transplanted mesenchymal stem cells.¹⁰ Thus, mitochondrial restitution may be a unifying feature of both mesenchymal stem cell-mediated and exogenous forms of MT.

These seminal studies in MT present many exciting basic science questions that are yet to be solved, which in turn will help to refine translational implementation to the benefit of patients with congenital heart disease. More extensive studies are needed to investigate whether there are genuine clinical benefits.

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Commentary: Energizing with ATP may be critical in ischemic pediatric hearts

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Ischemia-reperfusion injury (IRI) underlies the mechanism of myocardial dysfunction in various cardiac surgery settings. Altered mitochondrial architecture and function are hallmarks of IRI.¹ Serving as the final arbiter of life and

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Mitochondrial transfer may carry some benefit for the ischemic myocardium. Further studies are necessary to prove the efficacy and determine the applicability of this approach.

death, mitochondria are not only required to generate ATP but also can trigger apoptosis and necrosis.²

The current study by Guariento and colleagues³ demonstrates the potential effectiveness of autologous mitochondrial transfer (MT) therapy prepared from nonischemic skeletal muscles and injected directly into the ischemic myocardium in pediatric patients who require

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extracorporeal membrane oxygen (ECMO) support due to IRI. Ten patients received autologous MT and were compared with a retrospective cohort of 14 patients. MT was associated with better ventricular strain patterns following separation from ECMO and shorter duration to functional recovery after revascularization, based on echocardiographic interpretation. Although the rate of ECMO decannulation and the time from revascularization to ECMO decannulation was not different between the 2 groups, the freedom from ECMO reinstitution was in favor of MT group. However, the length of hospital stay, hospital mortality, and overall mortality remained similar between the 2 groups.

Despite the relatively small sample size and the lack of improvement in mortality rates and hospital stay duration, the trend of improvement in myocardial function might indicate the usefulness of this therapeutic modality. Of note, a preclinical animal study showed the possible benefit of MT therapy in cardiac IRI,⁴ although the injection was done before reperfusion, which may pose a question about different extents of injury at the time of treatment delivery. Interestingly, a protective effect of mitochondrial transplantation on another organ type was shown in a murine model of spinal cord IRI.⁵

These results raise several concerns and questions. Many variables are not accounted for but could play critical roles in the extent of injury and recovery. These include (but are not limited to) preoperative myocardial function and other factors that influence the extent of myocardial injury, such as crossclamp time, hypothermia, and the complexity of the repair. It is not clear whether the timing of the MT influences its effectiveness. However, as the authors discussed, multiple variables should also be considered. It is also possible that the observed recoveries could have been achieved without MT. Given the tremendous number of

variables in this patient population, this possibility should be investigated in a randomized controlled trial. Moreover, direct intramyocardial injections are invariably operator-dependent and require reopening the chest, which are major limiting factors affecting the generalizability and reproducibility of this technique in a multicenter setting for further studies and future adoption if it proves efficacious. The authors should be encouraged to further investigate the proposed intravascular delivery route as a more feasible and reproducible alternative.⁶

The study by Guariento and colleagues³ demonstrates the feasibility of this nontraditional therapeutic approach, which may have potential efficacy. Further extensive investigations and clinical trials should be adopted to assess efficacy and other aspects of treatment, such as the mode of delivery, timing, and dosing.

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