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PRECLINICAL RESEARCH

Improvement of Myocardial Function Following Catheter-Based Renal Denervation in Heart Failure

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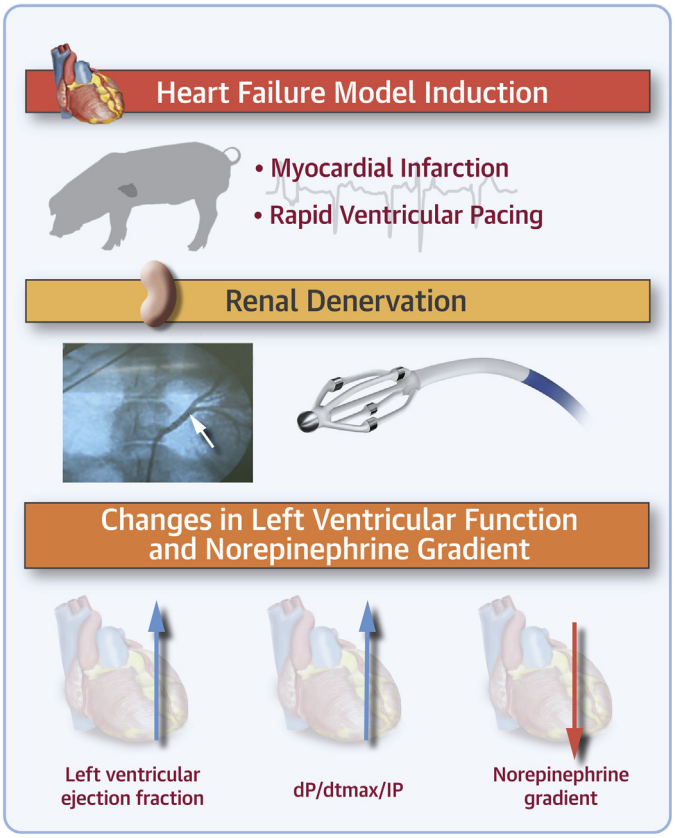
VISUAL ABSTRACT



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HIGHLIGHTS

- A porcine model of heart failure was induced by myocardial infarction followed by rapid ventricular pacing for 4 weeks.
- Catheter-based renal denervation was performed using an expandable basket with 4 electrodes to deliver radiofrequency energy. Histological examination showed significant denervation of the renal arteries after the procedure.
- Compared with the control group, animals that received renal denervation showed significant improvement of cardiac function as determined by LV ejection fraction, maximum rate of LV pressure rise normalized to instantaneous developed pressure, and reduction of myocardial and renal norepinephrine gradient at 10 weeks after procedure.

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SUMMARY

Renal denervation (RD) is a potential novel nonpharmacological therapy for heart failure (HF). We performed bilateral catheter-based RD in 10 adult pigs and compared them with 10 control subjects after induction of HF to investigate the long-term beneficial effects of RD on left ventricular (LV) function and regional norepinephrine gradient after conventional HF pharmacological therapy. Compared with control subjects, animals treated with RD demonstrated an improvement in LV function and reduction of norepinephrine gradients over the myocardium and kidney at 10-week follow-up. Our results demonstrated that effective bilateral RD decrease regional norepinephrine gradients and improve LV contractile function compared with medical therapy alone. (J Am Coll Cardiol Basic Trans Science 2017;2:270–81) © 2017 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ABBREVIATIONS AND ACRONYMS

ACE = angiotensin-converting enzyme

BNP = B-type natriuretic peptide

dP/dt_{max} = the maximum rate of left ventricular pressure rise

HF = heart failure

IP = instantaneous developed pressure

LV = left ventricular

MI = myocardial infarction

RD = renal denervation

TH = tyrosine hydroxylase

Heart failure (HF) is a major medical problem with substantial health care burden, and the associated mortality and morbidity of HF remain high despite advances in pharmacological and device management (1,2). There is thus a compelling need for new therapies that target the underlying pathophysiology of HF and further improve clinical outcome. In patients with HF, increased activity of the sympathetic nervous system is associated with progression of left ventricular (LV) dysfunction and increased mortality (3,4). Both renal afferent and efferent sympathetic nerves have been proposed to contribute to the sympathoexcitation in HF (5,6). In HF, increased central sympathetic neural outflow is associated with cardiac and renal efferent sympathetic nerve activations, and thus, cardiac and renal norepinephrine spillover (7–9). However, activation of renal afferent sympathetic nerves caused by renal hypoxemia and ischemia may also directly induce increased central sympathetic outflow (9,10). Recent development of catheter-based renal nerve ablation for treatment of refractory hypertension has led to a growing interest in renal denervation (RD) for treatment of HF (6,11–16).

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Prior studies showed that surgical RD improves LV function and prevents HF in rats after myocardial infarction (MI) (17–19). In large animal models of rapid pacing-induced HF, catheter-based RD also reduced systemic neurohormonal activation and renal norepinephrine content, and improved LV function and dyssynchrony (20–22). Nevertheless, the long-term beneficial effects of RD on cardiac function after conventional pharmacological therapy for HF have not been addressed in these studies. Here, we hypothesized that RD reduces the myocardial and renal norepinephrine discharge and improves LV function in HF. Accordingly, we investigated the long-term effect of bilateral catheter-based RD, using a multipolar electrode catheter, on LV contractile function and regional norepinephrine release in a porcine model of mixed cardiomyopathy treated with angiotensin-converting enzyme (ACE) inhibitor and beta-blocker.

METHODS

STUDY PROTOCOL. Female farm pigs weighing 35 to 45 kg (age 9 to 12 months) were used for this study. An animal model of HF induced by myocardial ischemia and rapid pacing (MI + HF) was created as described previously (23,24). In brief, all animals underwent baseline assessment of LV function using echocardiographic and invasive hemodynamic assessments. Acute MI was induced in all animals by coronary artery embolization to the left circumflex artery, followed by 4 weeks of rapid right ventricular pacing (150 beats/min) using a VVI pacemaker to induce HF. After ventricular pacing had ceased for 24 h, repeat echocardiographic and invasive hemodynamic assessments were performed. Animals with impaired left ventricular ejection fraction (LVEF) <45% were randomized to receive medication alone (control group, n = 10) or catheter-based bilateral RD (RD group, n = 10) after invasive hemodynamic studies and were followed for 10 weeks. During this period, all animals with or without RD were treated with daily oral metoprolol succinate (25 mg) plus ramipril (2.5 mg).

Serial echocardiographic examinations were performed at 2, 6, and 10 weeks following RD. At 10 weeks, final invasive hemodynamic studies were performed, and all animals were sacrificed for histological and immunohistochemical assessment.

Electrocardiographic parameters, including resting heart rate, corrected QT interval, and systolic and