

Mechanical circulatory support in lung transplantation: Cardiopulmonary bypass, extracorporeal life support, and *ex-vivo* lung perfusion

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Abstract

Lung transplant is the standard of care for patients with end-stage lung disease refractory to medical management. There is currently a critical organ shortage for lung transplantation with only 17% of offered organs being transplanted. Of those patients receiving a lung transplant, up to 25% will develop primary graft dysfunction, which is associated with an 8-fold increase in 30-d mortality. There are numerous mechanical lung assistance modalities that may be employed to help combat these challenges. We will discuss the use of mechanical lung assistance during lung transplantation, as a bridge to transplant, as a treatment for primary graft dysfunction, and finally as a means to remodel and evaluate organs deemed unsuitable for transplant, thus increasing the donor pool, improving survival to transplant, and improving overall patient survival.

Key words: Lung transplant; Cardiopulmonary bypass; Extracorporeal membrane oxygenation; Extracorporeal life support; Extracorporeal lung assist; Interventional lung assist; *Ex-vivo* lung perfusion

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Core tip: Numerous modalities of mechanical lung assistance may be employed throughout the course of a lung transplant patient. The use of cardiopulmonary bypass for lung transplantation is controversial and should be employed only when necessary for hemodynamic stability. Extracorporeal membrane oxygenation or extracorporeal lung assist devices improve survival to transplant as well as improve survival in patients with primary graft dysfunction. These techniques should be implemented early and appropriately according to patient factors. *Ex-vivo* lung perfusion has been shown to be safe in clinical trials and holds promise for increasing the donor pool and thus decreasing waiting list mortality.

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INTRODUCTION

Lung transplantation is the standard of care for end-stage lung disease refractory to medical management^[1,2]. There are an increasing number of patients awaiting lung transplant despite increases in lung transplant surgeries performed each year^[3]. Only 15%-20% of available donor lungs are deemed suitable for transplant^[3]. The shortage of suitable donor organs and extensive wait times have led to further progression of the recipient's native lung disease at the time of transplant, increased respiratory failure prior to transplant, and increased mortality while awaiting transplantation. Patient mortality may reach as high as 20% the first year on the waiting list and up to 40% after 2 years^[4].

Mechanical circulatory support may be required in the course of lung transplantation whether pre-operatively, intra-operatively, or post-operatively. Mechanical lung assistance (MLA) whether extracorporeal membrane oxygenation (ECMO) or extracorporeal lung assist (ECLA) has been used as a bridge to transplant in those patients undergoing respiratory failure prior to donor lung availability. The possibility of using ECMO in potential donors to increase the number of viable organs has also been proposed^[5]. The use of cardiopulmonary bypass (CPB) or ECMO during lung

transplant surgery is controversial. Lung transplant recipients who develop severe primary graft dysfunction (PGD) have increased early and late mortality, perioperative complications, and development of bronchiolitis obliterans syndrome^[6,7]. For those patients with PGD, ECMO and ECLA have been used as salvage therapies similar to their use in acute respiratory distress syndrome (ARDS). Furthermore, *ex-vivo* lung perfusion (EVLV) is an innovative technique, which may increase available donor organs by reconditioning previously untransplantable organs while allowing for continuous assessment of suitability for transplant.

USE OF CARDIOPULMONARY SUPPORT DURING LUNG TRANSPLANTATION

Overview

Mechanical circulatory support in the form of CPB or ECMO is frequently employed for lung transplantation^[1]. However, due to improvements in single-lung ventilation techniques and hemodynamic support, neither is always necessary^[1]. The components of a CPB circuit and an ECMO circuit are illustrated in Figures 1 and 2, respectively^[8,9]. The requirement for mechanical circulatory support during lung transplantation depends upon right ventricular function, pulmonary hypertension, and ability to tolerate single-lung ventilation^[1].

Indications

The most common indication for the use of CPB during lung transplantation is primary or secondary pulmonary hypertension, mean pulmonary artery pressure ≥ 25 mmHg^[10-12]. CPB is used in patients with pulmonary hypertension to prevent sudden and further increase in pulmonary artery pressure, which may lead to acute right ventricular failure during clamping of the pulmonary artery. Another common indication for CPB is *en-bloc* double-lung transplantation^[11,12]. Indications for unplanned CPB include: intra-operative hemodynamic instability, acute right ventricular failure, impaired gas exchange, technical difficulties, and increased pulmonary pressure^[10,12]. Gammie *et al*^[12] reports their most common indication for unplanned CPB as hypoxemia and hypotension during single-lung ventilation employed for contralateral hilar dissection, occurring in 5 out of 8 patients (62.5%). In their case series, Triantafyllou *et al*^[13] reported 11 out of 18 patients (61%) requiring CPB for instability after complete pulmonary perfusion was transferred to transplanted lung. Bronchiectasis has been flagged as a possible risk factor for requiring CPB with 3 out of 9 patients with this diagnosis (33%) requiring CPB in one series^[12]. One could speculate that this may be secondary to associated pulmonary hypertension.

Advantages of CPB

Proponents of CPB note maintenance of circulation and gas exchange, controlled reperfusion, and

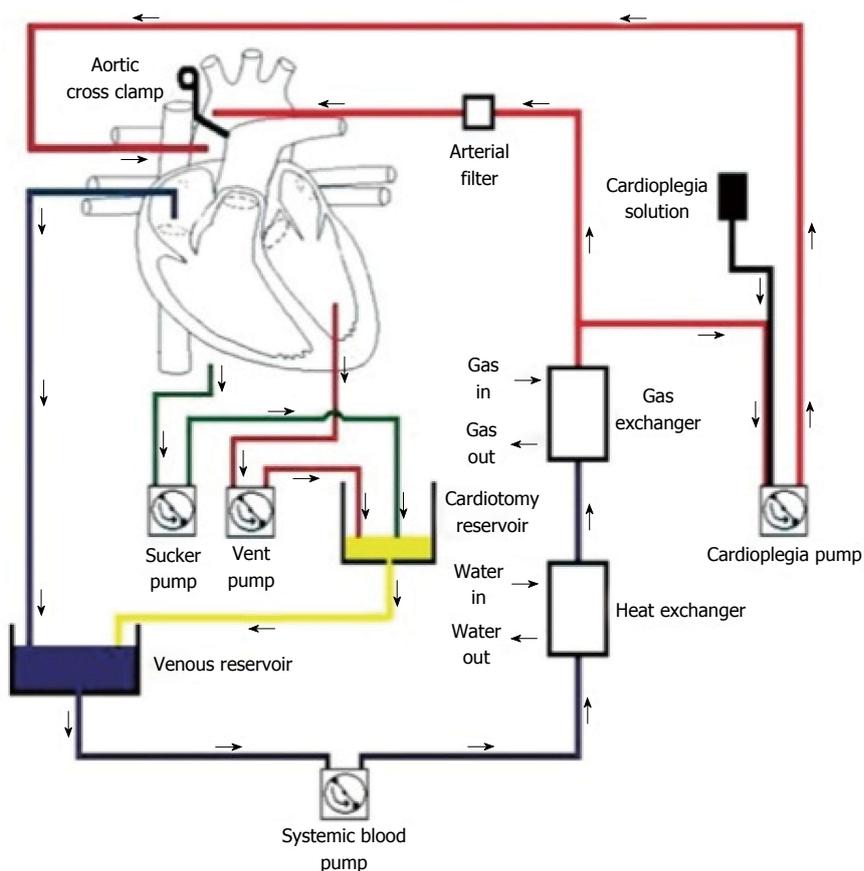


Figure 1 Cardiopulmonary bypass circuit is an open circuit in which venous blood drains into the venous reservoir by gravity (40-70 cm below the level of the heart) or siphonage. Cardiopulmonary bypass circuit is considered an open circuit: blood from the cardiotomy reservoir, blood transfusions, or other fluids may be added into the circuit. Blood then passes through an oxygenator or gas-exchanger and is returned to the arterial system by utilizing a roller or centrifugal pump^[8]. Figure from Machin *et al*^[9], with permission of Oxford University Press.

immunosuppressive effects as advantages of this approach^[11,14]. Marczin *et al*^[11] argue that controlled partial pulmonary reperfusion allowed by CPB may improve graft function. Studies have shown that reducing initial lung perfusion pressure can improve graft function^[11,14]. This then raises the question of sequential double lung transplant, in which the first lung transplanted will have to accommodate 100% of cardiac output during the implantation of the second lung, sometimes leading to PGD. In this situation, some authors suggest initiation of CPB after the implantation of the first lung, allowing for shorter CPB time and controlled reperfusion^[11]. Pharmacologic agents such as prostacyclin or nitric oxide have also been used to control reperfusion pulmonary artery pressures^[11]. Inhaled nitric oxide and inhaled prostacyclin are selective pulmonary vasodilators which decrease pulmonary vascular resistance through increases in intracellular cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) respectively thus decreasing pulmonary artery perfusion pressure^[7,15]. Szeto *et al*^[16] retrospectively reviewed 50 patients undergoing lung transplant for chronic obstructive pulmonary disease (COPD). They aimed to remove possible confounding of multiple disease processes and use of unplanned CPB. They

compared 14 patients undergoing elective CPB to 36 controls. They found no significant differences in duration of mechanical ventilation, ICU stay, length of stay, creatinine levels, PaO₂:FiO₂ at 1, 24, or 48 h, 30-d mortality, or 1 and 3-year survival. They concluded that CPB has no deleterious effects on early lung function or clinical outcome^[16]. Burdett *et al*^[17] performed a larger retrospective review comparing 53 CPB patients to 206 non-CPB patients. They similarly found no difference in PaO₂:FiO₂ ratios at 1 and 24 h post-transplant and no differences in duration of mechanical ventilation or transbronchial biopsy at 30 d^[17]. Pochettino *et al*^[18] found no significant differences in the following clinical outcome measures: duration of mechanical ventilation, re-intubation, re-operation for bleeding, sepsis, PGD, renal dysfunction, length of stay, or mortality. de Boer *et al*^[14] showed a significant survival benefit in emphysema patients when CPB was employed. This survival benefit was observed in patients with 2 HLA-DR mismatches as compared to those with 0 or 1 mismatches with immunosuppressive effects of CPB implicated as the source of survival benefit.

Airway management

Marczin *et al*^[11] suggest that CPB provides advantages

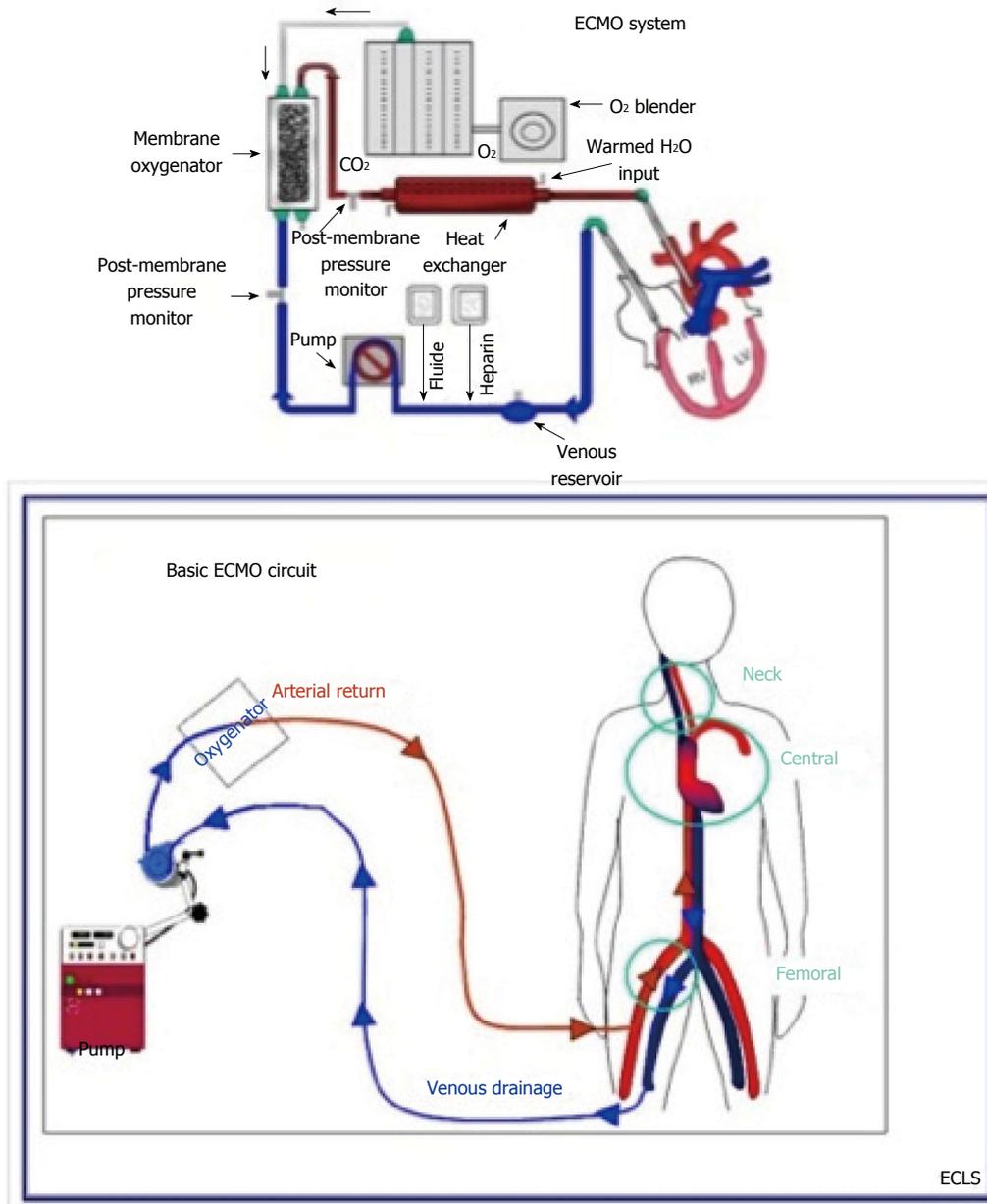


Figure 2 Schematic illustrating the components of an extracorporeal membrane oxygenation circuit: centrifugal pump, membrane oxygenator, inflow and outflow cannulas or cannula, and tubing with the potential to add ports for hemodialysis or ultrafiltration^[9]. ECMO: Extracorporeal membrane oxygenation.

in airway management, especially for small patients and those with suppurative lung disease in which double-lumen endotracheal tubes may present difficulties^[11]. They state a single-lumen endotracheal tube provides better access for removal of thick secretions. Pochettino *et al.*^[18] reported decreased perioperative pneumonia post-bilateral lung transplant in cystic fibrosis patients when CPB was employed ($P = 0.02$). They attributed this to decontamination of the operative field facilitated by CPB. CPB allows for simultaneous explantation of both infected lungs followed by lavage of native tracheal bronchial airways. Pochettino *et al.*^[18] commented on a different technique employed by the University of North Carolina in a similar study. Their group performed vigorous bronchoscopic washing of native lungs prior to explantation, thus

allowing for single-lung ventilation and avoidance of CPB.

Drawbacks of CPB

Use of CPB has been associated with early graft dysfunction due to activation of inflammatory mediators, increased operative and ischemic times, longer post-operative mechanical ventilation, increased pulmonary edema, increased mortality, as well as increased bleeding complications due to systemic heparinization^[1,10,12,19]. Pochettino *et al.*^[18] reported significant increase in fresh frozen plasma and platelet transfusions in patients undergoing CPB. Burdett *et al.*^[17] showed significant increases in blood transfusions ($P < 0.02$), and Szeto *et al.*^[16] showed significant increase transfusions of platelets and fresh frozen

plasma, each with ($P < 0.001$) in CPB groups^[16,17]. Gammie *et al*^[12] reported 11.4 units of perioperative blood transfusions in their CPB group compared to 6.0 units in their no-CPB group, ($P = 0.01$). Dalibon *et al*^[19] again showed significant differences in blood transfusions as well as duration of graft ischemia, duration of mechanical ventilation, pulmonary edema, and mortality at 48 h, 1 mo, and 1 year all being greater in CBP groups.

Inflammatory response to CPB

Inflammatory manifestations of CPB have been implicated in respiratory failure, ARDS, renal insufficiency, neurological deficits, and systemic inflammatory response syndrome (SIRS)^[20]. CPB alone invokes an inflammatory response thus far indistinguishable from ARDS and ischemia-reperfusion injury (IRI), including: activation of polymorphonuclear neutrophils (PMNs), macrophages, and monocytes; release of cytotoxic and chemotactic factors; increase in circulating cytokines such as endotoxin, interleukins, and tumor necrosis factor; complement activation; platelet activation and sequestration; and endothelial damage^[20-23]. Hypo-oncotic pressure resulting from large crystalloid priming volumes has been associated with endotoxin translocation^[24]. In recent years decreased priming volumes and use of colloid priming have been implemented in attempt to reduce this response. Reintroduction of activated blood from the surgical field into the CPB circuit leads to increased tissue plasminogen activator (tPA) and fibrinolytic activity^[24]. Interaction of blood cells with the CPB circuit results in complement activation. The balance of coagulation and anticoagulation remains a constant debacle in both ECMO and CPB. Thrombin plays an integral role in inflammation and coagulation and results in chemoattraction of monocytes and thus production of tissue factor as well as activation of endothelial cells, neutrophil adherence, and endothelial damage^[20,21]. Tissue factor leads to diffuse fibrin deposition throughout the microvasculature, followed by fibrinolysis which in turn leads to increased thrombin production, platelet aggregation and consumption^[21]. Anti-thrombin III (ATIII), identified as having potential anti-inflammatory and protective effects, may deficient post-CPB as well, possibly due to heparinization, hemodilution, or consumption^[20]. Systemic anticoagulation required for CPB compounded with often friable parenchyma and significant pleural adhesions may be directly responsible for increased peri-operative blood transfusions which come with their own share of inflammatory reactions, including transfusion related acute lung injury (TRALI). Transplanted lungs inevitably undergo cold and warm ischemia. Ischemia-reperfusion injury (IRI) has been shown to lead to pulmonary vasomotor dysfunction due to constriction of pulmonary vascular smooth muscle in the absence of hypoxia thus increasing

pulmonary vascular resistance (PVR)^[23]. Reperfusion of the transplanted lung with activated blood components from CPB circuit has been shown to exacerbate pulmonary vasomotor dysfunction in a dog model of autologous lung transplantation^[23].

Strategies are underway to help confront the inflammatory response to CPB. Aprotinin is a serine protease inhibitor, which has been shown to reduce bleeding and need for peri-operative transfusions, with possible anti-inflammatory effects related to inhibition of leukocyte transmigration through vascular endothelium^[20]. Heparin-coated circuits have reduced but not ameliorated complement activation^[22,24]. Baufreton *et al*^[24] prospectively evaluated the inflammatory response in 29 patients undergoing coronary artery bypass grafting and found that centrifugal pumps (CFP) resulted in increased intra-operative complement and neutrophil activation in comparison to roller pumps. Both groups showed significant increases in TNF- α , IL-6, and IL-8; however IL-8 was significantly greater at 2 h in the CFP group ($P = 0.02$)^[24]. Leukocyte depletion, and monoclonal antibodies are also being investigated^[21].

There is sufficient evidence to implicate CPB in lung damage on both a cellular level and in clinical outcomes. Both a multi-center prospective trial and a systematic review and meta-analysis found CPB to be a significant independent risk factor for PGD^[25,26]. A 10-year retrospective analysis yielded increased time on mechanical ventilation, pulmonary edema, blood transfusions, as well as 48 h, 1 mo, and 1-year mortality when CPB was compared to non-CPB^[19]. High-volume centers such as the University of Toronto are aiming to avoid CPB, which may be justified.

CPB and early graft dysfunction

The effects of CPB on early graft dysfunction is not a new question as evidenced by the retrospective review performed by Aeba *et al*^[27] on 100 lung transplant recipients from 1990-1992. They found significantly lower arterial/alveolar oxygen tension ratios of 0.48 ± 0.19 in the CPB group compared to 0.60 ± 0.22 in non-CPB group ($P = 0.025$). The CPB had more severe pulmonary infiltrates within 12 h after reperfusion than non-CPB group ($P = 0.034$). Prolonged intubation, > 7 d occurred in 29/55 in CPB compared to 8/45 in non-CPB group ($P = 0.003$). The non-CPB group showed better graft ($P = 0.05$) and patient ($P = 0.033$) survival at one month. Gammie *et al*^[12] retrospectively reviewed 94 double-lung transplantations and showed similar results. The reported significantly longer mean ischemic times ($P = 0.04$), increased perioperative blood transfusions ($P = 0.01$), worse arterial/alveolar oxygen tension ratios ($P = 0.001$), more severe pulmonary infiltrates ($P = 0.005$), and longer median duration of intubation in the CPB group ($P = 0.002$)^[12]. However, despite these findings, Gammie *et al*^[12] found no significant differences in 30-d mortality or

1-year survival between the two groups. It has been argued by proponents of CPB, that CPB groups are heavily weighted with patients having pulmonary hypertension, and perhaps the poor outcomes are not due to CPB. Gammie *et al.*^[12] performed a multivariate logistic regression analysis to address this concern, and pulmonary hypertension was not found to be an independent predictor of early graft dysfunction. Oto *et al.*^[28] noted that 80% of their patients requiring ECMO for PGD had undergone CPB, as compared to CPB use in only 16% of the patients not requiring ECMO for PGD, ($P = 0.0001$). Hartwig *et al.*^[29] similarly showed 66.7% of patients requiring ECMO for primary graft failure (PGF) had undergone CPB, compared to 16.2% in non-ECMO group ($P < 0.001$).

PGD

PGD a severe form of acute lung injury (ALI) occurs in approximately 10%-25% of lung transplant patients, with an 8-fold increase in 30-d mortality^[26]. Multiple strategies may be employed to minimize ischemia-reperfusion injury (IRI) and PGD. The Toronto group first removes the native lung with the least perfusion^[30]. Alveolar recruitment by holding sustained inspiration is thought to improve capillary recruitment and lead to decreased pulmonary vascular resistance (PVR). Toronto holds sustained inflation twice with a peak pressure < 25 cmH₂O, and positive end-expiratory pressure (PEEP) of 5 cmH₂O. They also remove their pulmonary artery clamp gradually over a 10-min period^[21]. Liu *et al.*^[26] performed a systematic review and meta-analysis of the clinical risk factors for PGD after lung transplant. Upon evaluation of 10042 patients, the following recipient risk factors showed a significant association with PGD: female gender, African American race, idiopathic pulmonary fibrosis (IPF), sarcoidosis, PPH, BMI ≥ 25 kg/m², and use of CPB. The following recipient factors were not found to significantly correlate with PGD: age, cystic fibrosis, secondary pulmonary hypertension (SPH), intra-operative inhaled nitric oxide (iNO), nor type of transplant, single vs bilateral^[26]. Diamond *et al.*^[25] performed a 10-center, prospective cohort study from March 2002 to December 2010, collecting data on 1255 patients, 211 (16.8%) of which developed grade 3 PGD by International Society for Heart and Lung Transplantation (ISHLT) criteria. They elevated recipient and donor factors, finding the following independent risk factors for PGD to be significant: donor smoking, FiO₂ during reperfusion, single lung transplant, use of CPB, overweight/obese BMI, sarcoidosis, and pulmonary artery hypertension (PAH)^[25].

CPB vs ECMO for lung transplant

ECMO has been used as an alternative to CPB in lung transplantation. The key differences between ECMO and CPB are peripheral vs central cannulation and duration of support. The details of ECMO circuits are discussed later in the ECMO section. ECMO

supports hemodynamic stability and gas exchange while allowing for lower doses of heparinization thus presumably decreasing bleeding complications. It also has the added benefit being able to provide support in all phases of transplantation.

Bittner *et al.*^[1] retrospectively reviewed 47 lung transplants performed at a single institution between 2003 and 2005. The purpose of their study was to compare the use of ECMO and CPB in lung transplant. Patients who underwent a combined heart-lung or lung-kidney transplant, coronary artery bypass, atrial septal defect repair, or emergency CPB support were excluded. Seven patients underwent CPB and 8 employed ECMO. Despite presumed benefits of decreased bleeding complications with ECMO, transfusion requirements for during the operation and 72 h afterward were 13.25 ± 1.6 units of PRBC for ECMO group vs 5.1 ± 2.8 for CPB group ($P = 0.02$). Activated clotting time (ACT) was kept > 450 s for CPB and between 160-220 s for ECMO group. Patients undergoing lung transplant without extracorporeal support received 2.7 ± 0.9 units PRBC in the same time period ($P = 0.001$). Indication for transfusion was hematocrit $< 30\%$; however later they state liberal blood product administration for intravascular volume. Weaning from mechanical ventilation was shorter in CPB group 3.9 ± 3.7 d vs 10.8 ± 6.6 d in the ECMO group ($P = 0.03$). Severe graft ischemia-perfusion injury, defined as ISHLT grade III, occurred in 9% CPB vs 13% in ECMO group, which is one patient per group. The ECMO patient survived after clot evacuation from thorax whereas CPB patient required ECMO support, massive blood transfusions, and passed on post-operative day 10 due to resistant coagulopathy, right heart failure, and intracranial bleeding. Similarly, Ko *et al.*^[31] concluded in their series of 10 single and 3 bilateral sequential lung transplantations that ECMO rather than CPB should be used.

MECHANICAL CIRCULATORY SUPPORT AS A BRIDGE TO TRANSPLANT

Due to extensive wait times, deterioration in pulmonary status while awaiting lung transplantation, and detrimental effects of mechanical ventilation, MLA is increasingly employed as a bridge to lung transplantation^[2,4]. There are two main forms of MLA, or extracorporeal life support (ECLS), which we will discuss, ECMO and ECLA. Let us first define each.

ECMO has become a general term, which now encompasses venoarterial (VA) and venovenous (VV) extracorporeal blood oxygenation and CO₂ removal. While venovenous ECMO is typically thought of for respiratory support, it may not be sufficient in pre-lung transplant patients, many of which have concomitant pulmonary hypertension and right heart failure. An ECMO circuit (Figure 2) contains a centrifugal pump,

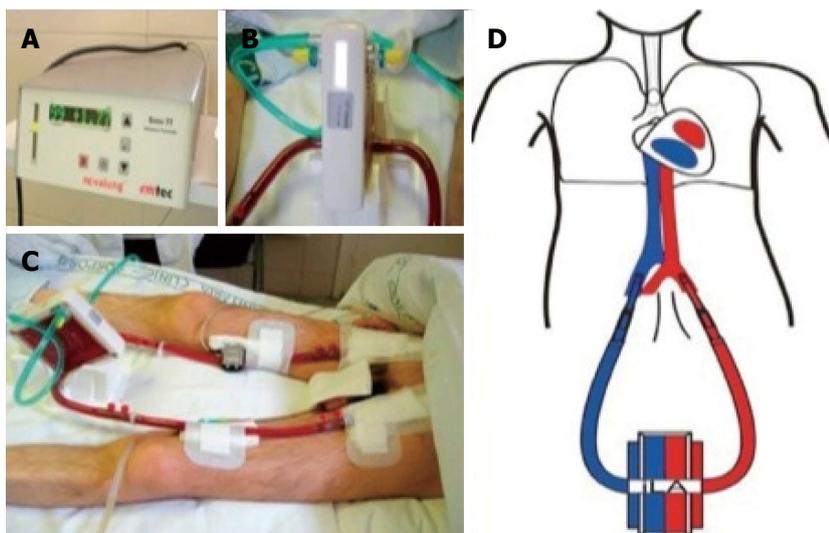


Figure 3 Extracorporeal lung assist, Interventional Lung Assist, or the NovaLung® System. A: Flow measure across the system, in this case 1.77 L of blood per minute; B: Arterial and venous lines, oxygen inflow, and extracorporeal membrane made of polymethylpentene which provides gas exchange by simple diffusion; C: Exchange membrane and arterial and venous cannulations; D: AV cannulation diagram for extracorporeal lung assist, note the absence of a pump^[52].

membrane oxygenator, inflow and outflow cannulas or cannula, and tubing with the potential to add ports for hemodialysis or ultrafiltration if needed^[3,9]. Peripheral cannulation for ECMO usually employs a combination of the following vessels depending on whether VA- or VV-ECMO is indicated: femoral artery, femoral vein, carotid artery, and internal jugular vein. A bicaval dual-lumen cannula is now available, which is inserted *via* the internal jugular vein, and potentially allows for increased mobility in awake VV-ECMO patients.

ECLA, the NovaLung® System (NovaLung GmbH, Heilbronn, Germany), sometimes referred to as Interventional Lung Assist (iLA) is illustrated in Figure 3^[32]. It is a pumpless, extracorporeal, biocompatible, membrane composed of polymethylpentene (PMP) fibers, which provides gas exchange *via* simple diffusion^[3]. ECLA is designed to function without a mechanical pump; however, one may be added if higher flows are needed. The device is typically implanted across an arteriovenous shunt between the femoral artery and femoral vein after heparinization. Flow rates of up to 2.5 L/min can be achieved depending on size of cannula and mean arterial pressure. Flow rates of 5.5 L/min may be achieved with the addition of an external pump. Because this device only receives approximately 15%–20% of cardiac output, it only oxygenates approximately 1/5 of venous return to the heart and is not recommended for severe hypoxia ($\text{PaO}_2/\text{FiO}_2 < 80 \text{ mmHg}$)^[33,34].

ECMO as a bridge to lung transplant

Early data on ECMO as a bridge to LTx were unfavorable^[33,35,36]. Fischer *et al.*^[4] reported a perioperative mortality of up to 60% in patients bridged to LTx with ECMO.

This could be attributed to the early attempts being in post-LTx patients with severe PGD, a pa-

tient population with severe immunocompromise and numerous other comorbidities. Over the last decade, technical advances in extracorporeal circuits such as centrifugal pumps, heparin-coated circuits, and polymethylpentene membrane oxygenators, among other advances have contributed to improved outcomes^[33]. Hayes *et al.*^[5] reports 1-year survival rates between 58% to 92% for patients bridged to LTx with ECMO.

Jackson *et al.*^[35] reported 3 cases in which ECMO was used successfully as a bridge to LTx; however each of these cases were complicated by bleeding requiring reoperation and massive transfusion in the post-operative period.

Bermudez *et al.*^[37] performed a single-center retrospective analysis of 1305 patients undergoing lung or heart-lung transplant between 1991 and 2010. Seventeen patients (1.3%) were bridged with ECMO, 5/17 (29%) between 1991–1993 and 12/17 (71%) after 2005. These patients were compared to non-ECMO control group. Statistically significant differences between the two groups included: double lung transplant 88% of ECMO group vs 54%, mean ischemic time 344 min for ECMO group vs 244, 48% of ECMO group required ECMO post-operatively due to PGD compared to 7.3% in control group. Increased post-operative ECMO for PGD was attributed to longer ischemic times and CPB or ECMO during transplantation. While ECMO group had increased perioperative morbidity, there were no significant differences in 30 d, 1-year, or 3-year survival or allograft function at 1-year^[37].

Lehmann *et al.*^[2] concluded that veno-arterial (VA) ECMO can be successfully used as a bridge to LTx as well as being utilized during LTx as a means for circulatory support. Lehmann *et al.*^[2] performed a retrospective analysis of 143 patients undergoing

LTx at their institution, 15 patients received MLA preoperatively, 14 ECMO, and 1 ECLA. Of the 5 ECLA patients, 4 were converted to ECMO after 10 d and one was weaned from MLA and went on to LTx. Two of the fifteen patients died prior to LTx due to intracranial hemorrhage and multi-organ failure (MOF). Eight patients from the MLA group were on mechanical ventilation, while 5 were awake and extubated. Six patients from the non-MLA group were on mechanical ventilation pre-transplant. Length of mechanical assistance pre-LTx ranged from 6 h to 30 d. There were no significant differences in demographic data, ischemia times, or intraoperative pulmonary arterial pressure (PAP). There were more sternotomies and bilateral sequential LTx performed in MLA group as well as 5 stroke events and 4 reoperations for bleeding. There was no significant difference in 30-d, 90-d, 1-year, and 5-year survival between MLA and non-MLA groups. Ten/13 (76.9%) survived to discharge^[2].

ECLA as a bridge to lung transplant

Fischer *et al.*^[4] reported on 12 patients with severe ventilation-refractory hypercapnia and respiratory acidosis, which were bridged to lung transplant with ECLA. At the time of Medical Advisory Secretariat Systematic Review in 2010, the Fisher case series was the only one to describe use of iLA as a bridge to LTx. It was compared to six studies using iLA for treatment of ARDS. While all studies showed an improvement in hypercapnia and acidosis, the pre-LTx group showed a drastic improvement over the first 6 h with PaO₂, pH, and PaCO₂ improving from 71 ± 27 mmHg, 7.21 ± 0.1, 128 ± 42 mmHg to 83 ± 17 mmHg, 7.34 ± 0.1 (*P* < 0.05), and 52 ± 5 mmHg (*P* < 0.05), respectively. However, these drastic improvements level off after 6 h whereas other groups continue to have significant improvements over subsequent days. These plateaus in the pre-LTx group may represent the inability of end-stage lungs for further improvement as compared to acute respiratory conditions associated with ARDS. Furthermore, PaO₂/FiO₂ ratio dropped after 24 h on iLA in pre-LTx group while continuing to improve in all other groups (135 pre, 150 2-6 h, 168 24 h, 139 2-7 d). Similarly, there was also an increased in PEEP requirements between 3-7 d in pre-LTx group from 6.8 ± 2.7 to 8.2 ± 1.4. iLA may be an effective bridge to LTx, improved survival and outcomes may be dependent on optimal timing of implementation^[4].

ECLA with a pulmonary artery to left atrial shunt (PA-LA) ECLS has also been proposed. Strueber *et al.*^[38] reported 4 cases of the use of PA-LA ECLS as a bridge to lung or heart-lung transplantation. All 4 patients survived to transplantation with mean time on ECLS of 17.5 d. Two patients required VA-ECMO for hemodynamic stabilization prior to PA-LA cannulation. They found that with PA-LA ECLS right ventricular function was able to recover, potentially eliminating the need for heart-lung transplantation. Extubation is

possible with PA-LA ECLS^[38].

Nosotti *et al.*^[39] reported on 4 cases in which ECMO was used as a bridge to transplant. While this is a small number of patients, they highlighted several key concerns in this patient population. Out of their 4 patients one had reoperation for hemothorax, one died from an ischemic stroke, and one had caval thrombosis adequately treated with heparin. This highlights the fine balance of coagulation management necessary in ECMO patients. They also commented on critical illness myopathy, which would likely be similar with mechanical ventilation in this same patient population, but again an important consideration. Furthermore, they commented that formerly healthy patients posted for emergent transplant do not have time to cope with being listed for organ transplantation and thus have significant psychiatric disturbances and depression^[39]. It could be argued that any patient undergoing salvage therapies such as ECMO may experience such disturbances. Awake ECMO may address the later two issues as well as avoidance of complications associated with general anesthesia, intubation, and mechanical ventilation such as hemodynamic collapse on induction and pulmonary and systemic inflammation associated with long-term ventilation^[40,41].

Awake/ambulatory ECMO as a bridge to lung transplant

This brings us to Olsson *et al.*^[42] who in 2010 were the first to report on five patients with cardiopulmonary failure secondary to pulmonary hypertension in which VA-ECMO was used in awake, spontaneously breathing patients. All patients were cannulated under local anesthesia without sedation, and with the exception of two patients who later required intubation secondary to bleeding complications, all patients were able to eat, drink, and participate in active physical therapy as well as psychotherapy. In this series, there were no reports of limb ischemia, hemolysis, platelet activation, systemic inflammatory response, or clinically evident embolic events; however 60% (3/5) of patients had significant bleeding events, two of which necessitated endotracheal intubation and one requiring repeat blood transfusions.

Fuehner *et al.*^[40] went on to report on 26 patients receiving awake ECMO as a bridge to LTx and compared these to 34 patients in whom mechanical ventilation (MV) was used as a bridge to LTx. Of note, 18 patients (53%) in the MV group were placed on ECLS prior to LTx (4 VV-ECMO, 12 AV-ECLA, and 2 PA-LA ECLA). Eight patients in the awake ECMO group (31%) required blood transfusion for bleeding complications (puncture sites, *n* = 6; epistaxis, *n* = 1; hemoptysis, *n* = 1). Seven patients (27%) required intubation and only 3 of these survived to discharge. Five (19%) developed sepsis, 1/5 survived to LTx. Patients in the ECMO group required significantly less days on MV after LTx (*P* = 0.04). ECMO group had an improved survival to transplant, improved survival

Table 1 Comparison of mechanical circulatory support modalities

	Open/closed	Pump	Cannulation	Indications	Phase of transplant
CPB	Open	Yes (Centrifugal or Roller)	Central (intrathoracic)	Hemodynamic instability Pulmonary hypertension Right ventricular failure <i>En bloc</i> double-LTx	Intraoperative
ECLS/iLA	Closed	No (Pump may be added)	Usually peripheral (also PA-LA)	Refractory: Hypercarbia (PCO ₂ > 80 mmHg)	Bridge to Tx (Awake)
VV-ECMO	Closed	Yes (Centrifugal or Roller)	Peripheral (BCDLC)	Refractory: Hypoxia (PaO ₂ :FiO ₂ < 80 mmHg) Hypercarbia PCO ₂ > 80 mmHg	Bridge to Tx (Awake) Graft Salvage
VA-ECMO	Closed	Yes (Centrifugal or Roller)	Peripheral (sometimes Central)	Hemodynamic instability Pulmonary hypertension Right heart failure	Bridge to Tx Intraoperative Graft Salvage

CPB: Cardiopulmonary bypass; ECLS: Extracorporeal lung support; iLA: Interventional lung assist; VV: Venovenous; VA: Venoarterial; ECMO: Extracorporeal membrane oxygenation; PA-LA: Pulmonary artery-left atrium; BCDLC: Bi-caval dual lumen cannula.

post-transplant, with overall 6-mo survival 62% ECMO group vs 35% MV group, ($P = 0.05$). If only those patients who received LTx are considered 80% ECMO group vs 50% MV group at 6-mo, ($P = 0.02$). Patients in the ECMO group also trended towards shorter ICU stays and shorter hospital stays^[40].

The myriad of extracorporeal support strategies available as a bridge to lung transplantation should be employed in the following order if possible: iLA (hypercarbia, respiratory acidosis), VV-ECMO (severe hypoxia, hypercarbia), VA-ECMO or PA-LA ECLS (need for hemodynamic support, pulmonary HTN, right heart failure) (Table 1). Oxygenation requires flows 3–5 L/min whereas CO₂ removal requires flows (0.5–1.0 L/min)^[43]. It has been suggested that even VA-ECMO does not successfully unload the right ventricle^[33]. Proponents of PA-LA ECLS state that this cannulation strategy may be employed in those patients who would benefit from an atrial septostomy as this decreases the work of the right ventricle and uses the elevated pulmonary artery pressure to drive flow across the oxygenator. By creating an oxygenating shunt PA-LA ECLS decreases right ventricular work while avoiding central hypoxemia created by an atrial septostomy. It is noted that patients with this degree of right ventricular failure will likely need peripheral VA-ECMO cannulation for hemodynamic support prior to induction of anesthesia.

Awake MLA has many benefits and should be employed whenever possible. In patients with pure respiratory failure VV-ECMO and ECLA offer safe bridging strategies. Hypercarbic respiratory failure may be bridged with ECLA, whereas hypoxic respiratory failure benefits from the higher flows provided by VV-ECMO. In patients with concomitant pulmonary hypertension and right ventricular failure, VA-ECMO and PA-LA ECLA are the two main options for bridging these patients to transplant. Olsson *et al*^[42] were able to achieve cannulation and successful bridging to transplant with VA-ECMO without sedation, intubation, or mechanical ventilation thus avoiding

the potential drawbacks of each. PA-LA ECLS provides immediate decrease in right ventricular afterload but has the necessity of general anesthesia, endotracheal intubation, and sternotomy or thoracotomy. None of the current case series provide hemodynamic data to assess improvement in right ventricular function. Further studies need to be done to assess the pros and cons of these two potential bridging strategies for this frequent scenario of pulmonary hypertension and right heart failure.

Post-transplant

Severe graft failure is the most common cause of death in the first 30 d post-lung transplant^[2]. The incidence of pulmonary graft failure (PGF) in patients post-lung transplant ranges from 13%–35%^[28]. PGF requiring ECMO support ranges from 2.1%–7.4% of lung transplants performed in the reported series^[2,28]. Use of MLA has been reported in 2.1%–5.5% of lung transplants for treatment of severe graft failure. PGF is defined as the inability of a pulmonary allograft to sustain ventilation and oxygenation despite full mechanical support^[44]. There are varying definitions of early PGF with some authors classifying it as < 7 d post-LTx and others within 24 h^[44]. Multiple factors have been associated with early PGF, including: prolonged ischemic time, ischemia-reperfusion injury, prolonged CPB, blood transfusions, circulatory arrest, significant active infection in recipient pulmonary bed, technical complications, and quality of donor lung^[28,44]. Of the possible contributors to early PGF, ischemia-reperfusion injury (IRI) is one of the most well-recognized complications of LTx, accounting for approximately one-third of 30-d mortality^[29]. Patients experiencing IRI may present with worsening compliance, hypoxemia, diffuse pulmonary infiltrates, and copious airway secretions^[29]. Late PGF is often multifactorial and may be irreversible^[28,44].

Glassman *et al*^[44] concluded that ischemia-reperfusion injury and acute graft dysfunction could be successfully reversed with early aggressive intervention.

They reported on 17 cases of ECMO support for severe graft failure in 16 patients between 1991 and 1993. These patients represented 7.4% of the 215 patients who underwent transplant during this time period. They noted significant differences in outcome depending on early (< 7 d post-LTx) or late (\geq 7 d post-LTx) initiation of ECMO support. In the early group, 80% (8/10) patients were weaned from ECMO and 70% (7/10) were long-term survivors, and 71% (5/7) had normal long-term lung function. In the late group, 0% (0/7) survived to discharge^[44].

Oto *et al.*^[28] reported on 10 (2.1%) of 481 LTx patients at their institution that were placed on ECMO for severe PGF. They compared 4 patients from (1990-1999) and 6 patients from (2000-2003). There was a significantly different time from transplant to initiation of ECMO support between these two groups with mean of 21 d in "early" group to a mean of 0.5 d for the recent group, ($P = 0.01$). PaO₂ 12 h post-initiation was significantly better in recent group 341 ± 90 mmHg vs 90 ± 23 mmHg, ($P = 0.03$). There was improved survival between "early" and recent groups; however this could be explained by observation of Glassman *et al.*^[44] above that ECMO is effective in early PGF, but not in late PGF. Oto *et al.*^[28] have the lowest reported incidence of ECMO use for PGF of any of the reported series, at 2.1% of their LTx cases. They attribute this to: (1) pretreatment of donor lungs with prostacyclin; (2) prospective T-cell and B-cell crossmatching; (3) less use of CPB; (4) inhaled nitric oxide during implantation; and (5) use of differential ventilation for unilateral PGF. While the incidence of bleeding improved from 50% in "early" group to 32% in recent group, the mortality rate for patients with bleeding complications was 100% suggesting that even with improved ECMO technology bleeding is still a significant problem^[28].

Hartwig *et al.*^[29] reported 23 patients requiring ECMO support for PGF. They compared those receiving VA- vs VV-ECMO. There were no significant differences in patient demographics, underlying pulmonary disease, or type of transplant between the two groups. However, there were significantly larger numbers of COPD/A1AT, Retransplant, and PPH patients in the ECMO group compared to non-ECMO group, with relative risk (RR) 0.272, 5.93, 5.76, respectively. CPB was used in 66.7% of those patients needing ECMO post-op as compared to 6.6% in the non-ECMO group, ($P < 0.001$). While not reaching statistical significance, ($P = 0.062$), donor/recipient BSA ratios indicated that the donor was smaller than the recipient in the majority of ECMO cases. VA-ECMO group had more complications, 30 of 39. VV-ECMO group had 87.5% 30-d survival, and a 3-year survival comparable to non-ECMO group. Survival data for VA-ECMO group was not explicitly provided. They concluded that VV-ECMO was associated with fewer complications and improved outcomes in comparison to VA-ECMO

and recommend early initiation of VV-ECMO in all LTx patients with severe IRI unless severe cardiac dysfunction refractory to VV-ECMO is present^[29].

Blood stream infections associated with mechanical circulatory support

Of the studies reviewed, very few comment on blood stream infections or the incidence thereof. Fischer *et al.*^[4] reported positive blood cultures in 7/12 (58.3%) of patients bridged to LTx with the NovaLung® iLA. In their case series of awake ECMO as a bridge to LTx, Olsson *et al.*^[42] reported 2/5 (40%) patients with infectious complications: one who died of septic multiorgan failure on the 8th day of ECMO support and one who died 2 mo post-LTx of septic multiorgan failure. Similarly, Bermudez *et al.*^[37] reported sepsis in 7/17 (41%) of patients bridged to LTx with ECMO. Of these 3 were bacterial and 4 fungal. Of the fungal infections 3/4 (75%) were caused by *Aspergillus*.

Fuehner *et al.*^[40] reported 5/26 (19.2%) with sepsis-like syndrome, all with negative blood cultures, 4 who went on to die of multisystem organ failure prior to transplant. In patients requiring ECMO post-transplant due to primary graft failure had the following reported rates of sepsis: Hartwig *et al.*^[29] 5/23 (21.7%); Oto *et al.*^[28] reported 2/10 (20%); Wigfield *et al.*^[45] 4/22 (18.2%). Fischer *et al.*^[46] queried the ELSO database and found 151 patients who underwent ECMO for PGD post-LTx, of these 15% were found to have septic complications.

Aubron *et al.*^[47] performed a retrospective review of 146 ECMO cases lasting greater than 48 h. They reported a 16.4% occurrence of blood stream infections (BSI), with *Candida* being the most common pathogen. Sequential Organ Failure Assessment (SOFA) score prior to cannulation [Odds ratio (OR) 1.23] and the duration of ECMO therapy (OR 1.08) were independent predictors of BSI. While BSI was associated with significant increase in ICU and overall hospital length of stay, it was not associated with increased mortality. Of note, these patients were not given prophylactic antibiotics but likely received antibiotics for underlying disease processes or surgical procedures. This study is of all ECMO patients at one institution and does not specifically represent lung transplant patients.

In a similar study, Pieri *et al.*^[48] retrospectively identified 46 patients undergoing ECMO (24 VA and 22 VV) for greater than 48 h in the time period reviewed. This study similarly found infection rate to correlate with SOFA score, duration of ECMO therapy, as well as ICU and hospital length of stay. Blood stream infection was identified in 8/46 (17.4%) of ECMO patients (4 VA and 4 VV). Causative organisms included: *Candida albicans* (2), *Candida parapsilosis* (2), *Klebsiella pneumoniae* (2), *Candida tropicalis* (1), *Corynebacterium minutissimum* (1), *Staphylococcus epidermidis* (1), and *Acinetobacter baumannii* (1). They note that 42% of ECMO centers use

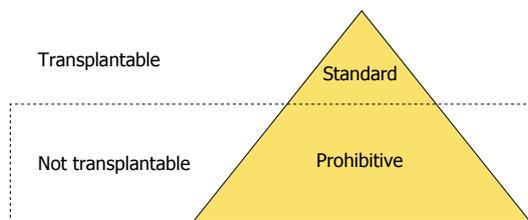


Figure 4 Only 15%-20% of donor organs meet standard criteria for lung transplant.

prophylactic antibiotics while only 2% report routine use of antifungal agents.

There have been no randomized controlled trials to evaluate the most appropriate prophylactic antimicrobial regimens for patients undergoing ECMO. This data could be beneficial in management of ECMO patients and could be combined with institutional antibiograms to provide the best possible prophylactic regimens for these patients.

EVLP

Shortage of suitable donor organs

The issue of critical organ shortage for lung transplantation has already been previously mentioned. In 2013, 1923 lung transplants were performed in the United States, and 174 patients died while on the waiting list^[49]. Only 15%-20% of offered organs meet criteria for transplantation^[3,50,51]. Figure 4 demonstrates the disparity between available organs and those meeting criteria for transplant. The International Society for Heart and Lung Transplantation (ISHLT) lists the following as the currently accepted "ideal" lung donor criteria: age < 55 years, ABO compatible, clear chest radiograph, approximate size match, clear chest X-ray, PaO₂/FiO₂ > 300 on 100% FiO₂ and positive end expiratory pressure (PEEP) of 5 cmH₂O, < 20 pack-year smoking history, absence of chest trauma, no evidence of aspiration/sepsis, no prior cardiopulmonary surgery, absence of organisms on sputum gram stain, and clear bronchoscopy^[52]. Failure of donor lungs to meet criteria is largely due to events leading up to death which result in poor organ, including: barotrauma, pulmonary edema, aspiration, and pneumonia as well as direct effects of brain death^[53]. Brain death is thought to lead to neurogenic pulmonary edema and inflammatory lung injury due to hemodynamic changes and cytokine storm associated with brain death^[53].

EVLP is an innovative use of mechanical circulatory support in an attempt to expand the available donor pool^[50]. This technology utilizes components of CPB or ECMO to isolate the lung and evaluate its function outside the body as a means of assessing suitability for transplant. The theorized mechanisms of benefit are removing interstitial fluid, washing out of inflammatory mediators, and allowing for alveolar recruitment at low airway pressures. Similar to the benefits observed

when ECMO is utilized for PGD, EVLP aims to provide a platform for organ reconditioning which will allow previously untransplantable organs to meet criteria for transplantation.

History of ex-vivo perfusion

First written ideas of ex-vivo perfusion are tracked back to 1812. In 1866, a frog heart was kept alive ex-vivo for 48 h, and a perfused liver ex-vivo was capable of producing urea. In 1935, Alexis Carrel successfully perfused a cat thyroid for 18 d using the Lindbergh pump, placing both men on the front of Time magazine^[54]. They performed several experiments showing that whole organs including ovary, thyroid, kidney, and heart could maintain functionality and cell proliferation ex-vivo^[53].

Support for use in humans

Animal models of EVLP showed no detrimental effects to the organ or recipient and additionally showed improved oxygenation, decreased mean airway pressure, pulmonary artery pressure, and inflammatory markers^[55]. In our own rat and porcine models, EVLP provides a platform for organ evaluation, reconditioning, disease modeling, and administration of therapeutic agents^[56]. Preclinical porcine models by Cypel *et al.*^[57] showed that normal and injured donor lungs could be maintained on EVLP for up to 12 h with excellent post-transplant lung function.

In 2001, Steen *et al.*^[58] published on the first ex-vivo perfused human lung transplant, a non-heart-beating donor lung transplanted into a 54 years old female with COPD yielding excellent function. Cypel *et al.*^[53] went on to perform a prospective, non-randomized clinical trial in which 23 high-risk donor lungs were placed on EVLP for 4 h and if physiologically appropriate, transplanted into human recipients. Three patients first underwent a safety and logistic feasibility study in which standard criteria donor lungs were transplanted, one with conventional methods and one after 1 h of EVLP with similar outcome. Twenty of the 23 high-risk donor lungs met criteria for transplant with improvement in median PO₂:FiO₂ from 335 mmHg donor lung to 414 and 443 mmHg at 1 and 4 h of EVLP, respectively ($P < 0.001$). These 20 lungs were transplanted and compared to 116 conventional lung transplants performed during the same time period. The incidence of PGD within 72 h of transplant was 15% for EVLP group, while 30% for control group. The EVLP group had no significant differences in length of stay, mechanical ventilation requirements, bronchial complications, and 1-year survival.

In a similar study conducted in Italy, incidence of PGD immediately after transplant and at 72 h was evaluated in EVLP ($n = 8$) and standard ($n = 28$) lung transplant groups^[59]. Eleven donor lungs initially underwent EVLP, 3 failed to meet criteria for transplantation, 2 secondary to infection, and 1 due

to poor gas exchange. They note that EVLP allowed for identification and confirmation of right lower lobe infection that was not evident on xray or CT scan performed on the day of donation. Increase in mean PaO₂:FiO₂ showed significant improvement at 1, 2, 3, and 4 h on EVLP ($P < 0.05$). Lung radiographs performed post-EVLP showed resolution of edema. In the standard lung transplant group, 50% (14/28) patients had PGD 3 at time zero, 7 of which continued through 72 h. Consistent with early mortality associated with PGD 3, 4 of these 7 patients did not survive to hospital discharge. In the EVLP group, 37.5% (3/8) patients had PGD 3 at time zero, all of which resolved by 72 h resulting in 0% PGD 3 at 72 h.

Sage *et al*^[60] performed a similar study in France in which 32 pairs of unsuitable donor lungs were reconditioned with *ex-vivo* perfusion per the Toronto technique. Of these, 31 were deemed suitable for transplant. One pair of lungs became progressively edematous with decreasing PaO₂:FiO₂. Reconditioned lungs were compared with 81 double-lung transplants performed during the same time period. EVLP resulted in a significant improvement in median PaO₂:FiO₂ ($P < 0.0001$). There were no significant differences in PGD at 72 h, length of mechanical ventilation, ICU or hospital length of stay, 30-d mortality, or one-year survival.

In utilizing unsuitable donor lungs reconditioned with EVLP, increased incidence of PGD was one of the primary concerns. These studies have shown that this concern is not validated, and in fact lungs reconditioned with EVLP may have lower incidence of PGD when compared with standard lung transplant controls.

Donor selection

EVLP seeks to make marginal donors a viable option. Marginal donors can be defined as those with arterial oxygen tension : fraction of inspired oxygen (PaO₂:FiO₂) ratios < 300, pulmonary edema, blood transfusions > 10 units, donation after cardiac death (DCD), pneumonia, or poor inflation/deflation at the time of procurement. Those with pneumonia or other active infection, severe mechanical lung injury contusions in more than one lobe, or gross gastric aspiration remain excluded.

DCD

In controlled DCD donors, graft assessment may occur prior to life support and therefore, EVLP is not typically employed for organ assessment^[61,62]. In uncontrolled DCD donors, duration of warm ischemia is often unknown and assessment prior to cardiac arrest is not possible. In these donors, EVLP provides a means of organ assessment and remodeling. Snell *et al*^[63] used a dog model to compare all Maastricht categories with varying preservation techniques with all groups achieving a PaO₂:FiO₂ between 472 to 586 mmHg without a significant increase in lung weight.

Similarly, Inokawa *et al*^[64] used a rat EVLP transplant model to compare four groups: heart beating donors (HBD), non-heart-beating donors (NHBD) without *ex-vivo* perfusion, NHBD perfused with Earle's solution, and NHBD perfused with Earle's solution supplemented with washed porcine erythrocytes^[64]. Blood samples obtained from the transplanted left pulmonary vein did not show significant differences in oxygenation between the two groups. At explantation wet-to-dry ratios were greater in left transplanted lungs as compared to native right lungs; however, there were no significant differences between the four groups. Steen *et al*^[58] were the first to report on clinical transplantation of DCD donor lungs after assessment by EVLP. In their review, Yeung *et al*^[62] list the following advantages provided by EVLP: (1) facilitates recruitment of atelectatic lung; (2) facilitates bronchoscopic clearance of airway secretions; (3) removal of clots *via* transient retrograde perfusion; and (4) improves ventilation/perfusion matching by avoiding interference of stiff chest wall and immobile diaphragm. As EVLP strategies improve, they are providing not only a means of assessment but a platform for organ remodeling and delivery of therapeutic agents.

Clinical trials

The HELP trial was a prospective, non-randomized performed from September 2008 through September 2009, which enrolled 102 lung transplant patients. Donor lungs initially rejected for transplant based on current criteria were placed on EVLP with Steen at 37 °C for 4 h. Rejected organs reaching a PaO₂/FiO₂ > 400 mmHg while on EVLP were transplanted into 16 recipients. These patients were compared to 86 controls receiving standard lung transplants during this same period. PGD scores, 30-d mortality, duration of intubation, length of ICU stay, and length of hospital stay were found to be equivalent in both groups^[50].

A multi-center prospective trial, NOVEL, is currently underway at 6 US lung transplant centers: New York Presbyterian-Columbia University Hospital, University of Colorado Medical Center, Brigham and Women's Hospital, Duke University Medical Center, University of Pennsylvania Medical Center, and University of Maryland Medical Center. This phase I clinical trial is funded by XVIVO Perfusion (Vitrolife, Inc, Englewood, CO) and will evaluate 30-d mortality, PGD, ICU length of stay, mechanical ventilation and ECLS utilization, and survival. We anxiously await the results of this trial in hopes that EVLP will achieve FDA support and help us decrease the number of patients dying while awaiting lung transplant.

CONCLUSION

There are numerous established and emerging mechanical circulatory support modalities that may be employed throughout the course of a lung transplant

patient. The use of CPB during lung transplantation is controversial. There are a paucity of randomized controlled trials to evaluate the utility of CPB in lung transplantation. The trials that have been reviewed here are inconsistent in their findings; further proving the need for higher powered studies. While the detrimental effects of CPB are well documented, right ventricular failure and/or hemodynamic instability are indications for the use of mechanical circulatory support during lung transplantation. VA-ECMO may also be used for this purpose and has the added benefits of peripheral cannulation and ability to span multiple phases of care, from bridging to post-operative support. Randomized controlled trials need to be performed to further investigate this controversial issue.

Extracorporeal support may also be required as a bridge to lung transplant as long wait times may result in respiratory failure prior to organ availability. To this avail, the least invasive modality should be employed if possible for the relative indication: iLA (hypercarbia, respiratory acidosis), VV-ECMO (severe hypoxia, hypercarbia), VA-ECMO or PA-LA ECLS (need for hemodynamic support, pulmonary HTN, right heart failure). These same modalities may be applied with the same order of preference for post-operative support or PGF. All of these modalities may be performed in awake patients and should be whenever possible.

While increased wait times necessitate bridging with mechanical circulatory support, EVLP may be emerging as the answer to increasing organ utilization and thus decreasing wait times. EVLP has shown excellent results in animal models as well as reproducible results in human studies around the world. We now anxiously await the results of ongoing clinical trials that may lead to the approval of EVLP for widespread use.

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