Mitochondria “muscle in” as a potential adjunct therapy in cardiothoracic surgery

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Surgery of the heart has probably reached the limit set by nature to all surgery; no new method and no new discovery can overcome the natural difficulties that attend a wound of the heart.

—Sir Stephen Paget, 1896¹

With each decade surpassing the previous since the first successful cardiopulmonary bypass operation in 1953, advancements in surgical procedure, surgical technology and apparatus, cardiac devices, imaging and diagnostics, pharmaceutical adjuncts, anesthesia, perioperative intensive care, and medical management have in combination markedly transformed outcomes for the cardiothoracic surgical patient. Despite how much has been achieved, will more than incremental improvement in cardiac patient outcomes be eventually limited by “the natural difficulties that attend a wound of the heart”? Fortunately, in the background there is basic research that is constantly challenging such technical constraints and that keeps augmenting our understanding of human biology and disease to establish a new baseline of medical accomplishment and practice.

The latest example involves mitochondria, the highly specialized organelles that house their own unique DNA and sustain oxidative phosphorylation-dependent energy production to support the majority of the heart's high work demand. Our exponentially growing understanding of the additional critical roles that mitochondria perform as dynamic regulators of adaptive metabolism and cellular homeostasis, cell survival, cell death, intracellular signaling, and intercellular communication in aging and disease have vastly expanded our capacity to target mitochondria-dependent cellular dysfunction that underpins numerous cardiovascular disorders.² Ischemic injury includes perturbations in mitochondrial structure and volume that lead to breaches in ionic homeostasis (particularly calcium) and involve loss of redox capacity, loss of reactive oxygen species management, and dysfunction caused by

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Central Message

Intraoperative transfer of autologous mitochondria isolated from viable tissue to injured myocardium may offer cardioprotective postischemic recovery of myocardial bioenergetics and viability.

See Article page 934.

oxidative and other epigenetic molecular modifications to proteins, lipids, and DNA.^{2,3} In addition, these processes are affected by cardiopulmonary bypass surgery stresses, many of which may be specifically targeted by intraoperative cardioprotection (Figure 1).⁴

In this issue of the *Journal*, Kaza and colleagues⁵ tantalize us with a conceptually bold effort to restore mitochondrial function and myocardial viability directly in a large animal (porcine) model of ischemia-reperfusion injury. After 24 minutes of regional ischemia induced by constriction of the circumflex artery, in the 25th minute, 8 0.1-mL injections of autologous mitochondria (approximately 1.3×10^7 mitochondria/injection) were delivered to the zone at risk. Subsequently, the snare was released to allow myocardial reperfusion. Mitochondria were rapidly isolated and purified under sterile conditions from a 30-mg skeletal muscle biopsy sample taken from the pectoralis major and prepared for injection. Most notably, after 4 weeks of recovery the myocardial infarct size was smaller (5.2%) than in the animals that received vehicle control injections (13%). Troponin I was also diminished by autologous mitochondrial treatment by 3 days after surgery, although not immediately after surgery. At 4 weeks of recovery, mitochondria-treated hearts exhibited no evidence of immune or inflammatory response, no difference in ultrastructural cell damage, and no evidence of effects on heart rate, atrial or ventricular arrhythmias, or electrocardiographic

FIGURE 1. A scheme summarizing the multiple roles of mitochondria in myocardial cells, in health and disease, and the potential of autologous isolated mitochondrial transfer in cardioprotection. CA, Calcium; SR, sarcoplasmic reticulum.

repolarization abnormalities. Importantly, Kaza and colleagues⁵ demonstrated mitochondrial uptake into cardiomyocytes, and the transplanted mitochondria were still present at 4 weeks after treatment.

This study is the culmination of previous validations and mitochondrial handling refinements performed in exacting detail by this group since their initial report in 2009.^{6,7} The mechanisms involved are not yet fully defined; however, their previous studies show that transplanted mitochondria exert extracellular and intracellular improvements in oxygen consumption and energy production. Mitochondria are endocytosed by an active actin-dependent process that differs from those conferred by tunneling nanotube or autophagosomal processes.⁶ Although in their earlier ex vivo ischemic rabbit heart studies contractile functional improvements were shown to be conferred by mitochondrial treatments,^{7,8} a significant limitation of this study was the inability to detect treatment differences in cardiac function with parasternal echocardiography.⁵ Kaza and colleagues⁵ state that this

limitation was due to the technically challenging size and positioning of porcine ribs and extended sternum, which limited resolution of the ultrasound window. Because the ischemic model used constriction of the circumflex rather than the left anterior descending artery, however, it is unclear whether mitochondrial cardioprotection can be afforded in the case of more severe ischemia that causes greater myocardial contractile dysfunction. Whether this failure to detect salvage of contractile performance is technical, related to severity of the injury, or perhaps shows absence of long-term benefit on ventricular function requires follow-up.

Ultimately, we must ask whether isolated mitochondria are safe to deliver to patients, and which patients are appropriate candidates. Can mitochondrial transplantation be cardioprotective in the patient who has cardiovascular disease and comorbidities related to diabetes, renal disease, obesity, senescence, and other conditions that may limit the viability of mitochondria sourced from the autologous noncardiac tissue? Are the mechanisms that permit mitochondrial uptake and survival in heart cells perturbed by the patient's

cardiovascular disease state, which may include long-term and evolving heterogeneous ischemia? What is the extent of contractile performance that can be salvaged? Assuming these crucial questions can be answered positively, the clinical refinement and translation of this novel method as a cardiac surgical adjunct may offer an enormous shift in the reach of cardiothoracic surgery to augment positive patient outcomes. In the meantime, more basic research must keep challenging “the natural difficulties.”

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