JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 72, NO. 21, 2018
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Renal Denervation Halts Left Ventricular Remodeling and Dysfunction in Heart Failure

New Shores Ahead*

Michael Böhm, MD, Sebastian Ewen, MD, Milan Wolf, MD

Chronic heart failure (HF) is the most common cause of hospitalization in the Western world. Even though major progress in treatment has been made, prevalence and incidence are steadily increasing. A raised sympathetic drive adversely affects cardiovascular outcome, indicated by circulating catecholamine and its association with poor prognosis (1,2).

Cardiac volume overload leads to release of A-type natriuretic peptide and B-type natriuretic peptide (BNP), which, in addition to diuretic effects, also have cardioprotective properties (3,4). Recently, enhanced production of neprilysin, enzymatically degrading potentially protective natriuretic and other bioactive peptides, was found to possibly contribute to the progression of left ventricular dysfunction. The elevation of neprilysin is associated with poor outcomes. Its inhibition with sacubitril/valsartan provides remarkable benefits in HF patients (5).

SEE PAGE 2609

In this issue of the *Journal*, Sharp et al. (6) investigated 25 Yucatan miniswine that underwent 75 min of left anterior descending coronary artery balloon occlusion to induce myocardial infarction, followed by reperfusion, and subsequently a catheter-based radiofrequency renal sympathetic denervation (RDN) using the EnligHTN multielectrode catheter (St. Jude Medical, St. Paul, Minnesota). In this preclinical trial, cardiac function was assessed by transthoracic echocardiography. At the end of the study, histological as well as biochemical examinations were performed to analyze cardiac remodeling, artery function, and neurohumoral activation.

The investigators showed that RDN reduces sympathetic activation assessed by decreased renal catecholamine levels (**Figure 1**). Furthermore, RDN led to a significant improvement in left ventricular longitudinal strain, a reduction of end-systolic volume, and a decline in cardiac fibrosis, resulting in an improvement of cardiac function. Interestingly, RDN reduced neprilysin activity, which was resulting in an increase of cardioprotective BNP concentrations. The authors should be applauded for exploring a novel pathway of maladaptive response associated with sympathetic activity in the development of HF. It would have been interesting to measure not only BNP, but also amino terminal (NT)-proBNP levels, as this is not cleaved by neprilysin. A direct comparison of those 2 substances could give more information of hemodynamic-dependent improvements due to RDN, because an improved hemodynamic should also result in a decrease in NT-proBNP, whereas an only neprilysin-dependent change should result in a neutral BNP level.

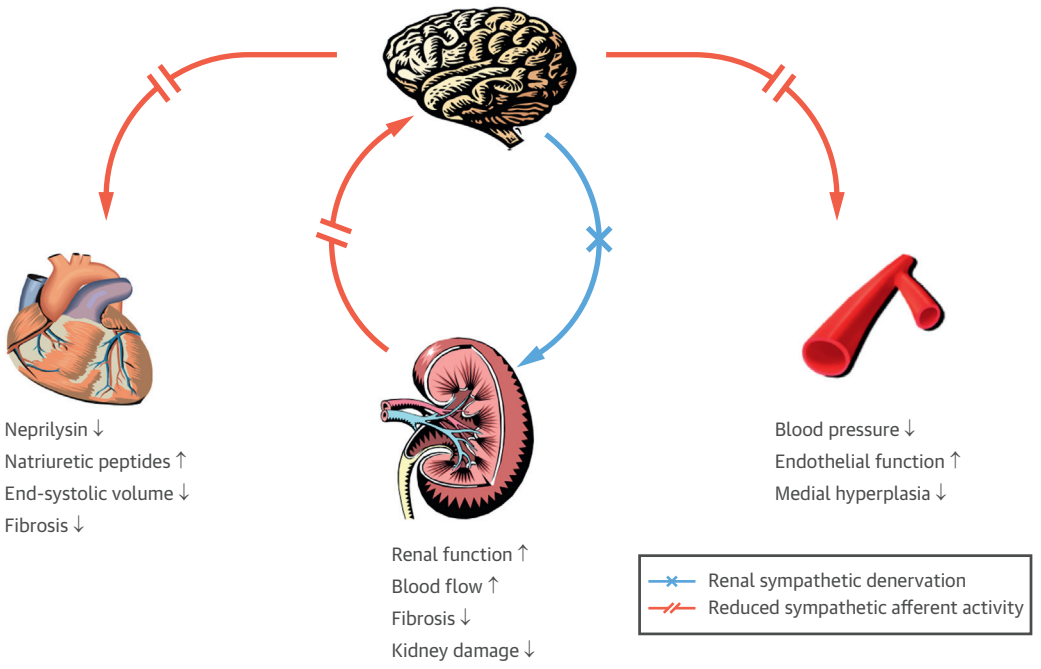
As recent studies have shown, RDN presents a safe and minimally invasive treatment option for patients with hypertension (7–9). However, the clinical evidence in the treatment of heart failure is very limited. This experimental work provides an

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Homburg-Saar, Germany. Dr. Böhm has served as a scientific advisor for and received speaker fees from Amgen, Bayer, Servier, Medtronic, Boehringer Ingelheim, Vifor, and Bristol-Myers Squibb. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2018.09.027

FIGURE 1 Effects of Renal Sympathetic Denervation



Sympathetic efferent activation is generated in the central nervous system. Efferent sympathetic nerves **(red lines)** target the heart, kidney, and vessels and produce neprilysin activation (new finding), inotropic effects, but also fibrosis, beta adrenergic down-regulation and contractile dysfunction. In the kidney, the vasoconstriction increases renin activation and enhanced sodium water retention, contributing to fibrosis and kidney damage. Peripheral arterial afterload increases by vasoconstriction and, in the long run, blood pressure is increased. Atherosclerosis is initiated, and media hyperplasia takes place. Interruption of afferent as well as efferent kidney nerve fibers by using renal sympathetic denervation **(red cross)** reduces sympathetic outflow **(interrupted red lines)** and potentially reverses these pathological findings.

in-depth insight into novel and potentially relevant mechanisms.

Up to now, there has only been 1 uncontrolled pilot study dealing with RDN in patients with heart failure, which showed no difference in blood pressure (as a beneficial contribution) and marked an improvement in 6-min walk test (10). These improvements are probably caused by reduced cardiac remodeling and improved cardiac function. Furthermore, echocardiographic studies showed that an interruption of renal sympathetic fibers resulted in a reduced left ventricular mass and improved diastolic function (11,12). A cardiac magnetic resonance imaging trial could even show a blood pressure–independent improvement in cardiac ejection fraction, left ventricular myocardial mass, and circumferential strain in patients with impairments at baseline (13). Nevertheless, mechanistic findings are still needed to determine how RDN is protective in heart failure. Therefore, the present aspect is of particular importance.

In summary, the investigators revealed in this preclinical trial how RDN elegantly combines the cornerstones of medical HF treatment, consisting of sympathetic modulation and inhibition of neprilysin activity. An in-depth investigation of how this minimally invasive, low side-effect method reduces the burden of HF is urgently needed. As RDN also has a positive effect on the most important comorbidities, such as atrial fibrillation (14), renal dysfunction (15), and diabetes (16), a prospective clinical trial is needed to scrutinize the potential beneficial effects of RDN in heart failure.

ADDRESS FOR CORRESPONDENCE: Dr. Michael Böhm, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Universitätsklinikum des Saarlandes, Kirrberger Straße, Geb. 40, 66421 Homburg/Saar, Germany. E-mail: Michael.Boehm@uks.eu. Twitter: @Saar_Uni.

REFERENCES

1. Florea VG, Cohn JN. The autonomic nervous system and heart failure. Circ Res 2014;114:1815–26.

2. Böhm M, Linz D, Ukena C, et al. Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? Circ Res 2014;115:400–9.

3. Stevens TL, Rasmussen TE, Wei CM, et al. Renal role of the endogenous natriuretic peptide system in acute congestive heart failure. J Card Fail 1996;2:119–25.

4. Epstein F, Levin E. Natriuretic peptides. N Engl J Med 1998;50:2357–68.

5. McMurray JJV, Packer M, Desai AS, et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993–1004.

6. Sharp TE III, Polhemus DJ, Li Z, et al. Renal denervation prevents heart failure progression via inhibition of the renin-angiotensin system. J Am Coll Cardiol 2018;72:2609–21.

7. Kandzari DE, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 2018;6736:1–10.

8. Townsend RR, Mahfoud F, Kandzari DE, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 2017;390:2160–70.

9. Azizi M, Schmieder RE, Mahfoud F, et al. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 2018;6736:1–11.

10. Davies JE, Manisty CH, Petraco R, et al. First-in-man safety evaluation of renal denervation for chronic systolic heart failure: Primary outcome from REACH-Pilot study. Int J Cardiol 2013;162:189–92.

11. Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol 2012;59:901–9.

12. Schirmer SH, Sayed MMYA, Reil JC, et al. Improvements in left ventricular hypertrophy and diastolic function following renal denervation: effects beyond blood pressure and heart rate reduction. J Am Coll Cardiol 2014;63:1916–23.

13. Mahfoud F, Urban D, Teller D, et al. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. Eur Heart J 2014;35:2224–31.

14. Linz D, Van Hunnik A, Hohl M, et al. Catheter-based renal denervation reduces atrial nerve sprouting and complexity of atrial fibrillation in goats. Circ Arrhythmia Electrophysiol 2015;8:466–74.

15. Mahfoud F, Cremers B, Janker J, et al. Renal hemodynamics and renal function after catheter-based renal sympathetic denervation in patients with resistant hypertension. Hypertension 2012;60:419–24.

16. Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 2011;123:1940–6.

KEY WORDS acute myocardial infarction, brain type natriuretic peptide, coronary vascular reactivity, neprilysin, renin-angiotensin system, sympathetic nervous system