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Commentary: Mitochondrial transplantation for ischemia-reperfusion injury—a new revolution or tilting at windmills?

Edward Buratto, MBBS, PhD,^{a,b,c} and
Igor E. Konstantinov, MD, PhD, FRACS^{a,b,c,d}

Edward Buratto, MBBS, PhD, and Igor E. Konstantinov, MD, PhD, FRACS

CENTRAL MESSAGE

Autologous mitochondrial transplantation is an elegant concept with a promising translational application.

The last 2 decades have been marked by explosive and exponential research activity aimed at regeneration and improvement of myocardial function in children. Stem cell therapies have been extensively trialed in the setting of ischemia-reperfusion injury, albeit without widespread clinical application.¹ In a detailed study recently published in *Nature*, injection of alive or dead stem cells or a chemical inducer of innate immunity all resulted in activation of innate immunity and improvement in myocardial function.² This suggests that the beneficial effects of stem cell therapy are likely related to activation of the innate immune response, rather than to stem cell engraftment.^{2,3} An elegant and more targeted approach to myocardial regeneration—autologous mitochondria transplantation—has been developed by the Boston group. This group previously demonstrated that the majority of transplanted exogenous mitochondria fuse with the endogenous mitochondrial network (Figure 1), with associated increase in adenosine triphosphate production.⁴ In a porcine model of ischemia-reperfusion injury, mitochondrial transplantation was associated with decreased

markers of myocardial injury and smaller infarct size compared with control animals. Furthermore, the presence of transplanted mitochondria was demonstrated for up to 4 weeks.⁵ The same group previously published their initial clinical experience with this autologous mitochondria transplantation technique in 5 children on extracorporeal membrane oxygenation (ECMO) support, demonstrating that mitochondrial transplantation is feasible and apparently safe.⁶

In this issue of the *Journal*, the Boston group report their further experience with injection of autologous mitochondria into the myocardium of children with ischemia-reperfusion injury.⁷ In 10 patients who required ECMO support following ischemia-reperfusion injury, autologous mitochondria were isolated from nonischemic rectus abdominis muscle and injected into the ischemic myocardium. These 10 subjects were compared with 14 historical controls. The patients treated with mitochondrial transplantation were more likely to successfully wean from ECMO and had better cardiovascular event-free survival and improved myocardial strain. Interestingly, the median age was lower in the treatment group (0.4 months [range 0.1–3.9 months] vs 11 months [range, 0.2–51 months]), although the difference did not reach statistical significance. The lack of statistical difference could be due to the small numbers alone. It should be remembered that mammalian neonatal myocardium has transient regenerative potential⁸; thus, it is likely that the myocardium has a greater capacity for recovery in younger children compared with older children. The results of the study

From the ^aDepartment of Cardiac Surgery, Royal Children's Hospital, Melbourne; ^bDepartment of Paediatrics, University of Melbourne, Melbourne; ^cHeart Research Group, Murdoch Children's Research Institute, Melbourne; and ^dMelbourne Centre for Cardiovascular Genomics and Regenerative Medicine, Melbourne, Australia.

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Address for reprints: Igor E. Konstantinov, MD, PhD, FRACS, Royal Children's Hospital, Flemington Rd, Parkville 3052, Australia (E-mail: igor.konstantinov@rch.org.au).

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FIGURE 1. Endocytosis of autologous mitochondria injected into the myocardium results in the uptake and subsequent escape of exogenous (green) mitochondria from the endolysosomal system and their integration into the endogenous (red) mitochondrial network. The process appears to increase adenosine triphosphate production in all 3 stages of exogenous mitochondrial release, and enhance myocardial recovery. *ATP*, Adenosine triphosphate.

are further obscured by the fact that all 14 patients in the nontreatment group were from a historical control cohort operated on between 2002 and 2015, whereas all 10 patients in the treatment group were operated on between 2015 and 2018. Some era bias could have affected the results.

Of note, there are currently at least 8 ongoing trials investigating the effect of stem cells in children with heart disease.¹ It is time for this promising concept of autologous mitochondria transplantation to be subjected to a randomized controlled trial. The great effort expended on research into protection against ischemia-reperfusion injury and myocardial regeneration over the last decades has proven somewhat quixotic, without delivering the expected clinical translation. One may hope that mitochondrial transplantation will not be lost in translation.

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