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Commentary: Protecting the powerhouse of the cell: The next frontier of myocardial protection?

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It appears that some 2 billion years ago, bacteria capable of aerobic metabolism were endocytosed by early eukaryotic cells and evolved into mitochondria. This symbiotic relationship conferred an enormous advantage by providing a means of aerobic metabolism for eukaryotic cells, paving the way for the evolution of complex multicell organisms. In normal conditions, the human myocardium is completely reliant on aerobic metabolism, which takes place in mitochondria. In ischemic conditions, such as those generated by aortic crossclamping in cardiac surgery or organ procurement, there is a switch to anaerobic metabolism. The process of ischemia–reperfusion causes mitochondrial injury that may be an important contributor to myocardial dysfunction. Recently, mitochondria have been recognized as a potential target for preventing ischemia–reperfusion related myocardial injury in several settings, including acute myocardial ischemia, organ transplantation, and right ventricular dysfunction.^{1–5}

Song and colleagues⁶ report the effects of a mitochondrial-specific antioxidant, Mito-Tempo, on an in vitro mouse model of cardioplegic ischemia–reperfusion. Mito-Tempo, which contains 2 compounds—triphenylphosphonium and piperidine nitroxide—is a lipophilic

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Mitochondria represent important new targets for protection during ischemia–reperfusion associated with cardiac surgery.

molecule. Being lipophilic, it can easily pass through the phospholipid membranes and accumulate within mitochondria where it acts as a superoxide scavenger, thus preventing oxidative injury. Song and colleagues⁶ demonstrate that treatment with Mito-Tempo had a range of beneficial effects on vessels including improved endothelium dependent vasodilatation, depressed intracellular calcium influx, and significantly reduced levels of reactive oxygen species within endothelial cells. Importantly, these beneficial effects were observed in both non-diabetic and diabetic experimental models, resulting in decreased microvascular dysfunction following ischemia–reperfusion.

Our current techniques of myocardial protection continue to rely on electrolyte induced cardiac arrest in diastole and hypothermia to minimise myocardial oxygen demand, with or without substrate enhancement, in order to reduce ischemia–reperfusion induced damage to the myocardium. These are essentially the same techniques described by the pioneering work of Buckberg and colleagues in the 1970s,⁷ with very few major advances in the intervening period. However, it appears that mitochondria may represent an important new target. It has previously been shown that mitochondrial transplantation into cardiomyocytes is a potentially effective strategy to improve myocardial recovery in the setting of ischemia–reperfusion, both in cardiac surgery and cardiac procurement for transplantation. Song and colleagues⁶ have added to this evidence by showing that protecting mitochondria from reactive oxygen species may preserve microvascular function in the setting of ischemia–reperfusion. Given the

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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 July 5, 2021; revisions received July 5, 2021; accepted for publication July 7, 2021; available ahead of print July 14, 2021.

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J Thorac Cardiovasc Surg 2022;164:e227-8
0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2021.07.009>

lipophilic properties of Mito-Tempo, it is possible it may also be able to diffuse into the myocardium and protect mitochondria within the cardiomyocytes from ischemia-reperfusion injury and, thus, directly protect the myocardium. The latter, however, is yet to be determined. The obvious benefit of Mito-Tempo compared to the more complex techniques involved in mitochondrial transplantation is the ease in which it could be incorporated into our current cardioplegia solutions.

Will therapies targeted at mitochondria provide a paradigm change in myocardial protection? This remains to be seen, yet the early pre-clinical data appear promising!

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Commentary: Targeting mitochondrial injury after plegic arrest: SK-ipping the endothelial tempo or not?

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In this issue, Song and colleagues¹ demonstrated that Mito-Tempo improved endothelium-dependent relaxation response and suppressed intracellular Ca^{2+} accumulation following cardioplegic hypoxia and reoxygenation. The authors suggest that these results are mediated by enhanced endothelial SK channel activity through inhibition of mitochondrial reactive oxygen species (ROS). The authors also concluded that coronary arteries of either normoglycemic

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Mito-Tempo improves endothelium-dependent relaxation response and suppresses intracellular Ca^{2+} accumulation after cardioplegic hypoxia/reoxygenation in vitro, yet in vivo studies are necessary.

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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 June 22, 2021; revisions received June 22, 2021; accepted for publication June 23, 2021; available ahead of print June 29, 2021.

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J Thorac Cardiovasc Surg 2022;164:e228-9

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2021.06.050>

or diabetic murine with Mito-Tempo showed enhanced endothelium-dependent relaxation in response to either a SK activator or an endothelium/nitric oxide-dependent vasodilator in a dose-dependent response.

Mitochondrial dysfunction plays a major role in myocardial injury following ischemia-reperfusion and is merely associated with ROS accumulation, which are byproducts of the altered metabolism of the cardiomyocytes.² Mito-Tempo is reported to be a mitochondria-targeted antioxidant providing protection either against