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Targeting Myocardial Energetics in the Failing Heart: Are We There Yet?

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It has long been recognized that key components of the cardiac energetic system are down regulated in the failing heart. Under normoxic conditions mitochondrial oxidative phosphorylation generates ~ 95% of the adenosine trisphosphate (ATP) content in the heart,[1] which is essential for the process of excitation contraction, as well as maintenance of membrane transport systems. Studies in patients with end-stage cardiomyopathy have shown that the total adenine nucleotide pool, (ATP, ADP, and AMP), creatine kinase activity (required for ATP synthesis), creatine phosphate (CrP) concentration, and the Cr/ATP ratio (a marker of impaired energy metabolism) are all decreased in the failing heart, which has given rise to the notion that the failing heart is an "engine out of fuel."[1, 2] Although multiple mechanisms have been proposed to explain the profoundly abnormal energetics in the failing heart, recent advances in our understanding of mitochondrial biology[3] have raised the intriguing possibility that mitochondria-targeted therapeutics may lead to improved energy production in the heart.[4] Accordingly, a study in this issue of the *Circulation: Heart Failure* by Daubert and colleagues,[5] which evaluates the safety of elamipretide, a novel mitochondria-targeted peptide, in heart failure patients with a reduced ejection fraction (HFrEF) is of considerable interest.[5]

Daubert et al conducted a double-blind placebo-controlled ascending-dose trial with elamipretide in HFrEF patients (< 35%) who were receiving evidence based medical therapies for heart failure. Patients were randomized to a single 4-hour IV infusion of elamipretide 0.005 mg/kg/hour (n=8), 0.05 mg/kg/hour (n=8), 0.25 mg/kg/hour (n=8), or placebo control (n=12). Safety and efficacy were assessed by measurement of clinical laboratories and 2-D echocardiography at pre-mid, mid, and end infusion and 6, 8, 12, and 24 hours post infusion. The primary end point of the study was the safety and tolerability of a single 4 hour intravenous infusion. The secondary end points included a pharmacokinetic analysis of elamipretide, evaluation of the effects of elamipretide on cardiac structure and function, and the effect of elamipretide on cardiac biomarkers. The authors found that a single IV infusion of elamipretide for 4 hours was safe and well tolerated. Blood pressure and heart rate remained stable in all cohorts. Peak plasma concentrations of elamipretide increased in a dose-proportional manner, with peak values observed at the end of the infusion, with no detectable plasma levels at 24 hours. Intriguingly, the authors report that

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compared to placebo, there was a significant decrease in left ventricular (LV) end-diastolic volume and LV end-systolic volume in the cohort that received the highest-dose. There was, however, no change in NT-proBNP or hsCRP at any time point among the elamipretide or placebo cohorts. Before discussing the significance of these findings, it is instructive to review what is known about elamipretide.

Elamipretide (also known as SS-31 MTP-131, Bendavia™) is a water soluble mitochondria-targeted tetrapeptide (D-Arg-dimethylTyr-Lys-Phe-NH2) that stabilizes cardiolipin by inhibiting the cytochrome C/cardiolipin peroxidase complex and also acts as a reactive oxygen scavenger.[6] Cardiolipin anchors cytochrome c to the inner mitochondrial membrane, thereby facilitating transport of electrons from complex III to complex IV. Because of its high content of unsaturated fatty acids and its location near the site of production of reactive oxygen species (ROS), cardiolipin is sensitive to oxidative stress. Oxidation of cardiolipin can lead to decreased electron transport, decreased ATP generation and release of cytochrome c into the cytoplasm, thereby triggering apoptotic cell death.[4] In experimental studies, treatment with elamipretide significantly improved myocardial mitochondrial ATP content, reduced myocardial infarct size and improved cardiac function. [7–9] Moreover, treatment with elamipretide improved LV systolic function, normalized plasma biomarkers of inflammation, and improved cardiac bioenergetics in a well-characterized canine model of HFrEF.[10]

Elamipretide has been studied previously in clinical trials, and was granted orphan drug status by the U.S. Food and Drug Administration (FDA) for patients with primary mitochondrial myopathy based on the encouraging results of the MMPOWER-2 Study (NCT-02805790).

Elamipretide has also been studied previously in a double-blind Phase 2a trial in patients who were undergoing a primary percutaneous coronary intervention following an ST-segment elevation myocardial infarction (STEMI). EMBRACE STEMI randomized 297 patients to elamipretide, infused at a rate of 0.05 mg/kg/h for 1 h, or placebo following a primary PCI. The primary endpoint of the trial was infarct size determined by measuring the area under the curve for elevation of creatine kinase-MB (CK-MB) 72 hours following PCI. Administration of elamipretide was not associated with a significant reduction in the primary endpoint, nor was it associated with an improvement in any of the pre-specified secondary outcome measures, including magnetic resonance imaging of LV structure and function, angiographic assessment of TIMI flow, resolution of ST-segment elevation, or circulating levels of NT-proBNP or measures of renal function. Importantly, administration of elamipretide was shown to be safe and well tolerated. Elamipretide has been tested in patients with heart failure with a preserved ejection fraction (NCT02814097). Although this study has been completed, the final results have not yet been reported at the time of this writing.

Targeting the myocardial energetics in heart failure: are we there yet?

There have been multiple attempts at restoring defective energy production in the failing heart, including improving myocardial oxidative capacity by increasing glucose utilization

(e.g., glucagon-like peptide 1 [GLP-1] agonists) or reducing fatty acid oxidation (e.g., trimetazidine), targeting excitation-contraction coupling (ranolazine), or restoring nitric oxide production. Although, encouraging results were observed in pre-clinical studies and small clinical reports, all attempts thus far to target myocardial energetics in HFrEF have not led to an FDA approved indication. Elamipretide and Mito-Q[11] represent a new class of mitochondria-targeted drugs that improve ATP generation in the heart. The study by Daubert and colleagues in this issue of the *Circulation: Heart Failure* shows that a short-term infusion of elamipretide is safe and well tolerated in HFrEF patients, which extends the overall safety profile of elamipretide by demonstrating that higher doses of elamipretide (0.25 mg/kg/hr) have an acceptable safety profile. The observed effects of high dose elamipretide on reducing LV volumes are interesting, but should be regarded as provisional because of the small numbers of patients that were studied, the wide confidence intervals for the changes in LV volumes, the absence of corroborating biomarker data to suggest reverse LV remodeling, and the lack of any adjustment for multiple statistical comparisons for the measurement of LV volumes, which raises the possibility that these findings may represent a type I statistical error. These limitations notwithstanding, the results of this phase I study with elamipretide in HFrEF patients are encouraging and suggest that targeting mitochondrial bioenergetics directly may represent a new and potentially exciting avenue for heart failure therapeutics.

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