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COMMENT

Renal denervation and perivascular adipose tissue browning

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The autonomic nervous system plays a fundamental role in regulating the cardiovascular system. Although the classification of "sympathetic" and "parasympathetic" applies only to efferent nerves, the term "sympathetic afferent" is sometimes used to describe the sensory nerve running along the efferent sympathetic nerve. The concept of interrupting the sensory nerves from the organs to relieve pain dates back to the 1930s. Page and Heuer [1] reported the outcomes of patients with nephritis who underwent surgical renal denervation. They observed blood pressure reductions lasting from weeks to months post-operation; however, the hypotensive effect was not permanent. It is likely that hypertension becomes resistant to renal sensory and sympathetic signals to and from the brain when the kidneys are severely damaged. Nevertheless, the study suggests a causal relationship between renal pain and hypertension. Renal afferent signals not inducing pain may also silently cause hypertension.

In 1951, a controlled study on surgical supradiaphragmatic splanchnicectomy reported that approximately 30% of patients with hypertension had blood pressure reductions outside the range of spontaneous variation [2]. The reduction in splanchnic vascular tone is likely the chief mechanism for this effect. The authors of that study foresaw splanchnicectomy as a routine treatment of established hypertensive disease not responding to medical treatments. However, surgical sympathectomy has not gained popularity, possibly due to its invasiveness and the development of various antihypertensive drugs.

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Animal studies have indicated that renal denervation reduces blood pressure in hypertension models, including spontaneously hypertensive rats (SHR) [3], deoxycorticosterone acetate (DOCA)-salt rats [4], and Dahl salt-sensitive rats [5]. However, the blood pressure in SHR with renal denervation eventually increases to levels comparable to that in sham-operated SHR, indicating that the neural mechanisms alone cannot account for the development of hypertension in SHR. Kidney cross-transplantation between SHR and normotensive Wistar–Kyoto rats clearly demonstrated that the kidneys play a critical role in the development of hypertension in SHR [6]. The control group is untreated in these animal experiments, making the hypotensive effect of renal denervation easily detected.

With the development of less invasive, catheter-based technology, renal denervation has regained interest as a treatment for drug-resistant hypertension. While the first large-scale clinical trial, SYMPLICITY-HTN3, did not show a significant reduction in systolic blood pressure in patients with resistant hypertension at 6 months after denervation as compared to a sham control group [7], the final follow-up demonstrated that the renal denervation group had significantly larger systolic blood pressure reductions from baseline to 36 months [8]. The variability in the hypotensive effect of renal denervation could be partly due to incomplete denervation [9], and renal denervation with refined procedures yields promising results. One difficulty in evaluating the results of the clinical trials is that a control group can exhibit unexpected blood pressure reductions [10], possibly resulting from habitual changes during the study period, such as improved medication adherence. Identifying the treatment mechanisms through fundamental research is still essential to determine patients who would benefit most from renal denervation.

Regarding the involvement of the sympathetic system in the treatment mechanisms, the sympathetic effect on the cardiovascular system through the neurotransmitter noradrenaline may be blocked by α- and β- adrenergic blockers.

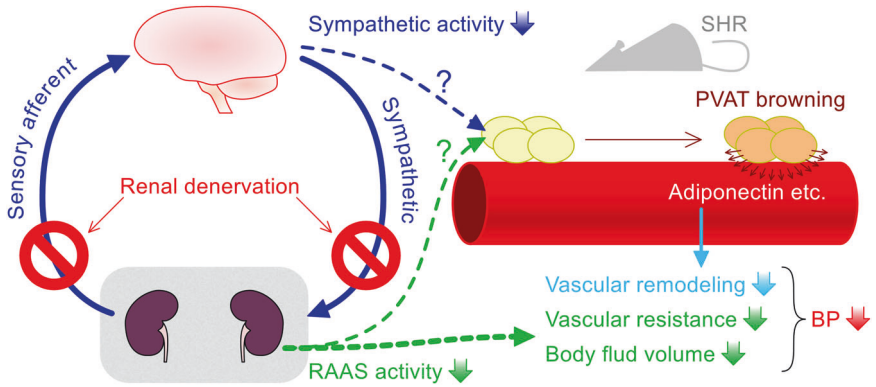

Fig. 1 Cardiovascular effect of renal denervation through PVAT. Renal denervation interrupts the afferent and efferent signals to and from the brain. While suppression of the renin–angiotensin–aldosterone system (RAAS) and sympathetic system may be a primary effect of renal denervation to reduce blood pressure (BP), the changes in perivascular adipose tissue (PVAT) can also contribute to reducing vascular remodeling in spontaneously hypertensive rats (SHR) as a pleiotropic effect of renal denervation

The effect through the renin–angiotensin–aldosterone system may be blocked by angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, and mineralocorticoid receptor blockers. Given these circumstances, why can renal denervation be more effective than pharmacological sympathetic blockade? One possible explanation is the relative potency of neural control as compared to pharmacological interventions [11, 12]. The neural control is so powerful that pharmacological blockade cannot eliminate the sympathetic effect, especially when the sympathetic system is overly activated under diseased conditions. Another explanation is a pleiotropic effect of renal denervation, which cannot be fully replaced by the current pharmacological interventions (Fig. 1).

The present study by Jiang et al. [13] reported the effect of renal denervation on vascular remodeling through the regulation of perivascular adipose tissue (PVAT) in SHR. Healthy PVAT exerts an atheroprotective effect by secreting adipokines such as adiponectin [14]. Removing PVAT promotes the development of neointima after a mechanical vascular injury. Moreover, obesity alters the profile of adipokines secreted from PVAT, enhancing neointimal formation. The present study demonstrated that renal denervation in SHR reduced vascular remodeling by inducing PVAT browning, altering adipokine secretion, and reducing the expression of reactive oxygen species in PVAT [13]. However, the cause of PVAT browning in SHR after renal denervation remains unclear. The possible sympathetic suppression after renal denervation may not be readily compatible with PVAT browning, because PVAT browning is typically associated with increased catecholamines [15]. Further investigations are required to determine whether the changes in PVAT are an essential component of the blood pressure-lowering effect of renal denervation and whether any pharmacological approach can reproduce such an effect on PVAT.

Compliance with ethical standards

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References

1. Page IH, Heuer GJ. The effect of renal denervation on patients suffering from nephritis. J Clin Invest. 1935;14:443–58.
2. Hoobler SW, Manning JT, Paine WG, McClellan SG, Helcher PO, Renfert H, et al. The effects of splanchnicectomy on the blood pressure in hypertension; a controlled study. Circulation. 1951;4:173–83.
3. Kline RL, Stuart PJ, Mercer PF. Effect of renal denervation on arterial pressure and renal norepinephrine concentration in Wistar-Kyoto and spontaneously hypertensive rats. Can J Physiol Pharm. 1980;58:1384–8.
4. Jacob F, Clark LA, Guzman PA, Osborn JW. Role of renal nerves in development of hypertension in DOCA-salt model in rats: a telemetric approach. Am J Physiol Heart Circ Physiol. 2005;289:H1519–29.
5. Nagata K, Tagami K, Okuzawa T, Hayakawa M, Nomura A, Nishimura T, et al. Comparison of the effects of renal denervation at early or advanced stages of hypertension on cardiac, renal, and adipose tissue pathology in Dahl salt-sensitive rats. Hypertens Res. 2024. https://doi.org/10.1038/s41440-024-01605-x
6. Bianchi G, Fox U, Di Francesco GF, Giovanetti AM, Pagetti D. Blood pressure changes produced by kidney cross-transplantation between spontaneously hypertensive rats and normotensive rats. Clin Sci Mol Med. 1974;47:435–48.
7. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N. Engl J Med. 2014;370:1393–401.
8. Bhatt DL, Vaduganathan M, Kandzari DE, Leon MB, Rocha-Singh K, Townsend RR, et al. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final

follow-up of the randomised SYMPLICITY HTN-3 Trial. Lancet. 2022;400:1405–16.
9. Sata Y, Head GA, Denton K, May CN, Schlaich MP. Role of the sympathetic nervous system and its modulation in renal hypertension. Front Med (Lausanne). 2018;5:82.
10. Kario K, Yokoi Y, Okamura K, Fujihara M, Ogoyama Y, Yamamoto E, et al. Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial. Hypertens Res. 2022;45:221–31.
11. Kawada T, Yamazaki T, Akiyama T, Shishido T, Miyano H, Sato T, et al. Interstitial norepinephrine level by cardiac microdialysis correlates with ventricular contractility. Am J Physiol. 1997;273:H1107–12.
12. Kawada T, Miyamoto T, Miyoshi Y, Yamaguchi S, Tanabe Y, Kamiya A, et al. Sympathetic neural regulation of heart rate is robust against high plasma catecholamines. J Physiol Sci. 2006;56:235–45.
13. Jiang T, Wei Y, Xu R, Jin Y, Song T, Wang H, et al. Renal denervation alleviates vascular remodeling in spontaneously hypertensive rats by regulating perivascular adipose tissue. Hypertens Res. https://doi.org/10.1038/s41440-024-01791-8
14. Tanaka K, Sata M. Roles of perivascular adipose tissue in the pathogenesis of atherosclerosis. Front Physiol. 2018;9:3.
15. Bartelt A, Heeren J. Adipose tissue browning and metabolic health. Nat Rev Endocrinol. 2014;10:24–36.