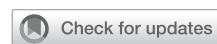


of these mitochondrial injections. That said, this is an important potential therapeutic pathway that warrants carefully considered future research.

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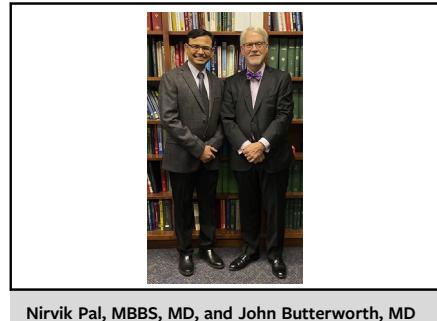
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Commentary: Mitochondria to the rescue?

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

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 colleagues¹ 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.



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CENTRAL MESSAGE

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

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Previous investigators showed that mitochondrial transplantation ameliorates myocardial injury in animals² 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

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 network¹⁰ 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.

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