Ischemia reperfusion induced acute lung injury: Using everything and the kitchen sink

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Severe primary graft dysfunction (PGD) continues to affect approximately 10% to 30 % of patients shortly after lung transplantation, and is associated with significant morbidity, risk of mortality, and inferior long-term outcomes.¹ Ischemia-reperfusion injury (IRI) is the presumed pathophysiologic basis of PGD, and represents a complex process with multiple overlapping pathways of injury.² The fact that no specific and effective therapy is available to counteract PGD is dismaying, despite the elucidation of numerous biochemical mechanisms of IRI.

Hashimoto and colleagues,³ from the Division of Thoracic Surgery at Toronto General Hospital, report their finding that a biologic agent, recombinant human Diannexin V, a homodimer of annexin V, ameliorates IRI in a rat lung transplant model. The authors administered the agent to the donor before procuring the lung, and to the recipient shortly after reperfusion. They observed significantly enhanced graft function, with improved oxygenation and carbon dioxide clearance, as well as a reduction in peak airway pressure. A mechanistic explanation for the observed benefits of the homodimer was suggested by the finding of a reduction in: fibrin deposition, markers of apoptosis, and release of inflammatory cytokines.

The challenge remains of how best to translate the results of this encouraging animal study into meaningful clinical outcomes. The field of IRI is replete with examples of promising strategies that seemingly solve the problem in experimental models, only to fall short in randomized clinical trials.^{4,5} Hashimoto and colleagues³ are optimistic about this agent, as it targets a very proximal event in IRI—the translocation of phosphatidylserine to the cell membrane.

The authors are correct to point out promising results with this agent in a phase II study of kidney transplantation, although the results of a follow-up phase II/III trial have yet to be made available. The hurdles to be overcome before the agent is clinically applicable in lung transplantation are likely to be high, given the substantial redundancy built

Lungs intubated and cannulated for ex vivo lung perfusion.

Central Message

Pharmacologic management of ischemic reperfusion injury in lung transplantation remains challenging.

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into pathways operating in IRI, as well as the complex interplay with other donor and recipient factors. Even more intimidating is the immense effort and expense required to test compounds in clinical trials.

The group at Toronto General Hospital is well positioned to surmount some of these challenges. A seminal and recent contribution of the group is the development and clinical utilization of extended normo-thermic ex vivo lung perfusion of lung allografts⁶ (Figure 1). Evaluation, and possibly reconditioning, of lungs previously considered unsuitable for transplantation, is now an opportunity.⁷ Compounds such as this homodimer can be added easily to the perfusate,

FIGURE 1. Lungs intubated and cannulated for ex vivo lung perfusion. ETT, Endotracheal tube; PA, pulmonary artery; LA, left atrium.

and tested for their effect on reperfusion ex vivo. Additionally, the necessity of simultaneous targeting of multiple pathways of IRI is quite plausible, as is the possibility that combination therapy tested in the “kitchen sink” of ex vivo lung perfusion will lead to successful clinical trials. Well designed animal studies, such as the one by Hashimoto and colleagues,³ will spur further development of agents and strategies to combat IRI in lung transplantation.

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