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Ex vivo lung perfusion (EVLP)

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Abstract The number of patients listed for lung transplantation largely exceeds the number of available transplantable organs because of both a shortage of organ donors and a low utilization rate of lungs from those donors. A novel strategy of donor lung management—ex vivo lung perfusion (EVLP)—that keeps the organ at physiological protective conditions has shown a great promise to increase lung utilization by re-evaluating, treating, and repairing donor lungs prior to transplantation. A clinical trial using EVLP has shown the method to be safe and to allow for reassessment and improvement in function from high-risk donor lungs from both brain death and cardiac death donors prior transplantation. When these lungs were transplanted, low rates of primary graft dysfunction were achieved, and the early outcomes were similar to those with conventionally selected and transplanted lungs. Pre-clinical studies have also shown a great potential of EVLP as a platform for the delivery of novel therapies to repair injured organs ex vivo, and thus further increase the donor lung utilization rate.

Keywords Lung preservation · Ex vivo lung perfusion · Reperfusion injury · Donor lungs · Ex vivo repair

Introduction

Lung transplantation (LTx) is a lifesaving therapy for patients suffering from end-stage lung diseases. However, the number of patients waiting for LTx greatly exceeds the number of donors available. An aggravating factor specific to LTx is the fact that only 15 % of lungs from multi-organ donors are deemed usable for transplantation [1]. Most potential lungs are considered unsuitable, due to the lung injury that occurs with brain death and intensive care unit (ICU)-related complications (i.e. barotrauma or lung edema associated with fluid resuscitation). Since primary graft dysfunction (PGD) is a complication that leads to severe early and long-term consequences for LTx recipients, transplant teams tend to be very conservative in selection of donor lungs. As a result, wait list mortality can be as high as 30 % [2, 3]. A novel strategy to overcome the shortage of donor lungs is the treatment and repair of injured donor lungs using normothermic EVLP (Fig. 1). This review will focus on rationale of normothermic preservation and recent developments with EVLP.

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Donor lung preservation

The current clinical practice of organ preservation is cold static preservation (CSP). During retrieval, a cold pulmonary flush using low potassium dextran preservation solution is coupled with topical cooling and lung ventilation [4, 5]. Lungs are then transported at 4 °C in a static inflated state. Hypothermia reduces metabolic activity to the point that cell viability can be maintained in the face of ischemia (5 % of metabolic rate at 37 °C) [6]. Cold temperature preservation is therefore the mainstay of lung preservation [7, 8]. However, the main limitation of the hypothermic preservation is the significant decrease in organ metabolic functions, which precludes the possibility of meaningful lung evaluation and recovery [6].

Development of EVLP

Ideally, further evaluation and even resuscitation of the lungs would be possible during the ex vivo phase of the organ before transplantation into the recipient. In order to achieve

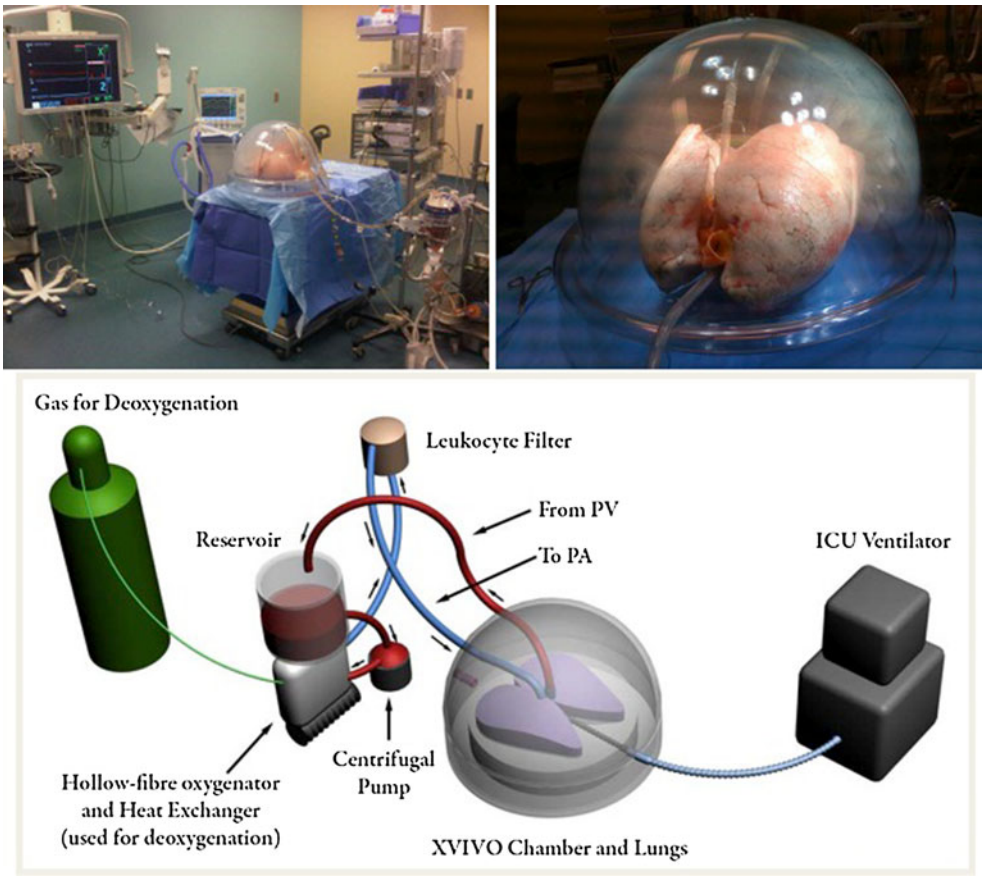

Fig. 1 The ex vivo lung perfusion circuit used in Toronto. PA = Pulmonary artery; PV = Pulmonary vein

this, organ preservation would need to occur at normothermic or near-normothermic conditions. One such strategy has been EVLP. This strategy attempts to simulate the in vivo situation by ventilation and perfusion of the donor lung graft. Originally proposed as early as 1938 by Carrel for organs in general and then in 1970 by Jirsch et al. for the evaluation and preservation of lungs in cases of distant procurement, attempts in those eras failed due to an inability to maintain the air/fluid barrier within the lung, leading to the development of edema and increased pulmonary vascular resistance (PVR) in the donor lung during EVLP [9, 10].

Driven by the objective of better evaluation of donation after cardiac death lungs, Steen et al. developed a modern ex vivo perfusion system with the intent of short term evaluation of lung function [11]. In doing so, they developed a buffered, extracellular solution with an optimal colloid osmotic pressure to act as the lung perfusate (Steen Solution, Vitrolife). This solution helps hold fluid within the intravascular space during perfusion and provides nutrients needed to maintain lung viability. The composition of Steen solution is quite similar to the current clinically utilized preservation solution of LPD-glucose (Perfadex®, Vitrolife), with human albumin as the major additional constituent. This protein is meant to maintain an optimal oncotic pressure to reduce the development of pulmonary edema during perfusion. Steen and colleagues utilized this solution mixed with red blood cells in combination with their circuit, and were able to successfully perfuse and evaluate lungs in a large animal model for one hour without the development of pulmonary edema and subsequent successful transplantation [11]. Following work in large animals, Steen's group was first to publish a case report of successful transplantation of a non-acceptable lung following a brief period of EVLP in 2007 [12]. Subsequently, this group has published a case series of six cases using short-term perfusion to evaluate rejected donor lungs [13].

The ultimate goal of Steen's studies was to utilize EVLP as a method for lung evaluation, and thus the perfusion times were short (60 min). For the application of EVLP for preservation, improved evaluation, and the goals of lung recovery and repair, more time is required. Erasmus et al. first attempted to extend the EVLP duration to 6 h; however, circuit induced injury again became problematic with increased PVR and airway pressures in the lung near the end of 6 h [14]. Our group first described successful long-term (12 h) ex vivo lung perfusion using a lung protective strategy for acellular normothermic perfusion and ventilation [15••].

To attain stable 12 h perfusion, several key lung protective strategies were employed [15••]. First, an acellular perfusate was utilized. We hypothesized that oxygen delivery to the

lung could occur mainly via the ventilator rather than via the vasculature. This concept is also supported by previous work where mere ventilation of a donor lung with room air at normothermia was demonstrated to preserve cell viability for 24 h [16, 17]. In addition, acellular perfusion is logistically simpler for clinical use and also avoids the problem of limited lifespan of red blood cells within the harsh environment of the perfusion circuit. Second, rather than subject the lungs to perfusion at 100 % of cardiac output, maximal flow was limited to 40 %. This lower flow aids in the reduction of hydrostatic edema caused by perfusion and, despite lower flows to non-dependent areas of the lung, histology and post-transplant function in EVLP lungs were shown to be normal. Third, we found that maintenance of a positive left atrial pressure of 3–5 mmHg to be important for the success of long-term perfusion. This small, but positive left atrial (LA) pressure tents open the capillaries and post-capillary venules and prevents collapse of the micro-vessels from occurring during increases in airway pressures and decreases of flow at inspiration [18]. Absence of positive LA pressures can lead to unstable alveolar geometry and results in decreased lung compliance [19]. Finally, we noted the importance of using a centrifugal pump. With ventilation, distension of the alveoli will place pressure upon the peri-alveolar vessels leading to cyclical increases in PVR with every breath. In contrast to roller pumps, increased PVR will result in decreased rotation and flow protecting lung vasculature. During perfusion, oxygen is removed and carbon dioxide is supplied via a membrane oxygenator as a simulation of normal cell physiology. Removal of oxygen allows for the measure of lung function by taking the difference between post-lung and pre-lung perfusate PO_2 and addition of carbon dioxide helps maintain the stability of the pH of the perfusate. Using this strategy, reproducible, safe 12 h normothermic ex vivo perfusion has been demonstrated in porcine and human lungs and this strategy of EVLP has been shown to interrupt ischemic damage caused by prolonged cold ischemia [15••, 20, 21].

Ex vivo lung evaluation

Current donor lung evaluation is a clinical process greatly dependent on the judgment of the surgeon. While some evaluation does occur prior to retrieval, i.e. chest x-rays and ICU bronchoscopy, the majority of the evaluation leading to the decision of utilization occurs at the time of organ retrieval. EVLP provides a more objective assessment of the lungs in an optimized environment. This is additionally important in donors after cardiac death where lung assessment “in vivo” is limited. Injury, as represented by the development of pulmonary edema during EVLP, is reflected in changes in compliance and airway pressure, and this precedes the effect on perfusate PO_2. [22]. Thus, during EVLP, these parameters should be monitored carefully and EVLP allowed to proceed over a period of at least 3–4 hours to allow for trends in compliance and airway pressure to be detected. To reduce the effect of atelectasis that might occur during donor lung transport, the baseline time point should be 1 h after warming the perfusate and after careful recruitment of the lung. All subsequent physiological measurements (compliance, airway pressures, PVR, and perfusate PO_2) can be compared to this time point. A cut-off, or normal value, is often sought for lung evaluation, but compliance and resultant airway pressure is based in part on lung volume and thus can fall within a large range of values. Thus, trends during the procedure are more informative, and at least stability of function is required for organ acceptance. We have generally used an EVLP delta PO_2 (pulmonary vein PO_2-pulmonary artery PO_2) of 350 mmHg (using FiO_2 100 %) as a cut-off value for lung acceptance for transplantation [23].

Using the EVLP strategy described by Cypel et al. and the evaluation strategy described above, a clinical trial was performed by the Toronto Lung Transplant program using EVLP for the assessment of high-risk lungs that otherwise would not be used [24•]. Lungs that originally did not meet acceptance criteria were transplanted after EVLP, and resulted in post-transplant outcomes equivalent to that of contemporary standard controls. This experience has now been extended to more than 50 clinical lung transplants after EVLP with improved outcomes, and the experience continues to grow [25].

Commercially available platforms for EVLP are now in various stages of development. Among them are the XPS system by XVIVO Perfusion, the LS1 by Vivoline Medical, and the OCS Lung by Transmedics. Of the three, the XPS system is the most faithful replication of the Toronto strategy and differs only by the addition of various in-line monitors to streamline organ assessment. The LS1 system resembles most closely Steen et al.’s system for lung evaluation and differs from the Toronto strategy by the use of a roller pump, an open atrium, and a blood-based cellular perfusate. A clinical trial is currently underway in the United Kingdom using this device [26]. The OCS Lung device is marketed as a mobile lung preservation system. This system also differs from the Toronto strategy by the use of an open atrium, a roller pump, bellow type ventilator, and a blood based cellular perfusate. Results following OCS lung preservation have been limited to case reports, but are now the subject of the international INSPIRE trial [27, 28]. This trial focus is the use of machine preservation for standard criteria lungs. The predication that cold ischemia is detrimental to the donor lung underlies the development of mobile normothermic perfusion solutions such as the OCS Lung system. However, it yet remains to be proven whether limited cold ischemia is truly detrimental. Even if normothermic preservation is utilized from retrieval to implantation, the need for some cold

ischemia is inevitable; cold flush and topical cooling at the time of donor cross-clamp and pre-implantation cooling are utilized to protect the lung and minimize warm ischemia during the actual surgical implantation. Compelling experimental and clinical data demonstrating that continuous mobile normothermic perfusion is superior to a combination of short intervals of cold ischemic preservation and normothermic evaluation and treatment will be needed to justify the conversion to this strategy, considering the logistical challenges and the added economic expenses needed for mobile normothermic perfusion of standard criteria lungs.

Biomarkers during EVLP

Biological markers in lung tissue, in bronchoalveolar lavage (BAL), or in perfusate could significantly enhance determination of organ quality and predictability of transplant outcomes. In the past decade, several biomarkers have been explored as important markers of donor lung injury. Cytokines such as IL-8, IL-1β and IL-6 seem to reflect injuries on different levels and IL-10 was shown to be protective [29–32]. Many other important markers have been discovered using high throughput analyses such as microarrays [33–35]. EVLP will greatly enhance our capability to bring biomarker assessment to a real time test in the clinical arena. Technology development to perform these diagnostic tests in few hours rather than in few days is also a parallel need, and this field has markedly evolved [36].

Ex vivo treatment strategies

Rather than aiming solely at minimizing cold ischemia, normothermic preservation instead demonstrates great promise for resuscitating injured donor lungs. Given that the majority of potential donor lungs are injured by a variety of mechanisms including brain death, contusion, aspiration, infection, edema, and atelectasis, one could imagine that targeted therapies for each of these injuries could be delivered ex vivo for repair and greatly increase the donor lung pool. The requirements for perfusion for repair compared to perfusion solely for evaluation differs by time. While the majority of lungs can be evaluated within 2–4 hours of perfusion, for repair, longer non-injurious stable perfusion will be required while potential treatments are administered.

Studies with the use of EVLP for lung repair have been recently reported. Each of these studies were targeted at a different form of donor lung injury and it is this breadth of exploration that will ultimately result in an arsenal of ex vivo lung therapy techniques applicable to each uniquely injured donor lung. Pulmonary edema is a common injury in donor lungs due to brain death physiology and/or ICU fluid management prior to retrieval. The use of terbutiline was found to accelerate the clearance of alveolar fluid during perfusion [37]. Another common mechanism of injury is aspiration. Inci et al. have attempted to improve porcine lungs injured by acid aspiration [38]. By lavaging the donor lung with surfactant during EVLP, they were able to achieve improved graft function when compared with controls. Due to the significant number of lungs rejected for suspicion of infection or pneumonia, delivery of high doses of antibiotics during EVLP is attractive. Both the Newcastle and Toronto groups have early data showing potential reduction in the burden of infection following EVLP antimicrobial therapy [39, 40].

EVLP based gene and cellular therapy have also been explored. Ex vivo gene therapy with an adenoviral vector is effective and additionally attractive because of reduced vector-associated inflammation. Furthermore, this strategy can easily fit into the logistical flow of clinical lung transplantation, simplifying adoption [41]. We have demonstrated that EVLP-based IL-10 gene therapy of rejected human donor lungs resulted in improved function and reduced biomarkers of inflammation, suggesting that IL-10 gene therapy could possibly increase the resilience of all donor lungs to reperfusion [21]. Lee et al. have shown that the delivery of mesenchymal stem cells to EVLP lungs can restore endothelial barrier permeability and alveolar fluid balance after endotoxin induced lung injury [42].

EVLP as bioreactor for lung regeneration

Recent work from Ott [43] and Petersen [44] has demonstrated a significant advance in the field of lung regeneration. To regenerate gas exchange tissue, they seeded decellularized scaffolds from rat lungs with epithelial and endothelial cells. To establish function, they perfused and ventilated cell-seeded constructs in a bioreactor simulating the physiologic environment of a developing lung. By day 5, constructs could be perfused with blood and ventilated using physiologic pressures, and they generated gas exchange comparable to that of isolated native lungs. Transplanted lungs performed gas exchange for up to 6 h. Although the methods described are only an initial step toward the long-term goal of generating functional lung tissue, the demonstration of an implantable organ that was able to maintain separation between the blood and airway compartments and that could participate in gas exchange for a period of time is very promising.

Conclusions

Ever since the development of clinical lung transplantation, transplant clinicians and scientists have sought to reduce injury and maximize safe preservation time during the storage

and transport of donor lungs. Key advancements in lung preservation in the form of hypothermia, inflated storage, and Perfadex flush have culminated in the maturation of lung transplantation into a standard of care for end-stage lung disease around the world. Today, the emphasis of lung preservation is shifting from slowing down organ death to that of facilitating organ recovery and regeneration prior to implantation using EVLP technology. Development of an ex vivo treatment arsenal ranging in complexity from pharmacologic to gene and cellular therapies will hopefully one day allow clinicians to utilize the full potential of the donor organ pool, improving outcomes of LTx.

Compliance with Ethics Guidelines

Conflict of Interest Marcelo Cypel declares no conflicts of interest relevant to this review article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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