Our understanding of the IR injury processes in the transplanted lungs is rather limited. This important basic science article provides another glimpse into the mechanism of the problem and offers a practical solution involving the nonselective removal of several molecular mediators of inflammation. Decreases in the concentrations of the various acute-phase reactants resulted in improved allograft function. Further studies will undoubtedly focused on more selective removal of proinflammatory mediators during the reconditioning of the lungs before implantation.

It is the hope of everyone in the field of lung transplantation that clinically important methods for reducing IR injury will be introduced into clinical practice as the severity of IR injury continues to increase, reflecting the current practice trends in the field of lung transplantation.

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Commentary: Double, double, toil, and trouble: Removing evil humours during ex vivo lung perfusion

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Removal of inflammatory mediators during EVLP may aid in preventing primary graft dysfunction.

The increasing number of patients diagnosed with end-stage respiratory failure has made the discrepancy between availability and demand more prominent despite the overall increasing number of donor lungs. Currently, the roadblock for those patients awaiting lung transplantation is organ utilization. The estimated rate of donor lung utilization is only roughly 20% both in the United States and the United Kingdom.[1] In response to this disparity, efforts have been made to determine ways to improve the utilization of donor lungs. Ex vivo lung perfusion (EVLP) has given hope to the field of lung transplantation with the potential to increase the number of available suitable donor lungs. To date, the clinical focus of EVLP has centered around its use as an organ assessment tool that has become widely available to transplantation centers. The future of the technology is the hope that lungs can be "resurrected" or improved to be suitable for transplantation.

CENTRAL MESSAGE

We comment on the promising work addressing the removal of inflammatory mediators from the perfusate during EVLP in a porcine model as a means of preventing primary graft dysfunction.

To address this hope, several groups are currently investigating how lungs can be manipulated on the circuit with the goal of improving quality or converting them to usable organs for transplantation. One of the issues critical to EVLP is its potential for promoting the ischemia and

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reperfusion (IR) process, which is heralded by release of inflammatory mediators into the perfusate.[1] In this issue of the *Journal*, Iskender and colleagues[2] present an evaluation of one such approach to IR promotion. They used a methodology involving a perfusate-adsorption process that reconditions the donor lung to IR injury, with the anticipation of providing more available allografts and decreased primary graft dysfunction. Their study in a porcine model provided evidence that use of the CytoSorb adsorber reduced the overall amount of cytokines in the allograft, thereby decreasing the inflammatory response during reperfusion.[2] These findings are of potential importance given what we know regarding the role of inflammation as a key mediator of IR injury.

IR injury is the most common cause of post-transplantation respiratory failure, with a 30-day mortality rate as high as 40%.[3] Increased expression of proinflammatory cytokines during EVLP has been associated with primary graft dysfunction in lung transplantation.[4] Minimizing the incidence of this adverse event will reduce the use of mechanical ventilation, length of hospital stay, overall cost, postoperative complications, and morbidity.

Iskender and colleagues provide a detailed assessment of their method using experimental metrics including pharmacokinetics, fluid and tissue analyses, inflammatory response, and radiologic/histological properties. The cytokine measurements in the perfusate of the adsorber group were significantly lower during the 6-hour EVLP period. In addition, the adsorber removed drugs such as meropenem and methylprednisolone. Plasma levels of interleukin-1Ra were significantly lower in the adsorber group, and cytokine filtration resulted in preserved graft function with improved gas exchange and pulmonary mechanics (ie, less edema, improved compliance, and decreased injury scores).

These short-term (immediate) results are certainly intriguing and raise further questions regarding the future implications of such a technology. What may be the implications for use of such a broad-spectrum absorber on the levels of other molecules in the perfusate? This will be especially important to further define in the clinical setting and the implications for a pretreatment protocol or variabilities in donor physiological/biochemical states.

It should be pointed out that this is not the first time this has been attempted. As the authors note, Kakishita and colleagues[5] explored the concept of cytokine removal during EVLP without improving lung function, suggesting that other factors may be involved in the lung injury seen during and after EVLP. The absorber device used in their study was substantially different, as were the experimental conditions, including the lack of addition of methylprednisolone and the initiation of EVLP following a short warm ischemic time. The Lixelle S-35 device used in the study of Kakashita and colleagues selectively removed ligands (β2-microglobulin, IL-8, IL-1β, IL-6, and tumor necrosis factor-α) from the perfusate. The CytoSorb device used in their study functions on size selectivity and surface adsorption.

Lung transplantation is the best option for the treatment of candidate patients with refractory end-stage lung disease. Potential progress with the next phases for EVLP research stimulate hope for expanding the donor pool for patients in need of this life-saving therapy. As such, use of the cytokine adsorber has clinical promise in potentially removing the "evil humours," thereby advancing the applicability of EVLP into the clinical setting.

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