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COMMENT

Beneficial effects of renal denervation on heart, kidneys, and adipose tissue beyond antihypertensive effect: is it independent of systemic sympathetic activity?

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Accumulating evidence supports the efficacy of renal denervation (RDN) as an antihypertensive treatment. However, it is still important to clarify the appropriate indications and predictors of responders to RDN in the treatment of hypertension. In fact, the antihypertensive effect of RDN depends on the hypertensive animal models [1]. Therefore, basic research using animal models is essential to supplement clinical studies for mechanistic insights. In addition, it can demonstrate the effects of RDN on organ damage beyond its blood pressure-lowering effect.

The present study by Nagata et al. reported the effects of RDN at early versus advanced stages of hypertension on blood pressure elevation and organ pathology, including kidney, heart, and adipose tissue, in Dahl salt-hypertensive rats fed 8% NaCl diet from 6 weeks of age [2]. The authors demonstrated that RDN at early stage (7 weeks of age) or advanced stage (9 weeks of age) attenuated blood pressure elevation. RDN at both stages ameliorated left ventricular (LV) diastolic dysfunction, fibrosis, and inflammation, although RDN at neither stage affected LV and cardiomyocyte hypertrophy. RDN at both stages also attenuated renal injury as well as downregulated the expression of renin-angiotensin system (RAS) components, such as angiotensinogen, angiotensin-converting enzyme, and angiotensin II type 1 receptor in the kidney. In the adipose tissue, RDN at both stages inhibited the gene expression of proinflammatory factors and RAS. As a difference in the effects of RDN between the early and advantage stages, the early intervention reduced both visceral fat mass and adipocyte size; however, the late intervention increased fat mass without affecting adipocyte size.

Renal nerves consist of sympathetic efferent nerves and sensory afferent nerves. Activation of renal sympathetic efferent nerves contributes to an increase in renin release, sodium reabsorption, and renal vascular resistance, contributing to hypertension and hypertensive organ damage [1, 3]. Afferent renal nerves relay the information from the kidneys to the central nervous system, including the brain nuclei that regulate sympathetic nerve activity [1, 3, 4]. Therefore, RDN, which denervates both efferent and afferent renal nerves, can decrease the activity of circulating RAS by reducing renin release through denervated efferent renal nerves and reduce central sympathetic outflow through denervated afferent renal nerves. This study by Nagata et al. showed that RDN at advanced stage decreased the parameters of circulating RAS, including plasma renin activity and plasma angiotensin II concentration, whereas RDN at either stage did not change the urinary norepinephrine level, an index of systemic sympathetic activity in the Dahl salt-sensitive rats [2]. In the heart and kidney, the local RAS operates in close interaction with the circulating RAS: the tissues may take up the circulating renin [5]. Circulating renin is mainly derived from the juxtaglomerular cells in the kidney, and the efferent renal nerves significantly control this renin secretion as well as renal tissue RAS [3]. Therefore, although RDN did not affect LV hypertrophy probably because of the only mild attenuation of salt-induced hypertension, its protective effect against renal injury related to the renal RAS inhibition might have contributed to the amelioration of LV inflammation and injury, possibly through attenuation of the systemic RAS, even without inhibition of central sympathetic outflow in the Dahl salt-sensitive rats.

Many clinical and animal studies, including this study by Nagata et al., have demonstrated that RDN exerts

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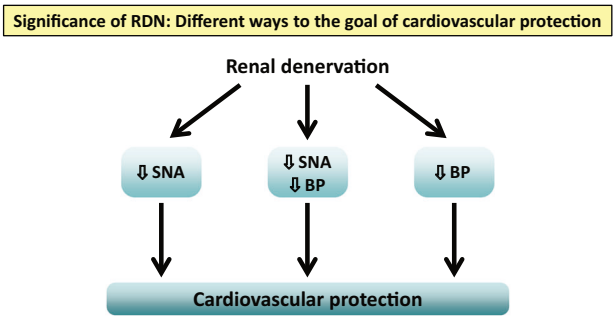

Fig. 1 How does renal denervation provide cardiovascular protection? Renal denervation (RDN) may provide cardiovascular protection through decreasing sympathetic nerve activity (SNA) and/or blood pressure (BP). It is often speculated that the organ-protective effects of RDN may be associated with its sympathoinhibitory effect; however, this remains unclear because most clinical and animal studies have not evaluated sympathetic activity. It will be important to evaluate sympathetic activity in future RDN studies

organ-protective effects in addition to the antihypertensive effect. The sympathetic nervous system plays a critical role in the pathophysiology of hypertension and cardiovascular disease [6, 7]. In addition, RDN can decrease sympathetic outflow through the inhibition of inputs from the afferent renal nerves. Therefore, it is often speculated that the organ-protective effects of RDN may be associated with its sympathoinhibitory effect; however, this remains unclear because most clinical and animal studies have not evaluated sympathetic activity. Interestingly, the present study by Nagata et al. demonstrated the cardiorenal protective effects of RDN without decreasing systemic sympathetic nerve activity [2]. We also demonstrated that RDN attenuated blood pressure elevation probably due to decreased activity of the circulating RAS by inhibition of efferent renal nerve activity, without decreasing sympathetic outflow in young stroke-prone spontaneously hypertensive rats [8]. On the other hand, RDN significantly lowered blood pressure and reduced LV hypertrophy while decreasing sympathetic outflow in adult spontaneously hypertensive rats [9]. As described above, the effect of RDN on sympathetic outflow may differ among the hypertensive animal models, and RDN appears to have a sympathoinhibitory effect under the pathological conditions where renal afferent nerves are activated due to renal damage [1, 10]. Sympathetic inhibition by RDN is not always necessary, but will still be critical for the beneficial effects of RDN on the target organs (Fig. 1). It will be important to evaluate sympathetic activity in future clinical and animal RDN studies.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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