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

CENTRAL MESSAGE

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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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

oxidative injury associated with acute liver or kidney injury or ischemic injury associated with endothelial dysfunction. Ischemia causes myocardial injury, and protecting the coronary endothelium in cardiac operations requiring cardiac arrest is pivotal for optimization of the outcomes. Although no alterations in SK3/SK4 protein expression were noted—the main channel subtypes in the cardiomyocytes—neither after cardioplegic hypoxia and reoxygenation with or without diabetes nor Mito-Tempo, it is speculated that SK activity instead of protein expression may be affected.

The authors used a transgenic model expressing the type 2 diabetic phenotype accompanied by mitochondrial dysfunction and increased susceptibility of the myocardium to ischemic reperfusion injury. This is quite important, given the common presence of comorbidities in patients undergoing open-heart surgery; yet, age and sex are 2 other factors—among others—that should be taken into consideration, given their impact on mitochondrial function and the subsequent clinical outcomes. Moreover, the authors attempted to elucidate a potential mechanism by which Mito-Tempo exerts its beneficial effects, focusing only on its impact on the SK channel activity following cardioplegic injury. Given the absence of SK protein expression changes after Mito-Tempo treatment, this assumption is likely flawed.

Additional pathways implicated in angiogenic or inflammatory responses of the injured endothelium should be further investigated.

Targeting mitochondrial-dependent ROS accumulation and the subsequent endothelial damage is a promising therapeutic strategy. Song and colleagues¹ should be commended for their novel work unveiling the favorable effect of Mito-Tempo treatment during cardioplegic hypoxic injury, yet in vivo assessment of this proof-of-concept study is necessary to evaluate the translational significance of these observed outcomes. Moreover, different types of cardioplegia are used in the clinical setting, an important aspect requiring further investigation. Before moving to preclinical and clinical studies, route of administration, dosage and dosing scheme should be investigated for optimal results following the establishment of the feasibility and safety of this treatment modality.

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