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Commentary: Recharging cellular batteries of the failing right heart: Mitochondrial transplantation

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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,¹ and studies have shown benefit from mitochondrial transfer therapy to improve left ventricle myocardial recovery after ischemia–reperfusion.² 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 colleagues³ describe a potent modality for mitigating cardiomyocyte apoptosis and fibrosis and preserving contractility in a

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CENTRAL MESSAGE

Autologous mitochondria transplantation supports the failing right ventricle in animal models. Further studies are needed to assess applicability in clinical settings.

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 autogenous 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.

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The authors should be commended on their study and their findings. However, there are still concerns that may limit clinical translation. First, the disease model used, which represents the early stages of adaptive changes in the RV following the onset of pressure overload, may not recapitulate the entire clinical physiology of RV pressure overload. More commonly, patients present at later stages of maladaptive RV hypertrophy and dilation that occur after years of RV pressure overload. It is unclear whether mitochondrial transfer will still be efficacious in the setting of a chronically dysfunctional RV. Second, the clinical application of an autologous therapeutic agent may be limited due to time, cost, clinical variables, and operator dependency. In addition, the study did not investigate the effect of hypothermia and cardiopulmonary bypass on the outcome of mitochondrial transfer in the dysfunctional RV. Furthermore, the postoperative inflammatory response that occurs following cardiopulmonary bypass may affect

the ability of mitochondrial transfer to improve RV function. These issues raise questions regarding the broad clinical applicability of autologous mitochondrial transfer in patients.

Despite the limitations of the study, these findings highlight a novel potential therapy for treatment of RV dysfunction in the situation of RV pressure overload. More mechanistic studies may drive this therapy to clinical success, ultimately enabling treatment of these clinically challenging patients.

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