Extended *ex vivo* lung perfusion—abridged expense

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Provenance: This is an invited article commissioned by the Editorial Office of *Annals of Translational Medicine*.

Comment on: Wei D, Gao F, Yang Z, *et al. Ex vivo* lung perfusion with perfusate purification for human donor lungs following prolonged cold storage. Ann Transl Med 2020;8:38.

Submitted Dec 02, 2019. Accepted for publication Jan 02, 2020.

doi: 10.21037/atm.2020.01.19

View this article at: http://dx.doi.org/10.21037/atm.2020.01.19

Currently, only 20% of donated lungs are being used for standard lung transplantation (1). Strategies such as ex vivo lung perfusion (EVLP) have shown promising results for improving lung utilization (2). In the clinical setting, most centers limit EVLP duration to between 3–6 hours with the main objective to assess suitability of the allograft for transplantation. However, the next frontier for EVLP is to move beyond evaluation to organ repair or therapy. One recent example from the Toronto group was the clinical use of ultraviolet C perfusate irradiation of hepatitis C-positive donors during EVLP resulting in lower viral loads within first week after transplantation (3). Future translational experiments and therapies might require significantly longer EVLP runs and so methods to safely extend an allograft's time on the circuit are needed.

In this edition of *Annals of Translational Medicine*, Wei *et al.* report a novel, modified method of EVLP to extend the EVLP run time to 12 hours in discarded human lungs (4) The group used a dialyzer-based modification of EVLP to purify and recycle perfusate within the circuit (PP group) and compared to standard hourly replacement of perfusate (control). They explored the effects of this modified system on lung function, physiological and inflammatory changes after 18–24 hours of cold preservation followed by a planned 12 hours of EVLP. This proof-of-concept study included 8 human right donor lungs rejected for clinical transplant. Four lungs were randomly assigned to the control circuit and 4 to the PP group. There were no differences between groups in EVLP functional characteristics of PaO_2, pulmonary artery pressure and airway pressures. Interestingly, 3 of 4 (75%) of the control lungs were removed early from EVLP given low PaO_2 and edema while all 4 (100%) of PP lungs completed 12 hours. The PP lungs showed improved physiological parameters of pH, lactate and electrolytes levels compared to the control group. Measured inflammatory cytokines were not statistically different between the two groups but notably, PP lungs showed less apoptosis.

Over the last decade EVLP has emerged as an important tool which has expanded the current donor pool for EVLP-capable centers. In North America, the University of Toronto program has pioneered the use of this technology (5). They have reported good outcomes with more than 20% of their total lung transplant surgeries being performed with EVLP reconditioned lungs (5). A recent meta-analysis of eight studies (n=1,191) showed post-transplant outcomes were similar in EVLP-treated and standard lung transplant groups (2). In addition, EVLP can allow the use of targeted therapies such as thrombolysis for lungs with clot burden without exposing the recipient to untoward side-effects (6). Another potential role is improving transplant team logistics in settings such as multiple concurrent transplants, donor instability with urgent procurement, reducing late night implants or in difficult recipient explants where concerns about prolonged ischemic time may be a factor.

One aspect limiting wide-spread adoption of EVLP is cost. In this paper, a specific aim of modifying the circuit to reuse perfusate was to mitigate the cost of replacing expensive perfusate every hour over the extended 12 hours of EVLP. This is novel thought with use of

existing technology to prolong EVLP run time in a cost-effective manner that could be widely applied. The cost of dialyzers and different perfusates would need to be factored into the overall cost effectiveness of this new EVLP model.

The translational impact of Wei and colleagues' study is limited given the small experimental groups and that post-transplant outcomes in the clinical setting are not addressed. However, the findings contribute to optimizing EVLP protocols to allow for extended runs while potentially lowering financial burden. Future directions could include larger studies with further modification of the EVLP circuit with a cytokine filter which has been shown in previous porcine EVLP experiments to have salutary effects (7). The authors should be congratulated for this interesting study which provides another advance in EVLP technology moving toward increasing lung transplantation prevalence and improving outcomes through improved organ assessment, rehabilitation and treatment.

Acknowledgments

None.

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.

Cite this article as: Grewal HS, Mehta AC, Bribiesco A. Extended *ex vivo* lung perfusion—abridged expense. Ann Transl Med 2020;8(3):42. doi: 10.21037/atm.2020.01.19

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