Sympathetic Activation in Chronic Kidney Disease
Out of the Shadow
Markus P. Schlaich

Chronic kidney disease (CKD) is a global and growing health problem. In the United States alone, an estimated 20 million people are affected by CKD, equating to \( \approx 13\% \) of the adult population.\(^1\) While carrying an increased risk for the development of end-stage renal disease (ESRD), the major threat to patients with CKD is the associated morbidity and mortality from cardiovascular causes, which is up to \( \approx 30 \) times higher than in the general population. Interestingly, the single most common cause of death in patients with ESRD is sudden cardiac death, mainly attributable to ventricular arrhythmias. This is perhaps not surprising given the substantially elevated sympathetic drive commonly encountered in ESRD patients. Indeed, elevated plasma norepinephrine levels have been shown to be predictive of both survival and incidence of cardiovascular events in this patient cohort.\(^2\) More recently, it was demonstrated that patients with CKD and known coronary artery disease are also at higher risk of sudden cardiac death, which was independently associated with the decline in estimated glomerular filtration rate (eGFR; hazard ratio of 1.11 per 10 mL/min decline in eGFR). Although this example intuitively suggests an important role of sympathetic nervous system activation in adverse outcomes associated with chronic and ESRD, there are several additional lines of persuasive evidence for such a role from recent clinical studies, as described below.

Increased concentrations of plasma catecholamines and enhanced sensitivity to norepinephrine paired with the observation of a pronounced hypotensive effect in response to adrenergic inhibition with clonidine provided initial evidence of sympathetic hyperactivity in patients with CKD. In 1992, Converse et al\(^3\) reported that muscle sympathetic nerve activity (MSNA), as assessed by microneurography, is increased in patients with ESRD undergoing hemodialysis. Interestingly, correction of uremia by renal transplantation did not result in normalization of sympathetic nerve activity,\(^4\) which was only abolished by bilateral nephrectomy, suggesting that sympathetic activation is driven by the diseased native kidneys.\(^3,4\) It then became evident that increased sympathetic nerve activity is already present in compensated chronic renal failure and, more recently, that increased MSNA is associated with a composite of all-cause mortality and nonfatal cardiovascular events in a small cohort of CKD patients.\(^5\)

Although striking, the described associations between sympathetic activation and moderate-to-severe chronic and end-stage renal failure do not necessarily establish a cause-effect relationship, nor are they proof of the concept that direct inhibition of sympathetic activation may translate into better outcomes in these patients. However, an elegant study by Grassi et al published in this issue of Hypertension\(^6\) provides further evidence for a crucial involvement of the sympathetic nervous system already in early stages of CKD.

In contrast to previous studies, the cohort under investigation included a relatively large number of hypertensive patients, 73, with normal or moderately impaired renal function as assessed by eGFR using the Modification of Diet in Renal Disease Study formula. All 42 of the patients with CKD had undergone renal biopsies to establish the cause of renal failure and were closely matched with the 31 hypertensive patients with normal renal function with regard to age, blood pressure, body mass index, and other potential confounding factors. Importantly, patients with renal and cardiac comorbidities assumed to independently affect sympathetic activation, such as autosomal dominant polycystic kidney disease, heart failure, and others, were excluded. Using microneurography, the investigators were able to demonstrate the following: (1) patients with CKD displayed MSNA values greater than controls; (2) MSNA increased progressively when patients were divided into tertiles according to the level of eGFR; and (3) MSNA was significantly and inversely correlated with the eGFR for the entire cohort \( (r = -0.59; P < 0.001) \). Although average plasma norepinephrine levels were higher in CKD patients, no correlation was evident between plasma norepinephrine and eGFR. This is perhaps not surprising given the limited value of plasma norepinephrine as a marker of sympathetic activation. Heart rate was also significantly higher in CKD patients, perhaps indicating increased sympathetic outflow to the heart in these patients. This would also be consistent with the more pronounced left ventricular mass index observed in these patients in view of the established role of norepinephrine as a cardiotrophic factor.

There are, however, also several limitations that need to be taken into account. First, volume status was only assessed clinically, which can be misleading and may have affected MSNA. Second, participating patients continued their antihypertensive regimen throughout the study with the exception...
of β-blockers, which were withdrawn 1 week before the study. The fact that the distribution of antihypertensive drug classes used was similar in the 2 groups does not rule out that CKD patients could respond differently to these drugs, particularly with regard to their effects on sympathetic activity, which can be reduced by renin-angiotensin system inhibitors and increased by calcium channel blockers. Third, the addition of a cohort of patients with CKD and normal blood pressure (without antihypertensive medication) would have been useful to render the results even more compelling.

Where to go from here? Is it time for routine use of effective strategies to target the sympathetic nervous system directly in patients with CKD? Are sympatholytic agents safe in CKD and ESRD? Will sympathetic inhibition halt or at least slow further deterioration of renal function and/or proteinuria? Will sympathetic inhibition beneficially influence cardiovascular outcomes in these patients?

Although some of these questions are not yet conclusively resolved, it appears inevitable to bring the sympathetic nervous system and its role in CKD out of the shadow and into the minds of the clinicians managing these patients. The clinical evidence for the adverse consequences of increased sympathetic activation is further accumulating and strongly supported by a large body of experimental evidence indicating that sympathetic activation, rather than being a consequence, is an early event in the pathophysiology of chronic renal failure and that various forms of renal injury even without alterations of renal function can activate the sympathetic nervous system, predominantly via afferent signals of sensory renal nerves.7 (Figure).

From a therapeutic point of view, centrally acting sympatholytic drugs such as the imidazoline-receptor agonist moxonidine have been shown to be safe and effective both in CKD and ESRD patients.8 In addition to the reduction in sympathetic nerve activity, there is evidence for a blood pressure–independent renoprotective effect of the drug as demonstrated by a reduced decline of eGFR in CKD patients when compared with an equipotent dose of a calcium channel blocker4 and by a favorable effect on microalbuminuria in the absence of blood pressure changes in patients with type 1 diabetes mellitus and optimal blood pressure control.9 Importantly and consistent with the data presented by Grassi et al6 in this issue, a previous study also found that sympathetic activity remains elevated in CKD patients despite adequate

**Figure.** The kidneys are strategically positioned to be both origin and target of increased sympathetic activation. Various forms of renal injury can stimulate afferent sensory nerve fiber signaling to central integrative structures in the brain (1). A large number of additional factors can further contribute to increased afferent signaling (2). Central integration of these afferent signals results in increased efferent sympathetic outflow to target organs, including the heart (3), the vasculature (4), the kidneys (5), and other organs with the consequences illustrated in the Figure. In addition to target organ damage, each of these effects can further aggravate the blood pressure elevations commonly seen in patients with CKD (6) and can contribute to the high morbidity and mortality from cardiovascular causes. Other than peripherally acting adrenoreceptor blocking agents (not shown), attractive therapeutic options include centrally acting sympatholytic agents that reduce central sympathetic outflow (7) to the periphery, including the heart, vasculature, and kidneys. Selective renal denervation as can be achieved by catheter-based application of radiofrequency energy may have additional benefit in that it not only reduces efferent sympathetic drive to the kidneys but also interferes with afferent signaling (8), thereby potentially targeting a major mediator of renal injury–induced sympathetic activation.
blood pressure control achieved by standard antihypertensive regimens, including renin-angiotensin system inhibition. The observation of a positive correlation between MSNA and increased left ventricular mass in these CKD patients indeed indicates that additional sympatho-inhibitory therapy may well be beneficial. Studies are currently being conducted to further substantiate the protective effects of direct sympatho-inhibitory treatment.

Lastly, the availability of a novel approach using catheter-based radiofrequency ablation technology to directly and selectively target both efferent and afferent renal nerves to functionally denervate the human kidney is likely to shed some more light into the pathophysiologic mechanisms underpinning the striking association between sympathetic activation and its adverse consequences in patients with CKD.

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