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EDITORIAL COMMENT

Targeting Mitochondrial Function in Heart Failure

Makes Sense But Will it Work?*

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Humans produce approximately their body weight equivalent adenosine triphosphate (ATP) (~65 kg) each day, and although the heart is only ~0.5% of body weight, it consumes roughly 8% of ATP generated (1). The heart possesses the highest content of mitochondria of any tissue. Approximately 90% of cellular ATP is used to support the contraction-relaxation cycle (2). Calcium sequestration into the sarcoplasmic reticulum also requires ATP. Production of energy in the human heart is a dynamic process because the heart stores only enough energy to support a few heartbeats. Mitochondria therefore must operate efficiently to respond promptly to the ever-changing energy needs as required by the rest of the body's function. Mitochondrial abnormalities and reduced capacity to generate ATP can have a profound impact in heart failure (HF). Abnormal mitochondria are also linked to myocyte injury because they are a major source of reactive oxygen species production that can induce cellular damage. Abnormal mitochondria also promote programmed cell death through the release of cytochrome *c* into the cytosolic compartment and activation of caspases (3).

Progression to HF is associated with a decline in energy reserve capacity that ultimately reaches a threshold after which compensatory mechanisms can no longer support the decreasing energy supply. Moreover, skeletal muscles also show mitochondrial dysfunction in HF, thus contributing to exercise intolerance (4). Mitochondrial dysfunction is also seen in patients with renal insufficiency (5) and in insulin resistance (6). Because patients with HF often have both renal insufficiency and insulin resistance, treating mitochondrial dysfunction in HF hold promise to help through cardiac and extracardiac mechanisms.

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In this issue of *JACC: Basic to Translational Science*, Chatfield et al. (7) describe mitochondrial function impairment in failing ventricular tissue and investigate the impact of elamipretide on mitochondrial and supercomplex function in failing pediatric and adult human hearts ex vivo. These investigators report that elamipretide improved mitochondrial oxygen flux, complex (C) I and IV activities, and supercomplex-associated CIV activity in failing human hearts, whereas the drug had no significant effect on normal mitochondrial function in nonfailing human hearts. Previous studies with elamipretide showed that the drug directly improved energetics in various animal models (8,9). The study by Chatfield et al. (7) is 1 of the studies to demonstrate direct acute effects of elamipretide on ex vivo human hearts.

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The study by Chatfield et al. (7) also gives additional insight into the mechanism of action of elamipretide, thereby suggesting that the drug improves human cardiac function through better coupling of supercomplex-associated enzyme complexes, CI, CIII, and CIV, instead of cardiolipin remodeling. The main mechanism of elamipretide benefits is believed to arise from stabilizing cardiolipin through inhibition of cytochrome *c*-cardiolipin peroxidase complex and thus allowing maximum energy production (10,11). However, Chatfield et al. (7) report that cardiolipin absolute amounts and the sum of all cardiolipin species were unaltered after elamipretide treatment, a finding indicating that the drug may improve mitochondrial function without an effect on cardiolipin. These findings should be considered with caution because the exposure time to the intervention was limited, and the concentrations of elamipretide needed to produce such results could well vary ex vivo and in vivo. The current study also highlights that elamipretide improves mitochondrial function independent of age and HF etiology, thus suggesting that mitochondria may represent 1 common final pathway in HF.

Although the study by Chatfield et al. (7) elegantly provides evidence that elamipretide improves myocardial energetics in failing myocardium, the question remains whether this mechanistic benefit will translate into clinical benefit, given that previous attempts to restore myocardial energetics have inconsistently led to clinical benefit. Fatty acid oxidation reduction with the use of trimetazidine and inhibition of excitation-contraction coupling with ranolazine did not improve HF outcomes (12,13). Although reactive oxygen species damage cardiolipin and result in mitochondrial dysfunction, none of the antioxidants have proved to be beneficial in HF; in fact, long-term supplementation of vitamin E (tocopherol) conferred an increased risk for HF (14,15). On the contrary, several trials have shown benefit of intravenous iron supplementation in patients with HF (16).

In the EMBRACE STEMI (Evaluation of Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients With Acute Coronary Events-ST-Segment Elevation Myocardial Infarction) trial, elamipretide did not improve the primary or secondary outcomes (17). In the randomized placebo-controlled trial of elamipretide in HF (18), the drug was shown to reduce left ventricular volumes; however, the confidence intervals were wide in this small study, and there were no changes in biomarker data. Elamipretide is currently being investigated (NCT02788747, NCT02814097, and NCT02914665) in larger HF studies to determine its effect on cardiac remodeling and clinical outcomes.

HF is a complex syndrome involving multiple altered physiological mechanisms and organ systems that interact. The results reported by Chatfield et al. (7) are encouraging, and mitochondria remain a promising therapeutic target. Data from carefully designed and conducted clinical trials are now needed to show whether the promise is actually fulfilled.

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