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See related article, "Liver Angiotensinogen Is the Primary Source of Renal Angiotensin II," on pages 1181–1189.

Renal Nerves and CKD: Is Renal Denervation the Answer?

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A role for renal nerves in the regulation of renal function has been recognized since the time of Claude Bernard.[1] It has also been clear that renal nerves have an intimate relationship with many forms of experimental hypertension,[2] and surgical splancnicectomy, with consequent renal denervation, was a recommended form of therapy for hypertension in humans before the introduction of effective pharmacologic agents,[3] despite the occurrence of serious side effects including orthostatic hypotension, erectile dysfunction, and gastrointestinal symptoms. Interest in renal denervation as an approach to the management of resistant hypertension in humans has recently been renewed with the introduction of an endovascular device, which uses the energy of a radiofrequency signal to ablate adjacent nerves in the vascular wall. When applied in a systematic manner in the lumens of the renal arteries, this approach results in sustained reduction in BP in patients with resistant hypertension.[4]

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Given the recognized role of efferent renal nerves in the regulation of renin secretion, tubular sodium reabsorption, and renal hemodynamics, the salutary effect of the radiofrequency ablation procedure on BP could readily be attributed to interruption of efferent sympathetic nerve impulses, resulting in a lowered rate of renin secretion, natriuresis, and improved renal hemodynamics. Surgical renal denervation also delays or prevents many forms of experimental hypertension, although interruption of efferent impulses is not always the basis for this antihypertensive action. The kidneys also have afferent nerve fibers that carry information from mechanoreceptors and chemoreceptors to the central nervous system. Activation of these afferents can increase central sympathetic outflow and cause elevations in BP. Selective deafferentation by cutting the dorsal roots from T9 to L1, called dorsal rhizotomy, interrupts signals from afferent nerves as they enter the spinal column, but leaves efferent pathways intact. This approach can be applied in experimental models of hypertension and has been used to demonstrate important roles of renal afferent nerves in preventing hypertension during ingestion of a high sodium diet[5] or after 5/6 nephrectomy.[6] It is obviously not useful in pursuing the roles of efferent *versus* afferent renal nerve activity in humans, because radiofrequency energy applied to the renal arteries will ablate afferent and efferent nerves.

Hypertension is an almost universal complication of CKD. In this setting, it has usually been thought to result from the interaction of impaired sodium excretion by diseased kidneys coupled with activation of the renin-angiotensin system. However, abundant evidence shows that CKD is a state of sympathetic nervous activation that contributes to hypertension, as well as participates in the progressive loss of renal function.[7,8] This sympathetic hyperactivity persists in patients with ESRD and was initially thought to be a consequence of uremia. However, it persists after renal transplantation when renal function has been normalized but is corrected when the native, diseased kidneys are removed,[9] indicating that the kidneys themselves are responsible for the hyperadrenergic state.[9,10]

Campese and colleagues[11,12] developed an interesting model of experimental hypertension in the rat, which clearly supports a major role for renal afferent nerves: the authors injected a small amount of phenol into the lower pole of one kidney and observed the prompt and long-lasting development of systemic hypertension accompanied by evidence of increased renal sympathetic nerve activity without any overall decrease in renal function. The hypertension and evidence of sympathetic activation did not occur in rats that had undergone dorsal rhizotomy, indicating that afferent traffic from the injected kidney led to the observed changes in CNS norepinephrine metabolism and increased sympathetic outflow.[12] This model provides definitive evidence that even small, functionally insignificant, renal lesions produce hypertension through renal afferent pathways.

The beneficial effects of the radiofrequency ablation procedure on BP in patients with resistant hypertension but with normal or near-normal renal function[4] led naturally to a consideration of its possible efficacy in patients with hypertension in the setting of CKD. As reported in this issue of *JASN*, Hering *et al.*[13] carried out a two-center pilot study of radiofrequency-mediated renal nerve ablation in 15 patients with moderate to severe CKD (creatinine-based estimated GFR [eGFR] 31 $\pm$ 9 [SD] mL/min per 1.73 m^2). Eleven of the 15 had type 2 diabetes, and all had resistant hypertension (average baseline office BP was 174$\pm$22/91$\pm$16 mmHg on treatment); their mean age was 61$\pm$9 years, and body mass index averaged 33$\pm$8 kg/m^2. Eight patients were followed for 6 months and five patients for 12 months. Importantly, there was no evidence of a decline in eGFR or effective renal plasma flow 6 months after the procedure, despite exposure to contrast material in some of the patients; the investigators did not analyze statistically the values at 12 months because of the small number of patients. Office systolic and diastolic BPs were significantly reduced at 3- and 6-month follow-up, although ambulatory BP monitoring over 24 hours did not reveal significant reductions. There was, however, a significant reduction in nighttime BP and in the night-to-day BP ratio, indicating an improvement in so-called dipping toward a more normal value. The authors also noted trends for improvement in hemoglobin A_{1C} and plasma brain natriuretic peptide concentrations, an increase in hemoglobin level, and decreases in urinary albumin-to-creatinine ratio, proteinuria, and the augmentation index (a measure of arterial stiffness), although none of these changes reached statistical significance. This pilot study in a small number of CKD patients thus suggests that radiofrequency renal denervation is safe, does not lead to appreciable deterioration of eGFR, and may have beneficial effects on resistant BP and cardiovascular risk factors in such patients.

Before accepting these conclusions, several issues need to be considered. First, were the kidneys successfully denervated by the procedure? Measurement of organ innervation in intact humans can best be done using the technique of norepinephrine spillover pioneered by Esler *et al.*[14] This is an isotope dilution method that determines the contribution of norepinephrine added to the circulation by individual organs and can be used as a marker of sympathetic efferent nerve activity to that organ. It has been successfully applied to the kidneys of hypertensive humans: in a proof-of-principal trial, radiofrequency renal nerve ablation in 10 hypertensive patients with normal renal function reduced renal norepinephrine spillover an average of 47% at 15–30 days after the procedure.[15] The gold standard of effective renal denervation when performed surgically in experimental animals is a reduction of renal norepinephrine content of >90%, so by that standard, catheter ablation may result in only partial efferent denervation. It will certainly be important to determine in future studies the effectiveness of the radiofrequency catheter denervation procedure on norepinephrine spillover in patients with CKD such as those studied in the current report.

A second issue is the possibility of reinnervation of the kidneys. Efferent renal innervation after surgical denervation

can be demonstrated to be complete after 3–4 months in both rats[16] and dogs.[17] Data in humans are sparse. Histologic study of transplanted kidneys showed axonal regeneration as early as 28 days after transplantation, which appeared complete by 8–12 months.[18] However, there was no assessment of the functional significance of these nerves, which were found primarily around the renal vasculature. Another study examined the renal hemodynamic response of transplant recipients *versus* normal controls to lower body negative pressure (LBNP), which reduced mean arterial pressure by 27 mmHg. The authors concluded that the transplanted kidneys remained denervated because the decline in renal blood flow was less than in the control subjects.[19] However, when renal vascular resistance (renal blood flow/arterial pressure) was calculated to factor in the fall in BP resulting from the LBNP, there was no difference between control and transplanted kidneys, suggesting at least partial reinnervation of the latter.[19] These limited data focused primarily on efferent sympathetic renal innervation. Data exploring the question of afferent renal nerve reinnervation after denervation or transplantion are virtually absent. One study in dogs measured the arterial pressure response to capsaicin injected into the renal artery after autotransplantation; in innervated kidneys, this injection raises BP through activation of renal afferent nerve pathways. Twelve to 35 months after autotransplantation, capsaicin produced an increase in BP of 10 mmHg, but this response was only one-third that seen in dogs with native innervated kidneys.[20] This suggests at least partial afferent renal innervation may have taken place after 1 year. These observations do not allow a clear conclusion about the reinnervation of human kidneys after renal denervation. However, the prolonged reduction in BP following catheter-based renal denervation argues that, even if reinnervation takes place, the benefits of the procedure persist for at least 1 year and are not overcome by compensations in other BP regulatory pathways, both in patients with resistant hypertension and near-normal renal function[4,15] and in patients with CKD and severe hypertension.[13]

It must of course be remembered that this is a small study with relatively short-term follow-up, and ultimate safety and efficacy of the catheter-based renal denervation procedure must await longer follow-up in a larger group of patients with CKD; indeed, of the five patients followed for 12 months, eGFR appears to have declined precipitously in one and more gradually in three others compared with the value at 6 months.[13] A trial in a larger group of patients is now underway prior to seeking approval from the Food and Drug Administration for approval of the radiocatheter device. Additionally, the preponderance of patients with type 2 diabetes (11/15) in this pilot study raises the question of benefit in patients with CKD from other causes or with a body mass index that is not so elevated. Not yet answered is the effect of the catheter-based renal denervation on the increased sympathetic tone accompanying CKD; in one case report, whole body norepinephrine spillover, a measure of overall sympathetic activity, was reduced 42% in a patient with resistant hypertension, although the patient's level of renal function was not presented.[21]

These issues notwithstanding, bilateral renal denervation using this modestly invasive technique appears to offer a new avenue to approach the treatment of resistant hypertension and may have particular utility in reducing the cardiovascular risk profile of patients with CKD. The results of the larger clinical trial now underway are awaited with keen interest.

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DISCLOSURES

None.

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