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EDITORIAL COMMENT

Cell Therapy for Heart Failure With Preserved Ejection Fraction*

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One-half of patients with heart failure (HF) have a preserved ejection fraction (HFpEF), and there is no proven effective treatment (1). The traditional thinking has been that left ventricular (LV) diastolic dysfunction caused by hypertensive ventricular remodeling causes the clinical syndrome of HFpEF. More recent data suggest that it is not so simple, and that other systemic processes such as inflammation, oxidative stress, and fibrosis play important roles in the pathophysiology (2,3). It is therefore hoped that interventions targeting inflammation and fibrosis might be effective to treat HFpEF.

Cell-based therapy for HF patients with reduced ejection fraction has been under investigation for nearly 2 decades, with mixed results to date (4). More recently, cardiosphere-derived cells (CDC) have emerged as a novel cell-based approach to treat various cardiac diseases (5). Unlike bone marrow-derived cells, CDCs are harvested directly from the heart via endomyocardial biopsy. These cells are cultured and plated to yield CDCs, which can then be injected by intracoronary infusion. CDCs are believed to exert pleiotropic salutary effects in the heart in addition to their stem cell-like regenerative behaviors (5). Although there is great enthusiasm that cell therapies could help patients where cardiomyocyte loss is the problem (like HF with reduced ejection fraction), it remains unclear whether patients with cardiovascular diseases without marked cardiomyocyte loss (like HFpEF) might also derive benefit.

In this issue of *JACC: Basic to Translational Science*, Gallet et al. (6) report exciting new data describing the effects of CDCs in an animal model considered by some to replicate human HFpEF. Dahl salt-sensitive (DS) rats age 7 weeks were fed a high-salt diet for 6 to 7 weeks to induce hypertension, with resultant concentric hypertrophy and diastolic dysfunction. These 54 rats were then randomly assigned to receive either allogenic CDCs or sham therapy, and were followed by echocardiography 1 and 4 weeks later to assess changes in Doppler parameters of diastolic function. At the completion of the study, diastolic function was assessed using gold standard conductance catheter-based techniques, followed by tissue harvesting for genetic and protein analysis. A separate cohort (n = 18) was fed a low-salt diet to serve as a control group.

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High-salt fed DS rats displayed hypertension, concentric LV hypertrophy, and diastolic dysfunction by echocardiography, indicating a HFpEF-like phenotype (6). Following intervention, the CDC-treated rats displayed an improvement in the Doppler E/A ratio, suggesting improved diastolic function that was subsequently confirmed invasively by enhanced relaxation relative to placebo-treated animals. In addition to positive effects on relaxation, CDC-treated animals displayed more compliant ventricles, manifest by a shallower slope in the LV end-diastolic pressure volume relationship. The salutary effects of CDC were accompanied by decreased LV fibrosis and inflammation and increased myocardial capillary density.

Intriguingly, these favorable changes occurred without a decrease in blood pressure or cardiac hypertrophy, suggesting a direct beneficial effect on myocyte function (6). This is important because it suggests that structural reverse remodeling is not necessary to see functional benefits, as has traditionally been believed. CDC therapy was associated

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with improved survival and also resulted in a decrease in circulating inflammatory cytokines as well as a reduction in genetic expression of markers of inflammation and fibrosis, providing intriguing mechanistic insight. The authors conclude that CDCs reverse HFpEF in rats by decreasing fibrosis and inflammation even in the absence of changes in LV load or chamber remodeling (6).

The multitude of positive effects observed from just a single dose of CDC therapy in this model is truly staggering (6). Previous studies testing cell therapy in rats after myocardial infarction have demonstrated an improvement in myocardial compliance (7), but no infarct was induced in the current study. Although the results certainly support further study, there are a number of important caveats to consider. One question is how well this rat model recapitulates what is seen in human HFpEF. In addition to hypertension, the DS rat model is characterized by significant renal dysfunction, causing massive volume overload, proteinuria, and cachexia. This is not typical of what is usually seen in human HFpEF, so one questions whether these benefits in rats will extend to what is seen in people with HFpEF in the community.

In fact, there is no widely-accepted animal model of human HFpEF, which is not surprising given the enormous complexity of this disorder. One key ingredient in human HFpEF is cardiovascular senescence, and it is very difficult to recreate this in an animal model. The authors demonstrate that diastolic dysfunction is present in the DS model (6), but it is now well-established that HFpEF is characterized by multiple other pathophysiological abnormalities beyond diastolic dysfunction alone (3), including systolic limitations (8-11), chronotropic incompetence (10,12), endothelial dysfunction (10), right heart and pulmonary vascular dysfunction (13-15), and abnormalities in the periphery (16,17). Indeed, it has been suggested that the tremendous mechanistic heterogeneity in HFpEF requires more rigorous subphenotyping to get the right treatment to the right patient (18,19). It would be interesting to see if CDCs might affect these other crucial components in the pathophysiology.

The data from Gallet et al. (6) suggest that improvement in fibrosis is a key component for the beneficial effects from CDC in the DS model. However, recent data have raised questions regarding the centrality of myocardial fibrosis in the pathophysiology of HFpEF. In a human autopsy study, histopathological fibrosis was not markedly different between HFpEF and control hearts (present in 58% vs. 43%, median area of fibrosis 9.6% vs. 7.1%), suggesting that factors other than interstitial fibrosis (such as intrinsic cardiomyocyte stiffness) may be more relevant (20).

Given this complexity, it may seem overly optimistic to think that a therapy like CDCs will work for all patients experiencing HFpEF. However, a subgroup of people who had inflammation and fibrosis play the dominant role may be in the best position to derive benefit from this promising therapy. Perhaps this is the group to enroll first in early phase trials. Right now, we can say that cell therapy appears to work for rats with diastolic dysfunction. We do not know if cell therapy is going to work for people with HFpEF, but the data from Gallet et al. (6) is giving us new hope that it might. Now it is time to find out. Stay tuned!

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