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.

References

1. Kimura W, Nakada Y, Sadek HA. Hypoxia-induced myocardial regeneration. *J Appl Physiol*. 2017;123:1676-81.
2. Fine B, Vunjak-Novakovic G. Heart regeneration in mouse and human: a bioengineering perspective. *Curr Opin Physiol*. 2020;14:56-63.
3. Bittle GJ, Morales D, Parchment N, Parsell D, Ambastha C, Sharma S, et al. Exosomes isolated from human cardiosphere-derived cells attenuate pressure overload–induced right ventricular dysfunction. *J Thorac Cardiovasc Surg*. 2021;162:975-86.e6.
4. Kaushal S, Wehman B, Pietris N, Naughton C, Bentzen SM, Bigham G, et al. Study design and rationale for ELPIS: a phase I/IIb randomized pilot study of allogeneic human mesenchymal stem cell injection in patients with hypoplastic left heart syndrome. *Am Heart J*. 2017;192:48-56.

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

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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

Progenitor Cells in Patients With Single-Ventricle Physiology (TICAP)² and Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease (PERSEUS)³ trials showed the potential for intracoronary infusion of cardiospheres to improve ventricular function, reduce fibrosis, and improve health-related quality of life in a small number of patients with HLHS.

Although cardiosphere injections may have therapeutic benefit, it has recently been recognized that they may act primarily through paracrine effects rather than differentiation into cardiac myocytes.⁴ In the current issue of the *Journal*, Bittle and colleagues⁵ investigate the possibility that exosomes derived from cardiospheres can yield similar clinical effects as the entire cardiosphere structure. To do so, an established model of porcine pulmonary artery banding was used with concomitant intramyocardial injection of cardiosphere exosomal isolates or control solutions. On serial postoperative echocardiography, the authors observed significant improvement in RV function in the treatment groups compared with the stably debilitated control group. Immunohistologic assessment demonstrated reduced cardiac myocyte hypertrophy in the exosomal-injection group. The authors conclude that intramyocardial injection of cardiosphere-derived exosomes mitigates pressure-induced injury and preserves RV function, with significant potential implications for the single-ventricle population.

The findings of this study are important, as they narrow the search for the exact cellular mediators of cardiac myocyte regenerative therapy. Although multiple previous studies have suggested that cell signaling rather than myogenic differentiation is the key mechanism of cardiosphere-derived cell therapy, this is the first study to show in a large animal model that extracellular vesicles harness the key therapeutic elements. Delivery of acellular exosomal preparations, as opposed to live cells, may significantly simplify the application of stem cell therapy

(Figure 1). As the authors explain, however, exosome content is heterogeneous, and future investigation to better define the key mediators within exosomes will be crucial.

Although the study provides encouraging data for exosomes derived from cardiosphere-derived cells, it also raises questions about potential clinical applications. Histologic changes in the study group included reduced cardiac myocyte hypertrophy, suggesting that exosome isolates may signal to prevent hypertrophy after a pressure load rather than improve function of previously injured cardiac myocytes. Further, in the absence of intracoronary delivery, clinical application may be limited to the prophylactic treatment of high-risk single-ventricle patients with intramyocardial injection during index palliation procedures rather than postoperative treatment for patients who develop RV dysfunction later in life. Given that only a minority of patients with HLHS go on to develop RV dysfunction soon after surgical palliation, the treatment effect and clinical benefit of a prophylactic therapy will likely be harder to prove in real-world practice.

References

1. Simsic JM, Bradley SM, Stroud MR, Atz AM. Risk factors for interstage death after the Norwood procedure. *Pediatr Cardiol*. 2005;26:400-3.
2. Tarui S, Ishigami S, Ousaka D, Kasahara S, Ohtsuki S, Sano S, et al. Transcoronary infusion of cardiac progenitor cells in hypoplastic left heart syndrome: three-year follow-up of the transcoronary infusion of cardiac progenitor cells in patients with single-ventricle physiology (TICAP) trial. *J Thorac Cardiovasc Surg*. 2015;150:1198-208.e2.
3. Shuta I, Shinichi O, Takahiro E, Daiki O, Maiko K, Yoshihiko K, et al. Intracoronary cardiac progenitor cells in single ventricle physiology. *Circ Res*. 2017;120:1162-73.
4. Li T-S, Cheng K, Malliaras K, Smith RR, Zhang Y, Sun B, et al. Direct comparison of different stem cell types and subpopulations reveals superior paracrine potency and myocardial repair efficacy with cardiosphere-derived cells. *J Am Coll Cardiol*. 2012;59:942-53.
5. Bittle GJ, Morales D, Parchment N, Parsell D, Ambastha C, Sharma S, et al. Exosomes isolated from human cardiosphere-derived cells attenuate pressure overload-induced right ventricular dysfunction. *J Thorac Cardiovasc Surg*. 2021;162:975-86.e6.