Are stem cells the next frontier for hypoplastic left heart syndrome? What are the promise, the reality, and the future?

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Half of what you learn in medical school will prove to be false. The only problem is no one knows which half. As a medical student in the early 1980s, we were taught that cardiomyocytes are postmitotic, do not divide, and live as long as the organism. Subsequent research has shown that cardiomyocytes are in fact capable of cell division in adults, albeit at a very slow rate.¹ It is well understood that the loss of cardiomyocytes because of myocardial infarction or other cardiomyopathic processes leads directly to mortality and morbidity.² Obviously, the ability to induce cardiomyocyte regeneration would be a revolutionary leap forward. Regeneration of the heart can be demonstrated in lower vertebrates, such as zebrafish and in neonatal mouse hearts.^{3,4} In the zebrafish, a small population of cardiomyocytes give rise to the majority of new heart muscle. Perhaps if a population of the correct kind of cells could be placed in the adult human heart, regeneration would be possible.⁵ In 2001, Orlic and colleagues⁶ reported 68% regeneration in infarcted mouse hearts with bone marrow-derived stem cells injected into the peri-infarct zone. Although the results of that study could not be duplicated, human studies quickly followed. In the last 2 decades, more than 30 randomized controlled trials of stem cell treatment for acute myocardial infarction have been completed.⁷ Although not every study has shown benefit, altogether stem cell treatment was observed to improve left ventricular ejection fraction significantly, and this improvement is maintained over intermediate-term follow-up. Some studies have shown a reduction in left ventricular end-systolic and end-diastolic volumes, as well as infarct size. Although these results are encouraging, so far no one has been able to demonstrate an improvement in mortality or morbidity.

After this initial exploration of stem cell therapy for acute myocardial infarction came studies of stem cells in congenital heart disease and pediatric heart failure. Both cardiomyopathy and congenital heart disease are being studied, but hypoplastic left heart syndrome (HLHS) is the most common congenital heart lesion to be the target

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Central Message

What is known, what is unknown, and what is the future of stem cell therapy for hypoplastic left heart syndrome?

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of stem cell therapy.⁸ HLHS remains a congenital heart lesion with poor prognosis. In the Single Ventricle Reconstruction Trial, the 12-month survival among more than 500 patients was only approximately 70%.⁹ Therefore, this common lesion with poor survival seems to be a reasonable target for a radical new kind of therapy. Several centers are actively investigating cell-based therapy for HLHS, including the Mayo Clinic, Duke University, and Okayama University. The group from Okayama have reported late follow-up of their phase 1 trial that has shown sustained improvement in terms of right ventricular function, growth, and brain natriuretic peptide levels.¹⁰ The challenges with interpretation of the results include the variable anatomy of HLHS and the fact that stem cell therapy is performed at the time of stage palliation. The study did not control for the stage at treatment or anatomic subtype. Although this is exciting, it would be easy to overinterpret the outcomes of this small phase 1 study in which efficacy was not the primary end point and for which these known confounding factors were not adequately controlled.

The overall results in adult studies show a modest benefit despite wide variation in the cells used. Current sources for cell-based therapy include mesenchymal stem cells, bone marrow, cardiosphere-derived cells, and c-kit⁺ cardiac

progenitor cells.¹¹ Experimental approaches in animals have suggested the possibility of using embryonic stem cells, induced pluripotent stem cells, reprogramming of fibroblasts, or even cardiomyocytes themselves as graft sources.¹¹ In addition, the dosing of cells has varied.¹² Regardless of the cell type, it is difficult to demonstrate an increase in cardiomyocytes. The stem cells spend very little time in the heart and are not the source of new cardiomyocytes.¹³ It seems that resident cardiomyocytes themselves are the most prominent source of new cardiomyocytes in the mature mammalian heart.¹¹ The potential for endogenous or exogenous stem cells to regenerate heart muscle is very low. Any benefit of stem cell therapy may be a paracrine effect, and the cells themselves could be completely unnecessary. The mechanism of action of stem cells could include immunomodulation, angiogenesis, antiapoptosis, antioxidation, and promotion of endogenous precursor cell migration, differentiation, and duplication.¹⁴

There is a great deal we do not know about stem cell therapy for heart disease. The studies thus far seem to show a benefit and the risks seem low, but follow-up is limited and the experience in the pediatric population is just starting. The relatively modest effects of stem cell therapy may be justification for continued human studies, but a great deal could be learned from more laboratory and animal studies. What is the mechanism of improvement in ejection fraction and reduction in infarct size? If the cells we are injecting are not implanting and only dividing at a vanishingly low rate, then how are they improving ejection fraction? Where are the cells going, and do they persist? Thus far, cell-based therapy seems to be safe in terms of neoplasia or disorganized growth, but there has been a report of malignant neoplasm attributed to stem cell therapy for lupus nephritis that required nephrectomy.¹⁵ If the paracrine factors are the most important effect of stem cell therapy, then shouldn't we identify those factors? Could those paracrine factors be the source for therapy that may be better in terms of targeting and safer than the current strategy? Stem cell therapy may be a blunt tool, and the mechanism remains elusive. An analogy may be the use of bloodletting for dropsy or heart failure (Figure 1).¹⁶ At a time when therapeutic options were limited, phlebotomy was sometimes successful because it resulted in a reduction in blood volume, thereby improving pulmonary edema and myocardial contractility by restoring more favorable Frank-Starling conditions. Certainly in desperate circumstances, lives were prolonged, but the loss of red cells and blood protein made ongoing therapy unsustainable. Ultimately, a better understanding of the pathophysiology and the discovery of diuretics resulted in a more sustainable treatment for heart failure. Perhaps we are at a similar point in time with cell-based regenerative therapies. For some very ill patient populations, ongoing human studies are justified, but broader application should await

FIGURE 1. Bloodletting occasionally benefited the individual with congestive heart failure (dropsy).

identification of the mechanisms with the goal of safer and more directed therapy.

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