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Commentary: Making lungs great again—introducing new modifications to the Toronto ex vivo lung perfusion protocol

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In clinical lung transplantation, ex vivo lung perfusion (EVLP) offers 3 critical advantages over conventional preservation methods. First, lung allografts, which reproducibly tolerate a limited time of cold storage, are reliably maintained with EVLP for 12 hours via the Toronto Protocol.^{1,2} Second, EVLP provides an opportunity to assess marginal organ performance before transplantation, facilitating expansion of the ever-limited donor pool. Early outcomes using EVLP have been promising, with initial experiences in the HELP¹ trial demonstrating equivalent survival and the INSPIRE (International Randomized Study of the TransMedics Organ Care System [OCS Lung] for Lung Preservation and Transplantation)³ trial identifying decreased rates of early primary graft dysfunction in patients receiving EVLP-preserved standard grafts. The NOVEL^{4,5} and EXPAND^{6,7} trials subsequently affirmed the utility of EVLP when used for extended criteria grafts.

Third and most importantly, however, EVLP offers the enormous potential to improve both marginal and standard grafts. Notable preclinical approaches have included gene therapy,⁸⁻¹⁰ novel drug delivery,¹¹⁻¹⁴ hepatitis C virus inactivation,^{15,16} antibiosis,¹⁷ stem cell therapy,¹⁸ and thrombolytics^{19,20} to optimize grafts. In addition, anatomic interventions, including lung lavage for aspiration injury²¹ and bronchial artery perfusion,²² have been

CENTRAL MESSAGE

New strategies in ex vivo lung perfusion extend preservation to 24 hours—an achievement that will enable surgeons to better allocate, evaluate, rehabilitate, and eventually enhance lung allografts.

proposed to improve graft function before transplant. Many of these interventions, however, will require extended normothermic perfusion beyond 12 hours.

One commonality among these diverse experimental approaches is the intention to emulate complex homeostatic mechanisms present in vivo that are suddenly lost during EVLP. Mechanisms regulating fluid and electrolyte balance, metabolism and nutrition, neuroendocrine regulation, and immune responses all remain largely ignored during preservation. Recently, the principle of establishing full physiologic support ex vivo was elegantly described with extracorporeal cross-circulation, which extended preservation of porcine lungs to 4 days²³ and repaired discarded human grafts in a xenogeneic model.²⁴ Clinical application of this approach, however, introduces new immunologic challenges in potential recipients, as well as ethical considerations for the animals—or patients—who would serve as organ “hosts.” As such, EVLP systems will likely remain a powerful tool in clinical transplantation for years to come despite current limitations.

In this issue of the *Journal*, Takahashi and colleagues²⁵ demonstrate 3 separate modifications to the Toronto Protocol to extend preservation time to 24 hours. This noteworthy achievement will enable clinicians to continue using EVLP to better allocate, evaluate, and investigate treatment strategies for marginal grafts. One strength of the study includes the straightforward clinical adaptability of their methods by replacing and/or supplementing the perfusate. These interventions are also relatively inexpensive. The authors demonstrate the modifications improve glucose and electrolyte homeostasis, and improve pulmonary function

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Disclosures: Dr Hartwig consults for Bridge to Life, Paragonix, Medtronic, Biomedinnovations, and Intuitive Surgical. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Aug 6, 2020; revisions received Aug 6, 2020; accepted for publication Aug 6, 2020; available ahead of print Aug 10, 2020.

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J Thorac Cardiovasc Surg 2021;161:1974-5

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2020.08.016>

compared with the current protocol. One limitation of the study is that grafts were not transplanted to demonstrate viability; however, a thorough histologic and cytokine analysis suggests these interventions mitigated inflammation and cellular injury. Second, not all grafts in the experimental groups were considered viable at 24 hours, indicating that although 24-hour EVLP is now achievable, it is not yet fully reliable. Finally, these experiments use the acellular Steen perfusate. Others have shown that a cellular perfusate may lead to better maintenance of the lungs on EVLP, and so these findings may not be universally applicable to other perfusion systems.²⁶ Nonetheless, these new iterations to the Toronto Protocol refine the practice of EVLP and bring us closer toward a physiologic perfusion platform to support novel organ rehabilitation strategies.

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