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MINIREVIEWS

Extracorporeal membrane oxygenation in lung transplantation: Indications, techniques and results

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Abstract

The use of extracorporeal membrane oxygenation (ECMO) in the field of lung transplantation has rapidly expanded over the past 30 years. It has become an important tool in an increasing number of specialized centers as a bridge to transplantation and in the intra-operative and/or post-operative setting. ECMO is an extremely versatile tool in the field of lung transplantation as it can be used and adapted in different configurations with several potential cannulation sites according to the specific need of the recipient. For example, patients who need to be bridged to lung transplantation often have hypercapnic respiratory failure that may preferably benefit from veno-venous (VV) ECMO or peripheral veno-arterial (VA) ECMO in the case of hemodynamic instability. Moreover, in an intra-operative setting, VV ECMO can be maintained or switched to a VA ECMO. The routine use of intra-operative ECMO and its eventual prolongation in the post-operative period has been widely investigated in recent years by several important lung transplantation centers in order to assess the graft function and its potential protective role on primary graft dysfunction and on ischemia-reperfusion injury. This review will assess the current evidence on the role of ECMO in the different phases of lung transplantation, while analyzing different studies on pre, intra- and post-operative utilization of this extracorporeal support.

Key Words: Lung transplantation; Extracorporeal membrane oxygenation; Bridge to transplantation; Support; Primary graft dysfunction; Ischemia-reperfusion injury

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Core Tip: Extracorporeal membrane oxygenation (ECMO) is the most used support in lung transplantation as it allows a complete spectrum of support (blood oxygenation, decarboxylation and cardiocirculatory support). Due to its versatility it can be used in a pre-operative setting (bridge to transplantation) and might be prolonged intra- and/or post-operatively. All these factors, in combination with a growing experience in its use in lung transplantation, usually in a multidisciplinary team, has resulted in good outcomes derived from several experiences reported in the literature by high-volume transplant centers. This paper aims to systematically review current evidence on pre, intra and post-operative ECMO in lung transplantation.

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INTRODUCTION

Lung transplantation (LTx) is an established option for patients with an end-stage lung disease unresponsive to any medical option. Despite some significant advances in medical therapy and in the organ allocation policy, such as the introduction of the lung allocation score (LAS) in 2005[1], the number of patients on the waiting list far exceeds the number of available organs, consequently the mortality remains high.

The LAS score effectively prioritized the candidacy of the sickest patient[2,3] and for this reason, in the past decades, there has been an increasing number of acute patients across transplant centers and a more frequent use of bridging support strategies, such as mechanical ventilation and extracorporeal membrane oxygenation (ECMO). Since then, in several transplantation centers, ECMO is routinely offered to patients with a rapidly declining end-stage disease as a bridging strategy to transplantation or, in the case of instability or inadequate graft function, as intra- and/or post-operative support. No randomized trials have ever been conducted to validate which one of these indications is the best; therefore, the preferred indication is for its utilization needs to be adapted on the single center's experience and on the patient's clinical conditions.

Recently, given the strong interaction between multidisciplinary teams and the increased experience in its use and in patient selection, ECMO is being extensively utilized in high-volume lung transplant centers[4] with good results[5,6].

Different configurations of ECMO, shown in Table 1, can be applied in LTx depending on the required support.

Veno-venous ECMO

Veno-venous (VV) ECMO is used in refractory respiratory failure and requires the placement of peripheral catheters. Usually, deoxygenated blood is drained from the femoral catheter and, after oxygenation, it is returned *via* the jugular vein. This configuration has no impact on cardiac function. In LTx, it can be used in patients, who do not present with significant hemodynamic compromise, with hypercapnic respiratory failure (low flow) or with significant hypoxia (full flow). This setting can be used as a bridge to LTx, especially in patients with end-stage pulmonary hypertension (PH), as it can increase right ventricular preload reducing the after-load and improving hematosis, and as a continuous support during transplantation. In a setting of bridging to lung transplant, the VV configuration is the most popular as it has several advantages compared to veno-arterial ECMO, for example, a lower rate of vascular and neurological complications. On the other hand, it provides only respiratory assistance without cardiac support (Figure 1A).

Veno-arterial ECMO

Veno-arterial (VA) ECMO is used for hemodynamic support with or without respiratory failure (Figure 1B). The cannulation can be performed centrally [drained from the right atrium and reinfused in the aorta (Figure 1C)] or peripherally (usually through femoral vessels). The use of bicaval venous cannulation has recently been described to configure a central VA ECMO in patients with severe cardiomegaly and

Table 1 Different ECMO configurations in lung transplantation

ECMO configuration	Cannulation	Support provided	Patient condition	Utilizazion in LTx
VV	Peripheral (double lumen cannula in the SVC *via* the jugular or subclavian vein or a single lumen cannula in the femoral vein or jugular and femoral veins)	Only respiratory	Hypoxemia	Bridge to transplantation; post-operative period
VA	Peripheral (femoral vessels; jugular/subclavian vein and subclavian artery) Central (from right atrium to aorta)	Respiratory + circulatory	Hypoxemia and cardiac failure	Bridge to transplantation; intra-operative; post-operative period
VVA	Same as VV ECMO + an additional cannula in the subclavian artery	Respiratory + circulatory	Severe right heart dysfunction with hypoxemia	Bridge to transplantation; intra-operative; post-operative period

VV: Veno-venous; VA: Veno-arterial; VVA: Veno-venous arterial; ECMO: Extracorporeal membrane oxygenation, LTx: Lung transplantation, SVC: Superior vena cava.

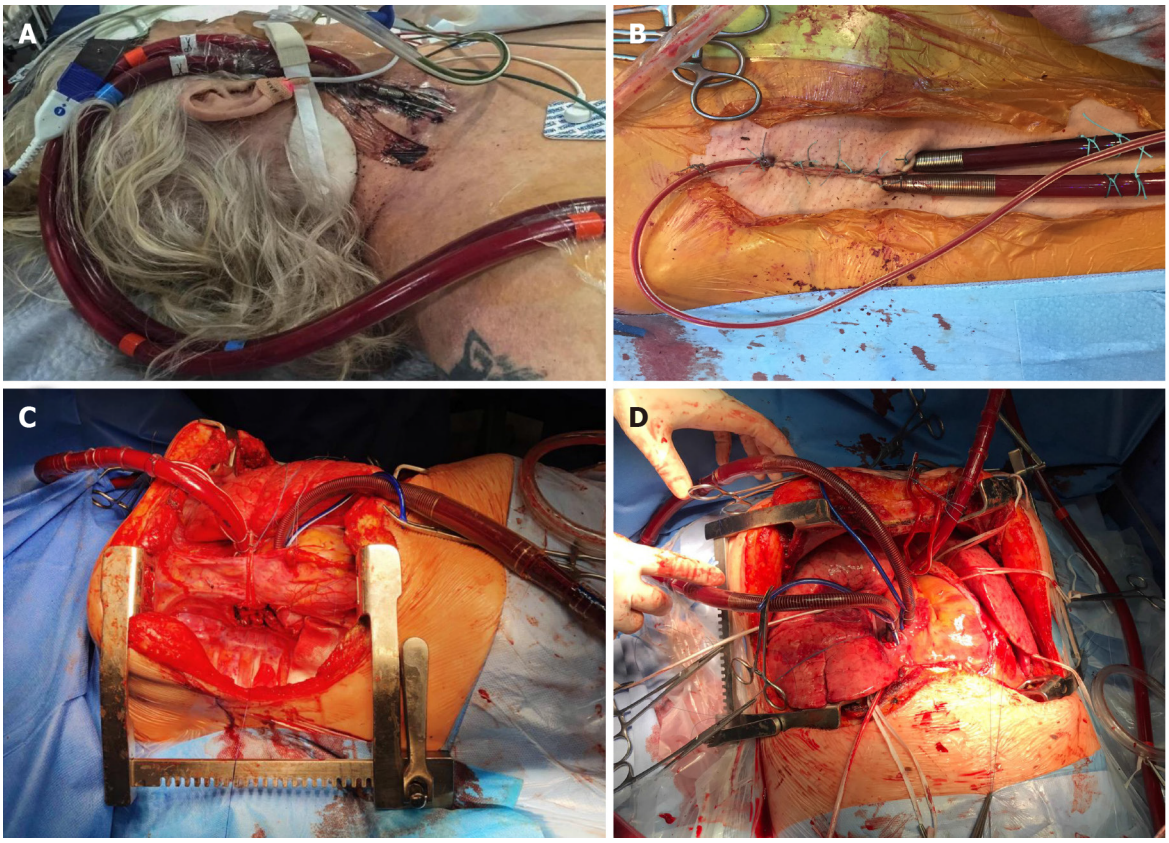

Figure 1 Different extra-corporeal membrane oxygenation configurations. A: Veno-venous extra-corporeal membrane oxygenation (ECMO) with jugular cannulation; B: Veno-arterial ECMO with peripheral cannulation, with the cannula for distal perfusion of the leg; C: Veno-arterial ECMO with central cannulation, the blood is drained from the right atrium and reinfused into the aorta; D: Central bicaval veno-arterial ECMO configuration.

pulmonary arterial hypertension in order to obtain optimal cardiac support and allow lung implantation without severe hemodynamic repercussions during cardiac manipulation (Figure 1D)[7]. Either central or peripheral VA ECMO can be used as intra LTx support, but the central setting has several advantages as it ensures a higher blood flow, by using a large inflow cannula with a large outflow cannula, avoiding peripheral ECMO-related issues (blood flow insufficiency, limb ischemia, vessel injury and groin infection). The peripheral VA configuration delivers oxygenated blood to the coronary arteries and brain *via* retrograde flow to the aortic arch. If left ventricular function improves, the retrograde flow will compete with the ventricular ejection; consequently, the coronary arteries and brain might be perfused with deoxygenated blood coming from the failing lungs and ejected from the left ventricle. On the other hand, peripheral ECMO is less invasive and it can be established under local anes-

thesia, it does not necessitate a clamshell incision and it can be maintained in the post-operative setting[8].

Veno-arterial-venous ECMO

Veno-arterial-venous (VAV) ECMO can also be used in LTx especially in the case of severe right heart dysfunction, providing both respiratory and circulatory support. In this support configuration, blood is drained from veins, oxygenated and returned to the right atrium and a central artery.

A variant of VAV configuration is the "sport model"[9]; it describes an optimal cannulation for VAV ECMO that uses a double lumen cannula VV ECMO configuration with additional oxygenation directly to the aortic arch. This technique allows cardiac and pulmonary resuscitation with a total gas exchange of perfused oxygenated blood to the proximal and distal aortic arch, and the weaning from VA and VV ECMO and ambulation in a setting of bridging to LTx[10].

Other devices used in LTx are:

Interventional Lung Assist Novalung (Novalung, GmbH, Hechingen, Germany): This is a low resistance lung assist device designed for a pulsatile blood flow with tight diffusion membranes and a protein matrix coating[11]. It does not require a pump assistance, as it is driven by cardiac output. In recent years, this device has been widely utilized as an effective bridge strategy to LTx in patients with ventilation-refractory hypercapnia[12-15].

Extracorporeal carbon dioxide removal: This is a sort of "respiratory dialysis"[7]. By using small percutaneous catheters, it is indicated to correct isolated hypercapnic failure in chronic obstructive pulmonary disease, cystic fibrosis (CF) or fibrosis exacerbations[16].

In this paper, we conduct a review to assess current evidence on the use of ECMO as a bridge to LTx, in the intra-operative setting and as post-operative support in the field of LTx.

ECMO AS A BRIDGE TO LTX

General considerations

The use of a mechanical pump-oxygenator to support a heart-LTx was first described by Webb and Howard at the end of 1950s and, between 1972 and 1977, many centers reported the use of extracorporeal oxygenators in patients who died awaiting LTx[17, 18]. In 1977, the first successful case of ECMO as a bridge to LTx was reported by Vieth who described a patient with post-trauma respiratory failure who underwent bilateral LTx[19]; unfortunately, the patient survived for only 10 d. In 1982, another case of ECMO as a bridge to LTx for 19 d was reported in a patient successfully bridged to a single LTx with short-term outcome in terms of survival[20].

The first successful use of ECMO as a bridge to LTx was published by Jurmann *et al* in 1991[21]: They described the use of VA ECMO in two patients who developed severe primary graft dysfunction (PGD) after LTx and who underwent re-transplantation with ECMO support.

The selection of patients who can benefit from ECMO as a bridge to LTx is a crucial aspect: Highly urgent patients, with a predicted high pre-transplant mortality, are often the ones who would benefit the most from ECMO support but, at the same time, they represent the patients, which are too critical to be considered appropriate for ECMO. The guidelines of the International Society of Heart and Lung Transplantation report that extracorporeal life support should be recommended in the case of young age, absence of multiorgan dysfunction and good rehabilitation potential. On the other hand, ECMO is not indicated in the case of septic shock, multiorgan dysfunction, heparin-induced thrombocytopenia, obesity, severe arterial occlusive disease, advanced age, underlying irreversible neurological or neuromuscolar disease[22].

Patients who can derive the greatest benefit from ECMO bridge are those with cardiopulmonary dysfunction severe enough to limit their ability to maintain the necessary physical conditioning to tolerate a transplant, and, in general, it is recommended in patients who have already been evaluated as appropriate candidates for LTx[23].

After a patient is considered suitable for an ECMO bridge strategy, the circuit can be configured in multiple ways (such as VA, VV or VVA) with peripheral or central access, depending on the disease and pathophysiology of the patient, in order to

provide the easiest management. It has to be taken into consideration that peripheral cannulation is the simplest approach to a bridge to LTx. For example, in patients affected by CF, a VV ECMO is usually sufficient to improve oxygenation and reduce blood concentration of CO_2, whereas in the case of idiopathic pulmonary arterial hypertension VA ECMO represents the best choice.

Current evidence on ECMO bridge

An analysis reported by the United Network for Organ Sharing (UNOS) demonstrated a significant increase in recent years in the use of ECMO at the time of LTx, compared to previous decades (1970-2010). This finding is a direct consequence of the greater use of ECMO in patients awaiting LTx[24,25]. A study by Mason *et al*[26] reported a negative experience with ECMO bridge to LTx showing a worse survival in patients with ECMO support compared to unsupported patients (50% *vs* 79%). In more recent years, different authors reported experiences with the ECMO bridge with good outcomes in terms of percentage of successfully bridged patients and with satisfying survival rates. The outcomes of ten major studies on this topic are reported in Table 2. We decided to collect the most recent studies (published from 2017 to 2020) to provide updated evidence. As reported in Table 2, the median duration of ECMO bridge ranged from 2 d[27] to 17 d[28], the most frequently used configuration was VV ECMO[26-34] and the majority of patients were successfully bridged to transplantation. Biscotti *et al*[29] reported the lowest percentage of successfully bridged patients; on the other hand, two studies[27,30] had a 100% success rate with the ECMO bridge to transplantation. Various authors, as expected, reported post-operative bleeding as the most frequent complication[28,29,32,34,35] in the bridged patients. The reported in-hospital mortality was acceptable in the majority of the studies, except for Yeo *et al* [28] who had an in-hospital mortality rate of 42%, but it has to be taken in consideration that the clinical conditions of patients supported with pre-transplant ECMO are usually more critical than those of the general population waiting for a LTx not supported by ECMO. This may have a negative influence on their post-operative outcomes, increasing in-hospital mortality. Recently, better results have been published following maintenance of ECMO support with the patient awake to allow adequate physiotherapy training and avoid muscle deconditioning secondary to general anesthesia and prolonged curarization[4,36].

With regard to long-term survival, all the studies reported a satisfying 1-year (ranging from 57.9%[28] to 100%[27]) and 3-year (from 63%[34] to 83%[31]) survival rate. The outcomes of the studies listed in the table are difficult to compare as they represent different realities among centers from all over the world. Furthermore, the decision to use ECMO as a bridge to transplant in a specific patient is center-dependent and the maintenance of a patient's candidacy to LTx while undergoing ECMO is also subject to institutional variation in risk assessment. Despite these considerations, the good outcomes reported lead us to consider ECMO a successful strategy as a bridge to LTx with the objective of improving the pre-operative condition of patients by enhancing physical strength and reducing cardiovascular complications[37].

Obviously, careful patient selection, center transplant volume and the multidisciplinary team are the key factors in obtaining improvement in outcomes of ECMO bridge. Further studies are needed to validate these results.

ECMO IN THE INTRA-OPERATIVE SETTING

General considerations

ECMO has been extensively used as a valid alternative to cardiopulmonary bypass (CPB) in LTx to provide hemodynamic and respiratory support during the surgical procedure. Different studies have compared ECMO to CPB demonstrating that ECMO resulted in fewer complications such as shorter duration of mechanical ventilation, shorter intensive care unit and hospital length of stay and reduced post-operative bleeding[38,39]. All patients who are bridged to transplant on ECMO usually remain on ECMO throughout the procedure. ECMO can also be used ex-novo during the surgical procedure in the case of hemodynamic instability and PH, which is associated with a higher risk of PGD, and may necessitate control over the pulmonary arterial pressure and lung reperfusion at the time of graft implantation[40]. Intra-operatively, VA ECMO is preferred over VV ECMO, as the latter does not ensure adequate cardiac output in patients with right ventricular dysfunction. Intra-operative VA ECMO support can be extended into the post-operative period or converted to VV ECMO in patients with good cardiac function for the management of PGD.

Table 2 Outcomes of the main studies on extracorporeal membrane oxygenation as a bridge to lung transplantation

Ref.	Number of patients	Median duration of ECMO	Mode of ECMO	Complications	Successful bridge (%)	In-hospital mortality	1-yr survival	3-yr survival
Tipograf *et al*[31], 2019	121	12 d	VV (52%) VA (43%) VAV (2.5%) RA-LA (1.6%) PA-LA (0.8%)	ECMO site 11% Renal 8.3% Vascular 12% Cardiac arrest 9.9% Cerebrovascular 12%	59%	9%	88%	83%
Biscotti *et al*[29], 2017	72	12 d	VV (62.5%) VA (31.9%) VAV (4.2%) PA-LA (1.4%)	ECMO site 15.2% Renal 8.3% Vascular 15.2% Cerebrovascular 5.5%	55.6%	7.5%	90.3%	NR
Hakim *et al*[32], 2018	30	8 d	VV (80%) VA (16.7%) VVA (3.3%)	Bleeding 33% Cardiac arrest 13% Cannula fracture 3% Thrombocytopenia 23% Needing paralytics 27%	87%	NR	85%	80%
Benazzo *et al*[33], 2019	120	5 d	VV 34% VA 30% iLA 21.7% VAV 0.8% Other 13.3%	Vascular 3.3% Cannula related 6.6% IDC 0.8%	80%	23.3%	69%	NR
Todd *et al*[27], 2017	12	2 d	VV 92% VA 8%	NR	100%	0%	100%	NR
Yeo *et al*[28], 2017	19	17.5 d	VV 79% VA 16% VAV 5%	Bleeding 26% Infections 10.5%	73.7%	42%	57.9%	NR
Ko *et al*[30], 2020	27	11 d	VV 89% VAV 7.4% VA 3.7%	Bleeding 46.7% Infections 26.7% Airway 13.3%	100%	25.9%	75%	70%
Hoetzenecker *et al*[34], 2018	71	10 d	VV 42.3% VA 9.9% PA-LA 12.7% Other 33.8%	Cerebrovascular 4.2% Renal 31.7% Bleeding 34.9%	88.7%	NR	70%	63%
Ius *et al*[35], 2018	87	9 d	VV 73% VA 37%	Bleeding 21% Renal 27%	78%	15%	79%	NR

						Vascular 10% Cerebrovascular 2% Atrial fibrillation 13%	

ECMO: Extracorporeal membrane oxygenation; VV: Veno-venous; VA: Veno-arterial; VAV: Veno-arterial-venous; PA-LA: Pulmonary artery-left atrium; RA-LA: Right atrium-left atrium; NR: Not reported; iLA: Interventional Lung Assist.

Various studies have recently proposed the routine use of intra-operative ECMO in LTx to allow controlled reperfusion and protective ventilation of the graft during transplantation, while reducing the ischemia-reperfusion injury and improving post-operative PGD rates[6,40-42]. On the other hand, we know that ECMO support can be associated with specific complications such as bleeding, reoperations, infections, and vascular damage that may affect post-operative results. Ius *et al*[4] suggested that, in order to minimize these complications, the identification of patients who really need intra-operative ECMO is necessary *a priori*. Moreover, the implantation of ECMO in urgent conditions (for example during or after a pneumonectomy) should be avoided.

Current evidence on intra-operative ECMO

During LTx, the implantation of ECMO is usually taken into consideration if there is worsening of cardiopulmonary conditions during the first or the second clamp of the pulmonary artery. Indications for intra-operative ECMO include a combination of the following conditions[4]: (1) Hypercapnia; (2) Low arterial saturation (< 90%); (3) Low cardiac index (< 2 L/min/m^2); and (4) Significant increase in pulmonary pressure. Between 2017 and 2020, five studies reported detailed outcomes on the use of ECMO during LTx (Table 3)[41,43-46]. Central (c) ECMO is commonly used in the intra-operative setting. Glorion *et al*[43] reported that almost half of patients (47.5%) were assisted with peripheral (p) ECMO. They compared 54 patients who had cECMO to 49 patients who had pECMO and reported similar results between the two groups in terms of in-hospital death, long-term survival rates and number of chest re-openings, even though the pECMO group included more bridged patients, who received an emergency transplant and who were supposed to be in a more critical condition. The study by the Vienna Group[6], conducted on a larger cohort of patients, reported a 100% rate of the usage of cECMO in the intra-operative setting with superior results in survival, when compared to transplantation without any extracorporeal support. When considering the utilization of intra-operative ECMO, as for the ECMO bridge, the most frequent complication reported is bleeding requiring surgical revision (from 12%[46] to 35% of patients[4]). For this reason, the Hannover group[4] suggested the administration of half-dose protamine to antagonize the heparin effect.

Ius *et al*[4] reported a higher prevalence of major complications, a significantly higher PGD 2-3 rate and a worst overall survival in the ECMO group than in the no ECMO patients; similarly Cosgun *et al*[44] concluded their study with the assumption that LTx with intraoperative ECMO support is associated with poorer outcomes. In contrast to these findings, the Italian group[43] reported comparable outcomes between the two groups, despite a higher need for intra-operative transfusion in the ECMO population. Similarly, the Vienna group[6] reported a significant superior survival in the ECMO group without a significant difference in PGD rate between the two groups, but it is well known that the current PGD classification does not perfectly reflect the real graft function, as it is primarily based on chest radiography which may have many confounders.

Another important concept is the prophylactic intra-operative utilization of ECMO, introduced by the Vienna group[6] in 2018: If the transplantation is performed without ECMO support, the first implanted lung will be exposed to the full cardiac output with possible damage[44], which may lead to a higher rate of PGD. In this context, prophylactic intra-operative ECMO may provide optimal reperfusion by diverting a significant proportion of the cardiac output away from the lung. This evidence was also supported by their recent study[41] in which they have postulated that the routine application of intra-operative ECMO in all the patients, regardless of respiratory and hemodynamic conditions, improved graft function.

These findings on the routine use of intra-operative ECMO in LTx provide important considerations, but other studies on this topic will be necessary to validate these preliminary results.

ECMO IN THE POST-OPERATIVE PERIOD

General considerations

At the end of the transplant procedure, especially if arterial blood gas analysis and pulmonary arterial pressure are not satisfactory, ECMO can be prolonged in the post-operative period. Post-operative prolongation of ECMO is mandatory in patients with PH and in patients with questionable graft function at the end of transplantation. In the post-operative setting, ECMO can also be implanted ex novo in the case of hemodynamic instability or inadequate graft function. PGD, a form of acute lung injury characterized by infiltrates on chest X ray and an impairment in blood gas exchange, is one of the leading causes of death in the early post-transplant course[47,48]. The use of ECMO during the post-operative period may reduce the PGD grade by supporting gas exchanges and pulmonary hemodynamics, while reducing ventilator-associated lung injury in acute distress syndrome. Moreover, it provides support for patients with refractory hypoxemia or right ventricular failure, caused by severe PGD, by facilitating the use of a lung protective ventilation strategy[49,50]. Two different studies have demonstrated that early implantation of secondary ECMO in the case of PGD provides better results than later implantation[49,51]. In addition to this, several groups have recently demonstrated that pulmonary edema occurring in PGD is mainly related to diastolic dysfunction of the left ventricle than to right ventricle stress[4,52-55]. This consideration suggests that the implantation of a secondary VA ECMO or the prolongation of ECMO (particularly in the case of PH) may lead to excellent results by allowing controlled filling and recovery of the left ventricle, preventing an acute increase in venous pressure hence reducing the reperfusion injury causing the PGD [56]. For this reason, particularly in this subgroup of patients, the use of ECMO in the post-operative setting may be considered a routine procedure[6].

Current evidence on post-operative ECMO

Studies on the use of post-operative ECMO and outcomes are presented in Table 4. Mulvihill *et al*[57], in their study on de-novo ECMO based on the UNOS registry, reported the utilization of post-transplant ECMO in 5.1% of cases. They found that ischemic time and pre-transplant ECMO were statistically associated with the need for post-operative ECMO 72 h after transplantation; this evidence supports a direct role of prolonged ischemic time in the pathogenesis of PGD, as reported by other studies[58-60]. Hoetzenecker *et al*[6] extensively investigated the concept of prophylactic post-operative ECMO prolongation, particularly in patients with PH and with questionable graft function (oxygen tesion/inspired oxygen fraction > 100, mean pulmonary arterial pressure/mean systemic arterial pressure < 2/3) at the end of the implantation. The prolongation of ECMO support showed excellent survival rates, giving a survival benefit both with and without the inclusion of primary pulmonary hypertension (PPH) patients in the study cohort. Furthermore, they reported that half of the patients treated with post-operative ECMO had a negative chest X-ray with near normal tidal volumes at low ventilation pressure: this interesting evidence offers some considerations on PGD grading. Indeed, based on the past definition of PGD made by ISHLT [61], a grade 3 PGD was automatically assigned to patients on ECMO. This definition was revised in 2016, and patients who were still on ECMO at that time were classified as PGD ungradable. The conclusions drawn in this study suggested that the real function of those lungs did not correspond to a classic PGD 3. These observations were corroborated by short mechanical ventilation duration both in PPH and in non-PPH patients associating the concept of prolonged prophylactic ECMO with excellent outcomes.

CONCLUSION

The utilization of ECMO in LTx has multiple applications as it allows extension of transplant indications while decreasing the mortality rate in critically ill patients on the waiting list, when used as a bridge to LTx. An interesting field of investigation is the role of intra- and post-operative ECMO in reducing reperfusion injury and PGD. This evidence is needed to extend the use of ECMO as a routine procedure in the intra- and post-operative setting for LTx. Several randomized trials, correlated by histopathological analysis, are required to validate these findings.

Table 3 Outcomes of the main studies on extracorporeal membrane oxygenation for intraoperative support during lung transplantation

Ref.	No. of patients	Type of ECMO	Complications	PGD rates	In hospital mortality	1-yr survival	3-yr survival
Glorion *et al*[43], 2018	103	pECMO 47.5% cECMO 52.5%	Rethoracotomy for bleeding 21.4% Chest infections 5.8% Deep vein thrombosis 18.4% Lower limb ischemia 6.8%	72 h grade 1-2: 70.8% 72 h grade 3: 33%	12.6%	82.4%	65%
Pettenuzzo *et al*[45], 2018	15	NR	Bleeding/surgical revision 26.6% Pulmonary thromboembolism 6.7% Cardiogenic shock 13.3% Cerebrovascular events 6.7% Sepsis with MOF 6.7% Deep vein thrombosis 26.7%	NR	13.3%	NR	NR
Hoetzenecker *et al*[6], 2018	343	cECMO 100%	Revision surgery 35% Leg ischemia 0.6% Thromboembolic events 1.4%	72 h grade 0: 87.5% 72 h grade 1: 5.4% 72 h grade 2: 3.9% 72 h grade 3: 3.3%	NR	91%	85%
Cosgun *et al*[44], 2017	134	NR	Lymphocele 10.4% Limb ischemia 0.7% Revision for hemothorax 12% Local bleeding 0.7% Local infection 0.7%	48 h or 72 h grade 2 or 3: 7.3%	NR	84.2%	60%
Ius *et al*[4], 2018	281	NR	Rethoracotomy for bleeding 17.8% Cerebrovascular events 1.8% Vascular complications 9.6%	24 h grade 2-3: 31.3% 48 h grade 2-3: 35.2% 72 h grade 2-3: 28.8%	NR	NR	74%
Hoetzenecker *et al*[41], 2020	159	cECMO 100%	Wound infections 8.2% Evacuation of hemothorax 8.2% Thromboembolic events 0% Local bleeding 0% Local infection 3.2%	Grade 0: 48.4% Grade 1: 4.4% Grade 2: 3.1% Grade 3: 2.5% Ungrad: 3.1%	NR	86%	NR
Dell'Amore *et al*[46], 2020	38	cECMO 76% CPB 24%	Evacuation of hemothorax 16% Acute renal failure 21% Pneumonia 29%	72 h grade 3: 16%	18%	76%	69%

ECMO: Extracorporeal membrane oxygenation; MOF: Multiorgan failure; NR: not reported; c: Central; p: Peripheral; Ungrad: Ungradable; CPB: Cardiopulmonary bypass; PGD: Primary graft dysfunction

Table 4 Outcomes of the main studies on prolonged or de novo secondary extracorporeal membrane oxygenation implant after lung transplantation

Ref.	Number of patients	Type of post-op ECMO	Median time from LTx to secondary ECMO	Weaning of second ECMO (%)
Mulvihill *et al*[57], 2017	107	De novo 100%	3 d	NR
Song *et al*[58], 2017	73	De novo 25%	26 d	50%
		Prolonged 75%		
Hoetzenecker *et al*[6], 2018	123	Prolonged 100%	/	/

ECMO: Extracorporeal membrane oxygenation; LTx: Lung transplantation.

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