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Exploring the potential of renal denervation in heart failure therapy: new insights into right ventricular function and sympathetic nervous modulation

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Heart failure (HF) remains a highly prevalent and complex condition, marked by significant morbidity and hyperactive sympathetic nervous system that further deteriorates cardiac function. While renal denervation (RDN) is primarily known for its effects on lowering blood pressure, recent studies suggest its potential to impact the cardiac sympathetic nervous system, making it a promising candidate for HF therapy. However, the influence of RDN on HF, specifically on right ventricular (RV) function, has yet to be fully elucidated. This study aimed to fill this gap by examining the effects of RDN on RV performance, myocardial norepinephrine (NE) levels, and HF markers in a hypertensive rat model of HF induced by volume overload.

Our study utilized hypertensive Ren-2 transgenic rats with an aorto-caval fistula (ACF) to simulate HF with volume overload. RDN was achieved via phenol application to the renal arteries to reduce renal sympathetic nerve activity (both afferent and efferent). After a two-week period, RV function was evaluated through echocardiography and pressure-volume analysis, focusing on RV end-systolic and end-diastolic pressures and RV systolic function. NE concentrations were measured in the kidney, plasma, and RV to gauge the impact on sympathetic modulation, while molecular markers were analyzed to assess changes in oxidative stress and HF progression.

Our findings demonstrate that RDN significantly reduces both end-systolic pressure (ESP) and end-diastolic pressure (EDP) in the RV, and enhanced RV contractility with an increase in RV end-systolic elastance (Ees) and fractional area change (FAC), indicating a reduction in RV afterload and an improvement in overall RV function in this HF model.

To better understand the connection between RV improvement and sympathetic activity, we measured NE levels, which serve as a primary marker of sympathetic activation. RDN led to a significant decrease in NE concentrations in the kidney and plasma, suggesting a reduction in overall sympathetic tone. Interestingly, NE levels were partially restored and significantly increased within the RV myocardium, an effect potentially linked to the downregulation of monoamine oxidase A (MAO-A), an enzyme that degrades NE while producing reactive oxygen species (ROS).

Furthermore, our molecular analyses showed decreased expression of critical HF markers, including Nppa, Tgm2, and an improved Myh7/6 ratio, indicating a reduction in myocardial stress and fibrosis in the RV. We also observed increased expression of SOD2, an antioxidant enzyme that may contribute to reduced ROS-induced damage in the myocardium, offering additional protective effects.

In summary, this study sheds new light on RDN's potential beyond hypertension management by demonstrating its beneficial effects on RV function in HF. Through reductions in RV ESP and EDP, improvements in systolic function, modulation of NE levels, and downregulation of HF markers, RDN may offer targeted protection against RV strain in volume-overloaded HF. These findings highlight the promise of RDN as a novel intervention for HF with RV involvement, warranting further investigation in larger models and clinical trials to confirm its therapeutic potential.

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