Normothermic Ex Vivo Lung Perfusion: A Review of the Toronto Protocol

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Abstract

Traditional methods of lung preservation include cold storage of lungs on ice prior to transplantation. Previous reports have identified deleterious outcomes with regards to prolonged cold ischemic time. Herein, a novel technique has been developed to perfuse lungs at normothermia. This review highlights a Toronto team's experience with developing and utilizing this system known as normothermic ex vivo lung perfusion (EVLP). EVLP allows for the assessment of marginal lungs and for reconditioning through therapeutic intervention. Various clinical studies have shown equivalent post-transplant outcomes when using the system on lungs that would have initially been declined for transplantation. EVLP ultimately expands the pool of available donor lungs for transplantation and its potential is addressed in this review.

Introduction

Over the past 25 years, lung transplantation has become an established and increasingly successful treatment for patients with end-stage lung disease. However, the waiting list for donor lungs has progressively increased and currently exceeds the number of available organs. As a result, large transplant registries in Europe and the United States have reported wait list mortalities as high as 30-40%.[1-4] One of the main driving factors contributing to the lack of organs is the small quantity of potential donor lungs that fulfill donation criteria. This can be attributed to the fact that physicians are often conservative in selecting lungs for transplant due to the risk of graft dysfunction. Indeed, 15-20% of lungs continue to transplant from multi-organ donors, inferring that up to 85% of lungs are rejected in some regions for lung transplantation.[5]

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The current standard clinical method of lung preservation is cold hypothermic static preservation, which offers very limited opportunities for physicians to assess graft quality and function.[6] Briefly, this method involves performing a cold pulmonary flush using a low potassium dextran solution, paired with lung ventilation during organ retrieval. The lungs are then inflated, explanted, and stored at 4°C until they are ready to be transplanted into the recipient.[6] During this time, there is a rapid decline in lung metabolic function, which is the primary reason for low assessment ability.[7]

One strategy developed to overcome this limitation is normothermic ex vivo lung perfusion (EVLP). This technique allows for the maintenance of donor lungs in a physiological state, allowing lung cells and tissues to maintain their metabolic activity and viability for extended periods of time.[8] As a result, marginal graft lung function can be assessed prior to transplantation, allowing for higher organ utilization rates. The addition of EVLP also provides the opportunity for therapeutic intervention. The option of reconditioning marginal or otherwise declined lungs can greatly enhance organ viability and expand the pool of potential donor lungs. Figure 1 illustrates the potential increase in available transplantable lungs through the use of EVLP.

This review will provide a background on the EVLP technology and its current and future potential clinical applications. We will focus on the protocol developed by a group from Toronto known as the Toronto EVLP method. Initial strategies using EVLP were only able to preserve lungs for 60 minutes prior to the development of circuit-induced lung injuries.[9] The Toronto group has mastered the EVLP technique, becoming the first to achieve long-term stable perfusion times of over 12 hours.[10] As a result, this method has generated a large amount of research and clinical data in the literature.

The Toronto Protocol

There are currently three EVLP methodologies being used internationally. Similarities and differences between them are summarized in Table 1.

To begin the procedure, the donor lungs are retrieved and stored at 4°C in a cooler for transport. The pulmonary lung bloc is dissected to prepare for cannula insertion. A specific

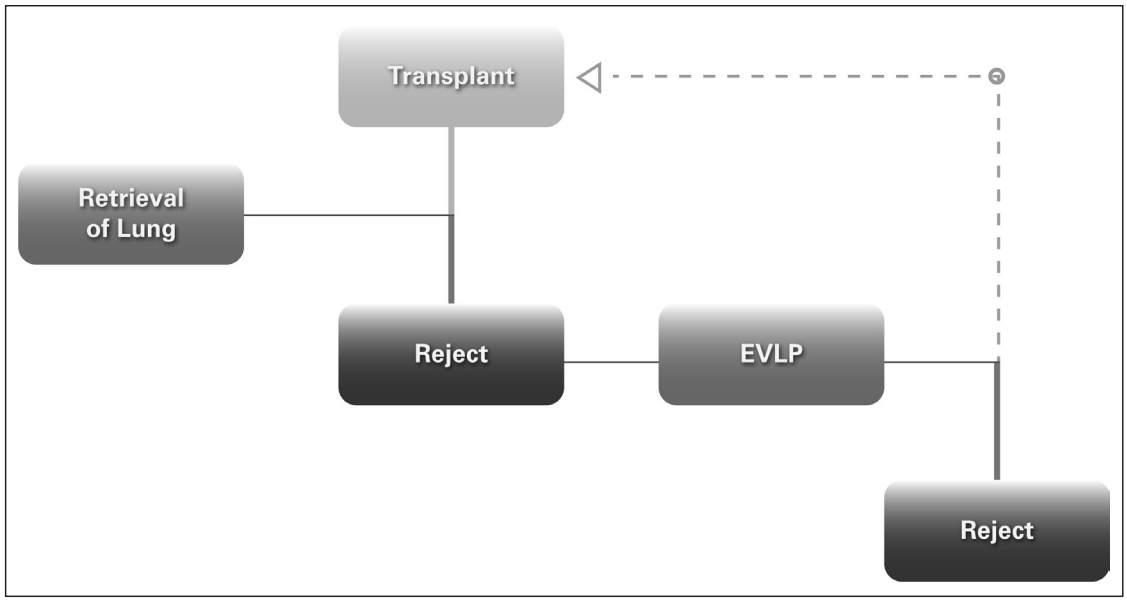

Figure 1. Flowchart of transplantable donor lung expansion using ex vivo lung perfusion (EVLP)

Table 1. Ex vivo lung perfusion methodologies[10-12]

	Protocol		
	Toronto	**Organ Care System (OCS)**	**Lund**
Flow			
Pump type	Centrifugal	Pulsatile	Roller
Flow at start of perfusion	150 mL/min	200 mL/min	100 mL/min
Target flow total	40% cardiac output	2.5 L/min	100% cardiac output
Ventilation			
Mode	Volume control	Volume control	Volume control
Tidal volume	7 mL/kg	6 mL/kg	3-8 mL/kg
Frequency	7 bpm	10 bpm	12 bpm
PEEP	5 cmH_2O	5 cmH_2O	5 cmH_2O
FiO_2	21%	21%	50%
Pressure			
Pulmonary artery	< 15 mmHg	< 20 mmHg	< 20 mmHg
Left atrium	3-5 mmHg	0 mmHg	0 mmHg
Temperature			
Perfusion start	25°C	32°C	25°C
Ventilation start	32°C	32°C	32°C
Evaluation start	37°C	37°C	37°C
Perfusion solution	STEEN™ solution	OCS solution + red cells (Hct 15-25%)	STEEN™ solution + red cells (Hct 10-15%)
Total perfusion time	Up to 12 hours	Transport time only	2-7 hours

cuffed cannula is stitched to the left atrium using two 4-0 polypropylene running sutures. A cannula is also inserted into the main pulmonary artery and secured using two heavy silk ties. The trachea is clamped and the tracheal staple line is opened to keep the lungs inflated. An endotracheal tube is inserted into the trachea and secured using two heavy silk ties, similar to that of the pulmonary artery. The endotracheal tube is then clamped, allowing for the release of the tracheal clamp. Before attachment to the circuit, the lungs are flushed (retrograde) with 1 L of a low-potassium dextran solution (Perfadex®). The full protocol is described by Cypel et al.[10]

The Toronto EVLP circuit consists of six components: an outflow line, a hollow-fiber-gas-exchange membrane, a centrifugal pump, a hard-shell reservoir, a leukocyte filter, and an inflow line. Additional components include a ventilator, a gas mixture (86% N_2, 8% CO_2, 6% O_2) cylinder, a heater, and a roller pump to recirculate leaked perfusate from the lungs (Figure 2).

The pulmonary artery and left atrial cannulas are connected to attachment sites on the circuit. The endotracheal tube is connected to a ventilator. Ventilation parameters are set to a tidal volume of 7 ml/kg of the donor's bodyweight, respiratory rate of 7 beats per minute, positive-end expiratory pressure of 5 cmH_2O, and FiO_2 of 21%. Ventilation is initiated only once the circuit has been primed.

The Toronto EVLP method uses an acellular perfusion solution known as STEEN™ solution. This is a low-potassium dextran solution supplemented with approximately 40% albumin. The addition of albumin optimizes the colloid pressure of the solution, allowing for fluid maintenance within the intravascular space. This perfusion solution was designed to prevent pulmonary edema, and provides nutrients for pulmonary homeostasis during perfusion.[14-16]

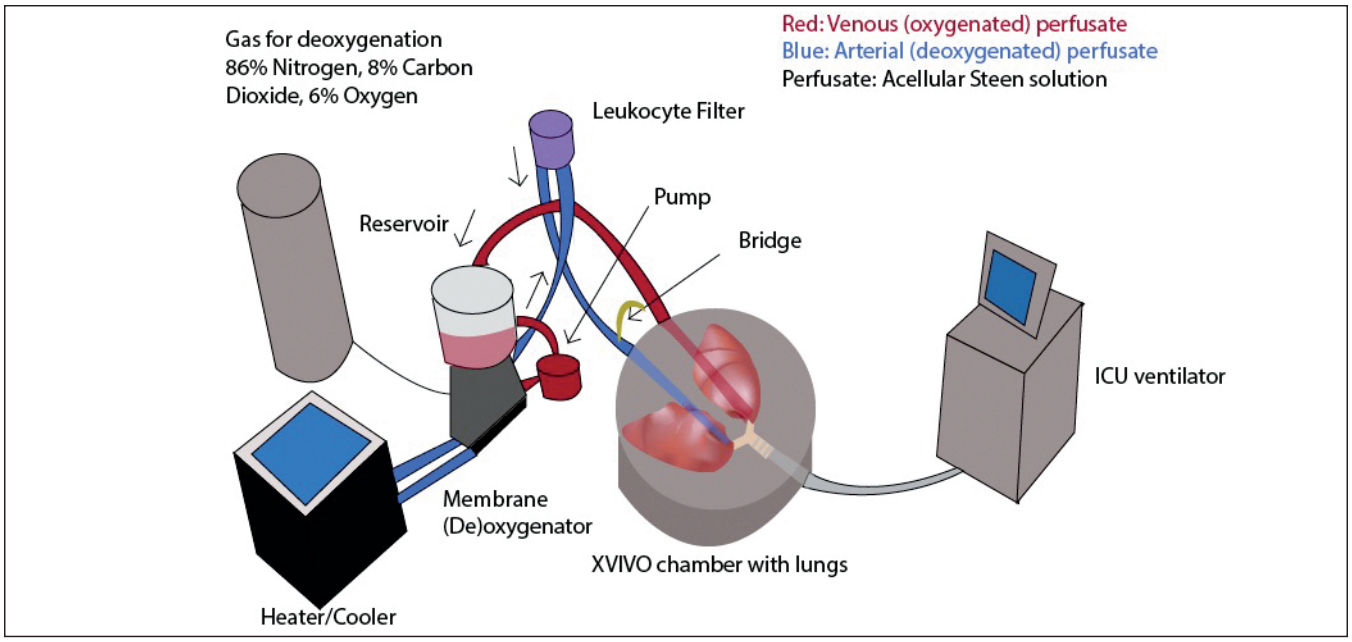

Figure 2. Schematic of the ex vivo lung perfusion circuit[13]

The EVLP circuit is primed with 2 L of STEEN™ solution, 500 mg methylprednisone (Solumedrol; Sandoz Canada, Boucherville, Canada), 3000 IU of unfractionated heparin (Organon, Canada), and 500 mg antibiotic (imipenem/cilastatin, Primaxin; Merck, Whitehouse Station, NJ, USA). The lungs are gradually warmed to 30°C after 10 minutes, and to 37°C after 20 minutes of perfusion. Perfusion flow rates are also gradually increased from 20% of the target flow rate, reaching 100% at the 1-hour perfusion mark. Once the lungs have reached 32°C, ventilation is initiated. Upon the initiation of ventilation, the gas mixture (86% N_2, 8% CO_2, 6% O_2) is turned on and applied at a sweep of 1 L/min. The target post-membrane partial pressure of carbon dioxide (CO_2) is between 35 and 40 mmHg. The first recruitment maneuver (up to 25 cm H_2O) is performed after 60 min of perfusion. STEEN™ solution in the circuit is partially exchanged hourly (500 mL the first hour, and 250 ml/hour thereafter).

The EVLP platform allows for the assessment of pulmonary artery pressure, left atrial pressure, peak airway pressure, plateau pressure, static compliance, and dynamic compliance. Perfusate gas analysis can be done in order to monitor glucose levels, lactate levels, and the standard blood gas analysis readings.[17]

EVLP as a Therapeutic Platform

Besides lung assessment, EVLP provides a platform for the use of a variety of therapeutic applications between the time of lung harvest and transplantation. More specifically, treatments can be administered to the airways with a bronchoscope or systemically through the perfusion solution. Strides have been taken to treat inflammation, pulmonary edema, infections, aspiration injury, and pulmonary emboli.[18-29] These studies will be discussed below. However, they are not exclusive to the Toronto EVLP method.

Inflammation

In 2009, Cypel et al. investigated the functional repair of human donor lungs using interleukin-10 (IL-10) gene therapy. Lung inflammation can lead to endothelial dysfunction and ultimately results in poor lung function. Therefore, methods to suppress inflammation to preserve lung function are attractive and effectively expand the donor lung pool. IL-10 is a known anti-inflammatory cytokine that is thought to function by inhibiting pro-inflammatory cytokines through inactivation of antigen presenting cells. Using adenoviral vectors, human IL-10 gene therapy was administered to human lungs unsuitable for transplantation. Gene therapy was able to improve lung respiratory properties and pulmonary vascular resistance.[18]

The issue of inflammation has also been addressed using mesenchymal stem cells (MSCs) in the EVLP circuit. Previous studies have shown that MSCs avoid allorecognition by generating an immunosuppressive environment through cytokine production and disrupting T cell and dendritic cell function.[19] One group investigated the use of MSCs to manage inflammation-induced symptoms in a human acute lung injury model. These pathologies include the destabilization of alveolar epithelial fluid transport.[30,31] Results showed that through the instillation of bone-marrow derived multipotent MSCs, these lungs exhibited a reduction of extravascular water, improved lung endothelial permeability, and restored alveolar fluid clearance.[20]

Pulmonary Edema

Pulmonary edema can be described as an excessive amount of fluid within the lungs. Weakening of the endothelial barrier leads to a leakage of fluid into the interstitial space and eventually across the epithelial barrier into the alveoli. This decreases the lung's ability to oxygenate blood. One tech-

nique aiming to address this issue is known as air space fluid clearance. In 2007, a group published data showing that a 43 +/-13% basilar alveolar fluid clearance per hour could be achieved using a β2-adrenergic receptor agonist (terbutaline).[21] Interestingly, rates were still as high as 19 +/- 10% per hour without the drug treatment.[21]

Another group sought to explore the effects of a β-adrenergic receptor agonist (salbutamol) on reducing edema in a pig EVLP model. This molecule works by increasing the amount of fluid clearance in the lung. The study found a reduction in pulmonary pressure upon administration of the drug during EVLP, as well as improved lung dynamic compliance.[22]

Infection

As previously mentioned, EVLP serves as a platform for the introduction of treatment through the lung's systemic circulation. The presence of bacteria and other pathogens can potentially injure lungs and lead to sepsis in the recipient. Removal of these species is advantageous in preventing these potentially negative outcomes. Researchers have aimed to provide high-dose antimicrobial agents during EVLP to reduce bacterial burden. A study investigating the use of broad-range high dose antimicrobial agents and anti-fungal treatments showed a reduction of pathogenic species in the bronchoalveolar lavage.[23]

In addition, a recent study was completed by Nakajima et al. using high-dose antibiotics (ciprofloxacin or azithromycin, vancomycin, and meropenem). They found a total decrease in bacterial counts and perfusate endotoxin levels in the bronchoalveolar lavage upon treatment instillation.[24] Treatment groups also had improved pulmonary oxygenation, compliance, and a reduction in pulmonary vascular resistance.[24]

Treatments for infection have also been addressed using multipotent MSCs. In a study mentioned above with regards to the treatment of inflammation, the researchers also observed bacterial killing with the use of multipotent MSCs.[20] They hypothesized that this was attributed to upregulation of a bacterial killing mechanism through keratinocyte growth factors.[20]

Aspiration Injury

In critically ill patients, it is common for gastric or oropharyngeal contents to aspirate into the lower respiratory tract. Consequently, these patients can develop pneumonia. This can contribute heavily towards the development of acute lung injury or acute respiratory distress syndromes. Surfactant therapy aims to protect patients from respiratory distress through administration of exogenous surfactant. Using a pig model, a group created an artificial lung injury with the use of a betaine-HCL/pepsin mixture. In this study, surfactant lavage was administered during EVLP of the aspiration-induced injured lungs. Results showed that surfactant therapy improved pulmonary vascular resistance, lowered oxygen indexes, and improved PaO_2/FiO_2 ratios in comparison to control groups.[28] Similar results were shown in a gastric juice induced aspiration ex vivo pig lung model, where surfactant therapy was able to recover lung properties such as PaO_2, pulmonary vascular resistance, and apoptotic cell percentage.[26]

The use of steroids to treat aspiration injury has also been explored. Using pig EVLP, Meers et al. explored preemptive therapy to aspiration-induced injured lungs using methylprednisolone. Aspiration injury was induced by instilling gastric juice into the airways. Results showed an improvement in lung gas exchange using steroid treatment prior to EVLP.[27]

Pulmonary Emboli

A pulmonary embolism can be described as a blockage of a lung artery. This can occur by many mechanisms, but is usually caused by the formation of blood clots. Fibrinolytic agents have been developed to dissolve these clots. Donation after cardiac death (DCD) donors run the risk of developing these clots as their lungs are exposed to deoxygenated blood circulated before retrieval. Acute pulmonary embolism formation can lead to graft dysfunction upon transplantation. A study published using a class of fibrinolytic agents known as urokinases showed improved pulmonary vascular resistance, gas exchange, and reduction of edema in DCD lungs.[25] A clinical case report published by Machuca et al. demonstrated the use of a fibrinolytic agent known as alteplase in order to successfully treat donor lungs with pulmonary emboli.[29]

Improving Transplantation to Date

Several promising studies using the Toronto EVLP technique are currently underway or have been recently completed. These studies are listed in Table 2. While the NOVEL, HELP, and Perfusix trials include extended-criteria donor lungs, the Vienna trial evaluated standard-criteria lungs.[32] In general, the results from these trials are encouraging.

Table 2. Four clinical trials using the Toronto EVLP technique[32-35]

Trial Name	Location	Donor Type	Portable	Sponsor	Status
NOVEL	United States	Extended-criteria	No	XVIVO	Completed
HELP	Toronto	Extended-criteria	No	Vitrolife	Completed
Vienna	Vienna	Standard	No	XVIVO	Completed
Perfusix	United States	Extended-criteria	Lung perfusion centre	United Therapeutics	Recruiting

The results from the HELP trial were published in 2011. Twenty lungs from 23 high-risk donors were transplanted after EVLP. In comparing the EVLP group to standard criteria lungs, there were no significant differences in hospital stay, ICU stay, 30-day mortality, primary graft dysfunction, or day in mechanical ventilation post-transplant.[34]

The group in Vienna published their EVLP experience in 2012, chronicling the results of 13 clinical EVLPs resulting in nine double-lung transplants.[35] Similarities were found in post-transplant outcomes including days on mechanical ventilation, hospital stay, ICU stay, and 30-day mortality when compared with 119 standard transplants without EVLP.

The NOVEL trial is a multicenter clinical trial, assessing EVLP for marginal donors. Their preliminary report outlined

results from 31 patients who received EVLP lungs. Results were comparable to 31 (non-EVLP) controls.[36] Updated results were described in 2014, after the completion of 42 lung transplants using EVLP.[33] Compared to 42 controls, early outcomes and 1-year survival rates were the same.

Most recently, a retrospective study by Yeung et al. investigated outcomes after transplantation of lungs preserved for more than 12 hours, including EVLP time.[37] The study reviewed 906 patients who received lung transplants at Toronto General Hospital from 2006 to 2015. Average preservation time outside of the body was 14.6 hours for 97 patients who received lungs after over 12 hours of preservation time, while 6.7 hours was the average preservation time for 809 patients in the under 12 hours of preservation time group. Early post-transplant outcomes were similar between the two groups despite high-risk lungs. No differences were seen in primary graft dysfunction or length of hospital and ICU stay between the two groups. These results are extremely encouraging, as lifesaving transplants can now be performed across larger geographic areas without the risk of poorer outcomes.

Future Potential

As technology continues to advance, it is evident that the applications of EVLP will expand along with it. Realistically, EVLP will be enhanced as a therapeutic platform to treat many other health-related conditions. In addition, it is realistic to believe that external organ repair centers will be made around the world. These centers will take on the responsibility of receiving marginal lungs and repairing them using the EVLP system. If deemed transplantable, these lungs will then be retrieved at the recipient's hospital. This concept has already been shown to be safe.[38]

The increased establishment of standard EVLP biomarker use is also expected to aid in lung assessment. Clinical assessments have their limitation, while lung biomarkers provide a more definitive approach for monitoring lungs during EVLP. Studies have been performed to find potential biomarkers of dysfunctional lungs through analyzing primary graft dysfunction (PGD) grade 3 lungs that were accepted for transplant, and lungs declined after EVLP.[39,40] Although promising, further validation studies must be done.

One aspect of EVLP currently being studied is extending perfusion times on the circuit. Keeping lungs stable using EVLP for over 12 hours will incur many benefits, including the consideration of a new range of therapeutic opportunities. For example, prolonged EVLP could become an optimal research platform to study acute lung injury. Studying acute lung injury ex vivo is attractive as it offers a clinically-relevant scenario of disease development and healing. Moreover, treatments with longer implementation times such as gene and cellular therapies can be considered, allowing for increased reconditioning potential.

EVLP has successfully increased the number of transplantable lungs and offers a range of potential opportunities for further expansion of the donor pool. As novel procedures and potential therapeutics in EVLP are developed, lung transplantation is set to become a reality for more patients suffering from end-stage lung disease.

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