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INVITED COMMENTARY

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The application of stem cells to pediatric patients with heart failure is now an emerging field with great potential. Originally, stem cell therapy was applied to adult patients with promising results, using first-generation stem cells.

However, there has been no set of guidelines for the adult stem cell field, which has impeded its general application to adult patients with heart failure. It is hoped that when the initial wave of phase 1 stem cell trials is completed in adults, there will be insightful lessons from these trials that will formulate future trials and, what is equally important, trials that will be initiated in children.

The clinical application of stem cells involves a multitude of steps, which include patient selection, preferable stem cell preparations, delivery systems, cell dosing, and regenerative clinical endpoints. All these steps require insightful experimentation in preclinical models to determine the optimal approach in assembling the best cell product. Preclinical animal models have been critical for answering these questions in adults but have not been studied extensively in animal models relevant to children.

Although a growing number of preclinical models and a recent phase 1 clinical trial have investigated the safety and efficacy of cell therapy for patients with congenital heart disease (CHD), no studies have been dedicated to identifying the optimal method of cell delivery as it relates to children. Thus, this study's evaluation of delivering cells during cardiopulmonary bypass (CPB) as a novel delivery strategy represents an important contribution to the clinical translation of stem cell therapy for patients with CHD [1]. For children with univentricular hearts, for example, the opportune time for cell delivery may be intra-operatively at the time of planned surgical reconstruction because this would afford maximal exposure to the heart and, as evaluated here, the potential to use the CPB circuit to drive intracoronary stem cell delivery.

The advantages of CPB-assisted cell delivery include a potentially broader myocardial biodistribution of cells and a relatively high-pressure mechanism of intracoronary delivery, which may facilitate cellular migration across the endothelium and into the interstitium. Indeed, the authors' findings are consistent with these potential advantages, because they have shown a distribution of cells through each of the chambers of the heart and numerous CD45⁺ or human antinuclear antigen-1⁺ cells located outside the vasculature and within the myocardium. Important remaining questions include how this method affects cellular retention compared with other commonly used techniques (intramyocardial injection,

catheter-based transc coronary delivery) and whether there are any safety risks beyond the immediate post-CPB period. An additional consideration is how to optimally distribute cells to a univentricular heart so that cells are preferentially directed to the coronary vasculature supplying the systemic ventricle. Yet, the present study heralds a new area of inquiry as it relates to the optimal technique for stem cell delivery in patients with complex CHD. This and other carefully performed studies should serve as the basis for the development of clinical protocols for children with CHD.

1. Brizard CP, Looi JYJ, Smolich JJ. Safety of intracoronary human cord blood stem cells in a lamb model of infant cardiopulmonary bypass. *Ann Thorac Surg.* 2015; 100:1021–9. [PubMed: 26209485]