

## *In-depth Review*

# Endovascular renal denervation: a novel sympatholytic with relevance to chronic kidney disease

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### Abstract

Endovascular renal denervation (sympathectomy) is a novel procedure developed for the treatment of resistant hypertension. Evidence suggests that it reduces both afferent and efferent sympathetic nerve activity, which may offer clinical benefit over and above any blood pressure-lowering effect. Studies have shown objective improvements in left ventricular mass, ventricular function, central arterial stiffness, central haemodynamics, baroreflex sensitivity and arrhythmia frequency. Benefits have also been seen in insulin resistance, microalbuminuria and glomerular filtration rate. In chronic kidney disease, elevated sympathetic activity has been causally linked to disease progression and cardiovascular sequelae. Effecting a marked reduction in sympathetic hyperactivity may herald a significant step in the management of this and other conditions. In this in-depth review, the pathophysiology and clinical significance of the sympatholytic effects of endovascular renal denervation are discussed.

**Keywords:** chronic kidney disease; renal denervation; resistant hypertension; sympathetic nervous system

### Overview

Chronic kidney disease (CKD) affects 7.2% of the world's population over the age of 30 years, and 23.4–35.8% of people over 65 years [1]. The disease is characterized by sympathetic activation, which increases in severity as the disease progresses [2]. Such sympathetic activation associates with the composite of all-cause mortality and nonfatal cardiovascular events [3]. Amelioration of sympathetic overload prevents both hypertension [4] and the progression of renal disease [5] in experimental models. These data have recently been replicated in humans following endovascular renal denervation [6]. Keen interest has been generated in the technique's sympatholytic effects [7, 8], particularly in CKD research circles. Potential translational research applications include reduction of glomerular hyperfiltration [9], glomerulosclerosis and albuminuria [10] and amelioration of glomerulonephritis [11]. The purpose of this article is to summarize what is known about endovascular renal denervation and give specific reference to use of the technique in CKD.

### Historical perspective

Thomas Willis first identified the sympathetic nervous system in 1664 [12], with Pourfois du Petit recognizing that the blood vessel calibre was under neural control some 60 years later [12]. Building on this work, Stelling

described vasomotor fibres in 1840 [12] before Bernard, Waller and Brown-Sequard fully detailed the pressor effects of electrical nerve stimulation and vasodilatation after nerve section [12]. Von Euler [12] brought things into the modern era with his description of the sympathetic neurotransmitter norepinephrine in 1946 with Ahlquist defining the concept of  $\alpha$ - and  $\beta$ -adrenergic receptors two years later [13].

With the increased understanding of the sympathetic nervous system came a desire to influence its effects for health benefits. In hypertension, recognition that increased peripheral vascular resistance was the principal haemodynamic abnormality [14] led to a concerted effort to ameliorate its effects. Hypertension represented a significant burden of disease. In the 1950s, 20% of the adult population had hypertension, hypertensive heart disease or both [15]. The risk of cardiovascular disease or death was increased in direct proportion to the elevation of blood pressure [16]. Malignant hypertension led to swift deterioration and death by uraemia, cerebral haemorrhage or uncontrollable heart failure [17]; less severe hypertension to an increased risk of atherosclerotic vascular disease [15].

In the 1930s, thoracolumbar sympathectomy had been developed for patients with severe hypertension. The procedure involved surgical section of the sympathetic trunks, along with removal of the great splanchnic nerves from the coeliac ganglion to the mid-thoracic level. The aim was to recreate the vasodilatory effect seen after experimental nerve section in order to reduce peripheral vascular resistance and hence blood pressure. Although the operation

improved all-cause mortality [18], the associated morbidity (severe orthostatic hypotension, impotence, urinary and faecal incontinence) reduced its universal acceptance. Ultimately, it was to fall out of favour as pharmacological alternatives were developed.

By the mid-1980s, it was clear that CKD patients had elevated levels of systemic sympathetic activity. Increased concentrations of plasma catecholamines [19] and a pronounced hypotensive effect in response to adrenergic inhibition with clonidine [20] substantiated these observations. In 1992, Converse *et al.* [21] first reported that muscle sympathetic nerve activity (MSNA), as assessed by clinical microneurography, is increased in patients who have end-stage kidney disease (ESKD) and undergo haemodialysis. Most interestingly, bilaterally nephrectomized patients had a sympathetic drive comparable with control subjects without renal failure and also had lower blood pressure (Figure 1) [21]. This was the pivotal clinical finding pointing to a role for afferent signalling from the diseased kidneys in sympathetic activation and hypertensive control.

### Endovascular renal denervation

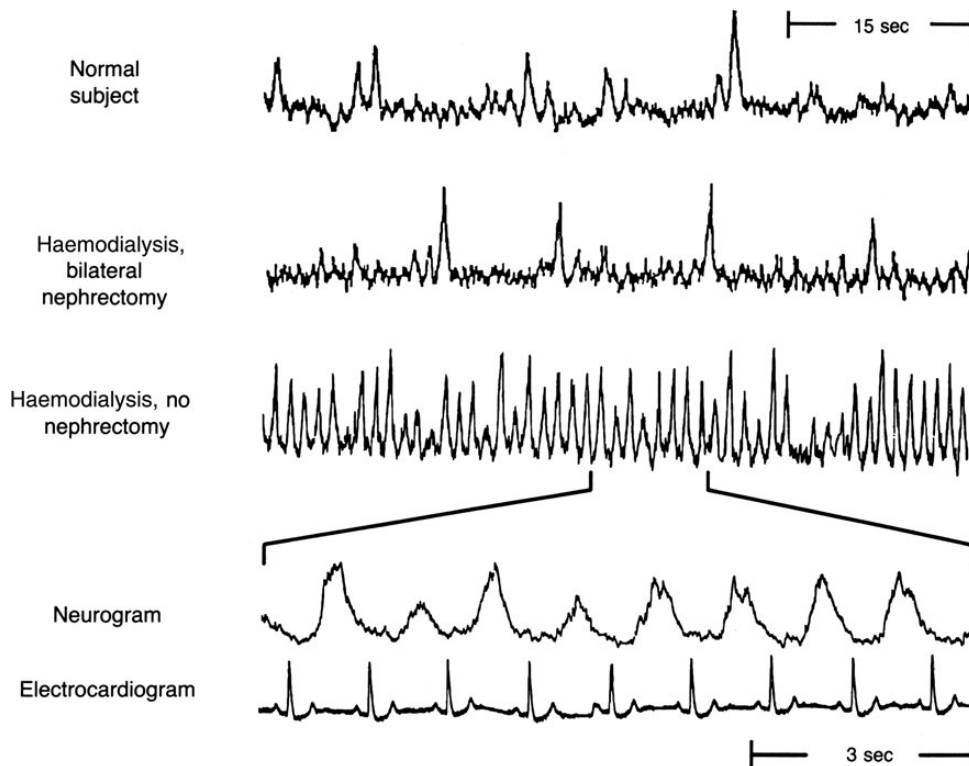
Recently, a novel procedure of endovascular renal denervation has been developed [22]. Unlike the traditional invasive surgical approach, this involves a percutaneous, catheter-based method, whereby radiofrequency waves are applied to the endothelial surfaces of both renal arteries. The treatment causes controlled burns through to the tunica adventitia, the location of the afferent pre-ganglionic and efferent post-ganglionic renal nervous supply. Nerve tissue is particularly sensitive to thermal injury. Post-ablation histology from pre-clinical swine studies reveals a pattern of nerve fibrosis,

replacement of nerve fascicles with fibrous connective tissue and thickening of the epineurium and perineurium [23]. In contrast, the renal arteries demonstrated fibrosis of 10–25% of the total media and underlying adventitia, with mild disruption of the external elastic lamina. Although thickened, the intima remained intact with complete endothelial coverage [23].

The first large clinical trial of endovascular renal denervation involved a case series of 45 patients with resistant hypertension [22]. This was defined as a blood pressure >140/90 despite three anti-hypertensive medications (including a diuretic) at maximal-tolerated dosage. A significant office-based blood pressure reduction at 1-month follow-up of 14/10 mmHg was followed by a sustained response at 12 months of 27/17 mmHg. Procedural complications were limited to one renal arterial dissection due to catheter manipulation (treated successfully with renal artery stenting) and one femoral artery aneurysm.

More recently, the Symplicity-HTN 2 trial [24] randomized 52 resistant hypertensive patients to catheter-based therapy in addition to conventional anti-hypertensive medications versus anti-hypertensive medications only. There was a significant difference in blood pressure from baseline to 6-month follow-up of 33/11 mmHg between treatment groups [24]. Following patient cross-over at 6 months, further analysis at 12 months [25] suggests that the antihypertensive effect is maintained. A single femoral pseudoaneurysm occurred in the treatment group and was successfully treated with ultrasound-guided compression. Transient bradycardia arose in seven patients, but no systemic side effects (such as postural hypotension or incontinence) have been reported.

Although not universal [26], the suggestion that sympathetic hyperactivity associated with resistant hypertension is



**Fig. 1.** Recordings of sympathetic nerve discharge to the vasculature of the leg muscles in a normal subject and in two patients receiving haemodialysis, one with and one without bilateral nephrectomy.

ameliorated by renal denervation [7, 8] offers some compelling prospects for research. Other clinical conditions where sympathetic activity is elevated may also benefit from this novel technique over and above resultant changes in blood pressure control.

## Sympathetic hyperactivity in CKD

### Pathophysiology

CKD is characterized by marked activation of the sympathetic nervous system, as evidenced by increased levels of circulating norepinephrine and an elevated number of sympathetic neural bursts recorded in the peroneal nerve via microneurography [2, 21]. The residual kidneys are critically involved in the pathogenesis of the sympathetic hyperactivity (Figure 2). In fact, evidence indicates that the sympathetic hyperactivity originates in the diseased kidney; MSNA in bilaterally nephrectomized patients on dialysis is comparable with that of healthy controls, and unilateral nephrectomy does not change MSNA [27].

Renal ischaemia is key to the pathogenesis. Ischaemia leads to sympathetic activation through the release of adenosine from proximal tubular cells [28]. Adenosine increases afferent renal nerve traffic, as can be shown during an adenosine infusion into the renal artery of uninephrectomized dogs [29]. In rats, induction of renal artery stenosis [30], partial renal ablation by arterial ligation [4] or intra-renal phenol injection [31] cause excitation of the renal afferent nerves, which results in neurogenic hypertension. Even a small injury in one kidney caused by intra-renal injection of phenol (an intervention that does not affect glomerular filtration rate but results in a local inflammatory response and scarring) leads to hypertension in association with an increased central sympathetic

activity [32]. In these animal models, dorsal rhizotomy (selective renal sympathetic denervation) results in a reduction or total prevention of hypertension. Additionally, in the phenol hypertension model, nephrectomy of the injured kidney several weeks after the induction of renal damage results in normalization of blood pressure [33]. From these experimental observations, it is clear that renal injury can lead to sympathetic hyperactivity and hypertension, and this hyperactivity is associated with activation of the renal afferent nerves.

Parallel activation of the renin-angiotensin system also occurs following ischaemic renal injury [27], resulting in increased peripheral and central sympathetic activity. Angiotensin II facilitates the pre-synaptic release of norepinephrine, inhibits its synaptic reuptake and enhances tissue response [34]. It also stimulates the sympathetic ganglia and adrenal medulla effecting an increase in circulating epinephrine and norepinephrine [34]. Finally, angiotensin II directly stimulates brainstem sympathetic signalling [34]. Aldosterone, acting via mineralocorticoid receptors, also increases sympathetic nerve activity by up-regulating the brain renin-angiotensin system components and induction of oxidative stress in the hypothalamus [35]. Consequently, there is up-regulation not only of peripheral, but also of central sympathetic activity following ischaemic renal injury.

Although renal ischaemia is key, it does not represent the complete pathophysiological picture. Autonomic dysfunction is frequently observed in patients with significant CKD [36]. This is accompanied by many cardiovascular disturbances, including dysfunction of the baroreflex arc [37] and hyporesponsiveness of adrenergic receptors. It is thought that afferent baroreflex arc dysfunction (exacerbated by the stiff vessels induced by vascular hypertrophy and calcification [38]) leads to enhanced sympathetic outflow, elevated plasma norepinephrine levels [39] and

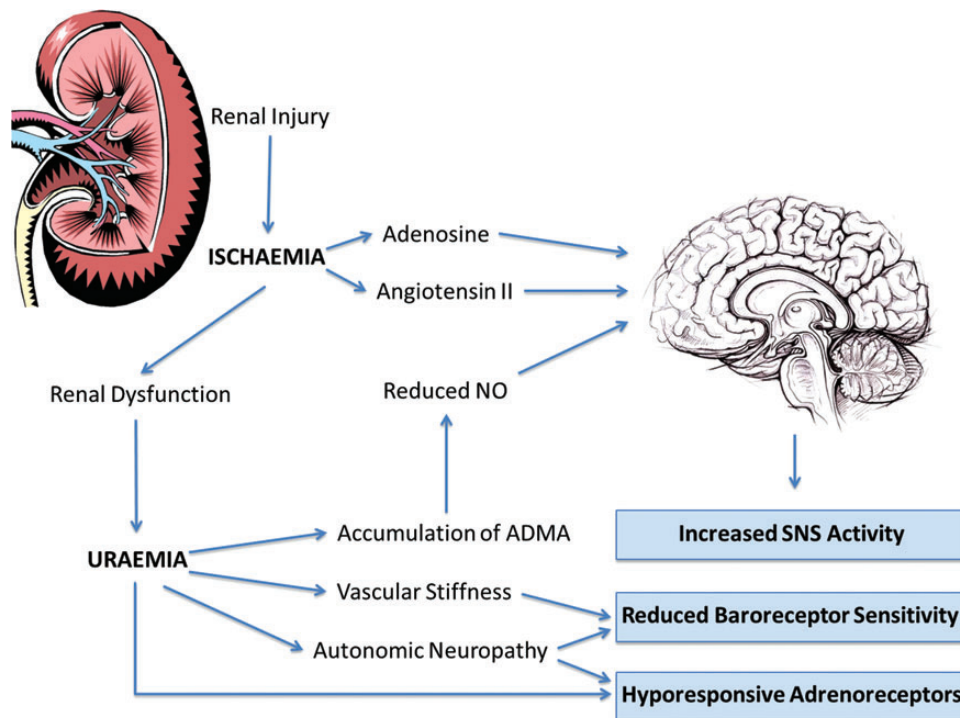


Fig. 2. The pathophysiology of sympathoexcitation in CKD.

resultant down-regulation of adrenoreceptors [40]. A co-existent defect in coupling between the  $\beta$ -adrenoreceptor and the effector enzyme adenylyl cyclase [41] and the reduced density and binding affinity of alpha receptors [40, 42] has also been demonstrated. Baroreceptor and adrenoreceptor dysfunction leaves patients with an impaired ability to react to changes in blood pressure, particularly an acute hypotensive episode, despite their elevated sympathetic tone. This is particularly relevant to the response to ultrafiltration for the haemodialysis population [43, 44].

uraemia cannot solely be blamed for the sympathetic hyperactivity in ESKD patients, as activity is similarly increased in patients who have undergone renal transplantation [45]. Accumulation of asymmetric dimethyl-L-arginine with inhibition of endothelial nitric oxide synthase and hence less nitric oxide production is therefore postulated as a contributory risk factor [46]. Neuronal nitric oxide is a major component of the signal transduction pathway involved in the tonic restraint of central sympathetic outflow [47].

### Clinical significance

The relationship between sympathetic nerve activity and CKD is not unidirectional; it is one of cyclical cause and effect. Sympathetic nerve activity is inversely correlated with estimated glomerular filtration rate (eGFR), implicating it as a causal agent in the progressive decline in kidney function seen in hypertensive CKD patients [2]. Furthermore, sympatholytic drug treatment attenuates albumin excretion in rats [10] and in patients with diabetic nephropathy [48]. Sympatholytic treatment has also been shown to prevent glomerulosclerosis in experimental hypertension [49]. Finally, selective renal sympathetic denervation improves experimental renal failure progression [5, 50], an effect that is partially blood pressure independent [50]. These results would seem to indicate that sympathetic hyperactivity is at least partially causal for the progression of CKD.

Pathological changes in sympathetic nervous activity also contribute to the higher incidence of sudden cardiac death in CKD and ESKD patients. Heart-rate variability (a marker of autonomic dysfunction) predicts ESKD- and CKD-related hospitalization [51] as well as haemodialysis patient mortality [52]. Plasma norepinephrine predicts survival and incident cardiovascular events in patients with ESKD [53]. Finally, MSNA associates with the composite of all-cause mortality and nonfatal cardiovascular events in CKD patients [3]. The mechanism for this relationship may well relate in part to left ventricular hypertrophy (LVH) and arrhythmogenesis [54]. LVH is an important, independent determinant of survival in patients receiving therapy for ESKD [55]. Sympathetic activity in CKD [56] and ESKD [57] patients correlates with left ventricular mass despite anti-hypertensive treatment. Endovascular renal denervation appears to reduce left ventricular mass and improves systolic and diastolic function [58], although this is based on a retrospective analysis using echocardiography and there have been no studies with these outcomes in a CKD or ESKD population to date.

### Endovascular renal denervation in CKD

Overall, there are scant data concerning endovascular renal denervation in the CKD and dialysis populations.

Hering *et al* [59] performed bilateral renal denervation in 15 patients with resistant hypertension and CKD Stage 3–4. The mean reduction in office blood pressure was 33/19 mmHg at 12 months, night-time ambulatory blood pressure significantly decreased restoring a more physiological dipping profile and no deterioration in renal function was observed.

Kiuchi *et al.* [6] recently performed denervation on 24 patients with resistant hypertension and CKD Stages 2–4. They observed a marked reduction in office blood pressure at 6 months (51/20 mmHg). Ambulatory blood pressure also fell substantially (19/7 mmHg), and there was an improvement seen in both microalbuminuria and glomerular filtration rate. This is in keeping with pre-clinical studies where renal denervation has been shown to prevent glomerular hyperfiltration [9] and halt progression of renal disease [5]. Further prospective data should be sought in humans to corroborate these potentially important findings.

Similar procedures have been undertaken in ESKD patients. Although somewhat more technically challenging due to the smaller renal arteries induced by atrophic kidneys, procedures have been on the whole successful, efficacious and safe [60–62]. One case even had an observed blood pressure reduction of 76/51 mmHg at 3 months without report of systemic side effects [62]. The most substantial dataset thus far comes from Schlaich *et al.* [63] who recently reported a case series of 12 ESKD patients, 9 of whom were successfully denervated (three failed due to atrophic renal arteries). They reported a significant reduction in office systolic blood pressure, although diastolic and ambulatory blood pressures were unchanged. Two of five patients had sympathetic nerve activity repeated post denervation, both demonstrated normalization of hyperactivity. Clearly, there is a scope for further investigation in this population, especially if axial imaging or a renal angiogram can be obtained prior to the procedure [63].

Outside the benefits of improved blood pressure control and the potential effects on left ventricular mass and function, it appears that renal denervation may also improve central arterial stiffness [64], central haemodynamics [64], baroreflex sensitivity [65] and arrhythmia frequency [66, 67]. The rate of death from cardiovascular disease in younger patients on dialysis is 180 times greater than that for people in the general population of the same age, but the rate of cardiac arrest (or 'sudden cardiac death') is thousands of times greater [68]. Most of these events are believed to be due to ventricular arrhythmias [69]. By reducing such terminal events, renal denervation has great promise in reducing the incidence of sudden cardiac death in dialysis patients.

### Endovascular renal denervation: further clinical relevance

Renal denervation has been demonstrated to disrupt afferent nerve signalling [7, 8]. As well as the anti-hypertensive benefits this affords, afferent disruption has also been demonstrated to be advantageous for renal pain control. Autosomal dominant polycystic kidney disease (APCKD) can be characterised by chronic and often severe abdominal, flank, or back pain. The enlarged cystic kidneys cause stretching of the capsule or traction on the renal pedicle, stimulating nociceptive afferent A $\delta$  and C fibres [70]. A recent case study has been presented where a woman with APCKD underwent renal denervation



for resistant hypertension [70]. As well as a substantial decrease in blood pressure (office BP reduction of 44/34 at three months), she had incidental but immediate resolution of five-year chronic flank pain. A further case report demonstrated the analgesic potential of the procedure in haematuria loin pain syndrome [71], this time applied electively and unilaterally. Confirmation of these findings in prospective studies is needed.

It is not just patients with renal disease that may benefit from denervation. Sleep-disordered breathing, a common comorbidity in dialysis patients [72], correlates with blood pressure and cardiovascular disease prevalence [73]. Obstructive sleep apnoea is also characterized by increased sympathetic activity [74] which is thought in part to be responsible for the pathophysiology. Ten patients with resistant hypertension and mild obstructive sleep apnoea underwent percutaneous catheter-based renal denervation. Six months later, 8 out of the 10 patients showed a reduction in apnoea-hypopnoea index (AHI) from 16.3 to 4.5 events per hour [75]. This was accompanied by significant decreases in blood pressure, plasma glucose concentration and HbA1c. The speculated mechanism for this change in AHI is an inhibition of the sympathetic nerve-mediated renal tubular sodium reabsorption throughout the nephron. As less fluid is reabsorbed, less fluid shifts from the legs to the neck with overnight recumbency and less apnoeic episodes result [76].

Changes in plasma glucose and HbA1c have been common findings post-denervation [77]. The significance of CKD in diabetes mellitus is well established [78, 79]. The specific effects of renal denervation on glucose metabolism have been studied by Mahfoud *et al.* in 37 patients [80]. At both 3 and 6 months, patients exhibited significant decreases in systolic and diastolic blood pressure and fasting concentrations of glucose, insulin and c-peptide. The homeostasis model assessment-insulin resistance (HOMA) index was also significantly decreased. Insulin resistance links hand-in-hand with sympathetic hyperactivity; insulin resistance activates the sympathetic nervous system with the resultant overactivity inducing insulin resistance via regional haemodynamic and possibly more direct cellular effects [81]. Although there is a demonstrably bidirectional experimental relationship, observational data suggest that sympathetic activation may in fact be the initial trigger [82]. Despite these encouraging data, it must be noted that Mahfoud's study was a retrospective analysis of Symplicity HTN-2 patients. Prospective data employing techniques such as the hyperinsulinaemic-euglycaemic clamp are needed before firm conclusions can be drawn in this area.

Mahfoud's group [83] has also reported reductions in blood pressure, renal resistive index and urinary albumin excretion following denervation, again without deleterious effects on the glomerular filtration rate. Their study was run in parallel to the Symplicity trials so studied a resistant hypertensive population with normal (eGFR  $\geq$  45) renal function. As such, an extrapolation of data is needed but as markers of glomerular hyperfiltration, clear relevance to the CKD and particularly the diabetic nephropathy population is apparent.

### Endovascular renal denervation: unanswered questions

Endovascular renal denervation is a rapidly moving field of research. Technological advances have already yielded

device progression. Multi-electrode baskets have been designed to reduce procedural time and increase procedural efficacy [84]. Radiofrequency ablation is also not the only option now; chemical denervation [85] and intravascular ultrasound [86] have been developed as alternative techniques. It is thought that over 50 different companies are developing competing systems. A search of the ClinicalTrials.gov website revealed 96 registered studies for 'renal denervation' at the time of writing.

The US Food and Drug Administration asserts that there are several issues that need to be addressed before denervation can be considered outside a research environment. Despite these concerns, some have been keen to extol the wider application of the technique as first-line therapy in essential hypertension [87] and make somewhat aspirational conclusions about cost-effectiveness [88]. It is interesting to note that of the estimated 5000 patients who have undergone renal denervation, only 250 were treated as part of clinical trials [89]. We would remind readers of the analogy with renal angioplasty to treat hypertension in the setting of renal artery stenosis, which now has very few clinical indications [90].

The chief concern amongst all other concerns is that the long-term safety of the procedure is unproven. Registry data have been presented for only 34 patients up to 3-year post-denervation [91]. A reassuring (albeit manufacturer-funded) global registry exists for over 1100 patients up to 12 months [92], although substantial data past this point are lacking. Case reports have demonstrated that late renal artery stenosis can occur [93], although with what frequency is yet to be established. Advanced imaging techniques also suggest that the sparse pre-clinical studies do not tell the complete picture regarding the effects of ablation on the renal arteries. Demonstrable intimal damage with intraluminal thrombosis has been seen via optical coherence tomography post-procedure [94]. Dual anti-platelet therapy for 3-6 months has consequently been proposed [94] with the risk of resultant renal ischaemia and microembolism unknown.

The efficacy of renal denervation is also unproven. True sham-procedure controls are yet to be utilized and little effort was made in the Symplicity trials to ensure medication concordance prior to or during the study period [95]. Both of these call into question the validity of the blood pressure drops observed. In addition to this, most studies of renal denervation have used office blood pressure as an outcome measure. In contrast, ambulatory blood pressure removes observer bias and measurement error, minimizes the white coat effect, and has greater reproducibility [95]. Moreover, in a cohort of 109 treatment-resistant hypertensive patients followed up for 4.8 years, higher ambulatory blood pressure values predicted cardiovascular morbidity and mortality, whereas office blood pressure had no prognostic value [96].

The effect of possible sympathetic reinnervation remains unclear. Studies of renal transplantation suggest that axonal regeneration of sympathetic nerves occurs as early as the fourth week post-surgical denervation [97], although the precise functional significance of this regrowth is less clear [98]. Most data suggest that endovascular denervation remains efficacious over the medium term [91], although it has been reported that treatment failure occurring at 12 months was responsive to repeat denervation [99]. This suggests that functional reinnervation may have occurred.

The results of Symplicity-HTN 3 are awaited with interest [100]. This trial of 530 patients in 27 locations involves a sham procedure and should offer some more clarity

regarding procedural efficacy and safety. Frustratingly, investigator blinding remains an issue with the trial design; masking randomization to patients will be difficult and planned follow-up remains short at only 6 months.

## Summary

Endovascular renal denervation offers a new and exciting therapeutic approach to resistant hypertension. It may also yield the benefit as a tolerable sympatholytic and confer an advantage over and above its blood pressure-lowering effect. Sympathetic hyperactivity is linked to both CKD progression and associated cardiovascular comorbidity. Further well-designed trials in the CKD population should focus on this therapeutic avenue, as well as considering any impact on blood pressure control.

*Conflict of interest statement.* None declared.

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