating for one-tool-fix-all? I am referring to the advocated intraoperative venoarterial extracorporeal membrane oxygenation (VA ECMO) support applied a priori to patients with pulmonary hypertension rather than a tailored approach according to the pathophysiology presented by each patient. For example, when addressing patients with secondary pulmonary hypertensions, which at times may respond to inhaled nitric oxide. Further, when the secondary pulmonary hypertension is a consequence of hypercapnic acidosis, which can be well managed by peripheral VV ECMO without the need of a central aortic cannulation or peripheral femoral artery cannulation.

Dr Matthew G. Hartwig *(Durham, NC)*. Thank you, Frank. I think that's a great question. These consensus documents I think are very difficult sometimes to develop, and sometimes the discussion can be quite contentious, as you can imagine, particularly with the lack of clear data. I think as people have an opportunity to go deeper into the manuscript once it's in publication and understand a lot of the conversation around each of the statements, a lot of that also will become clearer to them. But I definitely concur with your sense in general that we have a lot of options out there to support patients, and that patients have very particular reasons potentially for needing that support. So I think there are certainly going to be special cases that deviate from the relative norm and from certainly the idea that one consensus statement can fit all. I believe that the consensus document will allow for that flexibility so that surgeons can continue to provide the type of care and support that they feel is appropriate in each individual situation, absolutely.

Dr D'Ovidio. So along those lines, which were the more contentious statements that were difficult to come to an agreement?

Dr Hartwig. I think you could probably guess based on Dr McCurry's talk earlier, where some of that debate may

be. But I think there is still a lot of discussion around whether or not routine lung transplant truly benefits from any extracorporeal support whatsoever, and so that generated a lot of conversation. And then probably the other topic that people discussed the most (and certainly we got feedback on from the reviewers of the manuscript) was around the bridging of the COVID patients and the appropriateness of transplant in that patient population, particularly around timing of listing, timing of evaluation, and timing of transplant.

Dr D'Ovidio. And lastly, how frequently should we update these documents?

Dr Hartwig. That's a really good question. I think about this all the time, and as the theme for this year has been innovation and we know that this space—we've seen that innovation, and we can see it in the need to develop these statements. And I think this is going to be a document and a concept that we need to revisit quite frequently. And I don't know if it's 3 to 5 or so years, but this is definitely something that cannot sit on the shelf and not be reassessed in a regular fashion.

Dr D'Ovidio. Yeah, considering the rapidly evolving technology.

Dr Hartwig. Absolutely.

Dr D'Ovidio. Thank you.

Dr Hartwig. Thank you for your questions and comments.

Dr Usman Ahmad (*Cleveland, Ohio*). Thanks, Matt. Well presented, and congratulations on the work. I'd love to hear some discussion (and a lot of the panel members are in the room) around the use of our continuous use of VA-ECMO for idiopathic pulmonary hypertension patients. And if there is a strong sentiment about continuing support postoperatively, then should the arterial cannulation strategy be different in those patients so that the chest can be closed?

Dr Hartwig. That's also a very good question and not one that was I think addressed directly by any of the consensus documents. My personal opinion is for those patients who you know you're going to be—so if your strategy a priori is to leave the operating room on mechanical support, that certainly dictates how you would cannulate in the operating room.

Dr Walter Klepetko (*Vienna, Austria*). If I am allowed to answer your question with regard to transplanting patients with primary pulmonary hypertension on ECMO and potential postoperative prolongation, we have been setting up a protocol where we did this in every patient in the beginning. Later on, we realized that we're most likely overdoing it, and then we installed very clear criteria when to prolong postoperative ECMO. And these criteria do not differ for patients who have other indications or patients who have the indication of primary pulmonary hypertension. The outcome of this group is published, and it is excellent. So I think there is no need to prolong ECMO in PH patients, in every patient. You should do it only when there is a clear need for that and the criteria are available in the literature.

Dr Hartwig. I agree.

Dr Kenneth McCurry (*Cleveland, Ohio*). Indeed, Walter, that's an important point. If I may: Who in the audience, either in the case of idiopathic pulmonary arterial hypertension or in the case of IPF or secondary PH, who is putting in left atrial pressure lines and making decisions based on left atrial pressure lines whether to leave the patient on ECMO coming out of the operating room? No one? Everyone's seeing how the patient does and making a decision based on graft function before you leave the OR? That's what you do, Walter?

Dr Klepetko. Depends on pulmonary artery pressure, as well.

Dr McCurry. Yeah, that's what we do as well. Sounds like there's general consensus there.

APPENDIX 1. Author relationships with industry and other entities

Expert reviewer	Primary affiliation	Location	Have you received any support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.)? There is no time limit for this item	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/ or travel	Patents planned, issued or pending	Participation on a data safety monitoring board or advisory board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Matthew G. Hartwig, MD, Co-Chair	Duke University School	Durham, NC, USA		x		x	x						x		Transmedics, Paragonix, Biomedinnovations, Cystic Fibrosis Foundation, Qx Therapeutics
Victor van Berkel, MD, PhD, Co-Chair	University of Louisville School of Medicine	Louisville, KY, USA										x	x	x	Founder and board member of Breath Diagnostics, Inc.
Zachary Kon	Northwell Health	Manhasset, NY, USA				x	x	x		x			x		1) Moderna–Stocks, self 2) EConnect-1–Ownership interest, self 3) ProCure On-Demand–CEO/ ownership interest, self 4) Breethe/Abiomed–Consultant, self 5) Medtronic–Consultant, self
Kenneth R. McCurry, MD	Cleveland Clinic	Cleveland, Ohio, USA			x						x				XVIVO–commercial licensing agreement recently in place. Abiomed–payment for participation in advisory board.
Isabelle Opitz, MD FEBTS	Department of Thoraci	Zurich, Switzerland		x			x		x		x	x			Roche (Institutional Grant and Speakers Bureau), AstraZeneca (Advisory Board and Speakers Bureau), MSD (Advisory Board), Medtronic (Institutional Grant), Intuitive (Proctorship), SNF research council, Steering Committee IICT of SNSF; Chair Mesothelioma Group ETOP; Treasurer, President elect and Member Learning Affair Committee ESTS; Editorial Board ATS; Taskforce Mesothelioma, Staging Subcommittee MPM and N status for NSCLC IASLC; Board Member iMig;

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APPENDIX 1. Continued

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															Stiftungsrat Schulthessklinik.
Jasleen Kukreja, MD	University of California, San Francisco	San Francisco, CA, USA				x									Lung Bioengineering CareDx
Walter Klepetko MD	Medical University of V	Vienna, Austria													Nothing to disclose
Tiago N Machuca MD, PhD	University of Miami	Miami, FL, USA													Nothing to disclose
Konrad Hoetzenecker, MD PhD	Medical University Vie	Vienna, Austria				x									Medtronic
Olaf Mercier MD, PhD	Marie Lannelongue Hospital, Université Paris-Saclay	Le Plessis Robinson, France		x		x									Not related to lung transplantation (lung cancer and CTEPH) MSD for their CTEPH scientific group Astra Zeneca for consulting fees Edwards for clinical study PACEPORT
Michiel E. Erasmus, MD,PhD	University Medical Cen	Groningen, The Netherlands													Nothing to disclose
Hiroshi Date, MD	Kyoto University Graduate School of Medicine	Kyoto, Japan					x								Nothing to disclose
Dirk VAN RAEMDONCK, MD, PHD	University Hospitals Le	Leuven, Belgium													Nothing to disclose
Varun Puri, MD, MSCI	Washington University	St. Louis, MO	Academic time in the field of lung transplantation is supported by an NIH grant				x						x		PrecisCa, Intuitive Surgical

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APPENDIX 1. Continued

Expert reviewer	Primary affiliation	Location	Have you received any support for the present manuscript (e.g., funding, provision of study materials, medical writing, article processing charges, etc.)? There is no time limit for this item	Grants or contracts	Royalties or licenses	Consulting fees	Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events	Payment for expert testimony	Support for attending meetings and/ or travel	Patents planned, issued or pending	Participation on a data safety monitoring board or advisory board	Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid	Stock or stock options	Other financial or non-financial interests	All entities with whom the author may have the indicated relationships, and if payments were made to the author or institution.
Marcelo Cypel	Toronto General Hospi	Toronto, Ontario, Canada		x		x				x			x		Consultant to Lung Bioengineering, payment made to me Shareholder of Traferox technologies Inc.
Ankit Bharat, MD	Northwestern University	Chicago, IL, USA													

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Charles Hoopes MD, MPH	University of Alabama (Birmingham)	Birmingham, AL, USA							Nothing to disclose
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Jacob Klapper MD FACS	Duke University Medic	Durham, NC, USA							Nothing to disclose
Norihisa Shigemura, MD, PHD	Temple University Lewis Katz School of Medicine	Philadelphia, PA, USA							Nothing to disclose

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Errol L. Bush, MD	The Johns Hopkins Hos	Baltimore, MD, USA		x					VeraMedica Institute, LLC–medical-legal consulting related to environmental/occupational inhalation exposures.
Gabriel Loor	Baylor St Luke's Medical Center	Houston, TX, USA	x			x			Transmedics–grant support to my institution (BCM) for research related to EVLP Abiomed Breethe–grant support to my institution (BCM) for research related to Portable ECMO Synaptic Design–entitled to royalties for cardiac surgery simulator Medtronic–grant support to my institution (BCM) for research related to Heart Failure Atricure–grant support to my institution (BCM) for research related to cryothermy
Charles Hoopes, MD, MPH	University of Alabama	Birmingham, AL, USA							Nothing to disclose
Pablo G. Sanchez MD, PhD, FACS	University of Pittsburgh	Pittsburgh, PA, USA							Nothing to disclose