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Control of salt and volume retention cannot be ruled out as a mechanism underlying the blood pressure-lowering effect of renal denervation

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To the editor:

Catheter-based renal denervation (RDN) has been increasingly used to lower blood pressure (BP) in patients with treatment-resistant hypertension. However, the underlying mechanisms by which RDN is effective are not well understood.

In the advanced online edition of *Hypertension Research*, Kimura published a commentary¹ titled “Future of catheter-based renal denervation: key issues to solve”, which identified some key issues for future research on RDN. The author correctly pointed out that there exist salt- and volume-independent mechanisms underlying the BP-lowering effect of RDN, *e.g.* a decrease in renal vascular resistance, a decrease in renin-angiotensin system activity, and a decrease in afferent nerve activity². However, Kimura suggested that control of salt and volume retention is not the mechanism by which RDN lowers BP, based on what we consider two inappropriate pieces of evidence:

(1) The author stated that “RDN effectively lowered BP in a hypertensive model with non-salt sensitive hypertension, such as SHR (spontaneously hypertensive rats). In contrast, RDN could not lower BP in salt sensitive models, including DOCA-salt (deoxycorticosterone acetate) hypertension and 1K–1C (one-kidney, one-clip) Goldblatt hypertensive models³.” However, the cited reference³ stated that RDN can lower BP in all three models of hypertension mentioned above. The effectiveness of RDN in lowering BP in these three

models of hypertension is supported by other reports using SHR⁴, DOCA-salt⁵ and 1K-1C⁶ models of hypertension. These results suggest that RDN can lower BP independent of the status of salt sensitivity.

(2) Kimura stated that “three cases⁷⁻⁹ 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.” However, these patients with end-stage renal disease in those studies mentioned above still had residual renal function^{7, 8}, and RDN did not worsen the residual renal function during the study period. In addition, these three case reports using three individual patients complicated with end-stage renal disease were unable to address the importance of salt and volume retention in mediating the effect of RDN. Moreover, the majority of patients who have been treated with RDN were not complicated with end-stage renal disease. Thus, these studies did not rule out the importance of control of salt and volume retention in mediating the effect of RDN.

Different from Kimura’s opinion, evidence suggests that control of salt and volume retention may be one of the mechanisms underlying BP-lowering effect of RDN.

For example, RDN lowered BP in both SHR⁴ and DOCA salt-induced hypertensive rats⁵, which was accompanied by an increase in sodium excretion⁵ and a decrease in cumulative sodium and water balances, suggesting that efferent control of sodium and water balance contributes to BP-lowering effect of RDN in these models of hypertension.

In humans, RDN decreases BP which was accompanied by a decrease in noradrenaline spillover, a decrease in plasma renin activity and an increase in renal blood flow¹⁰. These findings suggest that control of salt and volume retention may be one of the mechanisms underlying the BP-lowering effect of RDN in humans. However, well-designed studies are needed to clarify this issue.

The importance of this mechanism varies in different models of hypertension. For example, in the 1K-1C model of renovascular hypertension, RDN decreased BP but did not alter renal sodium excretion⁶, suggesting that other mechanisms are responsible for the antihypertensive effect of RDN in renovascular hypertension. These mechanisms may include a decrease in plasma noradrenaline, a decrease in peripheral sympathetic nervous system activity and a decrease in the afferent renal nerve activity.

In summary, RDN lowers BP via multiple mechanisms, and control of salt and volume retention may be one of them.

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Conflict of interest

The authors declare no conflict of interest.

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