cell administration to young patients with systemic right ventricle pathology or pronounced abnormalities in structure, cellular composition, and functional responses to hemodynamic perturbations.^{5,8}

To avoid the mistakes of premature cell therapy trials in adult patients, proponents of pediatric cell therapy should ideally perform rigorous optimization of cell therapy in preclinical models of congenital heart disease. The resulting base of knowledge will provide the best opportunity for success in future clinical trials, preferably with adequately sized study populations and appropriate randomized, blinded trial design.

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Commentary: Defining the role of stem cell therapy in neonatal cardiac regeneration

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Over the past several years, preclinical and clinical studies about the potential cardiac application of stem cell therapy have been conducted extensively, primarily in adult ischemic heart disease.^{1,2} More recently, this potential therapeutic option has gained attention in the world of congenital heart disease. This has been due, in part, to the discovery that neonatal myocardium retains greater regenerative potential than adult heart tissue.^{3,4} Moreover, despite excellent surgical results in complex single-ventricle patients, we

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CENTRAL MESSAGE

Neonates have a higher cardiac regenerative potential when compared with adults, but much is yet to be learned regarding stem cell therapy in congenital heart disease.

have come to realize that it will take additional therapies to improve the long-term cardiac outlook for these children. Several cell types from many sources utilizing various delivery techniques are currently being investigated in multiple cardiac pathologies across the spectrum of patient age groups. Patients with single-ventricle physiology are deemed more suitable to study this potential treatment due to limited conventional options for treatment of their heart failure. It is important for cardiac care providers to

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understand these developing therapeutic strategies and possible mechanisms of cardiac regeneration.

Sano and colleagues⁵ provide an inclusive expert opinion on cardiac stem cell therapy with special attention given to the differences between neonatal and adult hearts. Emphasis is given to c-kit⁺ cardiac progenitor cells and cardiosphere-derived cells (CDCs), but much of the discussion can be generalized to all cardiac stem cells. Key points to keep in mind from this review are:

1. Age of the patient matters: Neonatal heart tissue has demonstrated more regenerative potential and tends to regenerate with limited scarring.
2. Age of the cells matter: The CDCs derived from neonatal hearts were more abundant, demonstrated more c-kit expression, and showed more proliferative and differentiation potential when compared with children aged >2 years.
3. Because of the above, the hope is that neonatal congenital heart disease patients are more likely to show measurable benefits from cell-based therapy.
4. The mechanism of action of stem cell therapy is not clearly understood, but the following pathways have been proposed:
 - a. Paracrine effect: By secreting growth factors and sub-cellular particles (exosomes) that promote repair, regeneration, and remodeling.
 - b. Immune modulation: By timely suppression or activation of the immune system to promote the healing process. This may influence the decision about the timing of cell therapy to get maximal benefit.
 - c. Angiogenesis: By activating endogenous endothelial progenitor cells or by secreting growth factors that promote neovascularization.
 - d. Cardiogenesis: By differentiation into new cardiomyocytes. However, this pathway has largely been debunked. Paracrine induction of endogenous cardiac progenitor cells may still be a possibility.

5. Clinical trials: To date, 2 phase 1 clinical trials of stem cell therapy in congenital heart disease have been completed, both of which did not show any major concern about the safety or feasibility of this therapy.^{6,7} One phase 2 clinical trial has shown improvement in ejection fraction in CDC-treated patients (+6.4% vs +1.3%) with single-ventricle physiology.⁸ Several other clinical trials are currently being conducted, most of which are focused on hypoplastic left heart syndrome and other single-ventricle lesions.

The authors present an excellent comprehensive review of the state of stem cell therapy in congenital heart disease. The increased regenerative potential of neonatal heart tissue is an encouraging discovery and promising for the development of novel therapeutic options. As we seek to define the role of stem cell therapy in congenital heart disease, much is still to be discovered about the best choices of patients, cell types, and methods (eg, route, dose, and timing) of administration of cell-based therapy.

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