Is perfusate exchange during *ex vivo* lung perfusion beneficial?

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Lung transplantation is a therapeutic option for patients with end-stage lung disease. The number of lung transplantations worldwide has been increasing since 2012 and has almost doubled over the last decade (1). Despite the increase in lung transplant rates, 326 patients died on the waitlist or became too sick to undergo transplant in 2017, and the overall waitlist mortality rate was 17.2 per 100 waitlist-years (2). Shortage of acceptable donor lungs remains a major limitation to lung transplantation. Ex vivo lung perfusion (EVLP) is an increasingly utilized technology to assess and recondition donor organs that are otherwise marginal for transplantation and may be used to expand the donor pool.

The EVLP system has multiple components, including a ventilator, endotracheal tube, perfusion solution, reservoir, oxygenator, pump, thermostat, and air filter. There are three main EVLP protocols: the Toronto protocol, the Lund protocol, and the Organ Care System™ (OCS) protocol (TransMedics, Andover, MA, USA). The Toronto protocol uses acellular Steen Solution (XVIVO Perfusion, Goteborg, Sweden), while the Lund and OCS protocols use solutions with the addition of red blood cells (cellular perfusate). Steen solution is designed to have the optimal osmolarity and high dextran content in order to coat the pulmonary endothelium and protect it from leukocyte interaction and other injuries (3). These EVLP protocols also vary with regard to perfusion flow rate and atrial pressure.

One potential benefit of EVLP is extending preservation time of donor organs with reports of successful preservation up to 12 hours and beyond. However, EVLP systems may have a limit on duration of lung support due to lack of systemic regulation of lungs and loss of homeostasis in the extracorporeal lung (4). There are reports of successful use of EVLP for 12 hours or more. In a retrospective study from Toronto comparing recipients who received lungs preserved more than 12 hours compared with recipients of lung preserved less than 12 hours, there were no differences in clinical outcomes including hospital length of stay, primary graft dysfunction, or overall survival (5). Of the lungs preserved greater than 12 hours, 95% underwent EVLP, suggesting that extended preservation with EVLP did not lead to worse early transplant outcomes. The EVLP protocol used for this study utilized Steen Solution with 100 mL of perfusate exchanged every 2 hours to maintain glucose levels and provide fresh perfusate components (6). Schiavon *et al*. (7) reported prolonged lung perfusion of 18 hours using the OCS system with subsequent successful transplantation.

There is no clear consensus as to whether cellular versus acellular perfusate is preferred for EVLP, particularly for extended preservation times. Prior studies of human and pig lungs undergoing EVLP for 12 hours showed similarities in oxygenation, airway parameters, and structural alterations using either cellular or acellular perfusates (6,8). However, both these studies used lungs with relatively minor damage. In a study of swine lungs which underwent 24 hours of EVLP using the OCS, acellular perfusion led to increased vascular resistance and edema, and acellular experiments had to be stopped by 6 hours. Perfusion with whole donor blood led to better pulmonary artery pressure and oxygenation compared with RBC perfusate (9).

The perfusate of lungs undergoing acellular EVLP had a steady increase in lactate concentrations over 12 hours (10). Lactate production is likely a result of metabolism from

glucose in the perfusate solution. However, lactate concentration and lactate to pyruvate ratio at the end of EVLP had no correlation to clinical outcomes after transplantation, including primary graft dysfunction scores or hospital length of stay (10). During 12 hours of EVLP, expression of proinflammatory cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), and granulocyte colony-stimulating factor (G-CSF) increase despite preserved lung function and lack of histologic injury (11). However, in another study, higher concentration of IL-8 in EVLP perfusate was associated with the development of primary graft dysfunction (12). Use of an absorbent filter to continuously filter the perfusate during 12 hours of EVLP has been performed using the Toronto protocol (13). When compared to lungs that underwent EVLP without filtration, lungs undergoing filtration had decreased glucose consumption, decreased perfusate concentrations of multiple cytokines, and less lung injury (13).

In the study by Wei *et al.*, the authors used 8 discarded human right donor lungs that had infection, low oxygenation, or abnormal imaging. All lungs underwent a target of 12 hours of EVLP using the Toronto protocol. Four of the lungs served as controls and underwent perfusate exchange with 250 mL of fresh solution every hour. The remaining four lungs had a modified circuit which utilized a dialyzer added to the reservoir (PP, perfusate purification group). Only 1 of the 4 lungs in the PP group completed the 12 hours of EVLP; the other 3 lungs had premature termination of EVLP due to severe edema and decreased oxygenation. There were no differences in airway pressures between the groups. Compared to the control group, the PP had stability of pH and a lower rate of increase of lactate. Cytokines concentrations increased in both groups over time and were not significantly different between the two groups.

Although this study was performed using human lungs, it is limited by the small number of lungs and the premature termination of the majority of lungs in the control group. It does not demonstrate a clear benefit of use of the dialyzer in terms of lung quality. In addition, since these lungs were not transplanted, there is no information about the clinical outcomes with use of a dialyzer for extended EVLP. Based on the previously mentioned studies, it is unclear whether differences in pH or glucose and lactate concentrations lead to differences in clinical outcomes. Lung compliance is an important parameter of quality, and because only a unilateral lung was studied, lung compliance could not be accurately determined.

In another study of swine lungs undergoing prolonged EVLP over 24 hours using a cellular perfusate, use of continuous hemodialysis of the perfusate during EVLP had similar effects on lactate concentrations (14). Lactate concentration increased more rapidly over time in the control group compared with the dialysis group. However, pulmonary artery pressures and pulmonary vascular resistance were higher in the dialysis group, and there were no differences in oxygenation and compliance between the groups. Taken together, both studies demonstrate that dialysis can remove lactate during EVLP using both cellular and acellular perfusates. However, more information is needed about the effects of dialysis on lung quality and clinical outcomes if the lungs are later utilized for transplantation. Given reports of successful transplantation after prolonged EVLP using standard protocols, it is unclear that use of perfusate dialysis adds clear benefit (5).

Both laboratory and clinical studies suggest that EVLP may allow for prolonged preservation periods for donor lungs. The ability to extend donor preservation time may allow for transport of organs over greater geographic distances, optimization of transplant logistics, and extended time for interventions to occur. Cross circulation is another technique that may allow for extended preservation times (15). The best approach to modify current EVLP protocols to extend preservation time still needs to be determined.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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