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PRE-CLINICAL RESEARCH

Cardiosphere-Derived Cells Reverse Heart Failure With Preserved Ejection Fraction in Rats by Decreasing Fibrosis and Inflammation

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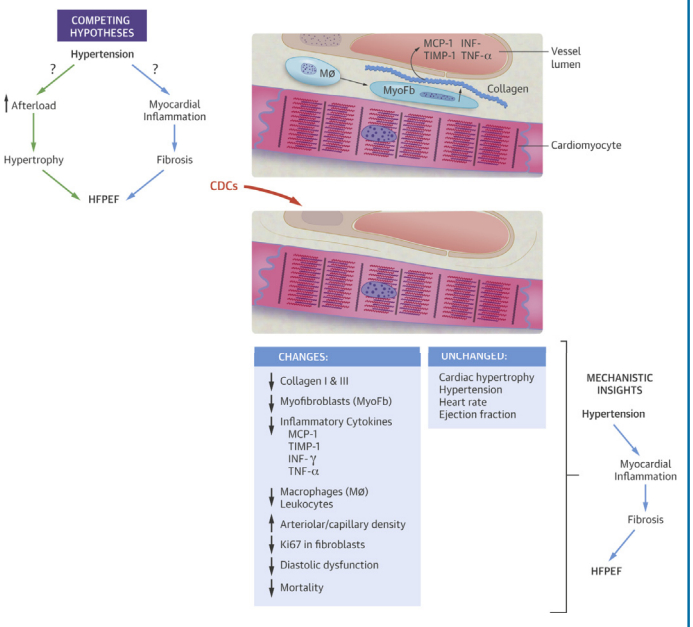
VISUAL ABSTRACT



Gallet, R. et al. J Am Coll Cardiol Basic Trans Sci. 2016; 1(1-2):14–28.

HIGHLIGHTS

- **The pathogenesis of heart failure with a preserved ejection fraction (HFpEF) is unclear.**
- **Cardiosphere-derived cells (CDCs) are heart-derived cell products with anti-fibrotic and anti-inflammatory properties, which have been implicated in HFpEF.**
- **Dahl salt-sensitive rats were fed a high-salt diet for 6 to7 weeks and randomized to receive intracoronary CDCs or placebo.**
- **Following CDC treatment, diastolic dysfunction resolved in treated rats but not in the placebo group. Treatment with CDCs also lower LV end-diastolic pressure, decrease lung congestion, and enhance survival.**
- **CDC treatment decreased LV fibrosis and inflammatory infiltrates, and reversed many of the transcriptomic changes associated with HFpEF, but had no effect on cardiac hypertrophy.**
- **By selectively reversing inflammation and fibrosis, CDCs may be beneficial in the treatment of HFpEF.**

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SUMMARY

The pathogenesis of heart failure with a preserved ejection fraction (HFpEF) is unclear. Myocardial fibrosis, inflammation, and cardiac hypertrophy have been suggested to contribute to the pathogenesis of HFpEF. Cardiosphere-derived cells (CDCs) are heart-derived cell products with antifibrotic and anti-inflammatory properties. This study tested whether rat CDCs were sufficient to decrease manifestations of HFpEF in hypertensive rats. Starting at 7 weeks of age, Dahl salt-sensitive rats were fed a high-salt diet for 6 to 7 weeks and randomized to receive intracoronary CDCs or placebo. Dahl rats fed normal chow served as controls. High-salt rats developed hypertension, left ventricular (LV) hypertrophy, and diastolic dysfunction, without impairment of ejection fraction. Four weeks after treatment, diastolic dysfunction resolved in CDC-treated rats but not in placebo. The improved LV relaxation was associated with lower LV end-diastolic pressure, decreased lung congestion, and enhanced survival in CDC-treated rats. Histology and echocardiography revealed no decrease in cardiac hypertrophy after CDC treatment, consistent with the finding of sustained, equally-elevated blood pressure in CDC- and placebo-treated rats. Nevertheless, CDC treatment decreased LV fibrosis and inflammatory infiltrates. Serum inflammatory cytokines were likewise decreased after CDC treatment. Whole-transcriptome analysis revealed that CDCs reversed changes in numerous transcripts associated with HFpEF, including many involved in inflammation and/or fibrosis. These studies suggest that CDCs normalized LV relaxation and LV diastolic pressure while improving survival in a rat model of HFpEF. The benefits of CDCs occurred despite persistent hypertension and cardiac hypertrophy. By selectively reversing inflammation and fibrosis, CDCs may be beneficial in the treatment of HFpEF. (J Am Coll Cardiol Basic Trans Sci 2016;1:14–28)

Heart failure with preserved ejection fraction (HFpEF) has become a major public health concern. Its increasing prevalence now exceeds that of heart failure with reduced ejection fraction (1–3). Outcomes of patients with HFpEF are poor (4,5), and so far, no treatment has been shown to decrease morbidity or mortality (3,6). HFpEF is associated with various cardiovascular risk factors (especially hypertension), extracardiac comorbidities, and aging. The net result is impaired diastolic relaxation and filling of the left ventricle, increased myocardial stiffness, impaired vascular compliance, and increased diastolic pressure (7,8). Myocardial fibrosis and inflammation have been associated with HFpEF (9–14) and with the transition from hypertensive left ventricular (LV) hypertrophy without HFpEF to hypertensive LV hypertrophy with HFpEF (15). Cardiosphere-derived cells (CDCs) are heart cell products with antifibrotic, anti-inflammatory, and angiogenic properties (16–20). CDCs, which are currently in phase 2 human trials for scar reduction after myocardial infarction (5), have been shown to be beneficial in models of ischemic (17,18,21) and nonischemic cardiomyopathy (16). Thus, we wondered whether CDCs might have disease-modifying activity in HFpEF.

Dahl salt-sensitive (DS) rats develop hypertension, hypertrophy, and, eventually, HFpEF on a high-salt diet (22–26). Increased fibrosis and inflammation underlie the development of HFpEF, with resultant cachexia, pulmonary congestion, and accelerated mortality (22,26,27). Therefore, this model has been widely used to test new treatments for HFpEF (23,27–31). Here, we tested the efficacy of CDCs in improving LV structure and function and overall outcome in DS rats with HFpEF.

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METHODS

An expanded "Methods" section is available in the Supplemental Appendix.

DS rats (Charles River, Wilmington, Massachusetts) were fed a 0.3% NaCl (low-salt) diet until 7 weeks of age. At that time, the diet was switched to an 8% NaCl (high-salt) diet in 54 rats by random assignment. DS rats fed the low-salt diet constituted the control group (n = 18). At 13 to 14 weeks of age, rats on the high-salt diet were randomized to

ABBREVIATIONS AND ACRONYMS

CDC = cardiosphere-derived cell

DS = Dahl salt-sensitive

E/A ratio = ratio of early to late ventricular filling velocity

HFpEF = heart failure with preserved ejection fraction

LV = left ventricular

LVEDP = left ventricular end-diastolic pressure

LVEF = left ventricular ejection fraction

MMP = matrix metalloproteinase

TIMP = tissue inhibitor of metalloproteinase