REVIEW ARTICLE

Extracorporeal membrane oxygenation and lung transplantation

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Abstract

The use of extracorporeal membrane oxygenation has had a positive impact on the outcomes after lung transplantation. Extracorporeal membrane oxygenation has a role in all phases of lung transplantation—preoperative, intraoperative, and postoperative periods. It serves as a bridge to transplantation in appropriate patients awaiting lung transplantation. Extracorporeal membrane oxygenation is used as a preferred method of cardiopulmonary support in some centres during implantation; and, after lung transplantation, it can be used to salvage the implanted lung in cases of severe primary graft dysfunction or as a planned extension of intraoperative extracorporeal membrane oxygenation onto the postoperative period. It has now gained acceptance as a mandatory tool in most lung transplant units. This article reviews the history of extracorporeal membrane oxygenation and lung transplantation, their subsequent development, and the current use of extracorporeal membrane oxygenation during lung transplantation. Our institutional practice and experience are described. The implications of the current global coronavirus disease pandemic on extracorporeal membrane oxygenation and lung transplantation are also briefly discussed.

Keywords Extracorporeal membrane oxygenation · Lung transplantation · Bridge to lung transplantation · Mechanical ventilation · End-stage lung disease · Primary graft dysfunction

Introduction

Lung transplantation (LT) is now the accepted standard of care for end-stage lung disease (ESLD) in appropriate patients [1]. The International Society for Heart and Lung Transplantation (ISHLT) has issued consensus documents for appropriate recipient selection [2]. LT was first performed by Dr. James Hardy in 1963 [3]. Subsequent attempts at LT were fraught with complications particularly bronchial dehiscence and there were no long-term survivors [4]. In the years that followed, world over, there were 38 attempts at LT with dismal results and no long-term survivors. LT failed to gain popularity as an acceptable surgical therapy for nearly 2 decades until 1983, when Dr. Joel Cooper reported the first long-term survivor after single LT. The technique of LT and use of cardiopulmonary support has evolved over the period of years—as described by Dr. Joel Cooper in his "Herbert Sloan Lecture" [5]. Advancements in our understanding of immunology, rejection, development of newer and efficacious drugs, and modification of surgical techniques led to superior outcomes and gradual adoption of LT as an accepted therapy for ESLD in appropriate patients.

Extracorporeal membrane oxygenation (ECMO) is an extension of the cardiopulmonary bypass (CPB) device used by cardiac surgeons, since 1953, to provide heart and lung support during surgical procedures on the heart. CPB, which was used only in operating theatres, was brought with modifications for use by the bedside in the intensive care unit (ICU). The first such use of ECMO was described by Hill in 1971 to provide successful respiratory support in a young man with adult respiratory distress syndrome (ARDS) following trauma [6]. The first neonatal patient with successful ECMO for severe respiratory failure was reported in 1975 [7]. In the early days, good outcomes after ECMO were seen only in the neonatal and paediatric age groups [8], with poor outcomes in adult patients. The first randomised controlled trial (RCT) for the use of ECMO in ARDS concluded that, while ECMO improved gas exchange, there was no long-term survival benefit [9]. Hence, it was not until the RCT of conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) in 2006 [10] and the superior results of ECMO used during the 2009 H1N1 influenza outbreak (which established the superiority of ECMO in the treatment of adult ARDS) in 2009 [11]

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that ECMO gained widespread acceptance for use in adult patients also. The history and evolution of ECMO have been reported previously [12, 13].

The first report of ECMO being used to support a patient as a bridge prior to LT was reported in 1977 by Veith [14]. However, the initial results were poor—both short-term and long-term results, with many centres abandoning its use. Eventually, with improvements in outcomes, it is now accepted as an appropriate therapy in selected patients with good long-term survival. Intraoperatively, the choice of type of cardiopulmonary support—either CPB or ECMO—during LT has been studied extensively. Despite conflicting data, ECMO is now emerging as a preferred modality of intraoperative support when compared to conventional CPB [15]. However, further trials are needed before advocating ECMO as a standard of care for providing intraoperative support during LT [16, 17]. The use of ECMO to support a grafted lung with severe primary graft dysfunction (PGD) after LT was described even prior to its use as an intraoperative support. In fact, it was the reports of successful therapy of PGD with ECMO that prompted use of ECMO intraoperatively. Now, ECMO is an established and perhaps the only rescue therapy to salvage a graft affected by severe PGD.

Use of ECMO—preoperatively—as a bridge to transplant (BTT)

Traditionally, mechanical ventilation (MV) has been the mainstay of offering respiratory support. However, the outcomes following MV especially in patients with end-stage interstitial lung disease (ILD) is dismal and nearly always fatal, unless LT is offered. MV as BTT had poor short-term survival with 2-fold increase in mortality in the first 6 months [18].

Veno-venous (VV) ECMO by optimising gas exchange offers pulmonary support as a BTT—until such time an organ is available. The first report of ECMO as a BTT in 1977 resulted in early death. Subsequently, the Toronto Lung Transplant Group reported the use of ECMO as BTT in a case of Paraquat poisoning. Following graft failure on the right side, ECMO was used again, in the same patient, as a bridge to left lung transplant. While the graft function was good, the patient succumbed to trachea-innominate fistula 71 days after the second lung transplant [19].

Early reports of ECMO as BTT were not encouraging due to higher complications and inferior survival when compared to patients without BTT [20]. Reports of successful use of ECMO postoperatively after LT in rescuing graft failure led to increased adoption preoperatively as BTT. Due to advancements in technology, improvements in ECMO equipment, and multidisciplinary team approach, the outcomes of ECMO therapy improved and ECMO evolved into an accepted

modality of cardiopulmonary support in the ICU [21, 22]. Table 1 lists the recent case reports which were reported in the last 6 years (from 2015 to 2020) comparing patients with ECMO as BTT to patients without BTT [23–31].

As per the 2018 Annual Data Report for Lungs by Organ Procurement Transplant Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR), there was an increase in the number of LT and an increase in the use of ECMO as BTT in 2018 when compared to 2013 [32]. ECMO with or without MV was used in 163 patients (6.4%) in 2018 as compared to 93 patients (4.9%) in 2013. Also, the number of patients with MV as BTT decreased from 91 patients (4.7%) in 2013 to 41 patients (1.6%) in 2018 as shown in Table 2.

The indications for ECMO as a BTT include refractory hypoxia, hypercarbia, or right ventricular failure despite maximal therapy, and which are otherwise eligible for LT. In the presence of any evidence of non-candidacy for LT, other irreversible organ failure, malignancy, active sepsis, or any other relative contraindications [33], the decision for ECMO needs to be carefully reviewed by multidisciplinary team after discussions with the family to avoid "bridge to nowhere" [34].

Typically, BTT involves two different cohorts of patients. The first cohort consists of patients already on the waitlist for LT who may suddenly suffer an acute exacerbation or may have a gradual downhill course with severe respiratory insufficiency. Such patients will need respiratory support. The second cohort is another group of patients, who present for the first time with acute respiratory deterioration in the background of ESLD, but who have not yet been assessed for LT. These patients not only require full respiratory support, but also need assessment for candidacy for LT while being supported in the ICU.

Survival after ECMO as a BTT has been studied extensively. While some studies report superior or similar outcomes between "bridged" and "non-bridged" LT patients [35–37], Schechter et al. [30] reported inferior outcomes when ECMO is used as a BTT compared to LT patients who did not have any support prior to transplantation. Nonetheless, these patients are so critically ill that their outcomes without ECMO would have been fatal. The practice of ECMO as a BTT was found to be quite variable across transplant units in the USA [38]. Centre volumes, too, were reported to have an impact on survival with better outcomes in high-volume centres [39]. While the reported duration on ECMO averages around 20 days (Table 1), there are also reports of prolonged bridging for longer periods of time [40], some even as long as 125 days [41].

MV has been compared to ECMO as a BTT and avoidance of MV has shown to be beneficial. Extubating patients once ECMO is established and allowing spontaneous breathing— "awake ECMO"—has been shown to improve outcomes. The

Table 1 Case series comparing LT patients with ECMO as BTT and those without ECMO

Authors	Year	Total patients	LT without BTT N (%)	LT with BTT (ECMO ± MV) N (%)	Duration of ECMO support	Grade3 PGD BTT Group N (%)	Grade3 PGD No BTT Group N (%)	Survival comparison between BTT and no BTT group
Ko et al. [23] (Korean Registry)	2020	112	85 (75.9%)	27 (24.1%)	27d (10.5–40.5d)	1 (3.7%)	15 (17.6%)	No difference
Oh et al. [24]	2019	61	28 (45.9%)	33 (54.1%)	14d (IQR 9–19d)	NA	NA	No difference in 1-, 3-, 5-year survival
Hayanga et al. [25]	2018	826	729 (88.2%)	97 (11.8%) (49 ECMO 48 ECMO +MV)	14d	NA	NA	ECMO +MV had better survival than no BTT
Ius et al. [26]	2018	917	830 (90.5%)	68 (7.4%)	9d (5 to 16d)	28 (42%)	93 (11%)	No difference in 1- and 5-year survival. But higher hospital mortality in BTT
Hoetzenecker et al. [27]	2018	1111	1040 (93.6%)	63 (5.7%)	10d (0–95d)	29 (46%)	NA	BTT slightly inferior to no BTT BTT (retransplant) is poor (comparable)
Todd et al. [28]	2017	93	81 (87.1%)	12 (12.9%)	103.6 h (19–395 h)	4 (33%)	21 (25%)	1-year survival BTT: 100% and no BTT 91%
Lees et al. [29]	2016	NA	NA	11	14d (4–40d)	NA	NA	1-year survival 64% No comparison done
Schechter et al. [30] (UNOS Database)	2016	11,607	11,423 (98.4%)	184 (1.6%) (65 ECMO and 119 ECMO +MV)	NA	NA	NA	BTT inferior to no BTT ECMO alone better than MV or ECMO +MV
Inci et al. [31]	2015	186	160 (86%)	20 (10.7%)	21d (1–81d)	6 (23%)	25 (15%)	1 year: 68% vs 85% 2 year: 53% vs 79%

d, days; *h*, hours

deleterious effects of MV include VAP (ventilator-associated pneumonia) and VILI (ventilator-induced lung injury) which comprise of volutrauma (alveolar overdistention), biotrauma (inflammation), and atelectrauma [42]. These ill effects due to MV are avoided during "awake" ECMO strategy.

"Awake" ECMO was conceived as a concept and practised since 2008 [27]. Langer et al. have published an excellent

article on the pathophysiology of "awake" ECMO and its benefits [43]. In one of the largest series comparing "awake" ECMO and ECMO with MV, Schechter et al. [30] analysed 11,607 patients from the UNOS Database who underwent LT. Of these, 65 patients underwent BTT using ECMO alone and 119 patients underwent BTT using ECMO with MV. Among the "bridged" LT patients, survival was better with "awake"

Table 2 Number and percentage of LT patients with BTT and without BTT

Characteristic	Year				
	2013			2018	
	Number of LT	Percent of LT		Number of LT	Percent of LT
ECMO bridge to LT	61	3.2		79	3.1
MV bridge to LT	91	4.7		41	1.6
ECMO + MV bridge to LT	32	1.7		84	3.3
No bridge to LT	1732	90.4		2343	92
TOTAL	*1916*	*100*		*2547*	*100*

Data from OPTN/SRTR 2018 Annual Data Report [32]

OPTN Organ Procurement and Transplant network, *SRTR* Scientific Registry of Transplant Recipients, *LT* lung transplantation, *BTT* bridge to transplantation

ECMO patients compared to ECMO patients who were also ventilated (3-year survival 64% vs 45% respectively).

Ambulatory ECMO Ambulation of patients on ECMO is beneficial [44]. It can be labour intensive and needs meticulous multidisciplinary team approach. While patients with groin cannulation can also be safely mobilised, a single ECMO cannula in the neck with two lumens offers obvious advantages. Dual-lumen cannula (DLC) was first described in adults in 2009 [45],wherein a single cannula (with two lumens) is inserted via the right internal jugular vein (IJV) under image guidance. Such a cannulation will aid in mobilising patients once extubated, since the groin is free of cannula. Yanagida et al. [46] described a series of 15 patients who underwent BTT with ECMO using a single DLC via right IJV, thereby demonstrating the feasibility of BTT using DLC for ECMO support. Cannulation using DLC can, rarely, be associated with injury to the superior vena cava (SVC) [45], right atrium (RA), or right ventricle (RV) [47], and therefore requires cautious placement under fluoroscopy or transesophageal echocardiography. Should an escalation to veno-arterial (VA) ECMO be required with DLC, easy cannulation of axillary artery has been described, thereby allowing prompt ambulation with VA ECMO. Mangi et al. [48] described the use of the axillary artery and vein for cannulation in VA ECMO. Such a technique, which uses upper limb vessels, allows safe and relatively easy ambulation while awaiting LT.

Intraoperative use of ECMO in LT

LT operation is often performed without use of CPB or ECMO, if there is no hypoxemia, hypercarbia or haemodynamic instability. In cases of bilateral sequential LT, the newly implanted lung supports the body when the second lung implantation is in progress. Lung protective ventilatory strategies have been described to safeguard the newly implanted lung during bilateral sequential LT.

Conventionally, CPB has been used to provide support during instances of hypoxemia or haemodynamic instability during LT [49]. Use of CPB involves higher degree of anticoagulation with heparin, exposure to air fluid interface in the venous reservoir and deleterious consequences of systemic inflammation. Successful use of ECMO as a BTT and as a rescue therapy for PGD after LT, prompted the intraoperative use of ECMO during LT. Thus, the use of ECMO as an alternative to CPB, to provide haemodynamic support and gas exchange during LT, evolved gradually [50]. Table 3 lists the case studies comparing intraoperative ECMO with CPB during LT [51–57].

In 2007, Bittner et al. [56] reported worse outcomes with use of ECMO including higher incidence of bleeding, requirements of blood products, and infection. Aigner et al. [57], in a larger series of patients, compared intraoperative ECMO with CPB and reported superior outcomes with ECMO. They suggested that CPB could, perhaps, be replaced by ECMO. Ius et al. [55] described their experiences with intraoperative use of CPB and ECMO. From 2010, they have adopted the use of VA ECMO as routine practice during LT, whenever the need for extracorporeal support arises. Over a 3-year period, on comparing CPB (46 patients) with VA ECMO (46 patients), they reported superior outcomes with VA ECMO and justified their "routine" intraoperative use of VA ECMO, whenever needed.

In 2017, Hoechter et al. performed a meta-analysis [58], looking at 6 studies comparing the use of ECMO and CPB during LT. They reported that ECMO was beneficial in terms of lesser use of blood products, shorter duration of mechanical ventilation, and ICU stay. The 3-month and 1-year mortality rates in the ECMO group were less than the respective mortality rates in the CPB group; however, only the reduced ICU stay in the ECMO group was statistically significant. The authors, while suggesting that ECMO may be beneficial, concluded that larger multicentre randomised trials were needed to confirm that ECMO is better than CPB.

The advantages of intraoperative ECMO over intraoperative CPB include lesser anticoagulation with lesser bleeding and lesser requirements of blood products. Avoidance of blood products is beneficial to LT recipients. The incidence of PGD is also less in LT patients who received intraoperative ECMO support. In a recent observational study by Hoetzenecker et al. [15], an analysis of 159 patients, who had intraoperative ECMO support during LT, between November 2016 and July 2018 revealed low rates of PGD and they recommended use of ECMO as intraoperative support, whenever needed during LT. Furthermore, superior results in survival in patients with intraoperative ECMO, both short and long term, have been reported. All these factors have led to many units using ECMO as their preferred choice of extracorporeal support, whenever needed [15, 55].

Types of ECMO used intraoperatively

Most often, VA ECMO is used when both haemodynamic support and adequate gas exchange are needed during the operation, as in patients with idiopathic pulmonary artery hypertension (IPAH) or severe pulmonary hypertension (PH). VV ECMO, alone, has also been used during LT intraoperatively [52]. VV ECMO has lesser incidence of vascular and neurological complications. During intraoperative initiation of VA ECMO, central cannulation has obvious advantages and can provide full haemodynamic and gas exchange support. Patients who are bridged with peripheral cannulation may be operated while on peripheral ECMO, though at times conversion to central cannulation may be required.

Table 3 Case series comparing intraoperative ECMO and CPB during lung transplantation

Authors	Year	Groups compared	Total pts	No Support	ECMO	CPB	Postop MV	PGD at T72h	Survival/mortality	Comments
Zhang et al. [51]	2020	ECMO vs No ECMO	138	94	44		No		*1-, 3-, 12-month survival* ECMO 90.9%, 72.7%, 56.8% No ECMO 95.4%, 82.7%, 73.6%	Preop factors for ECMO: age, high PA, preop MV
Hashimoto et al. [52]	2018	VV ECMO vs VA ECMO	34		VV 20 VA 11	3			1-year survival VA 90%, VV 73.1% No difference	
Machuca et al. [53]	2015	ECMO vs CPB	99		33	66	3 days vs 7.5 days		90-day mortality ECMO 6% vs CPB 15%	ICU, Hosp stay, and blood requirement less for ECMO
Biscotti et al. [54]	2014	ECMO vs CPB	102		47	55		ECMO 26 (56.5%) CPB 42 (76.4%)	No survival difference in 30 days or 1 year	ECMO required less transfusions and bleeding
Ius et al. [55]	2012	ECMO vs CPB	92		46	46			3-, 9-, 12-month survival CPB 70.59.56% vs ECMO 87,81,81%	ECMO less PRC, platelet intraop
Bittner et al. [56]	2007	ECMO vs CPB	47		8	7			Increased infections and mortality in ECMO	Higher blood product use in ECMO
Aigner et al. [57]	2007	ECMO vs CPB vs No Support	149		130	27			3-month, 1-year, 3-year survival ECMO 85.4%, 74.2%, 67.6% No ECMO 93.5%, 91.9%, 86.5% CPB 74%, 65.9%, 57.7%	ECMO is a valuable tool and can replace CPB

Some units have a planned policy of extending intra-operative ECMO onto the postoperative period [59]. In such cases, after the LT, the central VA cannulae are clamped and cut; the cut ends are connected to keep the ECMO circuit running and to be used in a subsequent peripheral configuration. After chest closure, peripheral ECMO is established by percutaneous cannulation of fem-oral artery and vein. Additional distal perfusion cannula is placed in the femoral artery.

Postoperative use of ECMO

The use of ECMO postoperatively, after LT, can be discussed under 2 heads:

(i) Instances where there is development of severe PGD and ECMO is used as a rescue therapy to salvage the graft.

(ii) Instances where there is planned continuation of intraop-erative ECMO into the postoperative period for varying periods, as in cases of recipients with IPAH.

Postoperative ECMO as a rescue therapy

After LT, the need for ECMO most commonly arises when severe PGD, not responding to any conventional measures, occurs. PGD refers to the condition with severe hypoxemia and radiological changes which usually occurs within 72 h after LT. Based on severity, PGD can be graded from grade 0 up to grade 3 as depicted in Table 4. The ISHLT has issued guidelines and consensus guidelines on definition and grading of PGD [60]. ECMO is now a recognised therapy for severe PGD. The report from the ISHLT Working Group for treat-ment of PGD [61] suggests that the best results are obtained when ECMO is initiated within 24 h of onset of severe PGD and recommends early institution of ECMO for grade 3 PGD. Table 5 lists the studies which compared post-LT patients with ECMO to post-LT patients without ECMO [62–67].

There has been an increase in the use of post-LT rescue ECMO over the years. The earlier studies, from 2000 to 2005 [65–67], reported use of postoperative ECMO in only 2 to 4% of patients, while the more recent studies reported higher use of postoperative ECMO in 5.8 to 13% of patients [62–64]. The

Table 4 The 2016 definition of primary graft dysfunction [60]

PGD grade	Pulmonary oedema on chest X-ray	PaO$_2$/FiO$_2$ ratio
Grade 0	No	Any
Grade 1	Yes	> 300
Grade 2	Yes	200–300
Grade 3	Yes	< 200

PaO$_2$ partial pressure of oxygen in arterial blood gas analysis, FiO$_2$ fraction of inspired oxygen concentration

survival after postoperative rescue ECMO in various studies is also tabulated in Table 5. The most recent study by Boffini et al. [62] reported an inferior overall survival after postoperative ECMO at 40% after 1 year and 30% after 5 years. However, when the data was analysed based on 3-month conditional survival, there were no differences in the 1- and 5-year survival rates (78% and 50% vs 80% and 60%) respectively between patients needing and not needing postoperative ECMO. Given the fact that patients suffering from severe PGD are a high-risk group with no chance for survival without ECMO, these survival rates justify the use of postoperative ECMO as a rescue therapy for grade 3 PGD. Hartwig et al. [63] reported similar survival rates, but pointed out that the graft function in the postoperative ECMO group was suboptimal with peak forced expiratory volume at 1 s (FEV1) being 58% and 83% in the ECMO and non-ECMO group respectively. The freedom from bronchiolitis obliterans syndrome (BOS) was an impressive 88% at 3 years.

Bermudez et al. [64] reported lower 1- and 5-year survival rates after postoperative ECMO (59% and 33%) compared to non-ECMO group (82% and 54%). However, among the postoperative ECMO patients, they found no difference in survival between VA and VV ECMO patients. Also, although 67% of the postoperative ECMO group were successfully weaned off ECMO, their long-term survival was inferior. In contrast to this study, Hartwig et al. [65] reported better outcomes with fewer complications in VV ECMO group compared to VA ECMO.

"Planned" continuation of intraoperative ECMO into postoperative period

In 2010, the Hannover Group [68] hypothesised that in cases of long-standing severe PH, the left ventricle (LV) is small and chronically underfilled with significantly reduced preload due to high pulmonary vascular resistance (PVR); and when the LV is suddenly exposed to normal preload due to sudden reduction in PVR in the newly transplanted lungs, it is unable to handle the sudden increase in LV preload. They, therefore, believed that a period of postoperative VA ECMO could provide time to allow adaptation of the LV to the new loading conditions. They analysed 53 patients with severe PH who underwent LT. Of these, 23 patients had intraoperative ECMO prolonged to the postoperative period for 5 days to allow the LV to adapt to the new loading conditions and

Table 5 Case series comparing postop ECMO and non-postop ECMO groups in LT patients

Authors	Year	Groups compared	Total LT patients	Postop ECMO	Survival	Comments
Boffini et al. [62]	2019	Postop ECMO vs non-postop ECMO	195	25	1-, 5-year survival ECMO 40%, 30% vs no ECMO 80, 60% On conditional 3-month survival, 1-,5-year survival ECMO 78, 58 vs no ECMO 80, 60	More transfusion, hospital stay
Hartwig et al. [63]	2012	Postop ECMO vs non-postop ECMO (for PGD)	498	28	30-dday, 1-year, 5-year survival ECMO 82%, 64%, 49% No ECMO 97%, 82%, 67%	Freedom from BOS at 3 years 88%, but peak FEV1was 58% in ECMO vs 83% in non-ECMO
Bermudez et al. [64]	2009	Postop ECMO vs non-postop ECMO (for PGD)	763	58	1-year, 5-year survival Postop ECMO 59%, 33% (VA and VV similar) Non-postop ECMO 82%, 54%	Although 67% of ECMO weaned off, long-term survival patients requiring ECMO was inferior
Hartwig et al. [65]	2005		522	23 VA −15 VV- 8	VV ECMO survival similar to no ECMO group	VV ECMO better than VA ECMO—better outcomes and fewer complications
Oto et al. [66]	2004	Early group (1990–1999) Recent group (2000–2003)	481	10	Early group ECMO initiated late— 4/4 all died; Recent group ECMO on 0–2 days— 3/6 discharged, 1 alive at 1 year	
Meyers et al. [67]	2000		444	12	4 not weaned and died. 8 weaned— out of which 1 died	

increased preload. The survival rates at 3 and 12 months were 100% and 96% respectively in the intraoperative and postoperative ECMO group compared to only 85% and 75% respectively in the group without postoperative ECMO.

In 2017, the same group [69] published mid-term results of planned ECMO extending onto postoperative period in 38 patients with severe PH. The 3-month and 1- and 5-year survival rates of the "planned" postoperative ECMO group of patients were no different from that of other LT patients without severe PH. Moreover, all the patients had excellent cardiac function, with disappearance of tricuspid regurgitation (TR) and improvements in LV dimensions 1 year after the LT. Other authors [59] [70] have also described similar survival figures.

Dell'Amore et al. [71] reported in 2020 their analysis of 38 patients who underwent LT and who had peripheral VA ECMO as a planned prolongation of ECMO into the postoperative period. They described lower incidence of PGD and improved survival in the postoperatively ECMO supported patients. Table 6 lists case series of patients with planned postoperatively extended intraoperative ECMO [59, 68–71].

Sites of cannulation for postoperative ECMO

For both types of postoperative ECMO—rescue ECMO and intraoperative ECMO extended postoperatively—the preferred cannulation site, in most units, is the groin. In case of extension of intraoperative ECMO, peripheral VA ECMO is established in the groin, thus enabling chest closure after LT. Distal arterial perfusion cannula is sited to reduce ischaemic complications of the leg. In cases of rescue ECMO, peripheral ECMO is initiated in the ICU

setting. While peripheral cannulation can be easily done, one should be mindful of its possible complications [72]—such as vascular injury, wrong vessel cannulation (artery for vein), or Harlequin syndrome.

Harlequin syndrome (differential oxygenation) occurs during peripheral VA ECMO [73] when lung function is extremely poor and deoxygenated blood from the lung is ejected by the LV. Simultaneously, the oxygenated blood from the ECMO pump retrogradely returns through the femoral artery and the site of mixing of oxygenated and deoxygenated blood may be variable. The mixing most often occurs at the descending aorta, resulting in deoxygenated blood being delivered to the coronaries and carotid. Conversion to veno-arterio-venous (VAV) configuration, which is achieved with an additional return cannula to the SVC or RA, may improve oxygenation to the upper body. Further modifications of VAV ECMO, by incorporating a second pump—"the slave pump"—has been described to regulate flow into the SVC [74]. Intravenous esmolol therapy has also been reported to help in Harlequin syndrome, by reducing the cardiac output and preventing the LV from ejecting a lot of deoxygenated blood [75].

Our institutional experience and practice

Preoperative ECMO as a BTT

We have instituted ECMO as BTT in 9 patients (8 patients had VV ECMO and 1 patient had VA ECMO). Of these, 4 patients underwent LT successfully and were weaned off ECMO in the

Table 6 Case series of patients with planned postoperatively extended intraoperative ECMO

Author	Year	Groups Compared	PGD3 at T72	Survival
Dell'Amore et al. [71]	2020	In IPAH recipients CPB (9) CPB + Postop ECMO (8) Intraop ECMO (14) Intra + postop ECMO (7)	Reduced incidence of PGD in postop ECMO supported patients	Improved survival in patients with postop ECMO in both patients supported by ECMO and CPB intra-operatively
Hoetzenecker et al. [59]	2018	No ECMO (116) vs Intraop ECMO (346) vs Intra+ postop ECMO (123)		1-, 3-, 5-year survival No ECMO 82%, 76%, 74% Intraop ECMO 91%, 85%, 80% Intra + postop ECMO 84%, 81%, 76%
Moser et al. [70]	2018	Intraop ECMO vs Intra +Postop ECMO		1-, 3-, 5-year survival Intraop ECMO 77.4%, 77.4%, 77.4% Intra + postop ECMO 90.2%, 87.4%, 87.4%
Salman et al. [69]	2017	IPAH recipients (38) (Intraop + postop ECMO) vs all other recipients	IPAH 15(39%) Vs Other LT 85(13%)	3-month, 1-year, 5-year survival same in both groups. Excellent heart function 1 year—TR disappeared in all with increase in LV dimensions
Tudorache et al. [68]	2015	Severe PH pts Intraop ECMO vs Intra +Postop ECMO		3 and 12 months: intraop + postop ECMO 100% and 96% vs no postop ECMO 85% and75% resp

operating theatre itself. Two of these patients recovered fully and are doing well 2 years after LT. Among the remaining 2 patients, currently, one patient is now slowly recovering from critical illness myopathy, having excellent graft function. The other patient had preoperative ECMO as BTT required postoperative VV ECMO for severe PGD after LT and is currently recovering in the ICU.

Of the 5 patients on ECMO awaiting LT, 2 patients died 8 and 10 days after ECMO, due to sepsis, before an organ was available. The remaining 3 patients are still supported by ECMO, of which two patients are extubated and ambulant on VV ECMO; and one patient required escalation to VA ECMO due to haemodynamic instability resulting from worsening right heart failure.

Intraoperative ECMO

Intraoperatively, since 2017, our practice has been to use central VA ECMO routinely for bilateral LT, keeping activated clotting time (ACT) around 160 to 180. In case of single LT, if the patient tolerates single-lung ventilation and trial clamping of the pulmonary artery, we proceed with the operation without extracorporeal support. We have performed 47 double lung transplants, 7 single lung transplants, and 27 combined heart and lung transplants. During assembly, a previously heparinised venous reservoir is incorporated as a safety precaution but is excluded from the ECMO circuit by double tubing clamps. This method is to enable quick conversion of ECMO to CPB should the need arise. In case of major bleed or haemodynamic instability, it is just a simple matter of releasing the tubing clamps to convert into cardiopulmonary bypass circuit. After the situation has been dealt with, the venous reservoir can again be excluded by tubing clamps—reverting to a VA-ECMO configuration again—allowing the ACT to drift down again.

Postoperative ECMO as a rescue therapy

We have instituted ECMO in 7 patients who developed grade 3 PGD. Out of these 7 patients, 1 patient required institution of ECMO in the operation theatre itself, while the remaining 6 patients had ECMO instituted in the ICU. All patients had peripheral VV ECMO and 1 patient required subsequent escalation to VA ECMO. Of the 7 patients on postop ECMO, 2 patients did not recover and died. The remaining 5 patients were weaned off ECMO and eventually discharged.

Impact of COVID on ECMO and LT

The current global pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has an ongoing, significant impact worldwide. It causes acute hypoxemic respiratory failure in a subset of patients with high mortality. Initial reports of ECMO in this population reported high mortality. A recent article by Barbaro et al. [76] looked at the outcomes of ECMO in COVID-19 in an international cohort of patients from the Extracorporeal Life Support Organisation (ELSO) registry. Out of 1035 patients in 213 hospitals across 36 countries, the 90-day mortality after ECMO initiation was 38%.

A proportion of patients who recover from acute respiratory failure have residual sequelae with progressive decline in lung function who may eventually be candidates for LT. The challenges for solid organ transplant during this COVID-19 are considerable ranging from a drop in the deceased organ donation rates and a rise in the number of offered organs being declined to acute shortages in healthcare delivery [77]. The resultant increase in waiting times has led to worsening of clinical condition of the recipients, which in turn has led to increase in need for ECMO as BTT. LT recipients form a vulnerable group for contracting COVID-19 and there have been anecdotal reports of COVID-19 infections in LT recipients [78].

There has been anecdotal reports of LT performed for respiratory failure due to COVID-19 in medical journals [79, 80], and social and print media. A balanced view is needed while offering LT to such patients, taking care to ensure that organs are used in appropriate cases; so that organ allocation is fair for everyone on the wait list for LT—both COVID and non-COVID patients. Cypel and Keshavjee [81] elaborated on ten valid points to be considered while deciding on candidacy for LT in post-COVID patients.

Conclusion

This review has shown that there is adequate evidence for the role of ECMO in LT as BTT and postoperative rescue therapy. The jury is still out as far as the intraoperative use of ECMO is concerned. While a few centres have adopted ECMO over CPB as their preferred choice for intraoperative extracorporeal support, larger randomised studies are required to confirm the superiority of ECMO over CPB for intraoperative extracorporeal support, whenever needed.

Compliance with ethical standards

Consent for publication   Not applicable.

Code availability   Not applicable.

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