

## Review Article

# Cardiorenal Protective Effects of Renal Denervation in Chronic Kidney Disease

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### Abstract

Hypertension and cardiovascular disease contribute to increased morbidity and mortality in patients with chronic kidney disease (CKD). As an interventional antihypertensive treatment, renal denervation appears to offer benefits beyond a simple blood pressure reduction. This review article will discuss the available experimental and clinical evidence on the application of renal denervation in CKD. Specifically, experimental studies suggest that renal denervation could reduce blood pressure in some but not all forms of CKD and that there is a differential contribution of the renal afferent nerves to high blood pressure in different conditions. A few clinical studies have documented a blood pressure reduction following renal denervation in CKD patients, but none of these studies are randomized, sham-controlled trials, potentially undermining the strength of this evidence. Experimental and clinical studies show that renal denervation is not only safe for CKD patients, but may offer renoprotective effects, such as attenuation in proteinuria, glomerular, and tubular-interstitial damage and slowing down decline in kidney function, but these benefits again await further substantiation in controlled trials. There is also preliminary evidence suggesting renal denervation might improve cardiac hypertrophy and autonomic function as assessed by heart rate variability, systolic blood pressure variability, and baroreflex sensitivity, in both animal models and patients with CKD. Despite therefore significant progress in the application and understanding of the mechanisms underlying renal denervation as a therapeutic procedure, ongoing work is required to confirm whether or not proposed cardiorenal benefits are associated with a reduction in the comorbidity of cardiovascular disease in CKD populations.

**Key words:** Blood pressure, cardiovascular disease, chronic kidney disease, kidney function, renal denervation

### Introduction

Chronic kidney disease (CKD) is a well-recognized public health problem, prevalent in approximately 10–15% of the general population worldwide.<sup>[1]</sup> Notwithstanding the risk of progression to end-stage renal failure (ESRD), CKD also brings with it an increased risk of cardiac and cerebrovascular disease due in part to the high incidence of hypertension in CKD. Indeed cardiovascular death is the most common cause of mortality in CKD patients<sup>[1]</sup> Resistant hypertension is a key feature in CKD patients<sup>[2]</sup> and is thought to be driven by multiple and interrelated factors. Evidence from experimental models suggests that the autonomic nervous system plays an important role in the development of hypertension and cardiovascular complications associated with CKD, with

evidence for both increased sympathetic efferent drive to the kidney<sup>[3]</sup> and increased afferent signaling from the kidney to the central nervous system<sup>[4]</sup> [Figure 1].

Catheter-based renal denervation is emerging as a potential antihypertensive strategy for resistant hypertension. The underlying rationale is based on a number of concepts arising from clinical and experimental studies:

1. Non-selective surgical sympathectomy, a procedure that removes the thoracic and lumbar ganglia, markedly reduced hypertension when it was in use prior to the advent of effective antihypertensive drugs,<sup>[5]</sup> and though it was not without adverse effects, for example, profound hypotension, supported the premise that hypertension is associated with sympathetic overactivity.

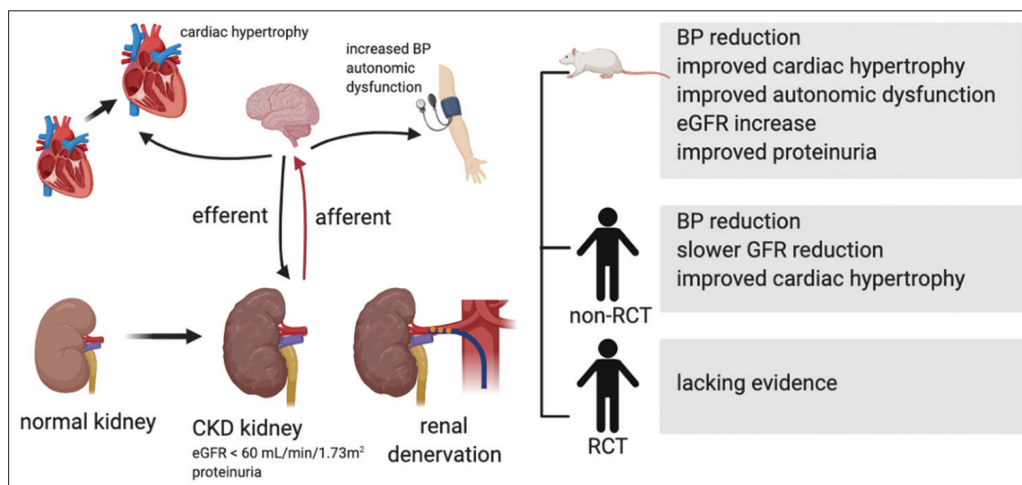
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Received 09-05-2020; Accepted 02-07-2020

doi: 10.15713/ins.john.0200





**Figure 1:** Summary figure illustrating CKD association with increased renal afferent (sensory) and efferent (sympathetic) nerve activity, their proposed contributions to the complications of CKD, and the available experimental and clinical evidence of the benefits of renal denervation. CKD, chronic kidney disease; BP, blood pressure; eGFR, estimated glomerular filtration rate; RCT, randomized clinical trial. Figure created with BioRender.com

- Chemical renal denervation can prevent the development, delay onset or attenuate the degree of hypertension in experimental animal models of hypertension,<sup>[3,6]</sup> and renal sympathetic activity, as determined by renal noradrenaline spillover, is elevated in patients with essential hypertension compared with normotensive controls,<sup>[7]</sup> with these two points collectively supporting increased sympathetic drive to the kidney as a key driver of hypertension.
- The renal nerve bundle, which consists of both renal afferent sensory and efferent sympathetic nerves, is readily accessible to radiofrequency energy emitted through a catheter in the renal artery lumen making a surgical approach feasible on a wide scale.<sup>[8]</sup>
- The technical development of interventional angioplasty for treatment of conditions such as acute myocardial infarction facilitated the development of devices suitable for renal denervation.<sup>[9]</sup>

Under these circumstances, the first-generation radiofrequency-generating catheter, which could be advanced into the renal artery to ablate renal nerves, was developed by Ardian and later put in a clinical trial under the executive of Medtronic.<sup>[8]</sup> Subsequent proof-of-concept studies demonstrated that renal denervation may have beneficial effects that reach beyond a simple reduction in blood pressure and for patients with CKD could have significant clinical impact providing both cardiovascular and renoprotective effects.<sup>[10,11]</sup> Of note is that in CKD patients, evidence of sympathetic overactivity alongside increased afferent signaling derived from the native injured kidneys<sup>[12]</sup> would suggest they are ideal candidates for the procedure. This review will summarize the current evidence for the potential cardiorenal protective effects of renal denervation in CKD [Figure 1].

## Effect of Renal Denervation on Blood Pressure

### Evidence from animal models

Renal denervation has been used in a variety of animal models of hypertension as an experimental approach to reduce blood pressure, with stripping of the renal nerves and periaxonal application of phenol to the renal artery, which removes both renal afferents and efferents, being shown to reduce blood pressure in models of two-kidney-one clip hypertension,<sup>[13]</sup> 5/6 renal ablation,<sup>[14]</sup> and polycystic kidney disease.<sup>[3]</sup> More recently, catheter-based renal denervation has been shown to reduce blood pressure in the fetal uninephrectomized sheep CKD model.<sup>[15]</sup> While there are studies in certain animal models where renal denervation has not had an impact on blood pressure, for instance, in the Ang II-salt model and deoxycorticosterone acetate (DOCA)-salt model induced with lower than typical doses of Ang II or DOCA, respectively,<sup>[16]</sup> these studies, and specifically their application to models of CKD, provide a strong foundation for the use of renal denervation in CKD patients.

In the clinical setting, however, it remains unclear whether the effect is mediated by removal of sympathetic nerves or sensory nerves or a combination of both. This applies equally to the use of renal denervation to treat hypertension arising from other causes. To answer this question, researchers have sought to selectively ablate the renal afferent sensory nerves by either dorsal rhizotomy<sup>[6]</sup> or periaxonal application of capsaicin.<sup>[4]</sup> Available evidence suggests that afferent renal denervation can attenuate hypertension in the 5/6 renal ablation model of CKD<sup>[6,12]</sup> and in the subtotal nephrectomized spontaneous hypertensive rat (SHR).<sup>[17]</sup> Sensory denervation of the kidney has also been shown to reduce blood pressure in the DOCA salt model,<sup>[4]</sup> but notably, not in the AngII-induced hypertension

model.<sup>[16]</sup> These results suggest two things: Firstly, that the renal afferents may make a differential contribution to hypertension in different disease states and importantly, not all forms of CKD may be responsive to renal denervation.

### Evidence from the clinic

The initial clinical trials undertaken to determine the efficacy and safety of catheter-based renal denervation in patients focused on patients with essential hypertension, excluding patients with moderate to severe CKD.<sup>[18]</sup> Following the initial promising results, a pilot study examining 15 patients with moderate to severe CKD found that renal denervation caused a marked blood pressure reduction at 1, 3, 6, and 12 months of follow-up without deterioration of renal function.<sup>[19]</sup> Subsequent single-center and multi-center prospective studies have shown a similar blood pressure lowering effect of renal denervation in CKD patients.<sup>[20,21]</sup> Moreover, a significant blood pressure reduction within 6 months of follow-up after denervation was also observed in ESRD patients.<sup>[22]</sup> Of note, however, is that a lack of central or 24-h ambulatory blood pressure reduction following renal denervation in CKD and/or ESRD patients has also been reported.<sup>[23]</sup> Importantly, none of these clinical studies were randomized sham-controlled trials, potentially undermining the strength of evidence. As such, whether or not renal denervation can truly produce a meaningful and sustainable blood pressure lowering effect in CKD cohorts needs further investigation.

### Renoprotective Effect of Renal Denervation

In addition to a blood pressure lowering effect, beneficial effects of renal denervation on kidney damage in CKD have been reported. In the 5/6 renal ablation model, both total and afferent renal denervation are reported to increase glomerular filtration rate (GFR), lower proteinuria, and ameliorate the development of glomerular and tubular-interstitial damage.<sup>[24]</sup> Similar findings are described in the uninephrectomized Dahl-salt sensitive model.<sup>[25]</sup> Interestingly, the attenuation of renal damage paralleled a reduction in blood pressure in the 5/6 renal ablation but not uninephrectomized Dahl-salt sensitive model of CKD, suggesting that renal denervation can provide renal protection independent of any effect on blood pressure.

In humans, observational studies suggest that renal denervation can slow or even halt the decline rate of estimated GFR (eGFR) in patients with CKD.<sup>[11,20]</sup> For instance, in a study consisting of 46 CKD patients, eGFR showed an annual decline of 3.5 mL/min/1.73m<sup>2</sup> for the 60 months before renal denervation but was stable during the 24 months after renal denervation.<sup>[11]</sup> The most recent study examining the impact of renal denervation on long-term renal function, published as part of the Global SYMPLICITY Registry, showed that over a 3 year period, there were no statistically significant differences in the decline in renal function between patients with and without chronic kidney disease.<sup>[21]</sup> Although these studies show promising benefits and indicate that there are no long-

term safety concerns associated with renal function after renal denervation, further large-scale multicenter randomized clinical trials are warranted to substantiate the observed renoprotective effects.

### Cardioprotective Effect of Renal Denervation

Cardiovascular disease is the leading cause of morbidity and mortality in CKD patients, and patients present with cardiac hypertrophy and fibrosis, arrhythmias<sup>[26]</sup> and abnormalities in autonomic function, namely sympathetic overdrive, parasympathetic insufficiency, and reduced baroreflex sensitivity (BRS).<sup>[27]</sup> Data available from both experimental and clinical studies suggest that renal denervation has cardioprotective effects and that this is also evident in CKD studies [Figure 1].

Improvements in cardiac hypertrophy and fibrosis have been reported after renal denervation in the SHR model<sup>[28]</sup> and in the fetal uninephrectomized sheep CKD model.<sup>[15]</sup> Renal denervation, however, failed to prevent the development of cardiac hypertrophy in the DOCA salt hypertension model.<sup>[29]</sup> In clinical studies, the beneficial effect of renal denervation on cardiac hypertrophy and fibrosis, reflected by reduced left ventricle mass, increased ventricular ejection fraction or decreased collagen turnover, have also been reported in patients with resistant hypertension<sup>[30,31]</sup> and importantly, those with CKD.<sup>[10]</sup> Similar to the renoprotective effects, the observed cardioprotective effects are associated with a lowering in blood pressure in some patients<sup>[30]</sup> but independent of such effect in others.<sup>[31]</sup>

Heart rate variability (HRV), systolic blood pressure variability (SBPV), and BRS have been measured in both experimental and clinical studies as indirect measures of autonomic activity and yielded inconclusive findings. In patients with resistant hypertension, an increase in all frequency components of HRV and reduction in low/high frequency ratio at 1 and 6 months post-denervation were present, suggesting a restoration of cardiac sympathovagal balance.<sup>[32]</sup> However, a lack of impact on HRV has also been reported in patients with resistant hypertension.<sup>[33]</sup> With regard to SBPV, reduced LF SBPV has been described after renal denervation in the SHR, indicating a reduced sympathetic control of blood pressure.<sup>[34]</sup> In human studies, the impact of renal denervation on cardiac sympathetic activity has been assessed through the uptake and washout of I<sup>123</sup> metaiodobenzylguanidine (MIBG), which is actively transported into sympathetic nerve terminals by the noradrenaline transporter. Using this method, Donazzan *et al.*<sup>[35]</sup> showed reduced cardiac sympathetic nerve activity 9 months after renal denervation in resistant hypertension patients. In contrast, van Brussel *et al.*<sup>[36]</sup> showed no impact on the cardiac sympathetic activity was observed at 6 weeks post-denervation using the same measure. The discrepancy between these studies could be caused by variable factors including the efficacy of the denervation procedure, differing baseline cardiac sympathetic tone and small sample size. To the best of our knowledge, there

have been no clinical studies examining the impact of renal denervation on these parameters in CKD patients.

A variable impact of renal denervation on baroreflex control has similarly been reported in animal models of hypertension and CKD. Renal denervation did not cause any significant changes in heart rate baroreflex curve parameters assessed by infusion of phenylephrine and sodium nitroprusside compared with sham controls in a sheep heart failure model,<sup>[37]</sup> while renal denervation of the clipped kidney in two-kidney-one-clip rats improved the arterial BRS upon infusion of sodium nitroprusside 10 days post the procedure.<sup>[13]</sup> Renal denervation did not improve impaired heart rate BRS, but did improve impaired renal sympathetic nerve activity BRS in a cisplatin-induced acute renal injury model rat 1-week post-denervation.<sup>[38]</sup> An improved heart rate and lumbar sympathetic nerve activity BRS were also reported in SHR 1-week post-denervation.<sup>[39]</sup> In 5/6 nephrectomy rats, total renal denervation partially recovered baroreflex control of heart rate in response to phenylephrine administration 8 weeks post-denervation.<sup>[14]</sup> Using spontaneous BRS as their measure, Hart *et al.*<sup>[39]</sup> showed that total renal denervation caused a significant albeit small increase in cardiac BRS within 24 h of denervation surgery in the SHR. Evidence of the impact of renal denervation on cardiac BRS in humans including CKD patients is sparse. The only evidence is from the work of Hart *et al.*,<sup>[39]</sup> who observed improved spontaneous BRS in patients with resistant hypertension 6 months post-denervation procedure. Interestingly, this improvement in BRS was not associated with a reduction in blood pressure, suggesting that the beneficial effect is independent of changes in blood pressure. Although Grassi *et al.*<sup>[40]</sup> documented an improvement in baroreflex control in muscle sympathetic nerve activity in patients with resistant hypertension at both 3 and 6 months after denervation, this was unrelated to the blood pressure reduction induced by the procedure. Whether the improvement in BRS following renal denervation could reduce the comorbidity of cardiovascular disease in CKD populations awaits future investigation.

## Conclusion

Hypertension and cardiovascular disease contribute to increased morbidity and mortality in CKD and are contributing factors to the progression to ESRD. While observations from clinical practice in hypertensive and CKD patients and a large body of experimental evidence suggests renal denervation could provide cardiorenal protection in CKD, no large scale randomized sham-controlled trials are available that so far to support these findings. Furthermore, the data suggest that not all forms of CKD may be equally responsive to renal denervation and specific cohort studies are required. Given that patients with CKD are at high risk for cardiovascular events, including heart attack, arrhythmia, and stroke, this is an important area of research that warrants close investigation.

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**How to cite this article:** Li S, Hildreth CM, Phillips JK. Cardiorenal Protective Effects of Renal Denervation in Chronic Kidney Disease. *Hypertens* 2020; 6(3): 142-146.

**Source of support:** Hillcrest Foundation Australia, **Conflicts of interest:** None

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