Commentary: Mitochondrial transplantation for myocardial failure, marvel remedy or wishful thinking?

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There is an everlasting argument between science and religion about the origin of humans that continues to date. The extremely complex and intelligent design of the human being, which continues by and large to mystify scientists, is a commonly used argument for the divine creation of God’s masterpiece, humankind. On the other hand, while scientists have not been able so far to completely solve the mystery of the human body, they have undeniably reached remarkable discoveries in the understanding and amendment of how the body works, with consequent groundbreaking advances in the fields of medicine and molecular biology. One of these extraordinary developments is the understanding of the role of mitochondria in normal cellular function and in the basis of various medical disorders.

The mitochondria are essential cellular organelles that play a crucial role in the generation of adenosine triphosphate that is necessary for cellular homeostasis, as well other mechanisms that affect cellular apoptosis and necrosis. Dysfunction of the mitochondria has been linked to several disorders that affect all body organs (eg, neuromuscular, endocrine, cardiac, renal, gastrointestinal, etc). Mitochondrial transplantation to cure such chronic disorders or reverse and mitigate acute organ injury is one of the new refined innovations and investigations in medicine. In the field of pediatric cardiac surgery, the team from Boston, led by James D. McCully, has explored techniques of mitochondrial transplantation to combat cardiac dysfunction associated with ischemia–reperfusion injury.1–3 In the current issue of the Journal, Weixler and colleagues present another contribution from Boston as they investigate the effect of mitochondrial transplantation in the treatment of right ventricle (RV) hypertrophy and failure.

In their article, Weixler and colleagues created a RV hypertrophy/failure model by banding the pulmonary artery in immature piglets. Four weeks later, the banded piglets (as compared with the control sham operation piglets) showed evidence of increased RV wall thickness, decreased RV fractioned area change, and decreased tricuspid annular plane systolic excursion, suggesting failure of the hypertrophied cardiomyocytes. At 4 weeks, the banded piglets were divided into 2 equal groups: one group received autologous mitochondrial transplantation from calf muscles and the other received vehicle, injected in the RV free wall. They noted that the group that received mitochondrial transfer continued to exhibit increased RV wall thickness in response to the band (while the vehicle group ceased to exhibit that), and that RV fractioned area change and tricuspid annular plane systolic excursion were increased again in the mitochondrial transfer group, to match that of the control (sham operation) group. Additional findings when the piglets were sacrificed at 8 weeks included the significant increased cardiomyocyte apoptosis and fibrosis in the banded compared with sham-operation piglets, although that difference was less pronounced in the ones that were treated with mitochondrial transplantation. They concluded that mitochondrial transplantation allowed for prolonged physiological adaptation of the pressure-loaded RV and preservation of contractility by reducing apoptotic

CENTRAL MESSAGE
Mitochondrial transplantation is promising but needs to be vetted more prior to clinical application.
cardiomyocyte loss. Consequently, they suggested a future role of mitochondrial transplantation in the potential management of patients with RV obstruction, hypertrophy and failure.4

Owing to the great resources and clinical and investigative expertise in Boston, this remarkable work is top-notch. Nonetheless, numerous questions remain to be answered to demonstrate the utility and practicality of mitochondrial transplantation in the management of patients with congenital heart defects such as those with RV obstruction, hypertrophy, and failure. (1) As the RV hypertrophy process often starts in utero or might be subtler than the relatively more acute banding model created in the immature piglets, can we ever conceive an optimal chronic RV failure model? Consequently, what is the proper timing and efficacy of mitochondrial transplantation in these real-life scenarios? (2) Considering that mitochondrial transplantation relies on the ability to conserve the mitochondria during the transfer process, the ability of this mitochondria to function and produce adenosine triphosphate that contributes to myofilament contraction, and the ability of this mitochondria to enter the cardiomyocyte and survive and function in these incorporating cells, how can we predict and control the number of mitochondria that would make it through all these obstacles and reach their final destination to provide positive effect on energy generation and prevention of apoptosis? (3) What is the mechanism that would allow long-term benefit in the treatment of chronic conditions? The previous work from the authors has focused more on acute ischemia–reperfusion models and while the cause–effect relationship between mitochondrial transplantation and the clinical improvement could be disputed, the benefit did not need to be necessarily prolonged, given the nature of acute injury; this is not the case in the chronic lesions affecting the RV.

In my mind, this is a very intriguing concept that is not yet ready for prime time and needs to be systematically scrutinized before clinical adaptation. This work might be in its infancy; however, by no means should this area remain uncharted and considered a “no-man’s land.” Back to the science and religion topic, they can both coexist, and collaborative efforts between talented scientists and clinicians as demonstrated by the group from Boston might help unlock the finest details of how the body functions and malfunctions, with ensuing remarkable advances to the well-being of humanity.

References