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Commentary: An idea with some muscle behind it

Danielle Gottlieb Sen, MS, MD, MPH, and
Bret A. Mettler, MD

Great ideas originate in the muscles.

—Attributed to Thomas A. Edison (1847-1931)

Six of nine species of cold-blooded animals have the capacity to regenerate their hearts during adult life. And even though adult human cardiomyocytes exhibit a nonregenerative response to injury, and subsequent systolic heart failure, many fetal mammals retain a regenerative response and demonstrate cardiomyocyte replication.¹ For those interested in treating systolic heart failure in children, these encouraging findings have fueled an effort to induce children's hearts to regenerate.

Of specific interest to congenital heart surgeons is the fragile group with single right ventricles (RV), whose outcomes are highly dependent on systolic function of the systemic RV. RV failure is addressed with the limited-supply solution of transplantation, and patients accumulate morbidities and compromised quality of life while awaiting a heart.

The view that the heart muscle cannot regenerate was upended with the discovery that bone marrow–derived stem cells could be utilized to regenerate heart muscle.

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Danielle Gottlieb Sen, MS, MD, MPH (left), and Bret A. Mettler, MD (right)

CENTRAL MESSAGE

Regenerative medicine, including stem cell–based therapies aimed at improving myocardial function, is advancing incrementally.

As scientists have established methods for the manipulation of stem cells, tissue-derived mesenchymal stem cells have emerged as an exploitable source of regenerative potential. Further insights into inducible pluripotent stem cells have led to differentiation and maturation techniques that allow the enrichment of cardiomyocyte progenitor populations. The field has subsequently experimented with multiple lineages of stem cells (bone marrow–derived stem cells, umbilical cord–derived stem cells, myocardial resident cardiac progenitor cells, and cardiosphere-derived progenitor cells) and, more recently, the secreted soup of incompletely understood products of cardiosphere-derived cell differentiation known as exosomes.²

Clinical trials have been completed in the field to date with 2 main delivery methods to the myocardium and variability in the timing of intervention, to approach the question of whether there are cell or cell-derived therapies that can ultimately change outcomes in univentricular hearts. Most trials have demonstrated modest improvements in right ventricular fractional area change, between 5% and 10%, through the duration of the trial.

In this issue of the *Journal*, Bittle and colleagues³ build on previous work exploring the potential of exosome-mediated paracrine mechanisms to restore systolic function in an animal model of RV pressure load–induced dysfunction. This current study builds on a series of investigations from this group and uses the group’s previously established swine pulmonary artery banding model to induce RV dysfunction.⁴

In this study, Bittle and colleagues³ separated a “soup” of exosomes into 3 fractions and injected each preparation into the myocardium of the RV at the time of banding. They performed echocardiography at 7 and 28 days, and at the 28-day time point, they demonstrated a 6% increase in right ventricular fractional area change relative to banded controls, with an acceptably minimal inflammatory response. Although this modest increase in right ventricular fractional area change was observed, cardiomyocyte proliferation was not measured, and thus no further mechanistic understanding was attained. The study therefore raises questions about

dose and number of injections that might be required for a sustained and clinically significant improvement.

Bittle and colleagues³ are to be congratulated for contributing a potentially promising, incremental step in the as-yet elusive goal of improving RV function. Until that juncture, anatomy is destiny, and newts maintain their regenerative advantage.

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Check for updates

Commentary: Cardiosphere-derived exosomes for single-ventricle heart disease: Are some of the parts greater than the whole?

Andrew M. Vekstein, MD,
Joseph W. Turek, MD, PhD, and
Nicholas D. Andersen, MD

Myocardial regeneration remains the holy grail of cardiovascular research in both the adult and pediatric realms.

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Acellular exosomes may prevent myocardial dysfunction in single-ventricle heart disease.

CENTRAL MESSAGE

Intramyocardial injection of acellular exosome preparations from cardiosphere-derived cells may simplify the application of stem cell therapy for patients with single-ventricle heart disease.

In pediatric patients with hypoplastic left heart syndrome (HLHS) and other forms of single-ventricle heart disease, progressive dysfunction of the systemic right ventricle (RV) remains a significant barrier to long-term survival.¹ However, the Transcatheter Infusion of Cardiac