COMMENTARY

Future of catheter-based renal denervation: key issues to solve

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Catheter-based renal denervation (RDN) has spread rapidly and widely.^{1,2} There are many positive reports^{1,2} showing significant blood pressure (BP) reduction; however, a negative result³ was published recently. Although this report, by Brinkmann *et al.*³, itself has an editorial commentary,⁴ I would like to discuss it further. First, BP decreased gradually until 6 or 12 months after RDN^{1,2} in contrast to the sudden and stable BP reduction thereafter with surgical splanchnic sympathetic denervation. These findings may suggest that RDN is not simply denervation but causes damage or degeneration of the renal nerve. Second, BP reduction after RDN appeared smaller in ambulatory BP monitoring measurements than office BP measurements.¹ As Brinkmann *et al.*³ measured BP at 3–6 months after RDN with an ambulatory BP monitoring device, the BP-lowering effect may have been masked, at least in part, in their study. RDN may strongly suppress BP elevation in response to a sympathetic stimulus under stress but not resting BP. Third, it is not clear why RDN has no effect on BP in ~10% of subjects.¹ As their study³ included only a small number of patients ($n = 12$), full effects could not be observed by chance, as observed in 10% of the entire population studied so far.¹ Fourth and most importantly, there is no definite method to detect the procedure or technical failure of RDN when a good BP response is not obtained. Therefore, we cannot exclude the possibility that they³ failed in the procedure in almost all subjects, although this possibility is low. Furthermore, it has not

yet been determined whether such patients with specific characteristics respond fully to RDN. Thus, it seems reasonable to simply conclude that most of their patients³ did not respond, despite technical success.

IMPORTANCE OF VOLUME-INDEPENDENT MECHANISMS

Brinkmann *et al.*³ showed that the degree of BP reduction by RDN tended to be proportional to the baseline BP level. As they included patients with a relatively low baseline BP, it might be possible that prominent BP reduction was not obtained, as they thought.³

In contrast, in animal models, the pressure–natriuresis curve was shifted leftward without changing the slope,⁵ indicating that salt sensitivity was not altered with RDN (Figure 1). In addition, RDN effectively lowered BP in a hypertensive model with non-salt-sensitive hypertension, such as SHR.⁶ In contrast, RDN could not lower BP in salt-sensitive models, including DOCA-salt hypertension and 1K–1C Goldblatt hypertensive models.⁶ These findings indicate that the relief of salt and volume retention is not the key mechanism for RDN to lower BP. Recently, three cases^{7–9} were described whose BP was

successfully lowered without reducing dry weight or body fluid volume in hemodialysis patients with no residual renal function to excrete urine. These findings also support the theory that the control of salt and volume retention is not the mechanism to lower BP. It should be noted here that if natriuresis is enhanced by RDN, the slope of the pressure–natriuresis curve should be enhanced, and the salt sensitivity of BP should be diminished.¹⁰ Instead, reduced renal vascular resistance may be the key mechanism for RDN to lower BP. It has been established that the shift of the pressure–natriuresis curve is primarily determined by preglomerular afferent arteriolar resistance,¹⁰ which is consistent with experimental results.⁵ It appears possible therefore that the patients from Brinkmann *et al.*³ are salt sensitive, making RDN ineffective.

FUTURE PROGRESS IN RDN AND ITS RELATED AREAS

From this discussion, the role of the renal sympathetic system must be clarified further in not only the basic and precise mechanisms of BP regulation^{11,12} but also essential hypertension. Of course, long-term benefits to reduce BP and cardiovascular events without any safety problems must be approved. BP-

Effects of Renal Denervation

1. Leftward Shift of Pressure-Natriuresis Curve without Affecting Salt-Sensitivity
 2. Effective in Non-Salt Sensitive Hypertension such as SHR
 3. Exceptionally Ineffective in Salt Sensitive Hypertension including DOCA-Salt and 1K-1C Goldblatt
- Reduction in renal vascular resistance = BP lowering mechanism

Figure 1 Effects of catheter-based renal denervation (RDN) on blood pressure (BP). (1) Animal experiments showed that the pressure–natriuresis curve was shifted leftward by RDN without affecting the slope, indicating that neither the salt sensitivity of BP nor the renal capacity to excrete sodium into urine was altered. In addition, (2) RDN effectively lowered BP in non-salt-sensitive types of hypertension, such as SHR, but (3) not in salt-sensitive types of hypertension, including DOCA-salt and 1 kidney–1 clip Goldblatt hypertension. Taken together, these findings suggest that the reduction of renal vascular resistance may be the key mechanism for RDN to lower BP.

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independent mechanisms of organ protection should also be studied to obtain a complete understanding of the role of systemic and renal sympathetic systems. We hope that RDN makes it possible to normalize BP without taking antihypertensive drugs in the future after the many important issues discussed above have been solved.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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