Commentary: Take two mitochondria and call me in the morning

Camille L. Hancock Friesen, MD

One of the rationales for timing of intervention in many valvar pathologies is that replacing a failed valve is possible, but replacing failed muscle is not. While that is still the case, there may be new methods on the horizon for improving the bioenergetics of failing cardiomyocytes. Weixler and colleagues1 present an interesting preclinical animal model in “Autogenous Mitochondria Transplantation for Treatment Of Right Heart Failure” that provides evidence that in a model of chronic right ventricle (RV) hypertension (pulmonary artery–banded neonatal piglets), autologous mitochondria derived from skeletal muscle can be injected locally into the RV and delay the onset of decompensated RV heart failure that is witnessed without the mitochondrial transplant. This is a very exciting proof-of-concept trial that shows that viable mitochondria can be harvested, isolated, transferred, and internalized in working form. The transplantation of mitochondria has been previously performed with evidence of positive impact in an animal model of ischemic injury but this is the first report of efficacy in a model of decompensated RV hypertension.2,3 Viable transplanted intracardiomyocyte mitochondria are visualized at 24 hours’ postinjection. The presence of proteins related to oxidatively competent mitochondria (proteomic functional annotation clustering) is used to provide evidence that the transplanted mitochondria are responsible for the preserved architecture and function of the right ventricle at 8 weeks postoperative, consistent with in vitro studies that show reduced late apoptosis and fibrosis in the study population.

Unfortunately, in this study there was no control arm of pulmonary artery–banded animals without injection of either vehicle or mitochondria. This lack of control arm leaves the question as to whether the injection of vector had a deleterious effect rather than that the injection of mitochondria had a positive impact. While the authors have shown convincingly that transplanted mitochondria are present and viable early post-transplant, they do not present data that confirm the presence of viable mitochondria at the late time points in the study and rely instead on the indirect evidence of protein expression in harvested RV tissue to indicate that viable function mitochondria are present and responsible for improved RV function.

The concept of specific genome editing to treat mitochondrial dysfunction is mentioned briefly in the state-of-the art armamentarium of therapies currently available to enhance bioenergetics in cardiomyocytes,4 although “three-parent” babies are now being engineered specifically for mitochondrial replacement to prevent hereditable mitochondrial defects.5 The authors of the current study are bringing exciting new technology and approaches to the congenital heart realm. It is invigorating to be part of a specialty that is at the cutting-edge of research and to think of the number of patients with congenital heart disease who we treat each day who might benefit from re-energizing tired-out cardiomyocytes.
Commentary: Recharging cellular batteries of the failing right heart: Mitochondrial transplantation

Mohamed Abdullah, MD, PhD, and Sunjay Kaushal, MD, PhD

There is growing interest in developing therapeutic interventions to preserve right ventricular (RV) function in the setting of maladaptive hypertrophy and dilation due to increased pressure overload. Mitochondrial dysfunction has been implicated in the pathophysiology of heart failure, and studies have shown benefit from mitochondrial transfer therapy to improve left ventricle myocardial recovery after ischemia–reperfusion. However, the utility of mitochondrial transfer to support RV function in the setting of pulmonary hypertension, RV outflow obstruction, or systemic RV associated with some congenital cardiac anomalies remains unknown at this time.

In this issue of the Journal, Weixler and colleagues describe a potent modality for mitigating cardiomyocyte apoptosis and fibrosis and preserving contractility in a pressure-loaded RV. The authors used a large animal porcine model of pulmonary artery banding leading to RV hypertrophy with a subsequent single injection of autologous mitochondria 4 weeks post-banding. Defined end points were then followed for another 4 weeks. Compared with the vehicle control group, the mitochondria-treated group displayed increased RV fractional area change, tricuspid annular plane systolic excursion, derivative of pressure over time max, and RV free wall thickness, as measured by echocardiography. At the histologic level, compared with the vehicle control group, the mitochondrial transfer group had significantly decreased myocardial fibrosis and apoptosis. Taken together, these results indicate that the mitochondrial transfer group remodeled the RV myocardium to improve clinically well-defined outcome measures.