Extracorporeal Life Support as a Bridge to Lung Transplantation

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KEYWORDS

- Bridge to lung transplantation • Extracorporeal life support
- Extracorporeal membrane oxygenation

HISTORICAL PERSPECTIVES

Lung transplantation (LTx) is effective life-saving therapy for patients with end-stage lung disease.[1] However, patients who are otherwise excellent candidates for LTx often die on the waiting list because they are too sick to survive until an organ becomes available. Currently, these patients are supported by maximal mechanical ventilation in the intensive care unit, but this can further aggravate the lung injury[2] and often leads to remote organ dysfunction with subsequent high mortality before or after LTx.[3] For many of these patients, refractory hypercapnia or hypoxemia will develop despite maximal ventilatory support and therefore extracorporeal life support (ECLS) is their only chance to survive until a compatible donor lung becomes available. Initial attempts at using ECLS as a bridge to LTx were hindered by a high rate of complications and poor outcomes.[4] In fact, the initial attempts of lung transplantation were frequently performed in patients on ECLS. In 1975, the first case of extracorporeal membrane oxygenation (ECMO) as a bridge to lung transplantation was performed for posttraumatic respiratory failure. The patient was successfully weaned from ECMO after the transplant; however, he died 10 days after the transplant from a combination of sepsis, bronchial anastomotic leak, and size mismatch. Subsequently, in 1982 in Toronto, a further case of ECMO as a bridge to lung transplant was attempted in a patient with severe paraquat poisoning, but the patient died 92 days after the procedure with a tracheal-innominate artery fistula.[5] Many centers came to view ECMO, and mechanical ventilation, as contraindications to lung transplantation as it was thought that both compromised bronchial healing, the Achilles heel of transplantation in the early days.[4] In addition, the use of adult ECMO for acute respiratory failure (ARF) significantly declined after a negative National Institutes of Health randomized trial in which survival after veno-arterial ECMO was only 10% in patients with severe ARF.[6] This combination of factors resulted in the concept of using ECMO as a bridge to lung transplant being largely discouraged. However, in the last decade, improvements in lung transplant outcomes and patient selection, a better understanding of ventilator-associated lung injury, and improvements in artificial lung device technologies have made it possible to bridge these sick patients to successful LTx.[7–11] In addition, recent studies have shown more promising results using ECLS for adults with ARF with survival rates ranging from 50% to 80%. This finding includes the experience from Michigan in 100 subjects,[12] the conventional ventilation or ECMO for severe adult respiratory failure trial,[13] and H1N1/Acute Respiratory Distress Syndrome (ARDS) reports.[14,15] The

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primary scope of this article is to review the indications, modes of application, and outcomes of ECLS when used as a bridge to LTx.

INDICATIONS

The main indications for ECLS as a bridge to LTx include patients with irreversible end-stage lung diseases presenting with rapid deterioration of respiratory status as reflected by refractory hypercapnic or hypoxemic respiratory failure (usually PCO_2 >80 mm Hg and PaO2/FIO2 <80 mm Hg). Another indication for ECLS in the pretransplant setting is in patients with severe pulmonary hypertension and hemodynamic collapse caused by severe dysfunction of the right ventricle.[10,16] Given the level of resource use and the scarcity of donor organs, careful patient selection is clearly needed. No specific criteria for this group of patients can yet be suggested because of the small number of reported cases, but in general, young age, absence of multiple-organ dysfunction, and good prospects for rehabilitation should be considered. Usually, these patients have already been assessed by the LTx team and listed for LTx; however, in exceptional instances, urgent assessments and listing can be performed. With increased experience, there is also a trend toward implementing ECLS earlier in the course of the respiratory failure to avoid the need for prolonged high-pressure mechanical ventilation leading to secondary organ dysfunction.[2,3] Furthermore, recent reports have shown the feasibility of ECLS as bridge to LTx in awake and nonintubated patients allowing them to ambulate and potentially be in better physical condition by the time of the transplant.[8,17]

CONTRAINDICATIONS

Contraindications for the use of ECLS in general include septic shock, multi-organ dysfunction, severe arterial occlusive disease, and heparin-induced thrombocytopenia type II. Unfavorable prognostic factors include acute renal failure, high vasopressor requirements, a long preceding duration of mechanical ventilation, advanced age, and obesity.[18]

COMPONENTS OF ECLS SYSTEMS AND TECHNOLOGICAL ADVANCES

The main components of the ECLS system include a membrane oxygenator, a pump, and tubing circuits (**Fig. 1**). In the last decade, several important advancements in technology have contributed to improved management and overall outcomes of these patients, as detailed later.

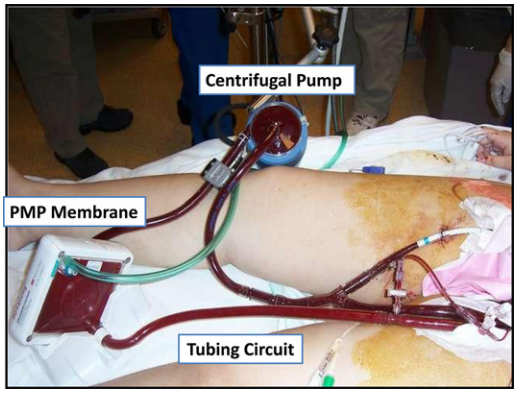

Fig. 1. Main components of a modern ECLS circuit.

Development of Polymethylpentene Membranes

In the past, most adult ECMO circuits used silicone membrane oxygenators and the remainder used polypropylene microporous oxygenators. Both these oxygenators had drawbacks. The introduction of polymethylpentene (PMP) membranes provided several technical advantages. Compared with silicone membrane oxygenators, the PMP oxygenator has reduced red blood cell and platelet transfusion requirements, significantly less plasma leakage, better gas exchange, lower resistance, and lower priming volume.[19,20] Compared with polypropylene microporous oxygenators, the PMP oxygenator has a reduced rate of oxygenator failure and can be functional for several weeks.[7] The PMP fibers are woven into a complex configuration of hollow fibers through which the oxygenated gas passes. The hollow fibers themselves are then arranged into mats and stacked into a configuration that allows blood to pass between the fibers with low resistance, which provides maximum blood/gas mixing and gas transfer can take place without direct contact with blood.

Introduction of Heparin-coated Circuits

Heparin-coated circuits led to reduced rates of platelet, complement, and granulocyte activation[8] and also significantly reduced heparin requirements.[21,22] Importantly, PMP oxygenators can also be readily heparin coated; whereas, the silicone membrane oxygenators cannot. Thus, the modern ECMO circuit can be entirely heparin coated and requires less systemic heparinization. In contrast, early ECMO circuits required full heparinization and consequently bleeding complications and daily blood product requirement were high.

Development of a New Generation of Centrifugal Pumps

Compared with traditional roller pumps, the centrifugal pumps have an improved performance and safety profile. They have virtually no risk of tubing rupture, require a smaller priming volume, do not require the use of a reservoir, and in general have a decreased incidence of hemolysis.[23,24]

MODES OF ECLS: CONFIGURATION OF DEVICE

In addition to the technical advances, device configuration can be individualized and tailored for specific patient ventilatory and hemodynamic requirements. The configuration and mode of ECLS will depend on the specific clinical scenario.

Hypercapnic Respiratory Failure

Refractory hypercapnic respiratory failure and acidosis is a common scenario in patients with cystic fibrosis (CF) waiting for lung transplantation. Noninvasive ventilation has become an important option as a treatment modality in ARF in CF, avoiding endotracheal intubation with its attendant complications.[25] If a suitable organ does not become available in time, respiratory failure progresses and mechanical ventilation becomes necessary. At that stage, management becomes increasingly difficult as high-pressure ventilation is required and alveolar hypoventilation and hypercapnia often persists despite it. Traditionally, patients with hypercapnia and respiratory acidosis required ECMO with the use of a pump. However, with the advent of an interventional lung assist device (iLA; Novalung, Heilbronn, Germany), the Hannover group demonstrated the feasibility of bridging these patients with the iLA in a *pumpless* arterio-venous (A-V) mode (**Fig. 2**).[7] This low-resistance (11mm Hg) PMP device is attached to the systemic circulation (usually femoral artery) and receives only part of the cardiac output (15% to 20% of cardiac output) for extracorporeal gas exchange, which allows prompt CO_2 removal and correction of respiratory acidosis. Varying the sweep of gas flow up to 15 L/min can control CO2 removal rates. The usual recommended rate of CO_2 clearance is 20 mm Hg/h. In order to use the pumpless device, patients must have an adequate mean arterial blood pressure to be able to sustain good flows through the device. Because only one-fifth of cardiac output is oxygenated in the membrane, PaO_2 is only augmented minimally with this mode of ECLS[7]; therefore, A-V iLA is not recommended in patients with severe hypoxia (PaO_2/FiO_2 <80 mm Hg). Cannulation is usually achieved percutaneously using a Seldinger technique in the femoral artery (13–15 Fr) and femoral vein (17 Fr). Because a centrifugal pump is not required, anticoagulation times (ACT) in the range of 150 to 180 seconds are acceptable.

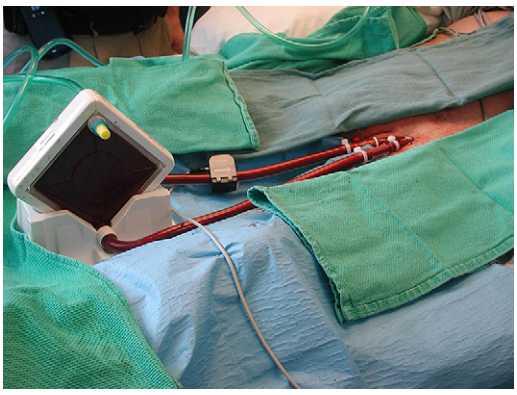

Fig. 2. Pumpless arterio-venous ECLS support. A low-resistance PMP device is attached to the systemic circulation (usually femoral artery) and receives part of the cardiac output (15%–20% of CO) for extracorporeal gas exchange. This procedure allows prompt CO_2 removal and correction of respiratory acidosis.

Hypoxemic Respiratory Failure

Although CO_2 removal can be achieved with low membrane flows (0.5–1.0 L/min),[26] substantial oxygenation requires more physiologic flows through the membrane (3–5 L/min). In order to achieve that, veno-venous (V-V) or veno-arterial (V-A) pump-driven ECLS support is required. V-V mode is the preferred choice if patients are hypoxemic but hemodynamically stable. The advantages of the V-V mode in comparison to V-A mode are the decreased rate of complications, such as bleeding, arterial thrombosis, and neurologic complications. Generally, a 22-Fr cannula is inserted into a femoral vein for drainage and a 17-F single-stage cannula is inserted into an internal jugular vein percutaneously for patient inflow. More recently, a dual-lumen, single-cannula system has been developed for V-V ECLS that has the advantage of simplicity, and importantly, allows for patient mobilization.[17] Using this cannula, the inflow to the ECLS circuit occurs from the tip of the cannula, which is located in the inferior vena cava, and from fenestrations in the proximal part of the cannula located at the superior vena cava-right atrial junction. The outflow from ECLS (oxygenated blood) is located at the midpoint between these 2 intake points and is directed medially toward the tricuspid valve. Visualization with fluoroscopy or transesophageal echocardiography is recommended to facilitate

accurate cannula insertion and positioning. In V-V mode, infused ECLS membrane oxygenated blood mixes with systemic venous return blood in the right atrium. At typical blood flow, the ratio of infused oxygenated blood to deoxygenated right atrial blood is usually around 3:1, which results in a hemoglobin saturation of 80% in the pulmonary artery. If there is no native lung function, this will be the oxygenation in the arterial blood. Although this can often be the case in ARDS, lungs from end-stage lung failure are often able to provide some degree of oxygenation contributing with better systemic saturation. One of the options to improve systemic hemoglobin saturation is to increase the pump flows, so that more blood flow bypasses the native lung. In all instances, hematocrit should be kept greater than 40% and cardiac function optimized to provide adequate systemic oxygen delivery. Usual ACTs should range from 160 to 200 seconds.

Hypoxemic Respiratory Failure and Hemodynamic Compromise

For patients with respiratory failure and hemodynamic compromise, V-A ECLS is the recommended option because it provides both cardiac and lung support. In fact, the initial experience with ECLS in LTx employed this mode.[5] Usually a femoral vein is cannulated for drainage and a femoral artery cannulated for blood return. Some investigators also propose the use of the axillary artery with an interposition graft.[27,28] Advantages of the axillary artery in this setting are the possibility of better patient mobilization and the low incidence of atherosclerosis in this vessel. Improved upper-body oxygenated perfusion is also an important advantage. During V-A femoral ECLS, fully saturated blood infused into the circulation from the ECLS circuit will preferentially perfuse the lower extremities and the abdominal viscera. Blood ejected from the heart will selectively perfuse the heart, brain, and upper extremities. As a result, the oxygen saturation of the blood perfusing the lower extremities and abdominal viscera may be substantially higher than that perfusing the upper body. Cardiac and cerebral hypoxia could exist and be unrecognized if oxygenation is monitored using blood from the lower extremity. Poor arterial saturations measured from the upper extremity should prompt adjustments to the mechanical ventilator to optimize pulmonary oxygenation or augmentation of blood flow through the ECLS circuit. Another option to improve central oxygenation is to insert another cannula into internal jugular vein and convert the circuit to a hybrid V (femoral vein)-VA (jugular vein and femoral artery) ECLS. Conversely, V-VA ECMO can also be used to provide partial cardiac support when cardiac function is depressed and does not improve with improved oxygenation on V-V support alone.[29,30]

A recent report demonstrated the application of V-A ECLS in awake and spontaneously breathing subjects, avoiding the drawbacks and complications associated with intubation and prolonged mechanical ventilation. 4 out of 5 subjects were successfully bridged to LTx.[8]

Pulmonary Hypertension and Right Ventricular Failure

A novel mode of ECLS is the recently described pulmonary artery to left atrium (PA–LA) ECLS.[10,31] Although progress has been made for isolated lung failure, no truly effective solution existed for patients with severe pulmonary arterial hypertension (PAH). Compared with patients with lung failure caused by isolated lung parenchymal disorders, patients with end-stage PAH develop severe right heart failure. V-A or V-V ECLS does not effectively unload the right ventricle. An atrial septostomy is sometimes performed in the setting of severe right ventricular dysfunction; however, this leads to desaturated blood being systemically ejected as a result of the iatrogenic right to left shunt. Alternatively, the authors have demonstrated that the connection of a low-resistance gas exchange device (Novalung; Novalung, Heilbronn, Germany) between the main trunk of the pulmonary artery and the left atrium in a pumpless mode creates an effective *oxygenating* shunt that unloads the right ventricle much like an atrial septostomy (**Fig. 3**). The advantage, in this case, is that the membrane oxygenates the blood and thus the central hypoxemia seen with a simple septostomy is avoided. In the authors' experience, patients improve dramatically as soon as flow across the Novalung is instituted.[10] The elevated pressure in the pulmonary arteries serves as the driving force for the device and obviates the need for a pump. From a technical standpoint, patients are usually so severely unstable such that they usually require femoral-femoral V-A ECLS support just before anesthetic induction. This procedure is followed by median sternotomy and cannulation of the PA (Medtronic arterial cannula 21-24 Fr; Medtronic, Minneapolis, MN, USA). The LA is cannulated by inserting a 17-23 Fr Pacifico cannula (Bard Inc, Salt Lake City, UT, USA) into the right superior pulmonary vein. Extubation, physiotherapy, and ambulation are achievable while patients are on pumpless PA-LA ECLS awaiting a compatible donor lung. Eight

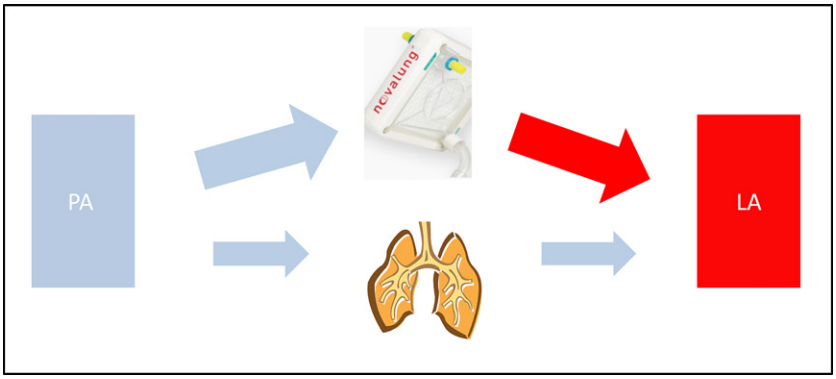

Fig. 3. Pumpless pulmonary artery to left atrium ECLS support for patients with pulmonary hypertension. An oxygenating shunt is created providing both right-ventricle decompression and oxygenation.

successful cases have been reported using this technique to bridge patients with PAH to LTx.[10,11,31] Of note, in most cases, heart-lung transplantation is not required because the unloaded right ventricle recovers on the Novalung and bilateral LTx provides ongoing remodeling and recovery of the right heart.[10]

PATIENT MANAGEMENT

Once ECLS is initiated, the ventilator should ideally be adjusted to resting lung settings with FiO_2 less than 0.6, end inspiratory pressure less than 35, PEEP 10 to 15, rate of 6/min. The ECLS flow should be maintained to sustain a venous blood saturation of 80% to 85% and an arterial saturation of 80% to 95%. Diuretics are given if required to maintain adequate urine output and remove excess fluid to maintain patients at dry weight (pre-illness weight). If negative fluid balance cannot be achieved with diuretics, hemofiltration should be initiated early. Neurologic status is frequently checked and any deterioration should prompt a head computed tomography scan. Cannulation sites and limb perfusion status are also frequently checked for bleeding and distal perfusion, respectively. Routine antibiotics and antifungal coverage should be given.

The general target guidelines used by the Toronto General Hospital ECLS/Lung Transplant Program are shown in **Table 1**.

OUTCOMES

The outcomes of patients bridged to LTx using mechanical support has been improving and is satisfactory considering the severity of their diseases and the overall survival of LTx recipients. A recent review from the UNOS experience totaling 51 subjects bridged to LTx from 1987 to 2008 using ECLS showed a 1-, 6-, 12-, and 24-month survival of 72%, 53%, 50%, and 45%, respectively compared with 93%, 85%, 79%, and 70% for unsupported patients, respectively.[32] Most recent reports from centers experienced in both LTx and ECLS have shown that 80% or more of patients can be successfully bridged to LTx and outcomes after LTx in these selected patients can approach that of conventional lung transplants.[7,8,10,11,33–36] These results demonstrate that outcomes in this patient population are better than the results of ECLS use to bridge patients to recovery from severe primary graft dysfunction after LTx,[18] although improved results have also been recently obtained in this latter group.[37,38] **Table 2** demonstrates reported case series of use of ECLS as a bridge to transplantation in which more than 4 subjects were included.[7,8,10,11,33–36]

Table 1
Target guidelines for patients on ECLS

Temperature	35.5°C–37.0°C
pH	7.35–7.45
pCO_2	35–45 mm Hg
pO_2	>100 mm Hg
Hemoglobin saturation	>85%
Hemoglobin	80–100 g/L
INR	<1.8 <1.5 if bleeding
Platelets	>80,000/mm^3 >100,000/mm^3 if bleeding
Fibrinogen	>1.5–4.0 g/L
Factor X concentration	0.4–0.6 u/mL
Anticoagulation time	160–200 sec
Pump flow	Aim 60 mL/kg/min

Abbreviation: INR, international normalized ratio.

Table 2
Experience with ECLS as a bridge to lung transplant (series with more than 4 cases)

Author	Number of Cases	Days on Device (Mean)	Mode ECLS	Bridged to LTx (%)	30-d Survival After LTx (%)	1-y Survival (%)
Fischer et al,[7] 2006	12	15.0	A-V pumpless	83	80	80
Olsson et al,[8] 2010	5	21.0	V-A	80	100	NA
Strueber et al,[10] 2009	4	17.0	PA-LA pumpless	100	100	75
Cypel et al,[11] 2010	12	7.0	V-A (3), V-V (1), A-V (4), PA-LA (4)	100	100	83
Yun et al,[33] 2010	7	7.0	V-V (5) V-A (2)	86	83	NA
Ricci et al,[34] 2010	12	13.5	A-V pumpless	25	NA	NA
Nosotti et al,[35] 2010	4	9.0	V-V	100	75	NA
Hämmäinen et al,[36] 2010	16	17.0	V-V (7) V-A (6)	81	100	92

Abbreviation: NA, not available.

COMPLICATIONS

The most common complications during ECLS include hemorrhage, complications at the cannulation site, renal failure, neurologic complications, and sepsis.[18] In an experience with 100 ECLS for ARF, cannula site and surgical site bleeding were the most common complications followed by arrhythmias and renal failure. In this series, 6 subjects died of gastrointestinal bleeding and 10 subjects developed irreversible brain damage caused by infarct or hemorrhage.[12] Patients on V-A ECLS have significantly higher rates of complications (especially neurologic complications and sepsis) when compared with V-V.[37]

SUMMARY

Although experience is still limited, ECLS clearly can be an effective tool to bridge patients to a life-saving lung transplant. Technological advances have permitted safer, less complicated application of ECLS for longer periods of time. Support can be tailored to minimize morbidity and provide the appropriate mode and level of cardiopulmonary support for each specific patient's physiologic requirements. Novel device refinements and further development of ECLS in an ambulatory and simplified manner will help to maintain these patients in better condition until transplantation. Further experience is required to ultimately define the optimal timing and criteria for initiation of ECLS in patients requiring bridging to lung transplantation.

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