Chapter 9

Extracorporeal Membrane Oxygenation During Lung Transplantation

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Additional information is available at the end of the chapter

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Abstract

Lung transplantation is increasing as a widely accepted surgical treatment for certain type of end-stage lung disease. Recent technical improvements in extracorporeal membrane oxygenation (ECMO) have been able to expand the role of ECMO during lung transplantation. The evolution of oxygenators, introduction of the new-type pump and tube, and improvement of percutaneous cannulation including dual lumen single catheter resulted in the technical renaissance of ECMO for lung transplantation. Now, beyond the traditional support for patients with severe primary graft dysfunction, ECMO can be established as essential perioperative roles for patients undergoing lung transplantation, such as preoperative lung protective support as a bridge to transplantation, replacement cardiopulmonary bypass during intraoperative support, and rescue of various life-threatening situations after post-transplant. After all, ECMO will be a fundamental, life-saving modality for patients during lung transplantation.

Keywords: Perioperative procedures, lung transplantation, Perioperative procedures, Ventilator-induced lung injury, Intensive care unit

1. Introduction

Recent expanded role of extracorporeal membrane oxygenation (ECMO) is switching the paradigm of organ transplantation, especially in the lung. Traditionally, the role of ECMO in the area of lung transplantation was focused in supporting patients with severe primary graft dysfunction (PGD) after post-transplant; however, as the technical ECMO environments such as new type of pump, oxygenator, catheter and tubing are improving, ECMO is now applied to the whole process of lung transplantation, from "bridge-to-transplant" to "rescue post-transplant" [1, 2].

The prevalence of lung transplantation has also increased over several decades especially in the specific end-stage lung diseases, such as cystic fibrosis, interstitial lung disease, and chronic obstructive lung disease. Contrary to successful early survival rate, the long-term survival rate of lung transplantation has still seen modest improvement. In addition, the mortality of patients on the waiting list is also concerning, consequently the interest in looking for alternative strategies for patients with end-stage lung disease who wait lung transplantation has risen considerably.

Mechanical ventilation has been applied to support the failing lung in peritransplant patients; however, per se can aggravate respiratory failure and hemodynamic instability by increasing the risk of ventilator-associated pneumonia and ventilator-induced lung injury [3]. Traditionally, mechanically ventilated pretransplant patients have been reported to have higher post-transplant mortality rates than nonventilated patients [4].

At this point, ECMO can be considered an alternative bridging strategy in lung transplantation, and now despite the complexity and side effects, the use of ECMO during lung transplantation has risen by 150% in the recent last 2 years compared to the previous decades (1970–2010; **Figure 1**). Besides the increase of amount, the characteristics of using ECMO are also evolving (**Table 1**) [5].

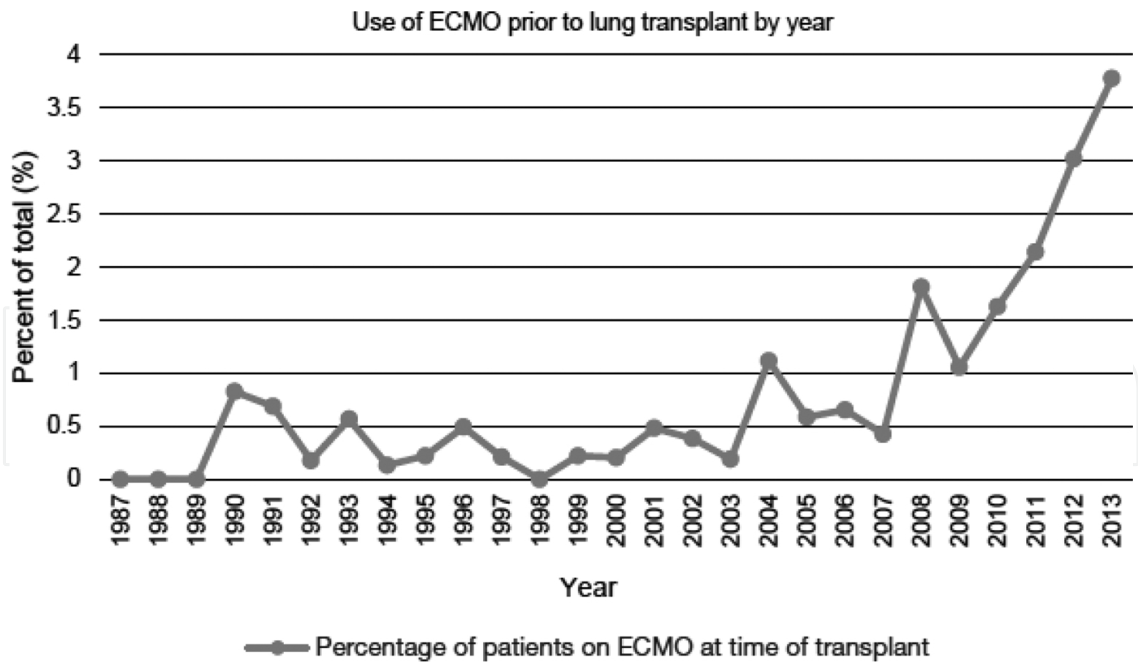

Figure 1. Percentage of patients on ECMO at the time of transplant by year. Data obtained from the United Network for Organ Sharing (UNOS) database 1987–2013. Adapted with permission from [1], © 2014 Gulack et al. Published under AME Publishing Company. DOI: 10.3978/j.issn.2072-1439.2014.06.04. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher AME Publishing Company.

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	1970s	1980s	1990–2000	2000–2010	2010–June 2011
Patients listed for lung transplantation on ECMO	1	1	22	104	58
Modes of ECLS used	VA	VA	VA	VV, VA, iLA™	VV, VA, iLA™, hybrid
Pump configuration	CPB	Roller pump	Roller pump	Centrifugal	Centrifigual
Oxygenator membrane	Silicone membrane	Polypropylene and silicone	Polypropylene	PMP	PMP
Cannulation approach innovation	Central	Central	Central	Peripheral Novalung®	Peripheral Avalon™

CPB, cardiopulmonary bypass; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ILA™, interventional lung assist; PMP, polymethylpentene; VA, venoarterial; and VV, venovenous.

Table 1. Evolution of ECMO as a bridge to lung transplant by decade. Adapted with permission from [5], © 2013 Diaz-Guzman et al. Published under Wolters Kluwer Health, Inc. DOI: 10.1097/MAT.0b013e31827461c2. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health.

2. Extracorporeal membrane oxygenation as a bridge to lung transplantation

The first report of the use of ECMO as a bridge-to-transplant was published in the 1970s [6]. The patient was successfully transplanted and wean from ECMO, he died at 10 days of post-transplant. Successful cases were reported in 1993 [7]; however, still controversies of using ECMO as a bridge-to-transplant were noted at that time because of poor clinical outcomes, for example, the estimated 1-year survival for the transplant of ECMO was only 40%. In addition, the resources have been considerable for a successful transplant through ECMO bridge, such as prolong intensive care and hospital stays, need of tracheostomy, substantial blood requirement, and consequent neuromuscular complications that also required prolonged periods of postoperative rehabilitation.

The lung allocation scoring (LAS) system, begun in 2005, can be attributable to increase the use of ECMO as a bridge-to-transplant. Contrary to it patients before 2005 would receive lungs only based on the length of time on the waiting list, both medical urgency and net benefit from transplantation were incorporated to create a standardized scoring system. Since the adoption of LAS system, patients receiving continuous mechanical ventilation get higher scores, more likely to receive a transplant. Simultaneously, issues were arisen that ventilator-dependent patient before transplantation may be too sick for transplantation, which may affect the post-transplant outcomes. Direct or indirect risk factors could be considered in these patients: one is the increased risk of "ventilator-induced lung injury (VILI)" or "ventilator-associated pneumonia" during waiting period, and the other is "ICU-acquired weakness."

ECMO has been associated with avoidance of mechanical ventilation and it facilitates perioperative rehabilitation. As far as minimizing VILI when using ECMO as a bridge-to-transplant, ECMO may be beneficial for the patients waiting lung transplantation who have refractory hypercapnic respiratory failure, which was followed by most patients with end-stage lung disease combined with hypoxic respiratory failure. Extracorporeal CO_2 removal (ECCO2R), more commonly called as this concept instead of ECMO, reduces mechanical ventilation requirements, enabling the use of low tidal volume and high PEEP at relatively lower respiratory rates. Recently, technological improvements, such as interventional lung-assisted device pumpless venovenous ECMO (NovalungGmbH, Germany), a low-resistance oxygenator that offers good decarboxylation, and the CardioHelp venovenous ECCO2R device (Maquet, Germany), have led to remove CO_2 selectively including partial or full oxygenation support [8].

a.

b.

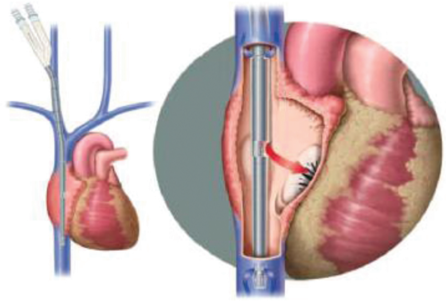

Figure 2. (a) Patient ambulating on venovenous-ECMO, (b) Avalon Elite Double lumen catheter and catheter placement. Adapted with permission from [5], © 2013 Diaz-Guzman et al. Published under Wolters Kluwer Health. DOI: 10.1097/MAT.0b013e31827461c2. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health.

Compared to the conventional mechanical ventilation strategy, patients who received "awake" ECMO as a bridge-to-transplant can be liberated from bed and participate in a preoperative "active" rehabilitation program, which consequently mitigated ICU-acquired weakness

(**Figure 2a**). For this purpose, new-type single catheters, configured by double lumen, such as "Avalon" (**Figure 2b**) or "Novatwin" cannula, can be preferable, which facilitate easier patient mobilization to prevent decline in skeletal muscle dysfunction in postoperative period. Although a direct causal relationship between preoperative rehabilitation enhanced by a bridge-to-transplant using ECMO and postoperative exercise tolerance with ultimate clinical outcomes has not been established, it is generally considered a standard of care to enlist all patients into an active pulmonary rehabilitation program before transplantation or a "destination therapy" like that seen with left ventricular-assisted devices in the area of heart transplantation. There appears to be a benefit even in a common selected group of extremely sick conditions before transplant despite the scarcity of data currently [9].

Until now, there are no randomized controlled trials showing the beneficial effect of ECMO as bridge to lung transplant, several retrospective studies reported acceptable survival and its feasibility. Because most of these analyses were composed of many heterogeneous patients' feature, whether ECMO as an alternative, rather than an adjunction, to invasive mechanical ventilation is a better bridging strategy during lung transplantation still remains an unresolved issue. A meta-analysis of 14 retrospective studies [10–23] reported from 50 to 90% of the post-transplant 1-year survival rate, which was significantly better in spontaneously breathing patients or when the ECMO bridge duration was shorter than 14 days.(**Tables 2** and **3**) [4].

Author, year	Patients, number	Age (years)	Sex male, *n* (%)	Diagnosis	Ventilation strategy	Bridge time (days)	Severity score prebridge
Mason, 2010 [19]	51	39±22	25 (49%)	PF 27%; COPD 1996; CF 12%; PH 9.8%; sarcoidosis 2%; other 20%	na	na	LAS 54±21
Bermudez, 2011 [11]	17	40±14	7 (41%)	PF 35%; Re-LTx 35%; CF 23%; COPD 6%	MV	3.2 (0–49)	na
Hammainen, 2011 [15]	16	41±8[a]	7 (58%)	PF 37%[a]; PH 15%[a]; CF 8%[a]; ARDS 8%[a]; IP 8%[a]; PVOD 8%[a]; BOS 8%[a]; PGD 8%[a]	na	12 (1–59)	na
Shafii, 2012 [21]	19	44 (23–60)	10 (53%)	IP 68%; CF 16%; PH 16%	MV 13	6±5	LAS 87 (64–95)
Nosotti, 2012 [20]	11	34±13	5 (45%)	na	Awake 7 MV 4	12.1±14.7	SOFA 4.9±1.4
Javidfar, 2012 [17]	18	34 (22–50)	8 (45%)	CF 44%; PF 33%; PH 11%; Other 11%	Awake 6	11.5 (6–18)	LAS 93(90–94)
George, 2012 [14]	122	48±16	74 (60%)	PF 29.5%; CF 11.5%; COPD 10.7%; PH 2.5%; other 45.8%	na	na	LAS 73.9±21.4
Fuehner, 2012 [13]	26	44 (23–62)	21 (81%)	PF 35%; PH 27%; CF 19%; BOS 12%; sarcoidosis 4%	Awake 19 MV 7	9 (1–45)	SOFA 7 (6–12)

Author, year	Patients, number	Age (years)	Sex male, *n* (%)	Diagnosis	Ventilation strategy	Bridge time (days)	Severity score prebridge
Hoopes, 2013 [16]	31	45±15	21 (67%)	PF 29%; CF 23%; ILD 13%; ARDS 10%; PVOD 10%; PH 6%; BOS 3%; IP 3%; CWP 3%	Ambulatory 18 13 VM	11 (2–53)	LAS > 50
Anile, 2013 [10]	12	na	na	CF 92%; histiocytosis 8%	Awake 2 MV 10	6±2.1	na
Toyoda, 2013 [22]	31	46±15[a]	10 (43%)[a]	Pf 33%[a]; CF 21%[a]; Re-LTx 13%[a]; scleroderma 13%[a]; bronchiectasis 8%[a]; COPD 4%[a]; sarcoidosis 4%[a]; PH 4%[a]	MV[a]	7.1±10	Las 87±9 [a]
Weig, 2013 [23]	26	36 (30–51)[a]	14 (54%)	PF 62%; CF 23%; COPD 4%; Re-LTx 4%; lung cancer 4%; sarcoidosis 4%	na	16 (88–25)[a]	SOFA 9 (8.5–10.5)[a]
Crotti, 2013 [12]	25	41±12	na	PF 52%; CF 16%; PH 16%; Re-LTx 12%; ARDS 4%	Awake 10 MV 15	5.8±4.5 versus 29.8±11.5[a]	SOFA 5.6±1.9
Lafarge, 2013 [18]	36	31 (22–48)	19 (53%)	CF 56%; PF 30%; other 14%	MV	3.5 (2–7)	na

Data presented in this table refer to patients underwent ECMO support with the intention to bridge to lung transplantation.
[a]Transplanted patients (when data for all enrolled patients are not available; Hemmainen et al., all data; Toyoda, all data; Weig et al., ECMO bridge time and SOFA; Anile, diagnosis). ECMO bridge time (days) and the prebridge severity score are expressed as mean± standard deviation or median and range. When no descriptive cumulative data for the overall population are provided, they are calculated from raw data presented in the original papers.
[b]Data refer to patients divided according to waiting time on ECMO: up to 14 days or longer.
Pts, patients; ECMO, extracorporeal membrane oxygenation; PF, pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; PH, pulmonary hypertersion; Re-LTx, Re-lung transplantation; ARDS, acute respiratory distress syndrome; IP, interstitial pneumonia; PVOD, pulmonary veno-occlusive disease, bronchiolitis obliterans syndrome; PGD, primary graft dysfunctions ILD, interstitial lung disease; CWP, coal workers, pneumoconiosis; MV, mechanical vertilation; LAS, lung allocation score; SOFA, sequential organ failure assessment; and na, not available.

Table 2. Characteristics of patients who underwent ECMO bridge to lung transplant. Reproduced from [4], © 2015 Chiumello et al. Published under CC BY 4.0 license. DOI: 10.1186/s13054-014-0686-7.

Author, year	Ltx/total patients, *n*	Died before Ltx, *n* (%)	Type of bypass	Survival at 1 year post-LTx (%)	Length of stay post-LTx (days)	MV (days post-LTx)
Mason, 2010 [19]	51/51	na	na	50%	24 (9–55) H	na
Bermudez, 2011 [11]	14/17	3 (17%): neurologic dysfunction, thrombosis	W, VA	74%	16 (3–40) ICU	12 (2–20)

Author, year	Ltx/total patients, *n*	Died before Ltx, *n* (%)	Type of bypass	Survival at 1 year post-LTx (%)	Length of stay post-LTx (days)	MV (days post-LTx)
Hammainen, 2011 [15]	13/16	3 (19%): septic MOF	W, VA	92%	22 (3–63) ICU	na
Shafii, 2012 [21]	14/19	5 (26%): septic MOF 2, DC 2, and anoxic brain injury 1	W, VA	75%	42 (19–175) H	22 (5–125)
Nosotti, 2012 [20]	11/11	na	W	87% and 50%[b]	47.6±21.9 H 30±20.4 ICU	27.1±20.7
Javidfar, 2012 [17]	10/18[a]	8 (44%): pneumonia 1, MOF 6, and CA 1	W, VA	60%	22 (18–33) H 47 (41–52) ICU	na
George, 2012 [10]	122/122	na	na	57.6%	32 (16.5–60) H	na
Fuehner, 2012 [13]	20/26	6 (23%): CA 2, septic MOF 4	W, VA	6 months 80%	38 (20–87) H 18 (1–69) ICU	14 (0–64)
Hoopes, 2013 [16]	31/31	na	VA, W	93%	31 (12–86)[e]H	na
Anile, 2013 [10]	7/12	5 (41%)	W, VA	85.7%	29 (15–59) H	<5
Toyoda, 2013 [22]	24/31	7(22%)	W, VA	74%	46 median H	na
Weig, 2013 [23]	13/26	13 (50%): acute liver failure 7, thoracic bleeding 3, cerebral hemorrhage 1, and PE 2	W, VA	54%	na	na
Crotti, 2013 [12]	17/25	8 (32%): MOF 3, septic shock 2, cardiogenic shock 2, and intestinal ischemia 1	W, VA	82% and 29%[c]	na	12.2±11.9[d]
Lafarge, 2013 [18]	30/36	6 (17%): GI bleeding 1, DIC 1, cerebral hemorrhage 1, CA 1, septic shock 1, and therapeutic limitation 1	W, VA,CPB	66.5%	na	na

Data are expressed as mean±standard deviation or median and range. Mason et al., Nosotti et al., and George et al. enrolled transplanted patients.
[a]Three of the eight patients who died had transiently recovered their baseline function and were weaned from ECMO support; they subsequently died before LTx.
[b]ECMO group: 87% awake (7 pts); mechanical ventilation ECMO group: 50% (4 pts);
[c]82% patients on ECMO bridge <14 days (early); 29% patients on ECMO bridge >14 days (late);
[d]12.2±11.9 days (early group) −45.3±33.5 (late group).
[e]LTx, lung transplant; CA, cardiac arrest; MOF, multiorgan failure; DIC, disseminated intravascular coagulation; Gl, gastrointestinal; VV, venovenous; VA, venoarterial; CPB, cardiopulmonary bypass; MV, mechanical ventilation; LOS, length of stay; H, hospital; and na, not available.

Table 3. Summary of outcomes. Reproduced from [4], © 2015 Chiumello et al. Published under CC BY 4.0 license. DOI: 10.1186/s13054-014-0686-7.

3. Extracorporeal membrane oxygenation during lung transplantation

There is little evidence or protocol about how to manage ECMO during intraoperative situation; however, the intraoperative use of ECMO may be necessary at any stage of developing hypoxia, hypercapnia, and/or hemodynamic instability. In bilateral lung transplantation, ECMO can stabilize hemodynamic variables and prevent "first lung syndrome," the hyperperfusion of the first implanted lung during implantation of the second lung. In addition, it can also be used at every phase during lung transplantation to enhance a protective ventilation strategy and avoid 100% oxygen so as to mitigate the reperfusion syndrome especially during one-lung ventilation or to support when there was a lung size mismatch, auto-PEEP, and dynamic hyperinflation [8].

Because of many advantages mentioned earlier, ECMO has replaced CPB as the first option for intraoperative support during lung transplantation in many transplant centers. A recent published study from Germany showed 5-year experience with intraoperative ECMO in lung transplantation since April 2010 [10]. Compared with patients who underwent lung transplantation without ECMO, overall survival at 1 and 4 years was not inferior in patients in whom the indication for ECMO support and the intraoperative use of ECMO did not emerge as a risk factor for mortality. Though small numbers were included, many studies showed overall clinical beneficiary of ECMO over CPB during lung transplantation, such as lesser intraoperative blood transfusion requirement, lesser mechanical ventilation requirement, shorter ICU stay, and higher postoperative complications.

Bermudez et al. [11] compared 49 VA-ECMOs with 222 CPBs using intraoperative lung transplantation. In this study, there was a higher requirement for reintubation, tracheostomy, and dialysis in the CPB group; however, the lack of significant differences in perioperative blood transfusion requirement and hospital length of stay may have been caused by the ECMO group including a sicker population, such as the higher LAS (73.3 vs. 52.9) and higher pretransplantation ECMO requirement (42.8% vs. 7.2%). Though most of these studies did not show any difference in the survival curve between two groups, one study [12] revealed the hospital mortality gain of CPB over ECMO (39% vs. 13%); however, it should be considered that there were more planned ECMOs than CPBs (61% vs. 28%) in this study, which may not be ignored showing the different mortality between two groups.

4. Extracorporeal membrane oxygenation as a rescue postlung transplant

In the postopertative setting of lung transplantation, early primary graft dysfunction (PGD), which is a syndrome consisting of lung injury during the first 72 hours following lung transplant defined as a physiologically decreased oxygenation and radiologically diffuse infiltrates, continues to be a major situation of morbidity and mortality. There is no doubt that ECMO has been applied as a pivotal management strategy to support severe PGD because none of interventions to ameliorate the effects of PGD on transplanted lung have been

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successful, including inhaled nitric oxide and prostaglandins. Although about 5% of lung transplantation requires ECMO support for PGD, this remains the most common indication for ECMO use as a rescue strategy and consequently it is reasonable that the concept of "bridge-to-transplant" has been arisen from the intermittent successes of a bridge to redo transplant in selected patients [1].

The goal of ECMO for severe PGD after lung transplant, same as mentioned in bridging-to-transplant, should be to minimize ventilator-induced lung injury such as elevated airway pressures or high inspired oxygen concentration by mechanical ventilation with positive pressure. While about this no uniform guidelines exist, one recommendation how to use ECMO to support PGD after lung transplant consists of initiating it when peak inspiratory pressure reaches up to 35 cm H_2O or 60% FiO_2 [13]. In addition, if possible, it could not be delayed greater than 48 hours to initiate ECMO after transplantation because of alleged worse outcomes. Hartwig et al. [14] reported surprising survival result in this group patients supported with VV-ECMO. Of the recipients from VV-ECMO following transplant, 96% weaned successfully with a 1-year survival of 64%.

Promisingly, *ex vivo* lung perfusion (EVLP), a novel technique used to evaluate and recondition marginal or rejected grafts, is also adapted during lung transplantation. The retrieved donor lung can be perfused in an *ex vivo* circuit, providing an opportunity to reassess its function before transplantation for the purpose of increasing successful transplantation with high-risk donor lungs. Cypel et al. [15] showed physiologically stable donor lung during 4 hours of *ex vivo* perfusion and its feasibility regarding less PGD event. Although the result was statistically not significant, this was the first report that demonstrates the possibility of *ex vivo* using ECMO for lung transplantation, remained and cited as the reference protocol. Recently, Boffini et al. [16] also revealed that the use of initially rejected grafts treated with EVLP did not increase severity of PGD after lung transplantation, suggesting a protective role of EVLP against PGD.

5. Conclusions

Recently, Biscotti et al. suggested the decision algorithm of how to use ECMO during entire lung transplantation (**Figure 3**) [2]. Though the details are not described in this chapter, the interhospital transport of lung transplantation candidate during ECMO is also feasible and this is opening a kind of new future episode [17].

Modern experience with ECMO and reported institutional experience on survival challenge historical assumptions about the treatment of end-stage lung disease and suggest that "bridging" to transplant with ECMO is both technically feasible and logistically viable. It is clear at this point that continued advances in the technologies and further research will help determine how best to include ECMO as a bridging strategy for lung transplantation.

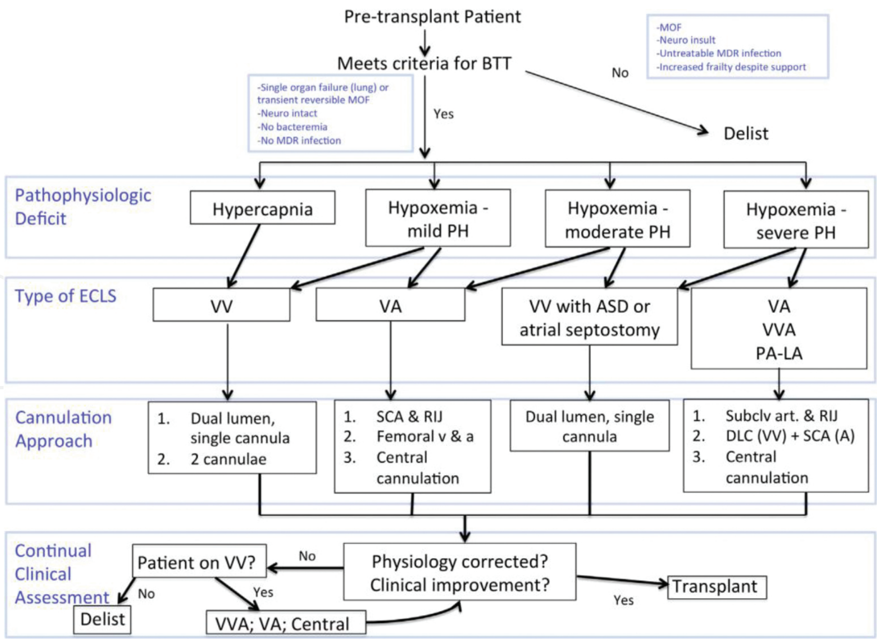

Figure 3. Decision algorithm of ECMO for lung transplantation. DLC, double lumen cannula; MDR, multidrug resistant; MOF, multiorgan failure; PALA, pulmonary artery to left atrium; PH, pulmonary hypertension; RIJ, right internal jugular vein; and SCA, subclavian artery. Adapted with permission from [2], © 2015 Biscotti et al. Published under Elsevier. DOI: http://dx.doi.org/10.1016/j.thorsurg.2014.09.010. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Elsevier.

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