We congratulate Hsu and colleagues³ for their excellent study, which adds a new therapeutic option for the treatment of PH.

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Commentary: Transplanting the powerhouse of the cell to enhance cardiopulmonary repair

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Waitlist mortality for organ transplantation remains unacceptably high.¹ Sustained efforts to address the limitations of donor organ availability have focused on transplanting donor cells—instead of whole organs—as restorative therapies for cardiovascular repairs.² Despite the promise of cell therapies for cardiovascular diseases, clinical translation is challenged by substantial regulatory barriers and suboptimal efficacy in controlled clinical trials.^{3,4} After decades of investigation into mechanisms of benefit, we now understand that transplanted cells' beneficial effects are a consequence of paracrine actions of their secreted elements.⁵ Do we need entire organs and cells, or can we more simply reduce some directed therapies to their subcellular

Vishnu Vasanthan, MD (left), and Ali Fatehi Hassanabad, MD, MSc (right).

CENTRAL MESSAGE

Organelle transplantation using mitochondria shows potential to improve cardiopulmonary repair and performance after injury.

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Disclosures: The 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 31, 2020; revisions received Aug 31, 2020; accepted for publication Sept 1, 2020; available ahead of print Nov 15, 2021.

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J Thorac Cardiovasc Surg 2022;163:e376-7

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2020.09.007>

elements? Perhaps for some applications, cell therapy is a big idea that could be even smaller. We can leverage only the most critical fragments of cells as a viable therapy.

Mitochondria are the cells' powerhouse, the cellular engine that drives energy production and sustains healthy metabolism. Organelle transplantation using mitochondria is now a promising new frontier to reverse end-stage organ dysfunction in the face of excessive hemodynamic stress. Chronic pulmonary hypertension can cause irreparable damage to the pulmonary circulation and myocardium of the right ventricle. Contemporary pulmonary artery hypertension management can improve hemodynamics, but novel therapies are necessary to reverse maladaptive pulmonary artery remodeling to prevent disease progression and reduce

the growing need for organ transplantation.⁶ Directed mitochondrial transplantation could be a synergistic therapy that promotes healthy structural remodeling in both the cardiac and pulmonary systems. In fact, mitochondrial transplantation has already shown benefit in cardiac ischemia-reperfusion injury in preclinical models and pediatric patients.^{7,8}

Hsu and colleagues⁹ explore the therapeutic potential of intravenously delivered mitochondria in a small animal model of chronic pulmonary hypertension. The novel repair strategy restored pulmonary arterial vasoreactivity, altered vascular wall protein expression, and improved remodeling and performance of the right ventricle.⁹ These results provide an early signal that mitochondrial transplantation may partially reverse the damage caused by chronic pulmonary hypertension. It offers a novel therapeutic approach to an age-old and refractory problem.

Targeted transplantation of subcellular organelles, such as mitochondria, may provide surgeons with new molecular tools to remodel and restore tissue function. We can speculate on the exciting possibilities for clinical translation of intravenous delivery of organelles as a therapy to restore damaged tissues. Adenosine triphosphate-related mitochondrial pathways are highlighted as a therapeutic target for pulmonary artery hypertension, and autologous donation of mitochondria from skeletal muscle is already feasible in clinical settings.⁸ Mitochondrial transplant therapy could be compatible with catheter-based delivery during in vivo lung perfusion, currently explored for selective chemotherapeutic delivery to damaged lungs (NCT02811523).¹⁰ This strategy could build on emerging

technologies and improve directed delivery of this therapy. Perhaps these approaches could be combined with other lung-specific therapies while minimizing potential systemic adverse side effects.

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