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COMMENT

Mechanisms underlying the effects of renal denervation in renovascular hypertension

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Arterial hypertension is a multifactorial disease that affects more than 1.5 billion individuals worldwide. While considered an expensive health problem that predisposes to other health complications, in a vast majority of the cases, its etiology remains largely unknown. In its complex etiology, a combination of environmental and genetic factors involves changes in the brain, kidneys, heart, blood vessels, and more recently in the gut microbiota [1]. Despite accumulating efforts in developing new therapies to control and treat arterial hypertension, single or multiple therapies using diuretics, calcium channel blockers, angiotensin-converting-enzyme inhibitors, and angiotensin II, as well as aldosterone receptor blockers, still represent the predominant clinical choice of antihypertensive treatment. Nevertheless, resistant hypertension affects as many as 20% of patients that do not respond to traditional therapy, highlighting the need for alternative therapies [2].

More than seven decades ago, one of the first approaches to treat hypertension was radical sympathectomy, involving sectioning both the splanchnic nerves and thoracic dorsal sympathetic chain, thereby interrupting sympathetic outflow resulting in decreased peripheral resistance and lowering of blood pressure [3]. Despite the promising but controversial results of sympathectomy due to its collateral effects [4], this approach was abandoned after the advent of antihypertensive drugs mentioned above. However, renal denervation (RD) has regained attention with the development of minimally invasive catheter-based technology to selectively ablate the renal nerves in humans [5]. Since then, several clinical and experimental studies have explored the therapeutic value of RD in hypertension and associated adverse complications [2, 6–9]. Notwithstanding, the data available are still controversial and the underlying mechanisms are not clear yet.

The kidneys have a crucial role in extracellular fluid and electrolyte homeostasis and hence in long-term blood pressure regulation and are innervated of both afferent and efferent nerves. The sympathetic efferent nerves influence the function of the preglomerular afferent arterioles, the granular juxtaglomerular cells, and the tubular epithelial cells along the nephron. Their main function is to modulate renal vascular resistance, renin secretion and tubular handling of solutes including sodium. The renal afferent nerves encompass nerve fibers projecting from the renal parenchyma to the hypothalamus, resulting in modulation of the sympathetic nervous system and nerve fibers that are pressure-sensitive receptors in the renal pelvis resulting in sympathoinhibition and mediating reno-renal reflexes whenever needed [2, 10]. Therefore, clinical and experimental studies aiming to understand the underlying mechanisms by which RD may influence blood pressure must take into consideration this reno-neural arrangement.

In this issue of Hypertension Research, Nishi et al. [11] brings important knowledge to the understanding of the mechanisms by which unilateral RD of the ischemic kidney in 2-kidneys-1-clip (2K1C) rats, an experimental model of renovascular hypertension, may contribute to antihypertensive effects. Using a combination of sophisticated in vivo and in vitro approaches, the authors elegantly demonstrated that unilateral renal denervation of the clamped kidney induced reduction of renal and splanchnic sympathetic nerves activity to the contralateral kidney, which was associated with reduction in oxidative stress in two key brain areas involved in sympathetic control (i.e., the paraventricular nucleus of the hypothalamus (PVN) and the rostral ventrolateral medulla (RVLM)), and significant reduction of renal injury. Importantly, these favorable effects were not observed in hypertensive 2K1C rats treated with the blood pressure-lowering drug hydralazine, thus

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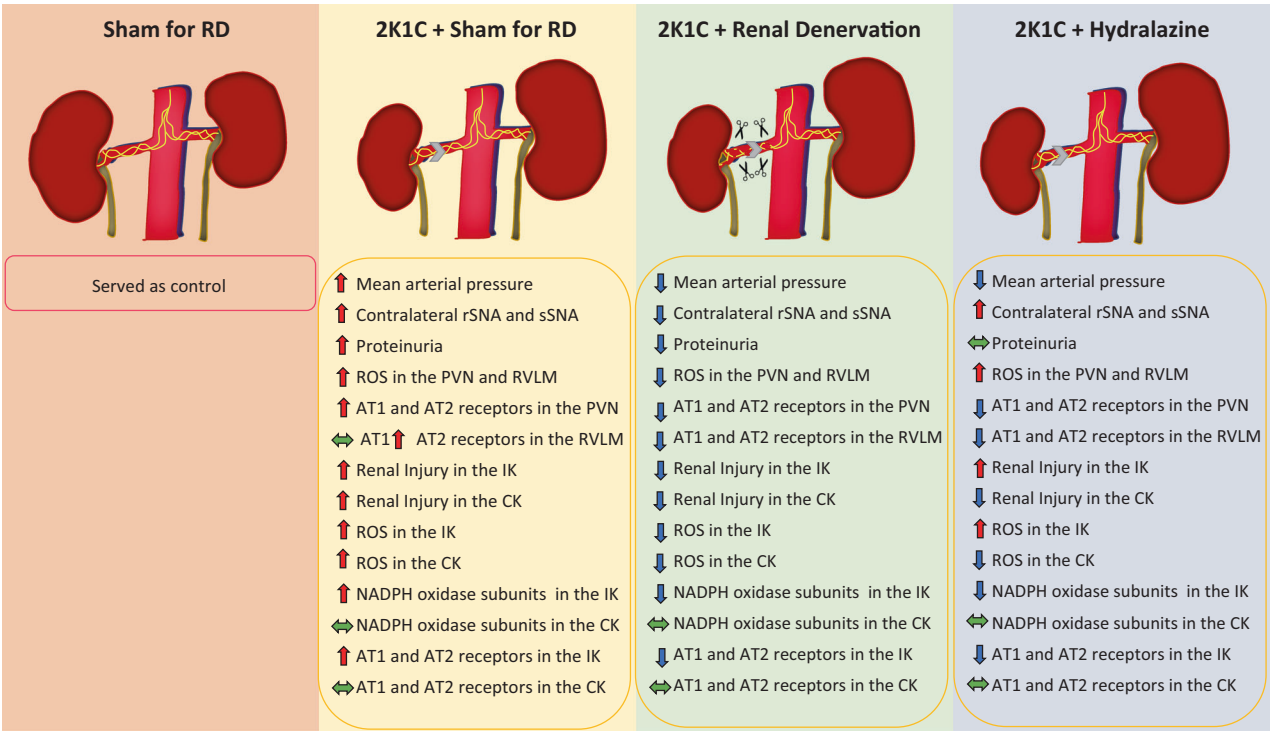

Fig. 1 Schematic drawing summarizing the findings by Nish et al. [11]. Authors suggest that nerves from the ischemic kidney may contribute to the development of hypertension, elevated contralateral renal sympathetic nerve activity (rSNA), and splanchnic sympathetic nerve activity (sSNA), leading to efferent nerve discharge and oxidative stress, followed by renal injury in 2-kidneys-1-clip (2K1C) hypertensive rats. Some of the important responses elicited by RD were dissociated from the fall in blood pressure as illustrated by the group 2K1C + Hydralazine. Red arrows are referred as "increase", blue arrows as "decrease" and double-headed-green arrows as "no change". Arrows indicate differences or not when the 2K1C + Sham for RD were compared to the control group and the 2K1C + RD or 2K1C + Hydralazine were compared to the 2K1C + sham for RD. RD, renal denervation; ROS, reactive oxygen species; PVN, paraventricular nucleus of the hypothalamus; RVLM, rostral ventrolateral medulla; AT_1 and AT_2, angiotensin II types 1 and 2 receptors; IK, ischemic kidney; CK, contralateral kidney

emphasizing the specific therapeutic value of renal denervation. The authors concluded that nerves from the ischemic kidney contribute to the increase in blood pressure, sympathetic efferent discharge, brain oxidative stress, and local renal alterations in renovascular hypertensive rats as summarized in Fig. 1.

Despite the undoubtable contribution towards the understanding of the mechanisms involved in the lowering of blood pressure by RD, as presented by Nishi and colleagues, some important questions remain unanswered and deserve future investigation(s). Firstly, it is impressive how unilateral denervation produces such a significant reduction in blood pressure in rats with 2K1C-induced renovascular hypertension (approximately 25 mmHg). In the most recent clinical trial, the SPYRAL HTN-OFF MED [8, 9], bilateral RD in hypertensive patients that were kept without the confounding effects of medication presented a more humble reduction in systolic arterial pressure, even 3 months after the procedure was performed (ranging from 5–10 mmHg). While the mechanisms that lead to the development of renovascular hypertension are very different from those related to essential hypertension, one potential explanation for such difference in the fall in blood pressure, that per se undermines the translational aspect of the study by Nishi and colleagues, is how blood pressure was recorded. While for the clinical trials, blood pressure was reported as averaged ambulatory 24 h-recordings, Nishi et al. performed a single acute measurement of the blood pressure in conscious, freely moving rats. Future studies in this matter should encompass blood pressure recordings using gold-standard radio-telemetry. By adopting that approach, in addition to allowing blood pressure recordings for 24 h, animals would be their own control and one would obtain measurements during baseline, after clipping the renal artery, to establish the degree of renovascular hypertension, and most importantly to evaluate the acute and chronic effects of RD compared with the sham-operated group. In the current study, the authors compared the effects between RD and sham-operation in rats with renovascular hypertensive, without confirmation that the degree of pathological changes (i.e., degree of hypertension, cardiac hypertrophy, renal hypertrophy of the contralateral kidney) was similar between the groups before the intervention was initiated.

Secondly, it is surprising that such strong protective effects were observed in the contralateral kidney since 4–5 weeks had elapsed before RD or hydralazine treatment was initiated. Although there is a relative short window for performing the measurements before reinnervation is considered to take place (i.e., 2–3 weeks), it would be interesting to perform RD at different time points along the development of renovascular hypertension rather than only after hypertension has been fully established. The rationale for that suggestion is that there is evidence that RD attenuates the development of cardiac hypertrophy presented in other forms of renal hypertension [12] and is clearly an important complication in 2K1C rats [13].

Thirdly, authors suggested that RD of the ischemic kidney blunts the increase of reactive oxygen species (ROS) in brain areas involved in cardiovascular control such as the PVN and the RVLM. The data presented are rather convincing and has helped to shed some light regarding the mechanisms leading to ROS accumulation along the SFO-PVN-RVLM axis in reno-neural hypertension. In addition, previous studies have reported that some forms of angiotensin II-dependent hypertension, including 2K1C-induced renovascular hypertension, involves the overexpression of angiotensin II receptors along the SFO-PVN-RVLM axis, particularly AT_1 receptors, leading to ROS accumulation and eventually increases in sympathetic nerve activity and blood pressure [14]. While this was true for the PVN, the authors were not able to detect increased expression of AT_1 receptors in RVLM from the 2K1C rats, which might be explained by the relatively small sample number in those experiments. The authors also acknowledged this as a limitation of their study. Importantly, even though no significant increase of AT_1 receptor expression were found in the RVLM of 2K1C, both RD and hydralazine were able to reduce AT_1 and AT_2 receptors expression, suggesting that overexpression of angiotensin II receptors in either the PVN or the RVLM is dependent on the increase in blood pressure and not related to the sensory inputs from the ischemic kidney.

Lastly, the favorable effects of RD on renal function, proteinuria and urinary angiotensinogen in rats with 2K1C were very impressive. Authors reported that renal injury, as shown by the alpha-smooth muscle actin expression and picrosirius red staining, and oxidative stress involve different mechanisms in the ischemic and contralateral kidneys of 2K1C rats. While ROS accumulation and development of renal injuries were dependent on the integrity of the renal nerves of the ischemic kidney, the abnormal changes of the contralateral kidney rather appeared to be related to the high blood pressure level per se. Considering that most of the ROS found in the kidneys would come from the angiotensin II-AT1 receptor-NADPH oxidase pathway, the mechanisms underlying ROS accumulation in the contralateral kidney remain elusive, since changes in AT_1 receptors and NADPH oxidase subunits were only found in the ischemic kidney and were sensible to either RD or blood pressure reduction by hydralazine.

Despite several remaining questions, as discussed above, the pioneering work by Nishi and colleagues [11] set the grounds for advancing the knowledge regarding the understanding of the mechanisms underlying the effects of RD in renovascular hypertension. Distinguishing the cause and consequences regarding the interrelationship between hypertension, central and peripheral SNA, activation of the renin-angiotensin system and oxidative stress is not trivial. The study by Nishi et al. has certainly provided novel knowledge to this field, which will certainly help driving further investigation to clarify important questions highlighted here. Furthermore, future placebo-controlled, prospective clinical investigations should be conducted in order to document the effective contribution of RD in patients with renovascular hypertension.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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