Therapeutic Effects of Renal Denervation on Renal Failure

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Abstract: Sympathetic nerve activity (SNA) is increased in both patients and experimental animals with renal failure. The kidney is a richly innervated organ and has both efferent and afferent nerves. Renal denervation shows protective effects against renal failure in both animals and humans. The underlying mechanisms include a decrease in blood pressure, a decrease in renal efferent SNA, a decrease in central SNA and sympathetic outflow, and downregulation of the renin-angiotensin system. It has been demonstrated that re-innervation occurs within weeks after renal denervation in animals but that no functional re-innervation occurs in humans for over two years after denervation. Renal denervation might not be renal protective in some situations including bile duct ligation-induced renal failure and ischemia/reperfusion-induced acute kidney injury. Catheter-based renal denervation has been applied to patients with both early and end stage renal failure and the published results so far suggest that this procedure is safe and effective at decreasing blood pressure. The effectiveness of renal denervation in improving renal function in patients with renal failure needs to be further investigated.

Keywords: Acute kidney injury, chronic kidney disease, re-innervation, renal denervation, sympathetic nerve activity.

INTRODUCTION

Renal dysfunction represents a significant global health issue associated with a high mortality and morbidity. Renal failure is frequently considered in relation to its onset as acute renal failure [now known as acute kidney injury, AKI [1]] and/or chronic renal failure [now known as chronic kidney disease, CKD [2]]. AKI accounts for 5-7% of hospital admissions [3], and the mortality is about 50-60% [4]. The prevalence of CKD is high in the elderly, affecting ~40% of people over the age of 70 years [2]. Renal failure contributes to significant health care costs, e.g., AKI is estimated to cost more than $10 billion per year in the United States [5]. There are relatively few effective treatment strategies for CKD with end stage disease being managed by dialysis; however maintaining on-going access for both hemodialysis and peritoneal dialysis is highly problematic [3, 4]. Currently available treatments to prevent renal failure progression are limited.

A large amount of evidence suggests that sympathetic nerve activity (SNA) is increased during renal failure [6-15]. SNA is positively correlated with disease severity in the early stages of CKD [10], and SNA is an independent predictor of death and cardiovascular events in patients with advanced CKD [16]. Pharmacological inhibition of SNA has been shown to have renal protective effects in both clinical [11, 17] and preclinical studies [18-21]. One approach to reducing SNA is renal denervation. A large amount of data suggests that renal denervation has beneficial effects during renal failure. This review summarized the preclinical and clinical evidence suggesting that renal denervation has benefits during renal failure.

INCREASED SNA DURING RENAL FAILURE

SNA is increased in patients that have CKD [6, 7, 9, 10, 12-15]. SNA is increased during both the early (mild to moderate degree, belonging to stages 3 and 4 of National Kidney Foundation Classification) [10, 15] and late stages of CKD [6, 7, 9, 14]. In patients with early stages of CKD, muscle SNA is positively associated with the severity of the renal failure as assessed by the decrease in estimated glomerular filtration rate (GFR). Increase in SNA during CKD has also been positively associated with disease outcome. It has been reported that in patients with advanced kidney disease, plasma norepinephrine (NE) is an independent predictor of all-cause mortality and cardiovascular events [10, 16]. Increased SNA has also been demonstrated in different animal models of renal failure such as the 5/6th nephrectomy-induced CKD [22] and lipopolysaccharide (LPS)-induced AKI models [18].

Pharmacological inhibition of SNA has been shown to have protective effects against renal failure in both preclinical and clinical studies. In patients with advanced CKD, the centrally acting imidazoline-I1 receptor agonist moxonidine delays the progression of renal failure as evidenced by a slower decrease in creatinine clearance [11]. Moxonidine can also reduce microalbuminuria in normotensive patients with type I diabetes [21]. β-blocker carvedilol also has beneficial effects in patients with dilated cardiomyopathy and renal failure requiring dialysis [23]. Carvedilol increased 2-year survival, decreased pathological remodelling and improved cardiac function in these patients [23]. In sub-totally nephrectomised rats, imidazoline-I1 receptor agonist moxonidine (1.5 mg/kg body weight/day) [19], α-adrenocceptor blocker phenoxybenzamine (5
Renal Denervation and Renal Failure

Renal afferent nerve activity influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control such as the heart and peripheral blood vessels, predominantly by modulating posterior hypothalamic activity [33, 38]. Abrogation of renal sensory afferent nerves has been demonstrated to reduce both blood pressure (BP) and organ damage caused by experimental renal failure [22].

**KIDNEY DYSFUNCTION INCREASES SNA**

Kidney dysfunction is associated with increased SNA. Muscle SNA is increased in renal transplant patients with good renal graft function [6] and patients on dialysis [7]. Bilateral nephrectomy decreases muscle SNA in these patients [6, 7]. In patients with renovascular hypertension percutaneous renal angioplasty decreases muscle SNA, plasma renin activity and plasma angiotensin II [39]. These results suggest that the diseased kidney plays a role in the increased SNA in humans.

Similar findings have also been observed in research animals. For example, an injury to the kidney produced by intra-renal injection of phenol, causes an immediate and prolonged (at least 4 weeks) rise in BP and NE secretion from the posterior hypothalamus [38, 40]. The increase in renal afferent nerve activity was confirmed by direct nerve activity recording [36]. The immediate and long-term effects of intra-renal injection of phenol on BP and NE secretion can be prevented by renal denervation [36, 38, 40].

Thus, renal afferent signals originating from the diseased kidneys are thought to be a major contributor in activating renal sympathetic outflow [41], which may facilitate the occurrence of the well-known adverse consequence of chronic sympathetic overactivity, such as hypertension [42], left ventricular hypertrophy [43], ventricular arrhythmia and sudden cardiac death. To directly support this notion, it has been reported that in humans bilateral nephrectomy leads to regression of left ventricular hypertrophy in a case report [17] and renal denervation [44] can decrease BP [44-48] and reduce cardiac hypertrophy [44].

Given that (1) SNA is increased in renal failure, (2) kidney afferent nerves regulate sympathetic outflow, and (3) diseased kidneys are a major contributor to the increased SNA, decreasing SNA by denervating the kidney has been suggested to be protective against renal failure. This will be discussed below.

**TECHNICAL ASPECTS OF RENAL DENERVATION USED IN PRE-CLINICAL RESEARCH ON RENAL FAILURE**

By searching the PUBMED database and hand searching of the reference lists of relevant articles we identified 18 studies in which renal denervation was performed in renal failure animal models and was reported to be protective against renal failure [18, 22, 38, 49-62] (Table 1). Among these 18 studies, three performed afferent renal nerve denervation by dorsal rhizotomy [22, 38, 62] and the rest performed both denervation of the afferent and efferent renal nerves. We also identified five articles in which renal denervation was reported to have no effect on [63-65] or further impair renal function [59, 66] (Table 1).
Table 1. Effects of Renal Denervation on Experimental Renal Failure

<table>
<thead>
<tr>
<th>Model</th>
<th>Animals</th>
<th>Renal Denervation</th>
<th>Effect of Renal Denervation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotoxemia 5 mg/kg LPS</td>
<td>C57BL mice</td>
<td>S/C renal nerves; Painting both kidney pedicles with 10% phenol in ethanol</td>
<td>↑ RBF immediately</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↔</td>
<td>NR</td>
</tr>
<tr>
<td>Endotoxemia in the presence of a COX inhibitor</td>
<td>Dogs</td>
<td>Unilateral denervation S/C renal nerves; Painting the pedicle with 95% ethanol</td>
<td>↓ Renal NE</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No electrical stimulation-induced ↓ in RBF</td>
<td>NR</td>
</tr>
<tr>
<td>Endotoxemia in the absence of a COX inhibitor</td>
<td>Dogs</td>
<td>Unilateral denervation S/C renal nerves; Painting the pedicle with 95% ethanol</td>
<td>↓ Renal NE</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No electrical stimulation-induced ↓ in RBF</td>
<td>NR</td>
</tr>
<tr>
<td>Cisplatin-induced AKI</td>
<td>Male SD rats</td>
<td>Unilateral denervation S/C renal nerves; Painting the vessels with 10% phenol in ethanol</td>
<td>↑ RBF</td>
<td>↔</td>
</tr>
<tr>
<td>NOS inhibition 4 w L-NAME</td>
<td>Male SD rats</td>
<td>S/C renal nerves of both kidneys; Painting the vessels with 10% phenol in ethanol</td>
<td>Renal NE content ↓</td>
<td>NR</td>
</tr>
<tr>
<td>NE-induced AKI</td>
<td>SD rats</td>
<td>Painting the renal arteries and veins with 10% phenol in ethanol for 30 min</td>
<td>Urinary sodium excretion ↑</td>
<td>↑</td>
</tr>
<tr>
<td>NE-induced AKI</td>
<td>Male SD rats</td>
<td>S/C renal nerves; Painting the vessels with 10% phenol in ethanol for 30 min</td>
<td>Urinary sodium excretion ↑</td>
<td>NR</td>
</tr>
<tr>
<td>Glycerol-induced AKI</td>
<td>Rats</td>
<td>Unilateral denervation S/C renal nerves; Painting the vessels with 10% phenol in ethanol</td>
<td>NR</td>
<td>↓</td>
</tr>
<tr>
<td>I/R</td>
<td>Male SD rats</td>
<td>S/C left renal nerves; Painting the vessels with 10% phenol in 70% ethanol</td>
<td>NR</td>
<td>↑</td>
</tr>
<tr>
<td>I/R</td>
<td>Male SD rats</td>
<td>Unilateral denervation S/C left renal nerves; Painting the vessels with 10% phenol in ethanol</td>
<td>NR</td>
<td>↑</td>
</tr>
<tr>
<td>I/R</td>
<td>Male Wistar rats</td>
<td>S/C renal nerves; Painting the vessels with 10% phenol in ethanol</td>
<td>NR</td>
<td>↔</td>
</tr>
<tr>
<td>5/6 nephrectomy</td>
<td>Male SD rats</td>
<td>S/C renal nerves; Painting the vessels with 10% phenol in ethanol</td>
<td>Uptake and fraction release of NE from cortical slices ↓</td>
<td>↔</td>
</tr>
<tr>
<td>5/6 nephrectomy</td>
<td>SD rats</td>
<td>S/C renal nerves; Painting the vessels with 10% phenol</td>
<td>NR</td>
<td>↔</td>
</tr>
<tr>
<td>5/6 nephrectomy</td>
<td>Male SD rats</td>
<td>Dorsal rhizotomy of T10 to L2</td>
<td>NR</td>
<td>↓</td>
</tr>
<tr>
<td>5/6 nephrectomy</td>
<td>Male SD rats</td>
<td>Dorsal rhizotomy of T10 to L3</td>
<td>BP and NE secretion from the PH ↓</td>
<td>NR</td>
</tr>
</tbody>
</table>
The technical aspects of dorsal rhizotomy were similar in the three studies identified [22, 38, 62]. Briefly, a dorsal incision was made, and the thoracic and lumbar regions of the vertebral column were exposed by gently pulling the musculature away from the vertebrae in male Sprague Dawley (SD) rats. An opening was made in the dorsal-lateral aspect of the vertebral bodies (T10 to L2 or L3) with a fine bone drill. The dura was opened, and the dorsal roots visualized, pulled with a hook and broken. Then the incision was closed and the animals were recovered for 5-6 weeks. The dorsal rhizotomy were performed at T10-L3 levels because the greatest concentration of afferent fibers from the kidney to the brainstem occurs at these levels [67].

The technical aspects of denervating both afferent and efferent renal nerves were similar in the identified studies. In brief, after the renal arteries and veins were exposed, all visible nerves around the renal arteries were cut and connective tissues passing next to and along the course of the renal arteries and veins were dissected and stripped off the adventitia. Then the renal arteries and veins were painted with a solution of 10% phenol in absolute ethanol. Some variations in this technique were reported. For example, 70% [57] and 95% [38, 63] ethanol were also used to dissolve the phenol in some studies. In one study 95% ethanol instead of phenol solution [49] was painted on the renal artery and vein. Bilateral renal denervation was most often performed. Some studies did involve unilateral renal denervation, e.g. when one kidney were removed [57, 60, 61, 65, 66] or the contralateral kidney was used as an intra-animal control [49].

In addition, other methods of renal denervation have been reported in the literature. For example, periarterial ethanol injection has been used to denervate renal arteries in pigs [68] although the effect of this procedure on renal failure has not yet been tested.

### Table 1. cont....

<table>
<thead>
<tr>
<th>Model</th>
<th>Animals</th>
<th>Renal Denervation Method</th>
<th>Renal Denervation Confirmation</th>
<th>Effect of Renal Denervation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/6 nephrectomy</td>
<td>Male SD rats</td>
<td>Dorsal rhizotomy of T10 to L2</td>
<td>NE concentration and turnover in the PH, the locus ceruleus ↓</td>
<td>↓ NR NR NR NR</td>
<td>[62]</td>
</tr>
<tr>
<td>Bile duct ligation</td>
<td>Male SD rats</td>
<td>S/C renal nerves; Painting with 10% phenol in 95% ethanol</td>
<td>Renal NE content ↓</td>
<td>NR ↔ NR NR NR ↔</td>
<td>[63]</td>
</tr>
<tr>
<td>I/R with ischemia pre conditioning</td>
<td>Male Wistar rats</td>
<td>S/C left renal nerves; Painting with phenol</td>
<td>Renal catecholamine ↓</td>
<td>↓ ↔ NR NR NR</td>
<td>[65]</td>
</tr>
<tr>
<td>I/R</td>
<td>Male Wistar rats</td>
<td>S/C left renal nerves; Painting with 10% phenol in ethanol</td>
<td>NR ↔ ↓ ↓ NR NR</td>
<td>[59]</td>
<td></td>
</tr>
<tr>
<td>I/R</td>
<td>Female NZ white rabbits</td>
<td>S/C left renal nerves; Painting with 10% phenol in ethanol</td>
<td>NR ↓ ↓ NR NR</td>
<td>[66]</td>
<td></td>
</tr>
</tbody>
</table>

AKI: acute renal failure; BP: blood pressure; COX: cyclooxygenase; d: day(s); h: hour(s); GFR: glomerular filtration rate; I/R: ischemia/reperfusion; L-NNAME: L-N^6^-nitroarginine methyl ester; NE: norepinephrine; NR: not reported; NZ: New Zealand; LPS: lipopolysaccharide; PH: posterior hypothalamus; RBF: renal blood flow; ref: reference; S/C: stripping and cutting; SD: Sprague Dawley; w: week(s).

The effectiveness of renal denervation was verified by different methods. Both functional and chemical parameters were used. For example, functionally, RBF [18] and urinary sodium excretion were increased immediately after renal denervation [52-55] and electrical stimulation-induced decrease in RBF was lost [49]. In addition, chemically, NE concentrations in the kidney [49, 51]; NE concentration [62], turnover [62] and secretion [38] from the brain; and uptake and fraction release of NE from cortical slices were decreased [60].

**EFFECTS OF RENAL DENERVATION ON EXPERIMENTAL RENAL FAILURE**

Surgical renal denervation has shown beneficial effects on AKI and CKD in various animal models including endotoxin-., cisplatin-., L-N^6^-nitroarginine methyl ester (L-NNAME)-, NE-, glycerol-, and ischemia reperfusion induced-AKI; and subtotal nephrectomy-induced CKD.

**Endotoxin-Induced AKI**

Administration of LPS induces AKI. It has been shown that 16 h after LPS administration, plasma NE, epinephrine and renin activity were increased; and glomerular filtration, filtration fraction and renal plasma flow were decreased compared with controls [18]. Bilateral renal denervation blocked the LPS-induced changes [18].

Unilateral renal denervation shows beneficial effect on LPS-induced AKI in the presence of cyclooxygenase (COX) inhibitors (indomethacin or meclofenamate), as denervation prevents the decrease in GRF and RBF compared with the contralateral innervated kidney [49]. However, in the absence of the COX inhibitors, renal denervation was no longer beneficial, suggesting that renal nerves play a protective role against renal ischemia and this is counterbalanced by the compensatory vasodilation of prostaglandins [49].
Cisplatin-Induced AKI

Single administration of cisplatin (5 mg/kg, i.p.) induced AKI in rats [50]. In this model, cisplatin impaired renal structure, as assessed by congestion in the renal interstitium, focal degeneration in the renal tubules, focal neutrophil accumulation in most glomeruli and cellular debris within renal tubules. Cisplatin treatment also impaired renal function, as evidenced by a decrease in RBF and an increase in vascular resistance [50]. All these abnormalities induced by cisplatin were attenuated by bilateral renal denervation [50].

L-NAME-Induced AKI

Administration of L-NAME (70 mg/100 mL in drinking water) to rats induces albuminuria, glomerular injury and intraglomerular platelet aggregation [51]. Bilateral renal denervation inhibited L-NAME-induced renal injury [51].

NE-Induced AKI

Infusion of NE (0.75 μg/kg/min for 40 min) into the renal artery of dogs [69] caused reversible AKI. One week after NE-induced AKI hemorrhagic reduction in systolic BP to 90 mm Hg caused marked impairment of autoregulation of RBF and histological evidence of ischemic injury including tubular necrosis and interstitial inflammation and edema [52]. Renal denervation prior to hemorrhage-induced BP reduction improved these parameters [52]. In a rat AKI model induced by intra-renal NE infusion, the RBF autoregulation was lost and the renal vasculature sensitivity to renal nerve stimulation was increased 1 week after AKI induction [53]. Renal denervation restored RBF autoregulation by attenuating NE efflux and renal vasoconstriction [53-55].

Glycerol-Induced AKI

Intramuscular injection of glycerol causes AKI [56]. Left kidney denervation has a protective role in this rat model of AKI, as evidenced by an increase in left kidney urine flow and inulin clearance at both 3 and 24 h after AKI induction [56].

Ischemia/Reperfusion-Induced AKI

Clamping renal arteries leads to ischemia and AKI in animals. For example, clamping the left renal artery for 90 min in a dog caused AKI, as evidenced by a 77% decrease in GFR 18 h after the ischemia procedure [70]. Similarly, clamping the renal arteries for 30-60 min also caused AKI in rats [58, 71, 72] and rabbits [66]. This model mimics the hypotensive AKI in humans. In this model, increased SNA might be involved in the disease progression, as decreasing SNA by β-adrenoceptor antagonist propranolol (1 mg/kg/h, i.v.) was reported to improve renal function, as evidenced by a decrease in serum creatinine and an increase in GFR [66, 72].

Clamping the left renal artery for 45 min followed by 24 h reperfusion caused AKI in rats [57]. Renal denervation attenuated renal dysfunction, as evidenced by an decrease in blood urea nitrogen and creatinine and an increase in creatinine clearance [57]. Renal denervation also decreased histological damage, as evidenced by a decrease in tubular necrosis and proteinaceous casts in the tubuli [57].

In rats with AKI induced by unilateral renal ischemia (due to clamping the left renal artery for 30 min followed by reperfusion) denervation decreased basal renal vascular resistance and increased urine flow rate, absolute and fractional sodium excretion, GFR and basal RBF [58]. Denervation also lowered medullary congestion and inflammation and tubular injury in this AKI model [58]. Bilateral renal denervation before the ischemia/reperfusion induced by occluding both renal arteries for 30 min followed by 60 min reperfusion, attenuated the decrease in GFR and RBF after the ischemia/reperfusion [59].

Subtotal Nephrectomy-Induced CKD

In 5/6th nephrectomy-induced renal failure in rats, renal denervation improved renal function as indicated by a decrease in serum creatinine [60] and albuminuria [61]. Renal denervation also attenuated renal histological damage, as evidenced by a decrease in glomerulosclerosis, tubulointerstitial and vascular damage [61].

5/6th nephrectomy-induced renal failure also resulted in cardiac abnormalities. For example, myocardial capillary supply was decreased [60]. Renal denervation completely prevented this decrease by preventing nephrectomy-induced down-regulation of cardiac VEGF mRNA expression [60]. In addition, renal denervation decreased the activation of cardiac interstitial and endothelial cells as evidenced by a decrease in proliferating cell nuclear antigen (PCNA)-positive cells in the myocardium [60].

Afferent renal nerves play an important role in the renal failure induced by 5/6th nephrectomy, as blocking renal afferent nerves by dorsal rhizotomy prevented the increase in (1) BP [22, 38]; (2) NE turnover rate in the posterior and lateral hypothalamic nuclei and in the locus ceruleus [62]; (3) NE secretion from the posterior hypothalamus [38]; and (4) the progression of renal disease as evidenced by a decrease in both serum creatinine and the severity of the glomerulosclerosis [22].

**EFFECTS OF CATHETER-BASED RENAL DENERVATION IN PATIENTS WITH RENAL FAILURE**

Recently, catheter-based renal denervation was introduced to control BP in treatment-resistant hypertensive patients. This approach is providing a good opportunity to assess the effectiveness of renal denervation on CKD [73-76].

**Procedure of Catheter-Based Renal Denervation**

A recent safety and proof-of-concept study for the first time applied a catheter-based technique to selectively denervate the kidneys in 45 patients with treatment-resistant hypertension [45]. Renal denervation was achieved percutaneously via the lumen of the renal artery using a catheter connected to a radiofrequency generator. After the catheter (Symplicity™, Aridian, Inc.) was introduced, four to six discrete radiofrequency ablations were applied both longitudinally and rotationally within each renal artery. During ablation, catheter tip temperature and impedance were constantly monitored during ablation and radiofrequency energy delivery was regulated according to a predetermined algorithm.
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The median duration of the procedure (from initiation to completion of radiofrequency delivery) was 38 minutes [45, 47]. Short term (14-30 days) [45] and longer term (up to 2 years after the procedure) [47] follow-up revealed no instances of renal artery aneurysm, stenosis or other major long term adverse events. The ablation procedure was typically accompanied by diffuse visceral non-radiating abdominal pain which did not persist beyond the radiofrequency energy application, and was managed by narcotics and sedatives treatment [45, 47]. These results suggested that this catheter-based renal denervation procedure had a reasonable vascular and renal safety profile.

The OneShot™ renal artery denervation system (Covidien) has been developed. This system has been shown to be effective in decreasing BP in a hypertensive patient and has a safe profile over a six-month follow-up period [77]. The major components of this OneShot™ system are the irrigated radiofrequency balloon catheter and a radiofrequency generator with an integrated pump. A monopolar silver electrode is mounted on the non-compliant balloon in a helical configuration ensuring delivery of radiofrequency in a spiral pattern using a single two-minute radiofrequency ablation without the need to manipulate the catheter. As the operator does not have to redirect the ablation catheter for multiple point-by-point ablations, delivery of radiofrequency is expected to be more predictable and consistent [77].

Catheter-Based Renal Denervation Decreases BP

Some non-randomized clinical trials have suggested that renal denervation resulted in a significant and sustained reduction in both systolic and diastolic office BP [44,47, 78]. It has been shown that renal denervation decreased BP for at least 24-months with a mean decrease of 20/10, 24/11, 25/11, 23/11, 26/14 and 32/14 mm Hg at 1, 3, 6, 12, 18 and 24 months, respectively [45, 47].

A randomized controlled clinical trial including a total of 106 patients with treatment-resistant hypertension (n=52 renal nerve ablation treatment and n=54 controls who were on conventional drug treatment) showed that renal denervation decreased seated office BP by 33/11 mm Hg (p<0.001 for both systolic and diastolic BP) [46]. Home BP recordings confirmed the observed office BP changes with a reduction in home BP by 22/12 mm Hg in the renal denervation group (p<0.001). BP control defined as systolic BP<140 mm Hg was achieved in 39% of the patients in the denervated group and in 3% of patients in control group. However, it is also important to note that there was substantial variability in regards to the BP effects and that the procedure fails to reduce BP in ~10% of treated patients. Whether this may be related to age of the patients, duration of hypertension, established target organ damage, the number of ablation treatment or other factors is currently unclear.

Effects of Catheter-Based Renal Denervation on Renal Failure and Renal Failure-Related Conditions

Renal denervation reduced mean NE spill over by 47% (95% CI 28-65%) 1 month after bilateral denervation [45]. It also decreased renin secretion and increased RBF [44]. This was confirmed by a study in which a hypertensive patient underwent renal denervation [44], as renal denervation increased renal plasma flow from 719 to 1126 ml/min. These results suggest successful denervation of efferent renal nerves. Renal denervation also decreased muscle SNA as assessed by peroneal nerve microneurography [44], suggesting the successful denervation of afferent renal nerves.

It has been shown that renal denervation improved GFR in 24% of patients that have treatment-resistant hypertension [45]. These findings suggest a protective effect of renal denervation on renal function. Two very recent studies carried out renal denervation in treatment-resistant hypertensive patients with end stage renal disease [73, 74]. In these studies renal denervation decreased BP by 38/30 mm Hg after 6 months [73] and 25/15 mm Hg after 1 months; and no adverse events occurred during the procedure or in the 6 months following the procedure. These studies suggest that catheter-based renal denervation is a safe and effective BP treatment in treating treatment-resistant hypertensive patients with end stage renal failure. Larger prospective studies are underway examining the safety and benefits in a larger cohort of patients with end stage renal disease [73]. Another recent study applied catheter-based renal denervation in 15 patients with moderate to severe (stages 3-4) CKD and showed a safe profile and effectiveness in decreasing BP [75]. The renal function (estimated GFR) remained unchanged after the procedure. However, this study had no control group and thus the beneficial effect of renal denervation in protecting renal failure progress needs to be further investigated. The effect of renal denervation on renal function should be included in future randomized clinical trials. To reduce the potential renal damage induced by contrast medium during the denervation procedure, a computed tomography scan-generated three-dimensional image-guided ablation procedure has been recently reported [76].

Renal denervation is reported to have beneficial effect on heart dysfunction and diabetes which are commonly associated with renal failure [48]. Renal denervation increased the cardiac baroreflex (from 7.8 to 11.7 msec/mm Hg) and reduced the LV mass (from 184 to 169 g, or from 78.8 to 73.1 g/m²) at 12 months [44]. In addition, renal denervation in patients with treatment-resistant hypertension has been reported to improve glucose metabolism and insulin sensitivity [48].

These results suggest that the benefits of renal denervation may protect against renal failure and renal failure-associated cardiovascular complications. However, the effectiveness of renal denervation in improving renal function in CKD patients will become clearer in future studies.

POSSIBLE MECHANISMS UNDERLYING THE BENEFICIAL EFFECT OF RENAL DENERVATION ON RENAL FUNCTION

Possible mechanisms underlying the beneficial effect of renal denervation on renal function include a decrease in (1) BP, (2) renal efferent SNA, (3) central SNA and sympathetic outflow and (4) the renin-angiotensin system (Figs. 1 and 2).
Fig. (1). The suggested mechanisms by which renal denervation has putative benefits on renal function. Denervation of efferent renal nerves leads to a decrease in NE content, reduction of salt and water retention and an increase in GFR and RBF. Denervation of afferent renal nerves leads to a decrease in brain SNA, and consequent decrease in sympathetic outflow to the kidney, heart and blood vessel. Thus, denervation of afferent renal nerve results in amelioration of renal failure-induced cardiac hypertrophy and renal damage. In addition, denervation of afferent renal nerves improves glycemic control. Both afferent and efferent renal denervation contributes to the decrease in BP and thus decreases hypertension-induced organ damage. Renal denervation also decreases the RAS, including downregulating renin synthesis and release, ACE activity and expression of AT1R. ACE: angiotensin-converting enzyme; AT1R: angiotensin II type 1 receptor; BP: blood pressure; GFR: glomerular filtration rate; NE: norepinephrine; RAS: renin-angiotensin system; RBF: renal blood flow.

Fig. (2). The possible molecular pathways underlying the beneficial effect of renal denervation. Enhanced SNA increases NE synthesis and release, which can lead to an increase in plasma renin activity. The increased renin activity promotes the conversion of angiotensinogen to angiotensin I which is further metabolized to angiotensin II by ACE. The increase in angiotensin II leads to an increase in aldosterone, consequently an increase in both water preservation and sodium retention. On the other hand, increase in NE and angiotensin II can constrict blood vessels. All of those changes may result in renal dysfunction. Denervating efferent nerves inhibits SNA; and denervating afferent renal nerve can also inhibit SNA via inhibition of sympathetic outflow. ACE: angiotensin-converting enzyme; NE: norepinephrine; SNA: sympathetic nerve activity.
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A Decrease in BP

Denervation of both efferent and afferent nerves leads to a decrease in BP. Denervation of renal efferent nerves relaxes blood vessels, reduces salt retention, restores the normal pressure-natriuresis relationship, all of which lead to a decrease in BP. Denervating efferent sympathetic nerves can decrease central sympathetic outflow and thus leads to a decrease in sympathetic drive to blood vessel, heart and kidney, which can lead to a decrease in BP.

Hypertension plays a key role in the progression of renal failure [79]. Elevated BP is a major determinant of decline in renal function [80] and BP lowering has renal protective effects [80]. Thus, renal denervation may provide beneficial effect on renal function via, at least in part, decreasing BP [73-76].

It is also clear that SNA inhibition can also protect against renal damage independent of changes in BP in preclinical studies [19-21, 81]. One clinical study has suggested that the decline in renal function observed 24 months after renal denervation is less than the predicted rate based on the BP response achieved [47]. Therefore other factors, in addition to lowering BP, likely mediate the beneficial effects of renal denervation on the renal failure.

A Decrease in Renal Efferent SNA

Renal efferent SNA is increased in renal failure. The increased NE in the kidney resulting from the increased SNA might promote renal failure, as intrarenal injection of NE causes AKI [52-55, 69]. Renal denervation decreases renal NE in animals [49, 51]. Human data also suggest that renal denervation decreases renal NE spillover [44]. These results suggest that the decrease in renal NE content may be one of mediators underling the renal protective effect of renal denervation.

The increase in sympathetic outflow to the kidney leads to sodium and water retention, renal vascular constriction and reduction of RBF [32, 33]. Thus, denervation of renal efferent nerves can decrease sodium and water retention, relax renal blood vessels and increase RBF and GFR.

A Decrease in Central SNA and Sympathetic Outflow

Renal afferent nerve projections to the hypothalamus can stimulate sympathetic outflow [29, 33]. Denervating the afferent renal nerves decreases central SNA as evidenced by a decrease in NE turnover in the brain [30, 62]. Renal denervation decreases whole body NE spillover and decreases sympathetic nerve traffic to the skeletal muscle vasculature [44, 82].

Decreasing sympathetic outflow to other organs can decrease renal failure-associated complications. For example, CKD can lead to cardiac hypertrophy, as bilateral nephrectomy regresses left ventricle hypertrophy within 12 months [17]. Importantly, renal denervation has been reported to reduce left ventricular mass from 184 to 169 g (78.8 to 73.1 per square meter of body surface area) in humans [44].

Renal denervation can improve glycemic control. In a recent randomised trial in patients with medication-resistant hypertension (n = 37 renal denervation and n = 13 controls) renal denervation improved fasting glucose (from 118±3.4 to 108±3.8 mg/dL), insulin levels (from 20.8 ± 3.0 to 9.3 ± 2.5 μU/mL) and calculated insulin sensitivity (from 6.0 ± 0.9 to 2.4 ± 0.8) and BP (-32/-12 mm Hg) at 3 months [48]. One of the possible mechanisms underlying the beneficial effect of renal denervation on insulin sensitivity and glucose metabolism is a decrease in SNA, as it has been shown that muscle SNA is positively correlated with insulin resistance [83]. Thus, renal denervation has beneficial effect on diabetes which is associated with renal failure [84].

A Decrease in the Renin-Angiotensin System

Renal denervation can decrease the renin-angiotensin system including renin, angiotensin-converting enzyme (ACE) and angiotensin II type 1 receptors.

Renin may play a role in the progression of renal failure. Plasma renin concentration has been reported to be increased in AKI in both humans [85] and animals [86]. Transgenic rats carrying an additional renin-gene displayed enhanced renal failure compared with BP-matched, stroke-prone spontaneously hypertensive rats in a subtotal nephrectomy model [87]. Renal denervation can reduce renin synthesis and release. Renal denervation in rats inhibits renin mRNA expression following ureteral obstruction [88]. The inhibitory effect of renal denervation on renin synthesis and secretion was also shown in mice with AKI induced by clamping the renal pedicle [89]. Renal denervation reduced the renal vein concentration of renin by half in this mouse model [89]. In humans, renal denervation has been reported to decrease renin activity 30 days after the procedure [44, 74]. Thus, decreasing renin concentration might in part mediate the renoprotective effect of renal denervation. However, the importance of this mechanism needs to be further investigated.

Angiotensin II plays an important role in renal failure progression. Both preclinical [90, 91] and clinical studies [92-95] have demonstrated the therapeutic efficacy of ACE inhibitors and angiotensin II receptor blockers in slowing the rate of renal failure progression. Renal denervation has been reported to decrease ACE activity in hemodialysis patient [74] and decrease the enhanced angiotensin II type I receptor expression in the renal cortex in rabbits with pacing-induced heart failure [96]. These results suggest that renal denervation might exert its renal protective effect partially through decreasing angiotensin II signaling.

Adenosine—a Putative Factor

Adenosine causes renal vasoconstriction and decreases renal blood flow [97, 98]. In renal failure (e.g. glycerol-induced AKI), the responsiveness to adenosine-induced renal vasoconstriction is enhanced [98]. Adenosine induces AKI by activating adenosine type 1 (A1) and type 3 (A3) receptors. Adenosine activates A1 receptors leading to renal vasoconstriction and decrease in RBF and GFR, and consequently ischemia and AKI [99-103]. Adenosine activates A3 receptors which can lead to degranulation of mast cells and an increase in plasma histamine and consequently renal histological damage [104]. Pharmacological inhibition of A1 [99-103] or A3 receptors [104] or knocking out A3 receptors [104] protects animals against AKI. In addition, adenosine inhibition has been
reported to protect against AKI in humans [97]. The importance of adenosine in mediating renoprotective effects of renal denervation on renal failure needs to be investigated in the future.

RE-INNERRATION

Renal re-innervation after denervation has been reported in research animals (Table 2). In rats, re-innervation of renal nerves appears to happen between the third and fifth week after denervation, as evidenced by an increase in perfusion pressure during renal nerve stimulation [105] and renal NE content [106]. Renal function appears to return to normal by 8 weeks, as evidenced by the findings that: (1) the response of perfusion pressure to renal nerve stimulation returns to normal at 5 weeks [105]; (2) BP is no longer different between the denervated and un-denervated rats at 5 [107] to 7 weeks after denervation [108]; and (3) sodium excretion returns to normal by 5 weeks [109]. Renal function does not completely return to normal by 8 weeks as supersensitivity to NE still exists at this time [109].

In dogs, the re-innervation process seems to take longer compared with rats. By week 6, renal NE in the denervated kidney has been reported to be only 5% of the un-denervated kidney [110]. Renal NE and plasma renin activity in response to salt depletion returns to normal around 16 weeks [110, 111]. Monoamine-positive varicose fiber is partially regenerated by 6-12 months [112]. However, renal re-innervation is still not complete up to 12 months as evidenced by the natriuresis and suppressed renin release reported [112].

In patients with transplanted kidneys the kidney does not appear to achieve functional re-innervation as evidenced by supersensitivity to circulating NE and an inadequate response of glomerular filtration rate to lower body negative pressure [113]. In humans renal denervation-induced BP decrease has been reported to be sustained for over two years, suggesting that re-innervation, if any, is not clinically relevant over a two years period [47].

In experimental animals, such as rats, effective repeated denervation has been performed at around 6 weeks after the initial procedure [107]. It is not clear how long catheter-based renal denervation is effective for in patients and whether repeat renal denervation is required in the long term.

RENALE DENERVATION HAS BEEN SHOWN TO BE INEFFECTIVE AT PROTECTION AGAINST RENAL FAILURE IN SOME EXPERIMENTAL MODELS

We identified five studies in which renal denervation did not show beneficial effect on renal failure [59, 63-66].

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Table 2. Re-Innervation after Renal Denervation

<table>
<thead>
<tr>
<th>Species</th>
<th>Setting</th>
<th>Re-Innervation Criteria</th>
<th>Observation</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Rats</td>
<td>1K-1C hypertension</td>
<td>BP ↑</td>
<td>4th w, BP ↑ 5th w, BP in denervated = BP in un-denervated</td>
<td>[107]</td>
</tr>
<tr>
<td>Male SD rats</td>
<td>DOCA salt</td>
<td>BP ↑ Renal NE content ↑</td>
<td>d 17 after DOCA salt, BP ↑ d 24 after DOCA salt, renal NE ↑</td>
<td>[106]</td>
</tr>
<tr>
<td>Male Wistar rats</td>
<td>Unilateral denervation</td>
<td>Changes in perfusion pressure during RNS and after administration of NE</td>
<td>24-32 d, response to RNS in denervated = 40% un-denervated; Supersensitivity to NE At 8 w, response to RNS in denervated = un-denervated; Supersensitivity to NE</td>
<td>[105]</td>
</tr>
<tr>
<td>Male SHR</td>
<td>Bilateral denervation</td>
<td>Fractional excretion of sodium ↓ BP ↑</td>
<td>5 w, renal NE ↑ Sodium excretion in denervated = undenervated BP in denervated = undenervated</td>
<td>[109]</td>
</tr>
<tr>
<td>Male New Zealand rats</td>
<td>Genetically hypertensive</td>
<td>BP ↑ Renal catecholamine (NE+epinephrine) ↑</td>
<td>1 week: Catecholamine in denervated = 17% of un-denervated; 4 w: up to 40% of un-denervated 7 w later, BP in denervated = BP in un-denervated</td>
<td>[108]</td>
</tr>
<tr>
<td>Mongrel dogs</td>
<td>Unilateral renal denervation of the left kidney</td>
<td>Monoamine-positive varicose fibers ↑ Renal natriuresis Renal NE ↑</td>
<td>1 and 3 m, no reinnervation was observed. 6 and 12 m, there was partial reinnervation of fibers. Lower renin and natriuresis was still seen in denervated kidney.</td>
<td>[112]</td>
</tr>
<tr>
<td>Dogs</td>
<td>Normotensive</td>
<td>Renal cortical NE content ↑</td>
<td>6 w, NE in denervated = 5% of un-denervated The values were 42%, 96% and 93% at 12, 16 and 21 w</td>
<td>[110]</td>
</tr>
<tr>
<td>Dogs</td>
<td>Bilateral nephrectomy</td>
<td>Renal cortical NE content ↑ PRA response to 3-6 day salt depletion</td>
<td>1-2 w, NE=0; 6 to 12 w, NE returned gradually to normal PRA ↑ first 3 m, and returned to normal at the 4th m</td>
<td>[111]</td>
</tr>
<tr>
<td>Human</td>
<td>Treatment-resistant hypertension</td>
<td>BP ↑</td>
<td>Up to 2 years, no sign of re-innervation</td>
<td>[47]</td>
</tr>
</tbody>
</table>
Renal Denervation and Renal Failure

Bile Duct Ligation-Induced AKI

Bile duct ligation, a model of obstructive jaundice, induces renal function impairment in rats as evidenced by a decrease in creatinine clearance and urinary sodium excretion, and an increase in urine flow [63]. Renal denervation has no effect on the changes induced by bile duct ligation in this AKI model [63]. In addition, renal denervation has little effect on increased sodium reabsorption that occurred after bile duct ligation in dogs [64]. These results suggest that renal sympathetic nerves play a small or no role in this type of AKI.

Ischemia/Reperfusion-Induced AKI

Although renal denervation has been reported to protect against ischemia/reperfusion-induced AKI [57-59], there are some contradictory reports. For example, in one study renal denervation did not protect against AKI induced by ischemia/reperfusion in rats although it inhibited the BP increase during and 1 min after ischemia injury [65]. In another two studies, renal denervation was reported to be harmful. One study reported that renal nerves mediate ischemic preconditioning-induced protective effects against ischemia/reperfusion-induced AKI [59]. Ischemic preconditioning (e.g. two periods of 3 min occlusion of the bilateral renal artery before a 30 min occlusion and 90-min reperfusion) improved renal dysfunction induced by ischemia/reperfusion injury, as evidenced by attenuation of both the increase in GFR and RBF and the increase in fractional excretion of sodium and urine flow. Renal denervation partially inhibited the renal protective effect of ischemic preconditioning [59]. Another study reported similar findings in a rabbit model. The investigators clamped the left kidney pedicle for 1h to induce AKI. Renal denervation was reported to increase renal failure as assessed by an increase in serum urea nitrogen (from 84 ± 10 to 120 ± 18 mg/dL) and creatinine (from 5.2 ± 0.8 to 8.6 ± 1.4 mg/dL) [66].

The mechanism underlying renal nerve-mediated protection of ischemic preconditioning and the reported discrepancies in the effect of renal denervation on ischemia/reperfusion-induced AKI needs to be further investigated [66].

CONCLUSION

Most current evidence suggests that renal denervation plays an important protective effect against renal failure in both animal models and humans. The underlying mechanisms include a decrease in BP, a decrease in renal efferent SNA, a decrease in central SNA and sympathetic outflow, and a decrease in the renin-angiotensin system including renin, ACE and angiotensin II type 1 receptors. It has been noted that re-innervation occurs after renal denervation in animals. However, functional re-innervation has not been observed in humans over a two-year period after renal denervation. Renal denervation might not be renal protective in some situations including bile duct ligation-induced renal failure and ischemia/reperfusion induced AKI. Catheter-based renal denervation decreases BP in both end stage and moderate to severe stages of renal failure. However, the effectiveness of renal denervation on renal function in CKD patients needs to be further investigated.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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