



Use of a cross circulation platform to regenerate lungs with induced gastric injury

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Lung transplantation is a therapeutic option for patients with end-stage lung disease for which no other treatments exist. Since 2012, the number of new candidates added to the wait list and the number of lung transplantations performed in the United States has increased (1). Despite an increase in the number of lung donor counts by 13.9% from 2015–2016, the overall mortality rate for candidates listed for lung transplant is 17.2 per 100 wait-list years (1,2). In particular, there may be underutilization of donors with donation after cardiac death (DCD) when compared to brain dead donors, with one-tenth the odds of utilization of DCD donors in the United States compared with brain-dead donors after adjusting for organ quality (3). A study of 29 pairs of rejected donor lungs were normal or had mild histologic abnormalities, had no or mild pulmonary edema, and 24% showed organisms on tissue gram staining (4). Overall, 12 of the 29 pairs of lungs were potentially suitable for transplant, suggesting that radiographic and clinical criteria used to select donor lungs may be insufficient in determining quality and lead to underutilization of donors.

Ex vivo lung perfusion (EVLP) perfuses and maintains lungs outside the body while maintaining temperature, moisture, and sterility of the lung preparation. Use of EVLP can increase the utilization of donor lungs and has become an increasingly utilized technology for assessment and reconditioning of donor organs not otherwise suitable for transplantation (5). In addition, EVLP can safely extend preservation times which are normally limited to less than 8 h with standard cold preservation. During EVLP, lungs are preserved at normothermia and therefore limit cold ischemic time. Recently, a transportable EVLP device,

the Organ Care System (OCS™), became available which eliminates the period of cold storage needed to transport lungs from the donor to the recipient hospital (6) and therefore potentially extend the distance between donor and recipient hospitals. Yeung *et al.* (7) found that use of EVLP to increase donor preservation time to greater than 12 h did not affect early transplantation outcomes. However, EVLP systems may also have a limit on duration of lung support due to lack of systemic regulation of lungs and loss of homeostasis in the extracorporeal lung (8). In addition to increasing preservation time, EVLP may be used to recondition the lung, and various therapies have been tested using EVLP in experimental models. However, there are scenarios where EVLP may not be effective. For example, gastric aspiration in donor lungs is a reason for declining lungs for transplantation. EVLP was ineffective in improving lung injury in piglets with induced gastric injury (9), although instillation of surfactant during EVLP improved lung function in a gastric injury model (10).

Cross circulation is an abandoned surgical procedure in which blood is exchanged between two bodies (11). During cross circulation, the donor provides support of its whole circulation to the second body or organ. The blood that returns from the recipient passes through the vital organs such as the liver and kidney of the donor's body (11). O'Neill *et al.* (8) utilized cross circulation between a recipient and healthy extracorporeal lungs in a swine model and successfully maintained the extracorporeal lungs for over 36 h with stability of the recipient. The authors used a biobridge constructed from the aortic arch of the donor with the brachiocephalic and left subclavian branches

ligated. This biobridge was connected to the left atrial cuff of the explanted lungs and served as a conduit for drainage of the pulmonary veins. The study also demonstrated that cross circulation allowed for the recovery of damaged lungs subjected to ischemia reperfusion injury. However, the extracorporeal lungs were not transplanted after support with the cross circulation platform.

In the subsequent study, Guenthart *et al.* (12) extended the application of the cross circulation platform to investigate its ability to regenerate lungs from a swine model of gastric aspiration. Lung injury was induced by instillation of gastric contents into a single lung via flexible video bronchoscopy, and the other lung served as a control. Gastric injury was confirmed by gross appearance at explant, chest x-rays, bronchoscopy, and histologic appearance. Both injured and control lungs were maintained via the same cross circulation platform for 36 h as described in the prior study. Therapeutic interventions were performed including bronchoalveolar lavage (BAL), surfactant replacement, and recruitment maneuvers. Assessment of the injured lung over time was performed including analysis of BAL fluid markers, lung injury scores, and histologic analysis. Over 36 h, injured lungs showed improvement in all parameters, including improvement in PaO₂ to FiO₂ ratio, pH, concentration of inflammatory cytokines in BAL fluid, lung injury scores, pressure-volume curves and lung compliance, and integrity of the alveolar epithelium.

The feasibility of the cross circulation platform to maintain injured lungs for 36 h as well as the effectiveness of therapeutic interventions to improve gastric injury in a swine model were demonstrated in this study. Can these findings be translated to the clinical setting? Choosing the optimal recipient to apply this procedure to might be difficult. Lung transplant candidates on the waiting list with a high lung allocation score (LAS) have a high risk of dying before transplant and therefore may benefit from technology that allows donor lungs to be reconditioned. However, lung transplant recipients with LAS greater than 70 also have higher risk of death when transplanted with standard donors, and the highest risk when transplanted using extended criteria donors (13). In addition, it needs to be investigated whether patients with end stage lung disease can handle the load of supporting the extracorporeal lungs during cross circulation, particularly patients with pulmonary arterial hypertension whose disease may cause a limitation in cardiac output. The logistics of maintaining the donor lungs and the recipient for 36 h during the cross circulation may also be difficult. Significant resources would

be required at the recipient transplant center, including appropriately trained staff, space, and monitors, to maintain the extracorporeal lungs and the recipient. These resources would also need to be available for the extended period of time required for cross circulation and the subsequent transplantation. Thus, it may only be feasible to perform cross circulation at large transplant centers. The optimal timing of administration and choice of drugs for immunosuppression administered to an unrelated recipient will also need to be determined.

The feasibility of performing assessments of the extracorporeal lungs in real time will also need to be investigated. Currently, the clinical use of EVLP to assess donor lung quality relies on simple criteria such as PaO₂/FiO₂ ratio, CO₂ content in the perfusion solution and exhaled air, perfusion pressure of the pulmonary artery, pulmonary arterial resistance, and lung mechanics (peak inspiratory pressure and compliance) (14). The lung may also be assessed macroscopically and via bronchoscopy. Measurement of markers in the BAL fluid such as inflammatory cytokine and exosome concentrations may not be readily available in all transplant centers and produce reliable results in a timely manner.

The cross circulation platform utilized by Guenthart *et al.* is a promising new technology to improve donor lung quality and increase donor lung utilization. In a swine model, it allowed for the reconditioning of lungs with gastric injury. However, the utilization of these lungs for lung transplantation and the translation to clinical practice must still be demonstrated. Additional factors such as optimal recipient selection for these cross circulation cases and the economic burden of performing cross circulation must also be investigated.

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Footnote

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conflicts of interest to declare.

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