of these mitochondrial injections. That said, this is an important potential therapeutic pathway that warrants carefully considered future research.

References

1. Acher C, Wynn M. Outcomes in open repair of the thoracic and thoracoabdominal aorta. *J Vasc Surg*. 2010;52(4 Suppl):3S-9S.
2. Corvera J, Copeland H, Blitzer D, Hicks A, Manghelli J, Hess P, et al. Open repair of chronic thoracic and thoracoabdominal aortic dissection using deep hypothermia and circulatory arrest. *J Thorac Cardiovasc Surg*. 2017;154:389-95.
3. Awad H, Ramadan ME, El Sayed HF, Tolpin DA, Tili E, Collard CD. Spinal cord injury after thoracic endovascular aortic aneurysm repair. *Can J Anaesth*. 2017;64:1218-35.
4. Frederick JR, Woo YJ. Thoracoabdominal aortic aneurysm. *Ann Cardiothorac Surg*. 2012;1:277-85.
5. Fedorow CA, Moon MC, Mutch WA, Grocott HP. Lumbar cerebrospinal fluid drainage for thoracoabdominal aortic surgery: rationale and practical considerations for management. *Anesth Analg*. 2010;111:46-58.
6. Fang SY, Roan JN, Lee JS, Chiu MH, Lin MW, Liu CC, et al. Transplantation of viable mitochondria attenuates neurologic injury after spinal cord ischemia. *J Thorac Cardiovasc Surg*. 2021;161:e337-47.
7. Scholpa NE, Schnellmann RG. Mitochondrial-based therapeutics for the treatment of spinal cord injury: mitochondrial biogenesis as a potential pharmacological target. *J Pharmacol Exp Ther*. 2017;363:303-13.
8. Sullivan PG, Krishnamurthy S, Patel SP, Pandya JD, Rabchevsky AG. Temporal characterization of mitochondrial bioenergetics after spinal cord injury. *J Neurotrauma*. 2007;24:991-9.

See Article page e337.

ADULT

Commentary: Mitochondria to the rescue?

Nirvik Pal, MBBS, MD, and John Butterworth, MD

Nirvik Pal, MBBS, MD, and John Butterworth, MD

CENTRAL MESSAGE

Another success story for mitochondrial transplant, but the basic biophysiologic mechanism remains unknown.

Precision medicine, machine learning, and artificial intelligence are the current buzz words of choice in medicine. To that list, we may soon add "organelle autotransfusion." In this edition of the *Journal*, Fang and colleagues[1] describe a novel potential treatment for ischemia–reperfusion injury in the spinal cord. In rat experiments, the authors harvested and isolated mitochondria, injected them intravenously during spinal cord ischemia, imaged the distribution of the mitochondria, and assessed motor function after restoration of circulation. The authors report spectacularly positive results. The isolation and harvesting procedures, requiring only approximately 30 minutes, make this technique potentially applicable to surgical patients.

Previous investigators showed that mitochondrial transplantation ameliorates myocardial injury in animals[2] and humans.[3,4] How do the transplanted mitochondria detect the target tissue? How do they migrate across plasma membranes? If they do not cross plasma membranes, how can they augment intracellular energy production? The authors harvested mitochondria from one rat and administered them to another; should we anticipate that allogenic mitochondria would generate some sort of immunologic response? Potential therapeutic mechanisms for mitochondrial transplantation include supplementation of bioenergetic substrates and antioxidants, or upregulation of enzymes for oxidative phosphorylation.[5] But in truth, we don't

From the Department of Anesthesiology, Virginia Commonwealth University School of Medicine, Richmond, Va.

Disclosures: Authors have nothing to disclose with regard to commercial support.
Received for publication Nov 26, 2019; revisions received Nov 26, 2019; accepted for publication Nov 26, 2019; available ahead of print Dec 14, 2019.

Address for reprints: John Butterworth, MD, Department of Anesthesiology, Virginia Commonwealth University School of Medicine, PO Box 980695, Richmond, VA 23298-0695 (E-mail: John.butterworth@vcuhealth.org).

J Thorac Cardiovasc Surg 2021;161:e350-1
0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.11.109

know the locus of action, how the mitochondria identify and access the locus of action, or the mechanism of the therapeutic effect![6,7]

Mitochondria are intracellular organelles accustomed to a milieu of reduced calcium ion concentrations. How do they survive the increased calcium concentrations encountered during harvesting and after intravenous injection? What is the dose-response relationship? What minimal number of mitochondria must be injected?[8] Other studies have shown less than 10% of injected mitochondria were internalized.[9] The authors wisely acknowledge many of these concerns as study limitations.

Spinal cord hypoperfusion during thoracoabdominal aortic aneurysm surgery remains a nettlesome challenge. Our understanding of spinal cord perfusion has evolved over time. We no longer expect a single artery of Adamkiewicz to be present in all patients; we now expect a collateral network[10] involving both intrathecal and extrathecal blood vessels as contributors to spinal cord perfusion. In clinical practice, we try to avoid spinal cord hypoperfusion by optimizing spinal cord perfusion pressure: We maintain an appropriate mean arterial pressure and reduce the intrathecal pressure by draining cerebrospinal fluid. We may also provide localized spinal cord cooling with cold epidural solutions, free radical scavengers (eg, systemic mannitol), membrane stabilizers (eg, magnesium or lidocaine), or anti-inflammatory agents (eg, steroids). Surgically, there are a variety of perfusion and shunting (partial bypass, left heart bypass) techniques for aorta repairs. We have limited evidence of efficacy for these maneuvers and drugs; the only thing we know with confidence is that shorter periods of ischemia are better. Therefore, it would be a monumental advance in patient care if this early evidence for spinal cord protection from mitochondrial transplantation were to be confirmed and the technique incorporated during those procedures in which spinal cord ischemia is a risk.

References

1. Fang SY, Roan JN, Lee JS, Chui MH, Lin MW, Liu CC, et al. Transplantation of viable mitochondria attenuates neurologic injury after spinal cord ischemia. *J Thorac Cardiovasc Surg*. 2021;161:e337-47.
2. Moskowitzova K, Shin B, Liu K, Ramirez-Barbieri G, Guariento A, Blitzer D, et al. Mitochondrial transplantation prolongs cold ischemia time in murine heart transplantation. *J Heart Lung Transplant*. 2019;38:92-9.
3. Emani SM, Piekarski BL, Harrild D, Del Nido PJ, McCully JD. Autologous mitochondrial transplantation for dysfunction after ischemia-reperfusion injury. *J Thorac Cardiovasc Surg*. 2017;154:286-9.
4. McCully JD, Cowan DB, Emani SM, Del Nido PJ. Mitochondrial transplantation: from animal models to clinical use in humans. *Mitochondrion*. 2017;34:127-34.
5. Gollihue JL, Rabchevsky AG. Prospects for therapeutic mitochondrial transplantation. *Mitochondrion*. 2017;35:70-9.
6. Gollihue JL, Patel SP, Rabchevsky AG. Mitochondrial transplantation strategies as potential therapeutics for central nervous system trauma. *Neural Regen Res*. 2018;13:194-7.
7. Bertero E, Maack C, O'Rourke B. Mitochondrial transplantation in humans: "magical" cure or cause for concern? *J Clin Invest*. 2018;128:5191-4.
8. Hammel JM. Mitochondrial autotransplantation: a "shot" in the dark? *J Thorac Cardiovasc Surg*. 2017;154:290.
9. Kumar SR. Mitochondrial transplantation: another miracle of molecular medicine? *J Thorac Cardiovasc Surg*. 2017;154:284-5.
10. Etz CD, Kari FA, Mueller CS, Silovitz D, Brenner RM, Lin HM, et al. The collateral network concept: a reassessment of the anatomy of spinal cord perfusion. *J Thorac Cardiovasc Surg*. 2011;141:1020-8.