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Review Article

Renal denervation benefits in chronic kidney disease: An updated review

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ABSTRACT

Hypertension (HTN) may not be properly controlled despite the ideal blood pressure (BP)-lowering drugs and good patient compliance. These scenarios emphasize the need for innovative approaches to treat HTN cases that are difficult to manage pharmaceutically. Numerous recent studies have documented the effectiveness of renal denervation (RDN) therapy in reducing sympathetic nerve system (SNS) overactivity. Although this therapy is invasive and expensive, its appropriate use in specific cases is still being refined. SNS overactivity is documented in HTN, chronic kidney disease (CKD), and end-stage renal disease patients. Over the past decade, RDN therapy has been used in different countries to treat HTN, with a positive response in most cases. However, some hospitals have no resources or interventionists to perform these procedures. Nonetheless, there is an increased number of physicians expressing interest in using RDN in sustained HTN therapy and prevention of CKD progression. There are no consensus guidelines worldwide; however, some societies have developed guidelines for using RDN based on updated information covering the BP-lowering mechanism, efficacy, patient selection, post- and preprocedural assessment, and procedural safety. In this review, we aimed to evaluate the effectiveness of the RDN procedure for treating HTN and prevention of CKD development and progression.

1. Introduction

Systemic hypertension (HTN) is a significant cause of escalating morbidity and mortality worldwide. HTN is the primary determinant of significant cardiovascular (CV) events. Moreover, HTN is a risk factor for CV disease (CVD), chronic kidney disease (CKD), eye complications, and cerebrovascular disease.[1] According to a study that included > 1.5 million people from 29 nations conducted by the International Society of HTN in 2019, the global prevalence of HTN was 34%.[2] Although several efficacious and secure drugs for reducing blood pressure (BP) have been developed recently, the proportion of hypertensive individuals who successfully achieve their BP objectives remains low in most global regions.[3,4] Inadequate compliance with polypharmacy therapy is the primary factor contributing to treatment ineffectiveness.[5] Nevertheless, certain cohorts of individuals with HTN continue to have unregulated BP levels despite their diligent adherence to many antihypertensive drugs. In addition, some individuals may encounter substantial adverse effects from certain drugs used to decrease BP, thus complicating

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its management. Consequently, scientists are now seeking innovative approaches or methodologies, other than drug therapy, to reduce BP in individuals with HTN.

Thailand surveys reported a decline in the rate of BP control among hypertensive individuals receiving antihypertensive therapy. The BP control rate decreased from 61% in a survey conducted in 2014 to 48% in a study conducted in 2020.[4] Data from a comprehensive survey conducted across Thailand revealed that 17% of individuals with HTN used three or more drugs to reduce their BP.[6] In the HTN clinic of a tertiary care university hospital, 33% of patients require three or more medications, including diuretic, to manage their high BP, suggesting the need for novel strategies to assist in controlling persistently high BP.[4] The first catheter-based renal denervation (RDN) treatment report was published in 2009.[7]

Renal denervation (RDN) (renal ablation) is a minimally invasive, therapeutical procedure for HTN that has not responded to > 3 antihypertensive medications, including diuretic agents. This type of HTN is labeled resistant HTN (RHTN). Multiple studies have shown that RDN may effectively reduce BP in hypertensive individuals. Nevertheless, the extent to which BP decreases following RDN differs across different studies. Owing to the invasive and expensive nature of RDN treatment, there is currently a focus on selecting the most suitable patients for this procedure. In addition, some factions of medical professionals and individuals seeking medical treatment are keen on using the RDN to maintain consistent BP readings over an extended period. This was done with the hope that prolonged BP management could be accomplished by consuming a minimum number of antihypertensive medications. Strangely, it was reported that the therapeutic benefits of RDN in patients with RHTN have been demonstrated in both clinical trials and experimental studies. This is contrary to meta-analyses and evaluations that did not show any substantial effect of RDN therapy on BP control.[1] It was evident that RDN reduces also the risk of CKD and CKD progression due to its effect on BP and sympathetic overactivity in CKD patients.[8,9]

This review will discuss RDN effectiveness, benefits, and complications in patients with RHTN and CKD. Different phrases, texts, and keywords such as renal denervation, renal ablation, RHTN surgical therapy, RHTN, autonomic nervous system denervation, BP control, nephrectomy, and HTN were used to search PubMed, Scopus, Google, EMBASE, and Google Scholar for articles related to kidney ablation in RHTN therapy.

2. Resistant Hypertension

Obesity and aging populations have caused HTN to become more common worldwide. Approximately 10% of people with HTN have RHTN, which is defined as a systolic BP of 140 mmHg or higher despite taking at least three maximally tolerated doses of antihypertensive medications from different classes, including a diuretic agent administered in an appropriate dose.[10–12] The European Society of HTN guidelines define RHTN as when lifestyle changes and pharmacological interventions with optimal or best-tolerated doses of three or more drugs fail to lower office BP < 140/90 mmHg.[13] Checking 24-hour BP outside the clinic should indicate poor BP management. True RHTN requires complete therapeutic adherence and exclusion of secondary causes.[13] Otherwise, it is called “pseudo-resistant” HTN.[8] RHTN patients are at increased risk of stroke, major CV events, and end-organ damage.[14] Various variables contribute to HTN in CKD patients and treating them may not control the BP.[8]

Renal artery catheter-based radiofrequency denervation is a therapeutic option for RHTN that has been adopted in clinical practice across countries.[15,16] Nonrandomized and unblinded randomized trials have shown significant reductions in BP during office visits following renal denervation.[7,17] Due to the study participants not being large enough, the absence of a sham procedure as a control, limited ambulatory BP recording, and lack of blinding made the results of those studies unreliable. To address these issues and increase the reliability of the findings, the SYMPLICITY HTN-3 study was designed.[18]

Several factors precipitate HTN, making its pathogenesis a complicated process. For many years, researchers have acknowledged the significant role of SNS in essential HTN pathogenesis. SNS plays a significant role in increasing cardiac output (CO), heart rate, and BP. Although SNS overactivity inhibition is a well-established pharmacological treatment for many HTN patients, its effectiveness in HTN control was not always established, especially in RHTN. Early treatments for HTN aim to decrease sympathetic tone through sympathectomy or sympatholytic medications. Interestingly, more recent studies have re-evaluated the roles of the afferent and efferent sympathetic renal nerves in the pathophysiology of HTN, particularly RHTN.[1]

The establishment of sympathetic crosstalk between the kidneys and the brain plays a significant role in the pathogenesis of RHTN.[19] Nonrandomized studies suggest that surgical sympathectomy may help some patients with uncontrolled HTN.[20] Sympathectomy, a surgical procedure that was conducted in the 1950s, has significant advantages in HTN management. Nevertheless, surgical sympathectomy is abended because of unbearable postural hypotension.[1] RDN is a more targeted approach than less-refined surgical sympathectomy and is supported by robust experimental evidence.[1]

Depending on how the clinical hypertensive phenotype is characterized, observational studies estimate a prevalence of 2–30% for RHTN.[13] To minimize office BP-related alarming features, rigorous anamnestic data collection

and assessment of ABP are necessary for appropriate diagnosis.[13] Some experts thought-resistant hypertensive conditions are pseudo-RHTN after extensive evaluation. Microneurographic examination of sympathetic nerve traffic showed that real RHTN had a more persistent sympathetic overdrive than pseudo-RHTN.[21] RHTN is more frequent in CKD and CV disease patients[22,23] and increases CV events compared to treated HTN.[13] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) sub-analysis showed that RHTN patients develop ESRD about 2-fold faster than normotensive individuals.[24] Fluid overload is a key hallmark of RHTN in dialysis-dependent patients;[25] however, it only explains a third of HTN.[8]

The pathophysiology of RHTN is attributed to intensified SNS activity. The renal arteries are innervated by afferent and efferent sympathetic fibers. Stimulation of the efferent SNS leads to renal vasoconstriction, a decrease in renal blood flow, and an increase in the release of renin and epinephrine, as well as sodium reuptake by the kidneys.[8] The stimulation of afferent sympathetic fibers through the renal sympathetic fibers results in a strengthening of central sympathetic activity. Given the fundamental role of renal sympathetic nerves in RHTN development, as shown by increased renal noradrenaline spillover and increased SNS activity of skeletal and smooth muscle, modulation of their activity could be a targeted treatment for this type of HTN.[26]

Stimulating the efferent nerves of the kidneys lowers BP by reversing the underlying cause of HTN. Sophisticated investigations using radiofrequency ablation or other techniques to denervate renal arteries have illustrated a decrease in systemic BP and SNS activity. The antihypertensive action of RDN has been attributed to a decrease in systemic vascular resistance. Therefore, RDN is a legitimate therapeutic technique for reducing BP and is applicable both in experimental settings and in clinical practice.[1]

HTN causes left ventricular hypertrophy (LVH), endothelial dysfunction, hyperplasia, and enlargement of vessel smooth muscle cells.[27] It has been reported that after administration of norepinephrine at sub-hypertensive doses, myocardial cell hyperplasia and LVH are observed.[28] Moreover, higher SNS activation without BP increase has been reported to cause hypertrophy and proliferation of blood vessels in smooth muscle cells.[28] Elevated SNS activation, independent of BP, can also cause exaggerated coronary vasoconstriction,[29] arrhythmogenicity,[30] impaired renal function,[31] glomerular podocyte injury[32] metabolic impairment, increased arterial stiffness, endothelial dysfunction[33] and atherosclerosis[34] increasing CV event risk.

It was reported that decreasing SNS activation without lowering BP protects the kidney.[35] Compared to untreated rats, partially nephrectomized rats treated with non-hypotensive moxonidine showed decreased glomerulosclerosis and urine albumin excretion.[35] In diabetics, modest dosages of moxonidine without BP changes lowered albuminuria.[36] These findings strongly suggest that sympathetic overactivity, regardless of the BP, may harm the heart, liver, and kidneys. Sympathetic overactivity in CKD is well-documented, although the causes of chronic sympathetic excitation in CKD are complicated and poorly understood.

3. Mechanism of Kidney Denervation Therapy for HTN

Modifications to the diet by lowering sodium consumption in hypertensive patients can be beneficial. However, it is challenging to create lasting dietary changes. Therefore, it is important to consider the risk of end-organ damage due to uncontrolled HTN. Reduced baroreflex sensitivity can increase BP variability, which may be exacerbated by a higher salt intake.[37] Chronic baroreflex failure can lead to adverse pressure-natriuresis response,[37] and age-related baroreflex failure can result in extended increases in BP levels and variability in higher salt sensitivity and intake.[38] Furthermore, the non-dipper and riser patterns of nocturnal BP depend on increased intravascular volume, which is associated with higher salt intake and sensitivity.

RDN is a practical approach for reducing BP in patients with uncontrolled HTN regardless of their clinical scenario, including those who are antihypertensive-naïve or have discontinued treatment.[38] Morning and nocturnal uncontrolled HTN pose a higher risk of CVD and stroke regardless of whether the patient's office BP is controlled.[39] The effectiveness of antihypertensive medication tends to decrease overnight before the regular morning dose, suggesting that nighttime and morning BP control may be a weakness of current antihypertensive medication regimens.[40] Consequently, RDN can be used as an adjunctive and alternative complementary therapy for HTN management.[38]

RDN influences efferent and afferent SNS sensory pathways, contributing to a reduction in BP.[41,42] By ablating sympathetic efferent nerves, RDN inhibits the RAAS, which leads to increased renal blood flow, decreased salt sensitivity, and reduced urinary sodium excretion.[38] The nocturnal non-dipping BP pattern primarily serves as a compensatory mechanism to promote excess sodium excretion in patients with increased blood volume.[43] Thus, RDN should be effective in populations with higher salt intake and sensitivity. However, further prospective studies are necessary to determine the direct effects of sodium concentration and volume status on the response to RDN. Additionally, ablation of afferent nerve suppresses central sympathetic outflow, which increases baroreceptor sensitivity and decreases overstated BP variability, such as sleep-triggered and morning BP surges.

In humans, sympathetic afferent and efferent nerve fibers are located inside the adventitial layer surrounding the renal arteries. The afferent sympathetic nerves carry signals from the kidneys to the hypothalamus, often in reaction to kidney damage. This leads to an increase in central sympathetic outflow, eventually resulting in elevated BP.[44] Efferent sympathetic nerves emerge from the central nervous system and subsequently innervate the kidneys. Efferent sympathetic nerves primarily exert three key actions on the kidneys: enhancing renin production, promoting salt reabsorption by the renal tubules, and inducing renal vasoconstriction that reduces kidney blood flow.[44] Thus, reducing sympathetic activity directed towards the kidneys may lead to a decrease in systemic BP.[45] Before the widespread availability of efficient drugs to decrease BP, surgical sympathectomy was performed to reduce BP.[4,46] Nevertheless, the impact of renal sympathetic outflow on increasing BP, the structure of easily reachable renal sympathetic nerves, and the need for a new treatment for HTN have motivated researchers to explore other methods for diminishing the sympathetic nerve fibers surrounding the renal arteries.

The initial purpose of developing a radiofrequency ablation catheter was to provide heat to eliminate nerves located in the adventitial layer of the renal arteries. Additional methods for ablating the renal nerve include intravascular ultrasound nerve ablation[47] and alcohol-mediated kidney nerve ablation using a Peregrine catheter.[48]

4. Indicators of Successful Renal Denervation

The strongest predictor of BP reduction following RDN was baseline systolic BP in post hoc analyses of the SYMPLICITY HTN-3 trial and meta-analysis.[49] SYMPLICTY HTN-3 concluded that the RDN group had a BP drop (-14.13 23.93 mmHg) and the Sham surgery (placebo surgery) group had -11.74 25.94, with a significant statistical difference of < 0.0001 for comparing the change from baseline in 553 patients who were distributed 2:1randomly. The BP-lowering efficacy of RDN therapy in HTN was derived from data from first-generation RDN studies that showed that RDN therapy effectively reduced BP in patients with RHTN.[49]

In 153 hypertensives post-RDN, BP progressively dropped by 18.9/9.4 mmHg after a month in 141 patients, and by 22/10.2 mmHg after 6 months in 144 patients, and after a year in 132 patients, the BP decreased by 26.5/13.5 mmHg. Interestingly, in a study conducted in Thailand to assess the efficacy of RDN in patients with RHTN, RDN was highly effective in reducing BP and was maintained for up to nine years in Thai patients with good outcomes.[50]

4.1. Indications and contraindications of RDN

Once the exclusion criteria are applicable, there is no contraindication, and the patient has RHTN, proper assessment can be initiated. Patients should be evaluated by a multidisciplinary team consisting of HTN specialists, cardiologists, physicians, specialist nurses, anesthesiologists, and social supporters. The indications for and contraindications to RDN are listed in Table 1.

In addition to uncontrolled HTN, the potential of RDN has been studied in other clinical scenarios. These include metabolic syndrome[51,52] [54-55)], sleep apnea, atrial fibrillation[53] ventricular arrhythmias[54] heart failure[55] and chronic kidney disease.[56] The positive results of pivotal trials suggest that RDN may have applications beyond HTN. Given the increasing metabolic syndrome prevalence in East and Southeast Asian countries[57] evaluating RDN's effects of RDN on this condition is particularly important. Similarly, sleep apnea is a promising target for CV risk reduction through RDN, owing to its association with neurogenic HTN. However, further long-term data are required.

5. Sympathetic Nervous System Activation Role in CKD Progression

Data have consistently reported that sympathetic hyperactivity is a common occurrence in patients with CKD. Growing evidence suggests that neurogenic changes may have a significant impact on both CV and chronic renal diseases prognosis.[58] With sympathetic overactivity, cardiac output and peripheral resistance increase, leading to HTN. This can be caused by direct activities on cardiac and vascular receptors or the effects of the renin-angiotensin system (RAAS) on renal salt retention and renin release.[59]

Initially, micro neurography was used to discover a reverse sympathetic hyperactivity in CKD and HD dependent patients.[38,60] However, subsequent research revealed a progressive increase in sympathetic activity during chronic renal failure, showing that adrenergic activation in HD patients is greater than that in simple essential HTN.[61] Some indirect data have shown that neurogenic signals from damaged kidneys produce sympathetic overactivity in ESRD patients.[62] ESRD patients on HD had more adventitia interior region nerve endings than those with normal renal function or milder CKD. Patients with CKD and ESRD with abnormal SNS activation have an increased risk of sudden cardiac mortality.[63] SNS overactivity is a persistent characteristic of CKD and ESRD, which elevates the risk of CV disease and mortality. Moreover, SNS overactivity does not only exacerbate HTN in CKD but also has a detrimental impact on CKD progression, regardless of its effect on BP.[8]

HTN and CKD are linked, and 80% of CKD patients had HTN.[64] HTN worsens CKD, and uncontrolled HTN

increases the risk of ESRD within five years.[65] Reduced renal function increases HTN incidence and severity.[64] Unfortunately, CKD and CV disease caused 4.6% of worldwide deaths in 2017.[66] RHTN occurs in 40% of CKD patients, making HTN control difficult (22). Physician reluctance to modify therapy, patient noncompliance, poor social support, and the complexity of managing several drugs in severe HTN contribute to this issue.[67]

HTN therapy depends on normal kidney function and in patients with kidney disease. Catheter-based renal denervation employing radiofrequency radiation, perivascular injection of neurotoxic drugs, or US has been examined in preclinical and clinical studies of patients with CKD. Recent recommendations and position statements from the European Society of Cardiology and European Society of HTN (ESC/ESH) incorporate renal denervation.[44,67,68] These therapies use technology at diverse stages of development, but several have been examined in sham-controlled trials to fulfill US regulatory approval standards.[69]

RDN lowers BP and prevents kidney impairment in hypertensive patients. The reason for this is to avoid excessive kidney-CNS interactions (Crosstalk). Renal nerves regulate renin secretion, nephron tubule salt reabsorption, and renal hemodynamics. When efferent neurons are stimulated, they decrease renal blood flow, renin release, and sodium and water excretion thereby increasing BP.[70] This mechanism also involves the afferent renal nerves; An increase in afferent signaling in the brain causes CNS-mediated arterial vasoconstriction. High sympathetic activity causes high BP and end-organ damage, including cardiac hypertrophy and renal dysfunction[71] Plasma noradrenaline levels in HD patients independently predict mortality and fatal and nonfatal CV events.[72]

The kidney regulates sympathetic activity in normal individuals and patients with CKD. Bilateral nephrectomy significantly reduces SNS activity, mean arterial pressure, and calf vascular resistance.[73] Further studies in renal transplant patients have shown that damaged kidneys might boost CNS activity. Even with good graft function, native kidneys show increased SNS activity in transplant patients without nephrectomy. Calf vascular resistance and muscle sympathetic nerve activity are considerably decreased in bilateral nephrectomy transplanted patients.[8]

RDN has been found to significantly reduce sympathetic muscle activity in hypertensive patients, with a substantial decrease observed after three months.[74] This intervention also lowers the activity of both single and multiple-unit muscles.[75] These results imply that RDN can decrease both efferent and afferent nerve activity, which may modulate the direct effect of renal signaling on BP and the indirect effect of afferent signaling on brain sympathetic activity outflow.[76]

6. Mechanisms of Sympathetic Nervous System Overactivity in Chronic Kidney Disease

6.1. Renin's Role in Sympathetic Nervous System Activation

Elevated plasma angiotensin II (Ang II) level is documented in CKD patients due to RAAS activation.[28,77] Ang II is a strong vasoconstrictor with several peripheral and central effects (31, 82). Ang II level controls peripheral SNS activation and vasoconstriction by increasing SNS terminal norepinephrine release, and Ang II level regulates brainstem sympathetic outflow.[28] It was reported that Ang II microinjection into the rostral ventrolateral medulla activates vasomotor sympathetic neurons, raising SNS activity in rats.[78] In addition, losartan (an ARB inhibitor) microinjection inhibits SNS impulse genesis.[79] Hence, it appears that Ang II regulates directly central SNS outflow.[28,80] Ang II receptor blockers and ACE inhibitors are the first-line therapy for HTN in CKD patients. Although their prolonged use lowers muscle SNS activity[81,82] after prolonged Ang II receptor blocker and ACE inhibitor therapy, muscle SNS activity in CKD patients is still greater than that in non-CKD hypertensive patients.[28] Thus, it is most probable that sympathetic overactivity in CKD patients is caused by processes other than the RAAS activation. This assumption needs to be investigated further.

7. Renal Afferent Sympathetic Nervous System Activation Role

The brain receives signals from chemoreceptors and baroreceptors in the kidneys to control the sympathetic outflow and systemic BP. Human investigations showed that kidney-originating neural impulses increase SNS outflow in CKD.[83] Renal ischemia increases adenosine synthesis, which excites renal afferent neurons and constricts afferent arterioles, lowering GFR.[84] It was found that smooth muscle SNS activity in renal transplant patients with intact native kidneys was equivalent to dialysis patients (stage 5 CKD).[85] In transplant patients who had bilateral native nephrectomy, smooth muscle SNS activity dropped to levels comparable to those in the controls. Thus, renal diseases may increase smooth muscle SNS activity through natural kidney signaling. Recent investigations have shown that lower renalase levels may contribute to higher SNS activity in CKD[86,87] The kidneys produce prorenalase, an inactive monoamine oxidase in the blood.[87] Renalase lowers BP by degrading catecholamines.[87,88] Renal failure and CKD patients have lower renalase levels, which reduce catecholamine breakdown, increasing SNS activity.[87]

8. Nitric Oxide Role in Sympathetic Nervous System Activation in Chronic Kidney Disease

Chronic SNS excitation in CKD may be caused by the diminished bioavailability of nitric oxide (NO) bioavailability. NO synthase (NOS) produces NO by oxidizing l-arginine to l-citrulline.[89] In healthy people, systemic NOS inhibition reduces NO and vasodilation, increasing arterial BP immediately.[28,90] In addition to vasodilation, NO inhibits platelet aggregation, smooth muscle cell proliferation, and leukocyte endothelium adhesion to maintain vascular homeostasis.[28,91] Additionally, endothelium-derived NO modulates vascular tone and arterial BP and helps maintain healthy vasculature. Although the significance of peripheral NO in vasodilation and BP control is well recognized, its central influence is less well understood.[28] NO seems to regulate brainstem sympathetic outflow as a signaling molecule, as animal investigations have shown.[92] Further research is required to prove the central effect of NO in BP control.

SNS activity decreased in early investigations, which extrapolated these results from direct central injections to systemic NO synthetase inhibitor infusions. In humans, systemic NOS inhibitors increase BP rapidly and significantly while decreasing SNS activity.[93] Inhibition of NO-mediated dependent peripheral vasodilation caused a rapid increase in BP. This BP increase stimulates arterial baroreflex and decreases SNS activity. Therefore, baroreflex-mediated SNS activation decreases the disguised sympathetic outflow increases owing to a decrease in central NO.

Elevated levels of asymmetric dimethylarginine (ADMA), the main endogenous NOS inhibitor, lowers NO concentrations in CKD.[94] In mild CKD, plasma ADMA concentrations increase as renal function diminishes.[95,96] Many studies have demonstrated that ADMA is a robust independent predictor of CV risk in CKD patients.[97,98] Plasma ADMA concentrations predict CV and all-cause mortality in patients with renal failure (105). ADMA concentrations in early-stage CKD predict mortality rate and CVD risk. In a large cohort of patients with stage 3–4 CKD, higher ADMA was strongly associated with CVD and modestly associated with CV and all-cause of mortality.[99] It is obvious that high ADMA plasma levels are related to CV risk, but most ADMA research has been correlational, focusing on NO's vascular endothelial characteristics of NO. ADMA may contribute to SNS overactivity in CKD given the growing functional evidence that NO is also a critical signaling molecule in the tonic control of central SNS outflow.

All cell types generate ADMA, which crosses the blood-brain barrier.[100] Arginine methyltransferase type I post-translationally methylates proteins to create it.[101] The dimethylarginine dimethylaminohydrolase (DDAH) enzyme metabolizes it, or the kidneys excrete it.[102] Although impaired renal ADMA clearance in CKD patients increases plasma levels, DDAH metabolism is the main method of ADMA elimination. Approximately 300 mol of ADMA is produced daily by the human body, with 250 mol processed by DDAH and a minor quantity eliminated by the kidneys.[103]

Elevated ADMA levels reduce central NO in CKD patients, which may increase brainstem sympathetic outflow.[104] In patients with stage 2–4 CKD, higher ADMA levels were associated with higher resting muscle SNS activity and lower eGFR.[28] This might be the reason for the high BP in CKD patients; however, further research is required on this topic.

9. Oxidative Stress Species Role in Sympathetic Nervous System Activation in Chronic Kidney Disease

CKD patients have greater levels of oxidative stress species (ROS).[105,106] which may cause persistent SNS excitation. ROS in the central nervous system regulates brainstem sympathetic output [(113)]. Animal investigations have observed that oxidative stress in the brain increases central sympathetic outflow by directly or indirectly scavenging NO.[107,108] Ang II activates NADPH oxidase, which increases ROS production.[109]

Reduced brain ROS with a superoxide dismutase mimetic tempol or overexpression of superoxide dismutase reverses enhanced central SNS outflow.[110,111] Tempol treatment with drinking extra water and systemic fluid infusion restores SNS activity and diminishes paraventricular parasympathetic neuronal activity in rats.[112]

ROS may produce direct and persistent SNS excitations. In addition to ROS direct effects, high ROS inhibits DDAH, which is the main ADMA breakdown mechanism.[113] This may boost the central SNS activation from ADMA. These findings show that ROS enhances brainstem sympathetic outflow and may cause higher SNS activity in CKD patients.

10. Renal Denervation in Chronic Kidney Disease Outcome

RDN reduces high BP via two major mechanisms. First, by depressing renal efferent neurons, renal blood flow, and increase in urine salt and water excretion.[114] Second, RDN reduces central sympathetic tone by interrupting renal afferents, which lowers total peripheral resistance and BP.[71] RDN has been studied for its effect on HTN for the past decade, and a recent network meta-analysis of 20 randomized controlled trials with 2152 patients showed that it lowers BP better than sham or antihypertensive therapy.[115]

Mohammad et al. examined the safety and efficacy of RDN as a possible therapy for HTN in CKD and

Table 1: Indications and contraindications for kidney denervation.

Recommended (51, 52).		RHTN (persistent BP > 140/90 mmHg with 3 drugs including diuretics). Not achieved BP control with maximum recommended antihypertensive drugs and full adherence. RHTN. Repeated H/O non-adherence despite numerous counseling sessions. Comorbidities need multiple medications. Multi-end-organ damage, with high CV risk. No good complaint with taking long-term pharmacotherapy Antihypertensive medication intolerance.
Indications	Potential	Type 2 DM/insulin resistance. Heart failure. Sleep apnea (53).
	Bleeding risk	Severe coagulation factors deficiencies. Severe anemia. Severe thrombocytopenia.
	Chronic diseases	CKD, eGFR < 40 mL/min/1.73m^{2}Type 1 DM.
Contraindications		Previous renal artery intervention (angioplasty, stent implantation).
	Vascular	Anatomic abnormalities and variants of renal arteries including: Renal artery aneurysms. Severe renal artery stenosis (diameter <3 mm). Excessive tortuosity.
Exclusion Criteria		Aortic aneurysm. White-coat HTN Secondary HTN (hyperaldosteronism) Pregnancy Young age (< 16 years)

Legend: HTN (HTN), Diabetes mellitus (DM), chronic kidney disease (CKD), and estimated glomerular filtration rate (eGFR).

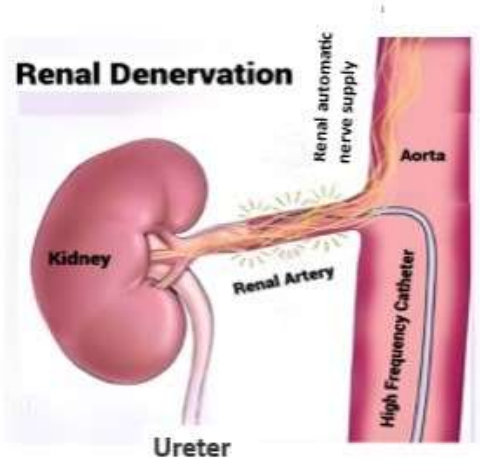

Figure 1: Renal denervation by Ureter radio frequency via the renal artery.

its effects on different renal function indicators. The authors noted that the incidence of RDN-related problems was 4.86% in CKD patients, making it a safe maneuver. RDN's use in numerous chronic conditions beyond HTN such as HFrEF therapy has advanced, and this article presents key evidence that supports its use as a therapy for RHTN and CKD.[9,104]

11. Sympathetic Nervous System Overactivity Clinical implications in Chronic Kidney Disease Treatment

CKD is characterized by sympathetic overactivity that requires treatment. There are identified routes that may increase SNS activity in CKD patients, which should be considered when evaluating treatment options to lower SNA in this high-risk group. ARB and ACEi diminish resting muscle SNS activation and BP, but neither normalizes muscle SNS activation in CKD.[81–92] However, additional treatments are required. Sympatholytic drugs, such as moxonidine, reduce muscle SNS activation in HTN patients (36), but adverse effects restrict their clinical use[116,117] Other therapies that decrease cholesterol, SNS activity, and ROS include statins.[118] Statins downregulate brain Ang II receptors and upregulate neural NO synthetase.[118] Even short-term statin medication reduces sympathetic overactivity[119] making it a promising treatment for CKD. In predialysis CKD patients, statin treatment lowered muscle SNS activation[120] delayed dialysis[121], all-cause mortality, and CV events.[122]

Another maneuver to reduce SNS overactivity in CKD is by reducing ROS. Decreased SNS activity

Table 2: Illustrate distinctions among simplicity study (I, II, III)

Study	Study type	M: F	Mean Age-years [SD]	No of Pts RNDT	Control	OSBP/ODBP-reduction-mmHg- RDN-therapy group		OSBP/ODBP - reduction - mmHg- - Control group		24AB- SBP/DBP reduction-RDN therapy group		24AB-SBP/DBP -reduction Control		Follow-up in months	Significance
SYMPL-ICITY-HTN-1 (158)	Open-label	1.6:1	57	153	NA	25 32 32	11 14 14	NA		NA	NA	NA		12 24 36	<0.0001
SYMPL-ICITY-HTN-2 (157)	Open-label	1:1.9	58+12	52 84 80 74 69 69 40	54	28+25.2 26.3+ 27.3 30.3+ 25.5 33.6+ 27.9 32.7+ 24.1	10.4+ 11.6 9.9+ 11.3 11.3+11 12.6+ 12.7 32.7+ 24.1	23.7+ 27.5 NA - 33+33 -	8.4+ 12.1 NA - - -	NA - - - -	NA - - - -	NA - - - -	NA - - - -	6 12 24 30 36	< 0.001
SYMPL ICITY-HTN-3(159)	Single blind	1.5:1	57.9 [10.7]	364	171	26.4	NA	5.7	NA	15.6	NA	0.3	NA	36	0.0001

Office systolic blood pressure (OSBP), office diastolic blood pressure (ODBP), renal denervation (RDN), hypertension (HTN), not available (NA), 24-hour ambulatory blood pressure (24-h AB S&DBP).

following ROS reduction has been proven in several animal studies, whereas patient investigations have had inconsistent outcomes.[123,124] This may be attributable to the antioxidant utilized in the study (vitamin E vs. vitamin C), the period of therapy (acute vs. chronic), the antioxidant dosage, and its efficiency in lowering ROS. However, the effect of ROS reduction in humans requires further assessment.

Pioglitazone lowers ADMA levels; hence, it may also help in CKD.[125] Lower plasma ADMA levels enhance central NO levels and decrease the brainstem sympathetic output. Thus, pioglitazone may reduce ADMA levels and sympathetic overactivity in CKD patients. In general, more studies are needed to identify pharmaceutical treatments for sympathetic overactivity in CKD and its beneficial and adverse effects.

RDN and carotid baroreflex excitation may help diminish SNS overactivity in CKD patients. RDN is mostly used to treat RHTN. In humans and animal models of HTN, renal denervation significantly reduced BP.[126,127] A major controlled clinical study (SYMPLICITY HTN-3) found that renal denervation reduced BP in HTN patients, similar to a sham control group.[128] Renal denervation may benefit patients with CKD, as bilateral nephrectomy in HD patients reduces resting muscle SNS activation.[85] Renal denervation lowers renin production, improves GFR, and lowers albuminuria in pilot investigations.[129,130] Despite these benefits, non-optimal renal artery diameter, contrast-induced nephropathy in CKD, and low renal blood flow must be addressed before RDN.[129,131]

Carotid baroreceptor stimulation may alleviate SNS overactivity in CKD patients. This procedure involves the implantation of a device to activate persistently carotid baroreceptors. In hypertensive individuals, this approach reduces BP by inhibiting SNS.[132,133] Chronic carotid baroreflex stimulation may benefit patients with CKD; however, further research is required.

12. Role of Sympathetic Nervous System in Chronic Kidney Disease Progression

The CKD and ESRD-related HTN involve multiple pathophysiological mechanisms that contribute to its development and progression. The sympathetic supply of efferent and afferent arteries plays an essential role in the development and progression of HTN in ESRD. Bilateral renal nerve ablation has shown promise in reducing BP in RHTN patients with normal kidney function. The native non-functioning kidney's neural excitatory influences on the central sympathetic drive can be reduced by denervation, potentially lowering the CV morbidity and mortality seen in ESRD.[8]

HTN is a major risk factor for ESRD and CV illness in patients undergoing chronic HD.[8,134] HTN affects 80–85% of patients with CKD and most patients with ESRD.[135] High BP, especially HTN, lowers GFR faster for any etiology of CKD, making HTN an independent factor for ESRD development.[8,135] HTN affects 50–60% of HD patients, depending on whether it is detected before or after dialysis and measured in an office or ambulatory setting.[8,135]

In a vicious cycle, uncontrolled RHTN increases the risk of ESRD over five years.[65] Multiple crosstalk mechanisms maintain CKD's inevitable high BP and contribute to elevated CV risk[8,135,136] In HD patients, sodium retention and volume expansion lead to HTN (143). Volume overload increases BP owing to cardiac output and systemic vascular resistance.[8,135] In 60% of HD patients, correcting volume overload by eliminating excess sodium and decreasing the target dry weight improves BP.[8,135] Endothelial dysfunction, RAAS activation, and SNS overactivity are prohypertensive pathogenic processes.[137] Recent studies have enhanced the significance of sympathetic neural variables and shed light on noradrenergic activation mechanisms.[58] Native kidneys may transmit afferent nerve signals to the CNS, causing sympathetic overdrive.[60,73] CKD development increases sympathetic activity[8,61] and intrarenal damage excites afferent renal neurons, which may affect the central sympathetic neural output.[138] Finally, renal sympathetic tone of efferent and afferent contributes to HTN development, and progression in ESRD patients, typically resulting in RHTN.[58]

13. Renal Denervation in End-Stage Renal Disease

Pioneering research 7 decades ago indicated promising HTN management following comprehensive surgical sympathectomy. These operations caused considerable comorbidities and adverse effects, despite better mortality rates. Native kidney nephrectomy reduces HTN and SNS hyperactivity in HD patients.[139] After partial nephrectomy in hypertensive rats, spinal rhizotomy reduced hypothalamic norepinephrine and HTN, proving that the kidneys are active neurologically and share neurogenic HTN.[140] Thus, inhibiting renal SNS overactivity in CKD may reduce HTN and delay kidney function deterioration. Bilateral nephrectomy is indicated in patients on HD with severe HTN. Because the therapeutic advantages of improving HTN seldom outweigh the substantial perioperative morbidity risk, it is rarely performed. However, rare non-compliant individuals with life-threatening HTN who cannot be treated using conventional methods may undergo bilateral nephrectomy.[141] In recent years, evidence of bilateral nephrectomy of native kidneys as an antihypertensive therapy has supported catheter-based renal SNS ablation in CKD patients and genuine RHTN. Experimental models have shown that ablation reduces SNS overactivity and prevents HTN and renal illness.

As kidney artery SNS ablation may help hypertensive CKD patients, nephrologists are interested in it because of emerging clinical evidence of its safety and effectiveness.

Preclinical and clinical studies have suggested that patients with CKD may benefit from nephroprotection. Therapeutic SNS ablation of native nonfunctioning kidneys in ESRD patients has poor safety and effectiveness. Pilot trials with limited sample sizes on ESRD and RHTN have shown promising evidence of renal SNS denervation over the last 10 years. Studies found that surgery was possible and successful in ESRD, despite reduced renal artery diameter and small atrophic kidneys.[131,142] One study reported the largest ESRD cohort with nine cases of successful denervation. Office systolic HTN and SNS traffic decreased after renal denervation, but ambulatory HTN did not.[131] A lower LV mass index was observed with decreased HTN. These effects were observed 3 months after treatment and lasted for 12 months.

In a nonrandomized investigation of HD patients with RHTN despite maximum pharmacological treatment and proven adherence, our group examined renal denervation.[143] Ambulatory systolic HTN decreased early during the follow-up period and remained low for 12 months. The sham-treated patients showed no changes in HTN. Renal denervation significantly lowered HTN during the day and night, indicating its benefits in patients undergoing HD.[131] A new meta-analysis of 238 CKD/ESRD patients with RHTN examined the effects of kidney SNS ablation. This study included patient data from 11 non-randomized, uncontrolled, single-center trials of CKD stages 1–5 and HD patients.[144] Research has shown that RDN reduces office and 24-hour ambulatory HTN after 24 months.[144] These patients should receive special follow-up, which should include monthly renal function assessments, clinical HTN checks, and 6-month ambulatory HTN monitoring.[13,44,145]

14. Blood Pressure Lowering Effects of Renal Denervation

After the initial non-randomized proof-of-concept research (SYMPLICITY-HTN1), many catheter-based renal nerve ablation clinical studies have been conducted. Different national and international scientific bodies have documented the procedure's major elements. The Italian Society of HTN emphasizes the importance of patient selection criteria.[145]

In five sham-controlled randomized studies, second-generation radiofrequency or ultrasound devices were safe and effective in patients who had or had no medical treatment.[8,146,147] Office systolic BP decreased by (9.0 to 10.8 mmHg), diastolic BP decreased (5.0 to 5.5 mmHg), and ambulatory BP decreased (4.7 to 9.0 and 3.7 to 6.0 mmHg), respectively.[44] In the final SYMPLICITY-HTN-3 study analysis, patients with renal RDN experienced substantially larger decreases in office and 24-hour ambulatory systolic BP from baseline to 36 months compared with the sham group.[148] These encouraging findings support the current recommendations of the European Society of HTN for the positive assessment of RDN.[13]

In addition to lowering BP, bilateral renal nerve ablation reduces SNS overactivity and systemic and renal norepinephrine spillovers.[8,75] Although the procedure reduced BP, a recent meta-analysis found a limited association between renal denervation-dependent SNS traffic reduction measured by microneurography and BP reduction.[149] Thus, processes other than noradrenergic inhibition may influence the BP-lowering effects of this RDN. Hence, further studies are mandatory to investigate the underlying mechanism(s) that interplay(s) in BP lowering effect of RDN.

15. Method of Kidney Denervation

RDN involves the destruction or damage of renal arteries' sympathetic innervation to the renal arteries. RDN can be done via renal artery cannulization, U/S high-frequency beam, or chemical SNS fiber ablation (Figure 1). RDN is the most common method of treating renal HTN, and radiofrequency (RF) ablation is the most common technique used for RDN. RF ablation involves damaging the renal arteries' nerve supply via the renal arteries, resulting in nerve discontinuity. To improve the RF ablation efficacy for RDN, several advances in techniques and procedures have been made. Over the years, RF ablation has been evidenced to be a mature and widely applicable method in both experimental and clinical settings. Figure 1 illustrates the high radio-frequency ablation via renal artery cannulization.

16. Ultrasound-Based Renal Denervation

High-frequency ultrasound (U/S) has been used to specifically induce selective RDN. Several empirical and clinical investigations have validated the potential efficacy of U/S-mediated RDN treatment. These investigations have shown that U/S use may cause specific damage to the kidneys and reduce SNS activity. Preliminary investigations in the USA have shown encouraging outcomes, similar to those observed with radiofrequency (RF) ablation. Similar to RF technology, advancements in U/S technology have been made to protect the vascular endothelium-independent of the size and shape of the renal artery. However, this method can be challenging for some individuals. The current discourse and empirical investigations seek to ascertain whether U/S-mediated RDN surpasses RF.

The RADIANCE-HTN SOLO study was conducted on 74 individuals with treatment-RHTN.[150] This study aimed to evaluate the long-term effectiveness and safety of US-guided RDN in reducing office BP and the use of antihypertensive drugs. At the beginning of the study, the OBP of the patients was assessed, and antihypertensive agents were initiated for a home BP of > 135/85 mmHg. After two months, the primary endpoint was reached, and the trial was double-blind after six months (patients and

physicians). The study found that overall office BP control improved from 29.4% at the screening stage to 45.1% at 36 months. Systolic office BP decreased by 10.8 mmHg at 36 months in patients with uncontrolled BP at the screening stage (n=36), while they were still on the same antihypertensive drugs. The study concluded that the safety and effectiveness of US-related RDN were durable for up to 36 months, with reduced OBP and improved office BP control despite a similar starting medication burden, and no new long-term safety concerns were identified.

17. Chemical Renal Denervation

Renal neurolysis, a type of chemical ablation, reduces both SNS activity and BP in animal models. This method entails deliberately damaging the renal nerves by administering chemicals such as alcohol, vincristine, and guanethidine, resulting in the loss of myelin from renal neurons. Although chemical denervation is sound biophysiological, there are presently no clinical data to substantiate its efficacy as a treatment for HTN in people. Chemical denervation, in comparison to radiofrequency ablation, generates lesions that penetrate deeper and lead to a more pronounced decrease in SNS impulses. Although chemical denervation shows potential, further studies are needed to thoroughly evaluate its safety before considering it as a viable therapeutic option.

18. Clinical Studies Assessed Renal Denervation

Clinical assessment of RF ablation for RDN commenced with the introduction of the first-generation SYMPLICITY catheter system. By employing a solitary unipolar electrode, this system facilitated the induction of RDN by rotating and guiding the catheter via the renal arteries using a helical template. SYMPLICITY HTN-1 was a major clinical study (including 45 patients) aimed at examining RDN in patients with HTN.[146] This study demonstrated a significant decrease in office BP records, which was sustained over up to 36 months. Additionally, a subset of patients exhibited reduced norepinephrine levels post-RDN, validating the fundamental pathophysiological concept.

In the SYMPLICITY HTN-2 clinical trial, patients with treatment-RHTN were treated with RDN therapy.[151] The trial demonstrated significant improvements in both office BP records and 24-hour ambulatory systolic BP. In this unblinded study, most patients responded positively to the RDN therapy. It is important to note that the results of both the SYMPLICITY HTN-1 and 2 trials were based solely on office BP records rather than ambulatory or home BP recordings. However, the absence of a sham control arm in both trials received widespread criticism.

The SYMPLICITY HTN-3 trial was a critical clinical research study that included a sham control group and mandated 24-hour ambulatory BP records for the study groups.[49] At the six-month mark, the BP records did not reveal a significant difference between RDN-treated and sham patients. Therefore, RDN was not superior to sham in treating RHTN. The decrease in BP in the sham group was substantial. The findings of the SYMPLICITY HTN-3 trial almost completely disqualified RDN as a therapeutic option for HTN. Several explanations, including incomplete denervation and a lack of operator experience, have been proposed for the failure of RDN therapy in the SYMPLICITY HTN-3 trial. To obtain additional comparative information, refer to the presented Table 2 which illustrates the distinctions among the three investigations.

19. Complications of Renal Denervation

The combined analysis showed no notable change in Scr and eGFR at 6, 12, and 24 months compared to the baseline, but other trials indicated improvements.[9]

Regarding complications, none of the studies reported renal artery dissection during surgery. One patient experienced post-RDN femoral bleeding.[152] Some patients developed femoral pseudoaneurysms that required surgery and hematomas.[9]

20. Limitations and Their Clinical Effects

CKD and uncontrolled HTN share a complicated pathophysiological mechanism that prevents medical treatment. A meta-analysis by Mohammad et al. and a comprehensive literature review indicated that CKD patients are the optimum cohort for RDN since it lowers BP and stabilizes eGFR and creatinine for 24 months in treating RHTN patients. Additionally, RDN may have distinct CV and renoprotective properties, which require additional studies in CKD populations. The procedure was safe and effective, with a complication rate of 4.86 %.[9]

The limitations of RDN in CKD patients have not been studied in gold-standard randomized control trials. There were 9 prospective observational and biased studies, making it difficult to assess the influence of RDN. Significant limitations: The limited study size (n = 226) may have exaggerated RDN's influence of RDN on BP and kidney function.[153]

Many variables contributed to heterogeneity in the meta-analysis. Study design, procedural methods, data collection, CKD stages, baseline population, dialysis, treatment-RHTN definition, medical therapy, and drug adherence assessment. This occurred during data pooling and was addressed using sensitivity analysis.[45] This heterogeneity was eliminated from 6 pooled results by sensitivity analysis. The heterogeneity was due to 63% of the patients with stage 2 CKD having the maximum mean eGFR of all included trials and using a new catheter type. In outcomes where the sensitivity analysis was found to be a cause

of heterogeneity, its removal did not impact the statistical significance.[45] From 4 pooled results, after Prasad study was excluded from the four pooled results.[154] This research may introduce heterogeneity due to the group having the lowest mean ODBP and 24-hour systolic and diastolic ABP. Both DOBP and diastolic 24-hour DABP were significant when the Prasad 2017 data were absent from the pooled analysis at 24 months.[154] However, these outcomes only had only 2 studies post-sensitivity analysis; therefore, definitive conclusions should be interpreted with caution. Scalise 2020 had 12 stage 5 CKD dialysis patients and caused variability in the two pooled outcomes. As its removal from the 12-month diastolic 24-hour ABP study had no impact, the significance was lost.

The findings of the Scalise 2020 review should be interpreted with caution. However, few CKD cohort studies on this innovative strategy show similarities in technique, intervention, and results. The pooled analysis offers a relevant literature overview with more evidence on RDN policy and future agreements on homogenizing larger comparative trials.

21. Conclusions and Perspectives

Renal denervation is proven to have a substantial reduction in both diastolic and systolic office blood pressure over 12 months, as well as a drop in 24-hour ambulatory blood pressure over 24 months in patients with chronic kidney disease and hypertension. The safety of renal denervation in patients with chronic kidney disease has been demonstrated, indicating its potential efficacy in treating patients with resistant hypertension and chronic kidney disease. This slows chronic kidney disease progression to end-stage renal disease. New studies are needed to identify how renal denervation affects estimated glomerular filtration rate, whether by reducing sympathetic overactivity or by other methods. If found, the other potential will change hypertension treatment in chronic renal disease and other non-hypertensive individuals.

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23. Conflict of Interest

None.

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