

Uses of Ex-Vivo Lung Perfusion in Pulmonary Translational Medicine

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ABSTRACT

Abbreviations: MSC: Mesenchymal Stromal Cells; MAPC: Multipotent Adult Progenitor Cells; LLL: Left Lower Lobes; RLL: Right Lower Lobes; BAL: Bronchoalveolar Lavage Fluid; NO: Nitric Oxide

Introduction

End-stage lung disease is treated with lung transplantation. The advancements in lung transplantation has allowed it to be applied to a greater number of pulmonary etiologies [1,2]. Unlike other solid organs such as kidney and liver, only 15-25% of lungs from donors are transplanted [3]. These low percentages are a testament to the delicacy of lungs. Because of the difficulty of obtaining lungs suitable for transplantation, multiple methods have been used to expand the donor pool. The recent advancement of ex-vivo lung perfusion (EVLP) has arguably the greatest impact on revolutionizing the evaluation of donor lungs and expanding the number of lungs suitable for transplantation. EVLP allows for lungs to be ventilated, oxygenated and perfused for assessment prior to implantation. By creating a physiologic and controlled milieu, EVLP can also be used as platform for reconditioning and repairing lungs [4-9]. In the realm of lung transplantation, there have been promising results in drug, gene, stem cell and medical gas therapy. In addition, EVLP can be applied to thoracic oncology and regenerative medicine.

Drug Therapy

Using the EVLP circuit, medications can be added in the pulmonary vessels and bronchus for directed therapy in study lungs. In the case of donor lungs, this would avoid systemic exposure and toxicity. One prime example of directed drug therapy for treatment

of donor lungs is in the case of pulmonary emboli, which is a contraindication for transplantation. Machuca and colleagues described a case in which a pulmonary embolism was causing hemodynamic compromise in the donor lungs. Using EVLP, directed thrombolysis with alteplase was done followed by multiple flushings to wash out any residual emboli [10]. Another contraindication for transplantation of donor lungs is pulmonary infections, whether it is associated with mechanical ventilation or aspiration. Using an EVLP, Nakajima and colleagues were able to show that high-dose antimicrobial agents added to the perfusates of lungs can significantly decrease microbial load [11]. Similarly, after a severe *Pseudomonas aeruginosa* infection was induced in the lungs of pigs, Zinne et al. placed these lungs on an EVLP circuit with added colistin to the perfusate. These lungs were kept on the circuit for treatment and re-implanted into the pigs. In the EVLP group, there was reduced overall mortality compared to conventional systemic intravenous antibiotic treatment of the pneumonia (control). The symptoms of infection were also less severe in the EVLP group. Therefore, though more research needs to be done, this could be an avenue of increasing the donor pool of lungs [12].

Gene Therapy

Much like drug therapy, directed gene therapy can also be done on the EVLP circuit. Anti-inflammatory cytokines can be used to treat donor lungs. Specifically, IL-10, which inactivates

antigen-presenting cells and inhibits the proinflammatory cytokine cascade, has been studied as gene therapy in EVLP. Machuca et al. [13] showed that treating lungs on EVLP with IL-10 transfected adenovirus is safe and improves post-transplant lung function and outcomes over EVLP alone in a porcine model [14]. This translated to a human model, as lungs from 10 donors deemed unusable for transplantation were treated with IL-10 gene therapy while on EVLP. Not only did these lungs had a more favorable anti-inflammatory cytokine profile, these lungs showed improvement in arterial oxygen pressure and pulmonary vascular resistance compared to the controls [14].

Stem-Cell Therapy

The interplay between pro- vs. anti-inflammatory cytokines and cellular profiles comes into significant play in transplantation. Studies have shown that mesenchymal stromal cells (MSC) or multipotent adult progenitor cells (MAPC) can affect this balance [15,16]. Using EVLP, Nakajima and colleagues delivered MSCs to the pulmonary artery of lungs and showed that apoptosis was decreased compared to control. Acute lung injury and pro-inflammatory markers were also decreased in the MSC group. Air movement was also improved, as peak airway pressures were decreased in the MSC group compared to control as well [17]. It has been hypothesized that MAPCs can decrease primary graft dysfunction in transplanted organs by decreasing ischemic-perfusion injury. La Francesca and colleagues bronchoscopically instilled MAPCs into the left lower lobes (LLL) and vehicle control into the right lower lobes (RLL) of donor lungs. The lungs were placed into the EVLP circuit and perfused and ventilated. After the EVLP run, the lungs were assessed for histologic injury and for inflammatory markers in bronchoalveolar lavage fluid (BAL) and lung tissue. La Francesca and colleagues showed that the LLLs treated with MAPCs had significantly decreased histological inflammation and decreased inflammatory markers compared to the RLLs [18].

Medical Gas Therapy

Various gas therapies can also be used to study lungs on EVLP. Inhaled nitric oxide (NO) is used quite frequently in the realm of lung transplantation as a pulmonary vasodilator [19,20]. There have been some discussions whether pre-transplant NO-ventilation could be helpful during the post-operative course. In a rat model, Dong and colleagues, ventilated rat lung with NO while on EVLP. They were able to show that lungs with NO-ventilation had significantly reduced wet:dry weight ratio, better oxygenation, and reduced pulmonary vascular resistance. There was also a maintenance of endothelial NO synthase (eNOS) and a better anti-inflammatory profile for lungs ventilated with NO [21].

EVLP Outside of Lung Transplantation

Thoracic Oncology

In 1958, Creech and colleagues used isolated lung perfusion with chemotherapeutic agents to treat pulmonary malignancies on an extracorporeal circuit much like EVLP. By using an EVLP

circuit, lungs stricken with cancer can be given higher doses of chemotherapy without exposing the rest of the body to toxic levels of chemotherapy. This was successfully shown by Weksler and colleagues. They showed that in-vivo isolated single lung perfusion in rats is feasible with low mortality and morbidity [22]. Reck dos Santos and colleagues used this concept in the setting of pulmonary metastases. Reck dos Santos cannulated the pulmonary artery and veins in pigs in vivo, with a circuit similar to EVLP. The left lung was perfused for 4 hours with doxorubicin. There was no systemic exposure to doxorubicin with homogeneous distribution in the lung. There was also no evidence of acute lung injury [23]. Though promising, further studies are needed to determine is long term efficacy on local recurrence, toxicity, pulmonary function and overall survival.

Regenerative Medicine and Bioengineering

Organ engineering is another method to increase the number of organs available for patients with end-stage lung disease. Ott and colleagues developed techniques to decellularize lungs from various animals. These decellularized lungs are left with extracellular matrix and architecture that serves as a scaffold for cellular deposition. Ott was able to generate functional pulmonary vasculature by repopulating the vascular beds with endothelial and perivascular cells [24,25]. Ultimately, this decellularized platform can be used to potentially "grow" lungs for possible transplantation. EVLP has been suggested as a bioreactor circuit for delivery of cells to for the artificial organ and for providing a physiological environment for proliferation. It can also then be used as an assessment tool for artificial lungs.

Conclusion

Currently, EVLP is predominantly used as a platform for assessment of marginal donor lungs. With the capabilities of EVLP to ventilate and perfuse lungs, it can be used as a potent platform for lung therapies in and outside the realm of lung transplantation. Marginal lungs can be treated on the EVLP circuit for optimization prior to transplantation. Meanwhile, the EVLP or circuits similar can be used for lung isolation for oncologic treatments, or as a bioreactor platform for the growth of artificial organs.

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