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PRECLINICAL RESEARCH

Renal Denervation Decreases Susceptibility to Arrhythmogenic Cardiac Alternans and Ventricular Arrhythmia in a Rat Model of Post-Myocardial Infarction Heart Failure

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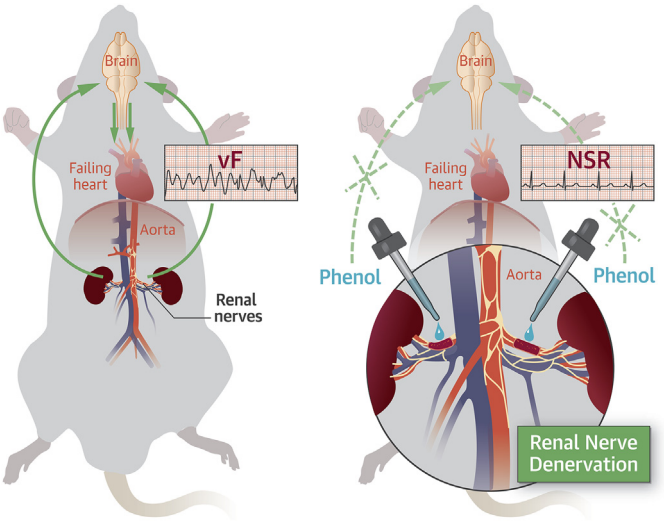
VISUAL ABSTRACT



Chang, S.-N. et al. J Am Coll Cardiol Basic Trans Science. 2017;2(2):184–93.

HIGHLIGHTS

- In systolic heart failure, decreased renal perfusion due to impaired cardiac pumping activates the renal nerves, which send a signal to the brain to call for help.
- The brain thus activates the neurohormonal system to increase organ perfusion, which may predispose the heart to ventricular arrhythmia.
- Chemical renal denervation with phenol cuts the signal sent to the brain and thus decreases the susceptibility to ventricular arrhythmia in rats with systolic heart failure.

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SUMMARY

Several studies have shown the beneficial effect of renal denervation (RDN) in the treatment of ventricular arrhythmia, especially in the setting of heart failure (HF). However, the underlying mechanism of antiarrhythmic effect of RDN is unknown. Arrhythmogenic cardiac alternans, particularly spatially discordant repolarization alternans, characterized by simultaneous prolongation and shortening of action potential duration (APD) in different myocardial regions, is central to the genesis of ventricular fibrillation in HF. Whether RDN decreases the susceptibility to arrhythmogenic cardiac alternans in HF has never been addressed before. The authors used a rat model of post-myocardial infarction HF and dual voltage-calcium optical mapping to investigate whether RDN could attenuate arrhythmogenic cardiac alternans that predisposes to ventricular arrhythmias, as well as the hemodynamic effect of RDN in HF. The HF rats had increased body weights, dilated hearts, and lower blood pressure. The HF rats also had longer ventricular APDs and a delay in the decay of the calcium transient, typical electrophysiological features of human HF. Susceptibility to calcium transient alternans, APD alternans, and spatially discordant APD alternans was increased in the HF hearts. RDN significantly attenuated a delay in the decay of the calcium transient, calcium transient and APD alternans, and importantly, the discordant APD alternans, and thereby decreased the incidence of induced ventricular arrhythmia in HF. RDN did not further decrease blood pressure in HF rats. In conclusion, RDN improves calcium cycling and prevents spatially discordant APD alternans and ventricular arrhythmia in HF. RDN does not aggravate hemodynamics in HF. (J Am Coll Cardiol Basic Trans Science 2017;2:184–93)

ABBREVIATIONS AND ACRONYMS

APD = action potential duration

APD-ALT = action potential duration alternans

Ca-ALT = calcium transient alternans

HF = heart failure

MI = myocardial infarction

RDN = renal denervation

PR = pacing rate

SCD = sudden cardiac death

VF = ventricular fibrillation

VT = ventricular tachycardia

Patients with heart failure (HF) still have a poor prognosis, and treatment for HF still remains a great challenge although pharmacological and device therapies have greatly improved in recent years. Compared with the general population, the presence of HF is associated with a 6- to 9-fold increased risk of sudden cardiac death (SCD) (1). The most common cause of SCD in HF is ventricular arrhythmias, such as ventricular tachycardia (VT) or fibrillation (VF) (1). There is clear evidence that activation of the sympathetic nervous system plays a major role in the pathogenesis and mechanism of ventricular arrhythmias in HF (2).

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The recent introduction of endovascular catheter-based radiofrequency ablation technology, renal denervation (RDN), has emerged as a treatment tool for patients with resistant hypertension. This catheter-based approach that targets the efferent and afferent renal sympathetic nerves has been demonstrated to result in a favorable blood pressure reduction through modulation of sympathetic activity (3,4). Recently, catheter-based RDN has also been studied in the treatment of other relevant cardiovascular diseases that are involved in activation of the sympathetic nervous system, such as HF, atrial fibrillation, and ventricular arrhythmias (5–9).

In 2012, Ukena et al. (7) first showed that RDN greatly decreased VT/VF episodes in 2 patients with HF due to cardiomyopathy and therapy-resistant electrical storm. One recent report also showed that RDN successfully treated repetitive VT/VF that were refractory to antiarrhythmic drug therapy and ablation in a patient with acute myocardial infarction (MI) and HF (8). In a recent small case series, a significant reduction of VT burden was observed after RDN in 4 patients with HF and VT despite maximized antiarrhythmic therapy and ablation (9). In all these patients, RDN not only was an effective treatment modality for suppressing or diminishing ventricular arrhythmias, but also was associated with a good safety profile.

The electrophysiological characteristics and the mechanisms of ventricular arrhythmias that occur during HF are complex and depend on the underlying diseases. In HF, intracellular calcium homeostasis is altered, and such calcium-handling impairment has been demonstrated to result in arrhythmogenic calcium transient alternans (Ca-ALT) and thus action potential duration (APD) alternans (APD-ALT) (10). Several lines of evidence have shown that arrhythmogenic APD-ALT is the major mechanism initiating ventricular arrhythmias and SCD in HF (11–13).

Based on the preliminary results of the small series of case studies showing the beneficial effect of RDN in the treatment of ventricular arrhythmia in HF and from a pathophysiological point of view, RDN may be an effective treatment for the prevention and treatment of ventricular arrhythmias in HF. However, the