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EDITORIAL

Commentary on: Restoring discarded porcine lungs by ex vivo removal of neutrophil extracellular traps

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In 2001, Steen and colleagues from Lund University in Sweden performed the first ex-vivo assessment of human lungs from a donor after circulatory death (DCD) to ensure acceptable lung function prior to transplantation. Six years later, the same team performed a lung transplant using donor lungs initially considered unacceptable, after they were reconditioned and evaluated on the ex-vivo system.[1] Ex-vivo lung perfusion (EVLP) has since gained tremendous attention for its potential applications in the field of lung transplantation. Two clinical trials – the first published by the University of Toronto, an institution that contributed significantly to the optimization of EVLP technique and established a model clinical EVLP program, and the second conducted across 17 lung transplant centers throughout the United States – demonstrated the safety and feasibility of lung transplantation following EVLP.[2] Both played key roles in attaining Food and Drug Administration (FDA) approval of ex-vivo perfusion systems in 2019. Since then, EVLP use has expanded as a clinical tool to help increase donor lung utilization. The ex-vivo perfusion systems provide both objective assessments of donor lungs that may otherwise have been deemed unsuitable for transplant and have the potential ability to rehabilitate marginal donor lungs. EVLP is also being studied as a platform for delivering therapeutic agents – including adenosine receptor agonists, inhaled anesthetics, and even mesenchymal stem cells – to the donor lung, resulting in a decreased inflammatory profile within the donor lung tissue.[3] These results support the possibility of using EVLP for increasing rehabilitation rates of marginal donor lungs and further expanding the potential donor pool.

Almost 2 decades after Steen's team pioneered the concept of EVLP for reconditioning of donor lungs, the Lindstedt research group continues Lund University's legacy of pushing the boundaries of EVLP. In their manuscript, Mittendorfer and colleagues ambitiously propose a new application of EVLP that could actively treat and promote lung recovery following acute lung injury (ALI) via the removal of neutrophil extracellular traps (NETs). There are 2 significant innovations associated with their proposal.

First, using EVLP as a platform for targeted removal of a noxious trigger, such as NETs, is a unique utilization of the EVLP system. It is well-established that neutrophils are a major mediator in the acute inflammation underlying the pathophysiology of ALI. One specific mechanism involves the release of NETs, which are webs of nuclear chromatin and protein released by activated neutrophils into the extracellular space. Although initially thought to be a protective mechanism against pathogenic agents, recent research has emphasized the role of NETs as a cause of inflammation in lung tissues. In line with their pro-inflammatory effects, NETs have been implicated in primary graft dysfunction and poor post-transplant outcomes as well as ALI.[4] Caldarone et al. further applied this finding to EVLP, showing that elevated NET levels in the perfusate of donor lungs on EVLP prior to transplantation may be associated with poor recipient outcomes.[5] In ALI specifically, studies have found that the presence of extracellular histones, which in turn suggests the presence of NETs, is associated with worse lung injury in both trauma and aspiration-induced models.[4] Mittendorfer's novel development combines chemical biology techniques with EVLP, running the perfusate through a column containing histone-

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Abbreviations: ALI, acute lung injury; DCD, donor after circulatory death; EVLP, ex-vivo lung perfusion; FDA, Food and Drug Administration; NETs, neutrophil extracellular traps; P/F ratio, PaO_2/FiO_2 ratio

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conjugated beads to bind chromatin fragments and thereby extract NETs from circulation. Compared to lungs that underwent standard EVLP only, lungs that underwent EVLP tailored for NET removal had lower cell-free DNA levels, lower levels of extracellular histones in the perfusate, lower concentrations of citrullinated histone H3 (Cit-H3) in broncho-alveolar lavage samples, and less visualization of Cit-H3 on immunohistochemistry staining of lung tissue. These results demonstrate the feasibility of successful removal of NETs through their elegantly designed EVLP system.

Second, there have been few attempts thus far at using EVLP as a direct therapeutic delivery platform to actively treat donor lungs after ALI. This new, active ex-vivo intervention that is designed to remove tissue-damaging NET particles captures an additional subset of potential donor lungs that could benefit from an EVLP therapeutic application and potentially contribute to the expansion of the donor pool. In this study, a porcine model of gastric aspiration-induced lung injury was evaluated. Compared to lungs that underwent EVLP only, lungs that underwent EVLP and NET removal demonstrated: less edema on wet-dry ratios of lung biopsies; less infiltration, alveolar wall thickening, and edema on histology; and improved PaO_2/FiO_2 (P/F) ratios after 4 hours, reaching an acceptable threshold for transplant (P/F $>$ 300) in 5 of 6 specimens. These early findings are very encouraging and provide critical data that help illustrate the potential impact of this process. This novel attempt to recondition donor lungs with ALI still requires additional study to help with the translation of NET removal into clinical practice. While the manuscript reports improvements on a cellular level and improved P/F ratios following NET removal, these measures are only the initial critical step in introducing such a new technique. Further reproducible and supporting clinically relevant data that also demonstrates non-inferiority of post-transplantation outcomes in animal models, are anticipated. Future studies should build on this important innovation and help create new strategies to successfully utilize donor lungs that previously were discarded for having clear evidence of acute lung injury.

Overall, we commend the authors on a truly novel application of EVLP and for bringing new donor lung populations into the realm of possible donor lung salvage. Given the crucial need to expand the donor lung pool, the field of EVLP warrants continued exploration from all perspectives – development of new therapeutic techniques as exemplified by Mittendorfer et al., assessment of outcomes, discovery of underlying molecular mechanisms, and creation of health systems that facilitate access to EVLP.

Disclosure statement

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