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COMMENTARY

What is the benefit of renal denervation?

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Heart failure is still a critical burden. It has already been determined that chronic overactivation of the sympathetic nervous and renin–angiotensin system worsens heart failure associated with progressive cardiac remodeling.[1,2] However, the 5-year survival rate in heart failure is still approximately 50%, despite advancements in various pharmacological and non-pharmacological therapies. Device therapies for sympathoinhibition, such as spinal cord stimulation, vagal nerve stimulation, baroreflex activating therapy and renal sympathetic denervation, have been a large focus of innovation. We expected renal denervation to be a focus because it has been reported to provide a beneficial depressor response in patients with resistant hypertension.[3–6] In addition, renal denervation has been shown to have a protective effect on chronic kidney diseases associated with hypertension.[7] Heart failure is strongly associated with renal dysfunction/damage; when co-occurring, cardiac and renal dysfunctions exaggerate multi-organ damage and progression to poor prognosis.[2] Therefore, influencing renal denervation could stop the vicious cycle of heart failure. Moreover, considering the pathophysiology of sympathoexcitation in heart failure, denervation of the renal afferent nerve could inhibit the regulation of the central sympathetic system and provide beneficial sympathoinhibition to heart failure.

In this issue of the journal, Watanabe *et al.*[8] reported the impressive and evocative study, 'Renal denervation mitigates cardiac remodeling and renal damage in Dahl rats: a comparison with β-receptor blockade' to *Hypertension Research*. Watanabe *et al.*[8] hypothesized whether renal denervation would ameliorate damage by improving renal function and sympathetic cardioregulation in hypertensive heart failure with renal injury. Dahl salt-sensitive hypertensive rats in the hypertrophic stage were subjected to renal denervation, sham operation, vehicle or β-blocker bisoprolol. In this study, Watanabe *et al.*[8] demonstrated the following results: (1) neither renal denervation nor bisoprolol altered blood pressure, but bidoprolol significantly reduced heart rate; (2) both renal denervation and bisoprolol significantly prolonged survival; (3) renal denervation and bisoprolol reduced left ventricular hypertrophy and improved left ventricular function, left ventricular myocyte, hypertrophy and fibrosis; (4) renal denervation increased tyrosine hydroxylase and β1-adrenergic receptors in the left ventricular myocardium, while bisoprolol increased α1b, α1d and α2c adrenergic receptors in the left ventricular myocardium and (5) both renal denervation and bisoprolol reduced renal damage and dysfunction accompanied by suppressing endothelin-1, renin and angiotensin-converting enzyme mRNA. Considering these impressive results, renal denervation exerts greater protective effects on the left ventricular sympathetic system compared with chronic β-blocker treatment; by contrast, β-blocker treatment caused a persistent heart rate reduction with increased expression of α-adrenergic receptors in both the left ventricle and the kidney. Watanabe *et al.*[8] concluded that renal denervation may hold therapeutic potential, especially in patients with heart failure and progressive renal impairment. Although renal denervation could not reduce blood pressure in the present study, further study should not be discouraged. Compared with previous studies, the present assessment provides further details because Watanabe *et al.*[8] clearly showed that renal denervation did not alter renal sodium excretion, daily sodium/water balance, cardiac output and vascular resistance, suggesting that renal denervation could not improve the renal pressure–natriuresis relationship. Moreover, Watanabe *et al.*[8] assessed diurnal blood pressure changes and demonstrated that renal denervation only decreased mean blood pressure during the resting phase, while the hypotensive effect of β-blocker lasted for 24 h. These important results were conceptually consistent with a previous clinical study[9] and demonstrated the benefits of renal denervation on protection against hypertensive organ damage in heart failure. We should consider that the renal denervation improves the quality of blood pressure, such as nocturnal dipping, which is ultimately more important than mere blood pressure reduction during the daytime.

Treatments for hypertension should aim to protect hypertensive organ damage, especially in cardiac hypertrophy and hypertensive renal damage. To achieve this blood pressure reduction is essential. However, the direct effects on left ventricular hypertrophy and renal damage independent of blood pressure reduction would be reasonable to treat heart failure. Watanabe *et al.*[8] demonstrated the prospective benefits of renal denervation. Urine noradrenaline, excretion as a parameter of sympathoexcitation, decreased, and noradrenaline content, tyrosine hydroxylase protein expression and β1-receptor expression in the left ventricular myocardium were restored in the Dahl salt-sensitive rats treated with renal denervation. These results focused on the effect of renal denervation for central-sympathetic regulation by disrupting the renal afferent nerve. For renal protection suppressing efferent renal sympathetic nerve activity decreases renin secretion and sodium reabsorption or increases renal blood flow.[10] Watanabe *et al.*[8] demonstrated that renal denervation exerts direct renal effects by suppressing local neurohormonal factors,

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such as endothelin 1, renin and angiotensin converting enzyme, independent of blood pressure. These results made us consider whether renal denervation would mitigate cardiac and renal hypertensive damages without significant blood pressure reduction.

Interestingly, bisoprolol, not renal denervation, reduced heart rates and restored α1b and α1d adrenergic receptor expression and increased α2c adrenergic receptor expression.[8] As suggested by Watanabe *et al.*[8] the reduction in oxygen expenditure associated with the heart rate is quite central to the benefits of β-blockers. In contrast, bisoprolol did not restore noradrenalin content, tyrosine hydroxylase protein or β1-receptor expression in the left ventricular myocardium.[8] Although the improvement of survival in Dahl salt-sensitive rats was similar between renal denervation and bisoprolol, the beneficial mechanisms differed greatly between the two treatments in Dahl salt-sensitive rats.[8]

Now, we wonder about the interpretation of SIMPLICITY HTN-3, 'What is the benefit of renal denervation?'.[7] As perspective and clinical implications, Watanabe *et al.*[8] first described the procedural competency and suboptimal renal denervation, and proposed the suggestive comment, 'It is now more important than ever for the basic mechanisms underlining renal denervation to be clarified'. In addition, Watanabe *et al.*[8] concluded that renal denervation holds therapeutic potential in patients with heart failure and progressive renal damage, independent of blood pressure-lowering responses, as shown in Figure 6. To prove this concept, future long-term clinical trials and further animal examinations are needed to determine whether renal denervation could improve survival against left ventricular hypertrophy and renal damage in patients with heart failure. However, the results in Watanabe *et al.*[8] encourage us to advance towards the future of renal denervation.

What is the benefit of renal denervation? We better think again about the essential aims of the treatment for heart failure.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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