Renal denervation and patients with CKD: current evidence and future perspectives

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The intensive crosstalk between the brain and the kidney has been a point of interest in many different fields. The research into the significance of afferent signaling from, and efferent sympathetic firing towards the kidney has recently gained attention. Some conditions, most notably chronic kidney disease (CKD), increase efferent signaling. On the other hand, afferent signaling escalates related to renal damage, ischemia, or other functional impairment. This raises sympathetic activity throughout the body, significantly impacting the heart and other organs. Increased sympathetic activity combined with renin secretion and sodium retention raises blood pressure, with a detrimental impact on cardiac functioning and subsequent cardiovascular complications.

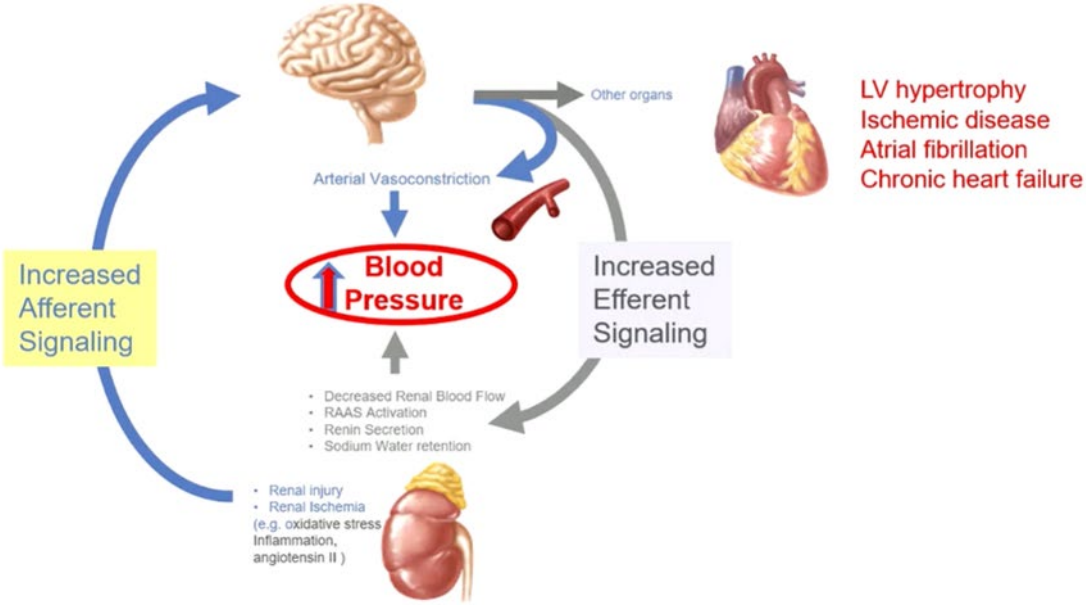

Figure 1. Importance of afferent signaling from and efferent sympathetic firing to the kidney

The first attempts to interfere with this kidney-brain relationship were recorded in 1972, employing a surgical procedure – bilateral nephrectomy, which resulted in a mean arterial blood pressure decrease. In 1992, the same procedure was employed in a London-based study, resulting in a dramatic reduction in the mean sympathetic nerve discharge and a significant decrease in vascular resistance and mean arterial blood pressure. There has been evidence that bilateral nephrectomy in patients after kidney transplantation also causes a decline in MSNA and a subsequent decrease in cardiovascular reactivity. Therefore, from surgical experience, it is necessary to tackle the sympathetic nervous system to attenuate the progression of not only renal disease but cardiovascular disease as well.

Renal denervation (RDN) is an endovascular device-based therapy that interferes with the renal nerves, i.e. interrupts the kidney-brain communication. The research led by Guido Grassi looked at muscle sympathetic neuronal activity (MSNA) in hypertension by using the microneurographic method and found an overall decrease in sympathetic activity post-RDN. Likewise, the group led by Markus Schlaich, focused on single unit MSNA, which is more specific to the vasoconstrictive fiber nerves activity, and three months after renal denervation similar effects have been observed. The measurement of the spillover of norepinephrine from the renal sympathetic nerves to plasma following renal denervation showed a reduction of 47% in humans and 85% in the swine model. Therefore, endovascular RDN not only reduces sympathetic activity in the kidney, but in the entire body as well.

Experiments on sheep models tested the effects of RDN on blood pressure and other impacts on the organs. The procedure helped to preserve the glomerular filtration rate and improve mean arterial blood pressure. Also, renal denervation prevented albuminuria and reduced left ventricular mass in hypertensive CKD patients. Immunohistochemistry staining after RDN in CKD showed a decrease in the efferent sympathetic innervation of arcuate vessels and sensory afferent innervation in the pelvic wall.

The research on catheter-based radiofrequency RDN also included the hypothesis that RDN may cause an increase in nitric oxide, consequently decreasing blood pressure and preserving renal function. Schäufele et al. found reduced basal nitric oxide activity and increased oxidative stress in chronic glomerular disease. Singh et al. recently found that urinary NO_x (nitrate + nitrite) excretion was significantly increased 2 months after RDN and remained elevated at 30 months in CKD sheep models. The same group investigated the effect of RDN on blood pressure, glomerular filtration rate (GFR), albuminuria, and left ventricular mass in the same ovine models. A series of follow-up experiments in normotensive and hypertensive CKD sheep after RDN or sham procedures showed that RDN improves mean arterial pressure, prevents albuminuria, and reduces left ventricular mass in hypertensive CKD animals. Furthermore, a reduced anatomical and some functional reinnervation of renal nerves were observed in hypertensive sheep 30 months after the procedure.

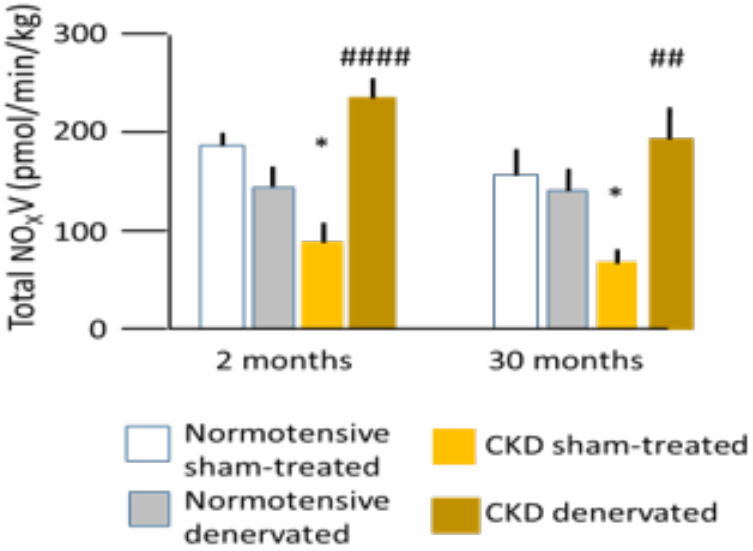

Figure 2. Levels of urinary NOX (nitrate + nitrite) in normotensive and CKD sheep after RDN or sham procedure

Results from humans are still scarce. A series of three pilot studies have been conducted in Erlangen, Melbourne, and Sao Paulo respectively to investigate the effects of RDN in humans. The Erlangen study observed no notable decrease in eGFR in CKD patients one year after RDN, but the values of serum creatinine compared to the values registered three years earlier showed an evident decrease in eGFR of over 4.8 ml/min/year. The Melbourne and the Sao Paolo studies obtained similar results, indicating that RDN is an efficient tool to target increased sympathetic activity in CKD patients. Recently, the Global Symplicity Registry was established to collect and analyze real-world data on the safety and efficacy of RDN procedures, covering more than three thousand subjects. The registry follows patients with and without CKD, with an estimated glomerular filtration rate (eGFR) above and below 60. At one, two, and three-year follow-up, systolic 24-hour ambulatory blood pressure (ABP) appeared to decline to the same extent in primary and secondary hypertension.

Patients with the end-stage renal disease treated with dialysis represent yet another group that needs consideration when exploring the effects of RDN. The experience from a single-center pilot study led by Christian Ott showed a decrease in mean 24-hour ambulatory blood pressure in hypertensive patients on hemodialysis and an improvement in other parameters six months after the procedure. The randomized study conducted in Milan, Italy, followed 24 hemodialysis patients with resistant hypertension for approximately six years and recorded similar results related to blood pressure decrease after RDN.

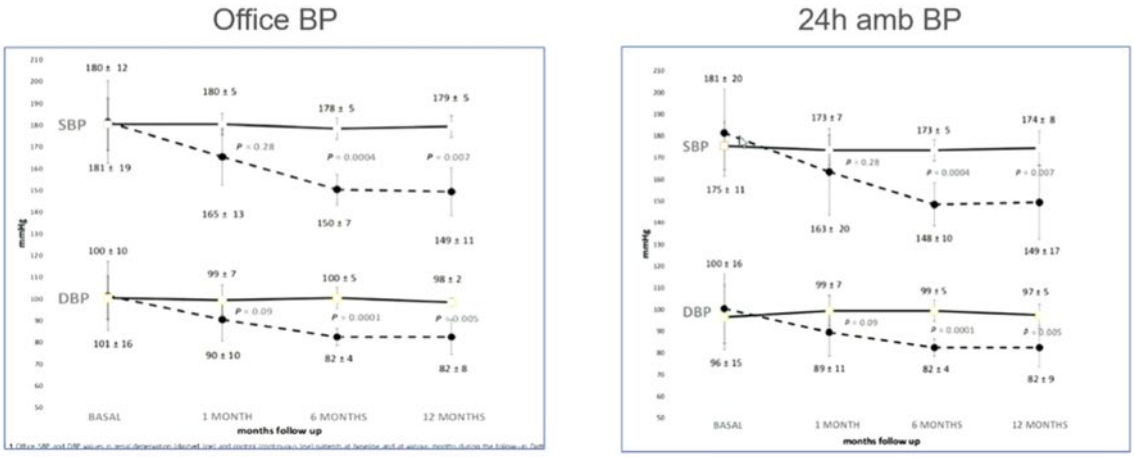

Figure 3. Post-RDN blood pressure in patients with ESRD and resistant hypertension on long-term hemodialysis

The major safety concerns related to the RDN procedure were endothelial damage, new renal artery stenosis, contrast-induced nephropathy, and eGFR loss in the long term. However, beyond a few femoral access complications (hematoma, pseudoaneurysm) no acute adverse safety events (e.g. acute renal failure, dissections, perforations, bleeding) were observed in the sham-controlled randomized clinical trials. Similarly, a meta-analysis showed no statistically significant changes in eGFR at follow-up that could not be attributed to aging.

The durability of the procedure is still not completely known but is estimated to be at least three years. Histological analyses in a swine model study 7 and 180 days after the RDN procedure showed mature fibrotic infiltration and persistent axonal destruction, proving that no renal re-innervation took place. Also, the physiological assessment looking at the axon density showed a significantly lowered

norepinephrine concentration in the tissue of the RDN group, which is a marker of the sympathetic drive to the kidney. The pilot study on the long-term effect of RDN on blood pressure reduction in patients on antihypertensive medications (SPYRAL HTN-ON MED) found that the impact of the RDN procedure remained over six months, with a striking effect of a subsequent decrease in blood pressure values after the six-month primary endpoint.

Key points

1. RDN is becoming an important adjunctive treatment modality in the management of patients with hypertension.
2. RDN is considered a safe and well-tolerated endovascular intervention in the CKD population (with limited data in eGFR<45mL/min/1.73m^2).
3. In patients with CKD, RDN effectively reduces blood pressure to the same extent observed in primary hypertension.
4. The potential of RDN to provide additional benefits in CKD patients through preserving renal function should be further explored.

Further reading

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(4) Schmieder RE, Kandzari DE, Wang TD, Lee YH, Lazarus G, Pathak A. Differences in patient and physician perspectives on pharmaceutical therapy and renal denervation for the management of hypertension. *J Hypertens*. 2021;39(1):162-168. doi:10.1097/HJH.0000000000002592

(5) Singh RR, McArdle ZM, Iudica M, et al. Sustained Decrease in Blood Pressure and Reduced Anatomical and Functional Reinnervation of Renal Nerves in Hypertensive Sheep 30 Months After Catheter-Based Renal Denervation. *Hypertension*. 2019;73(3):718-727. doi:10.1161/HYPERTENSIONAHA.118.12250

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