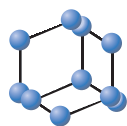


## REVIEW ARTICLE

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SCIENCE

## Renal Innervation in Resistant Hypertension: A Review of Pathophysiology and Renal Denervation as Potential Treatment



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**Abstract: Background:** Advances in treatment and increased awareness have improved the prognosis for many patients with hypertension (HTN). Resistant hypertension (RH) refers to a subset of hypertensive individuals who fail to achieve a desired blood pressure (BP) despite concurrent use of 3 different classes antihypertensive agents, one being a diuretic, and proper lifestyle changes. The prevalence and prognosis of RH are unclear owing to its heterogeneous etiologies, risk factors, and secondary comorbidities. Previous research has provided evidence that increased renal sympathetic nerve activity (RSNA) within the renal artery contributes to RH development. Renal denervation (RDN) is a procedure that attempts to ameliorate the effects of heightened RSNA via ablation renal sympathetic fibers. BP reductions associated with RDN may be attributed to decreased norepinephrine spillover, restoration of natriuresis, increasing renal blood flow, and lowering plasma renin activity. Early clinical trials perpetuated positive results, and enthusiasm grew exponentially. However, recent clinical trials have called into question RDN's efficacy. Numerous limitations must be addressed to discern the true effectiveness of RDN as a therapeutic option for RH.

**Objective:** We aimed to review the current understanding of RH, the anatomy of renal arteries, physiology of RH on renal arteries, anatomical pathways of the sympathetic involved in RH, RDN as a treatment option, and all relevant clinical trials treating RH with RDN.

**Methods:** We piloted a MEDLINE<sup>®</sup> database search of literature extending from 1980 to 2017, with emphasis on the previous five years, combining keywords such as "resistant hypertension" and "renal denervation."

**Conclusion:** A plethora of information is available regarding heightened RSNA leading to RH. RDN as a possible treatment option has shown a range of results. Reconciling RDN's true efficacy requires future trials to increased sites of nerve ablation, standardized protocol, increased anatomical understanding per individual basis, stricter guidelines regarding study design, increased operator experience, and integrating the use of a multielectrode catheter.

**Keywords:** Resistant hypertension, renal denervation, renal artery, renal sympathetic nerve activity, nerve ablation, stroke.

### 1. INTRODUCTION

Hypertension (HTN) is defined as a BP greater than 130/80 mmHg [1]. Despite advances in diagnosis, treatment, and public awareness, HTN affects more than 1 billion individuals worldwide [2, 3]. By the year 2025, it is projected that 29% of the world's population will have HTN. BPs higher than 140/90 mmHg, seen in HTN, are major risk

factor for stroke, coronary heart disease, heart failure, vascular disease, and chronic renal failure [2, 3].

HTN is divided into two major categories; primary and secondary HTN [4, 5]. Although exact etiology of primary HTN remains unclear, a variety of factors increase the risk of development. Major risk factors include poor lifestyle choices, age, and genetic factors. Secondary HTN may develop as a result of a variety of medical conditions, iatrogenic factors, and illicit drug use [4, 5].

Current treatment options for HTN include both non-pharmacological and pharmacologic treatment. Nonpharmacological therapies include lifestyle changes such as limiting

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dietary salt intake, increasing exercise, dietary modifications, weight loss, limiting alcohol intake and enhancing patient education [6]. Pharmacologic treatment is determined empirically based on the degree of BP reduction, tolerability, and safety [6]. There are five major classes of pharmacologic treatments that may be used as monotherapies or in combination. Antihypertensive medication regimens should be adjusted according to the patient's needs and desired BP reductions [6, 7]. Briefly, these include thiazide diuretics, long-acting calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and, in rare cases, beta blockers [6, 7].

Unfortunately, there is a subset of individuals with HTN, which are unresponsive to conventional treatments. Patients with resistant hypertension (RH) fail to attain BP below 140/90 mmHg despite optimal pharmacotherapy, medication adherence, and lifestyle changes [8]. The exact prevalence of RH remains unclear, as the current epidemiological studies are based on varying diagnostic criteria, inadequate adherence to anti-hypertensive therapies, ineffective treatment regimens, and suboptimal BP measurements. A study by Persell [9] has provided information that 8.9% of patients with HTN met the criteria for RH. Additional research using the National Health and Nutrition Examination Survey (NHANES) estimated an increase in the prevalence of RH from 15.9% (1998-2004) to 28.0% (2005-2008) [10].

Sustained increases in the activity of the sympathetic nervous system (SNS) have been strongly implicated in the development of RH. Pharmacological manipulation of the SNS has proven difficult to accomplish in patients with RH. Medical therapies include the use of alpha- and beta-blockers; however, favorable responses from these medications occurs in a small proportion of patients with RH. Patients with RH tend to achieve insignificant beneficial responses to medical therapies, thus making SNS control difficult [11, 12]. Recent findings have also implicated a connection between RH and angiotensin II type 2 receptors (AT2Rs) residing in the cardiovascular control centers of the brain. The most pertinent areas of the brain involved in cardiovascular regulation of BP include the paraventricular nucleus of the hypothalamus and the nucleus of the solitary tract within the dorsal medulla oblongata. Stimulation of these receptors has provided decreases in BP in patients with HTN of neurogenic origin, as AT2R stimulation may ameliorate heightened SNS activity in the central nervous system (CNS) [13]. Thus, AT2R stimulation may be a viable option for the treatment of RH, however further studies are needed to discern its ability as a therapeutic [13].

The renal arteries are densely innervated by efferent sympathetic nerves of the SNS and afferent sensory nerves relaying signals from the kidneys to the CNS [14]. Efferent sympathetic fibers utilize adrenoceptor signaling within the renal vasculature, tubules, and juxtaglomerular cells to facilitate changes in renal blood flow, glomerular filtration rate, renin levels, and sodium and water reabsorption. The majority of the afferent sensory fibers are located within the renal pelvic wall. Afferent fibers can sense deformation and distension of stretch receptors, elicit an inhibitory renorenal

reflex response, and participate in a negative feedback loop that leads to inhibition of efferent sympathetic nerves [14].

Collectively, the degree efferent and afferent sympathetic fiber innervation are referred to as renal sympathetic nerve activity (RSNA). Chronically elevated efferent RSNA and inappropriate afferent signaling may lead to increased catecholamine spillover. Specifically, norepinephrine spillover in the renal arteries increases in circulating blood volume, arteriolar vasoconstriction and systemic blood pressure contributing to the development of RH [11].

In attempts to obliterate the dysfunctional RSNA, the rationale behind renal denervation (RDN) was developed. RDN utilizes a catheter to ablate the nerves in the main body of the renal artery and thus, decrease sympathetic tone. A variety of RDN catheters have been developed since its inception during the 1950s, with the future looking towards multipolar catheters that may increase the surface area, and thus the nerves being ablated [15].

Currently, results from clinical trials present conflicting data regarding the ability of RDN to significantly decrease BP in patients with RH [16, 17]. We performed a comprehensive review the current literature *vis a vis* the role of renal innervation in RH and the implications of RDN in the treatment of RH.

First, current information regarding the background of RH, anatomical basis of the renal arteries, the anatomy of renal innervation and its physiology are summarized. Subsequently, potential causes and risk factors of RH are outlined. Finally, the methods of RDN, types of catheters in current use, all clinical trials to date have been discussed, and possible future directions of the use of RDN in RH.

## 2. MATERIALS AND METHODS

A comprehensive MEDLINE® database search of the literature extending from 1980 to 2017, with particular emphasis on the previous five years, was conducted combining keywords such as “resistant hypertension” and “renal denervation” with the following search criteria: “etiology”, “risk factors”, “renal anatomy”, “renal innervation”, “renal physiology”, “mechanism of action”, and “clinical trials”. No specific exclusion criteria were set. Included are all current clinical trials that have been performed. Publication quality was assessed using the relative citation ratio derived from iCite bibliometrics.

## 3. DEFINITION OF RESISTANT HYPERTENSION

RH is a clinical pathology defined by the American Heart Association as an uncontrolled BP that remains above the desired levels despite the concurrent use of three different classes antihypertensive medications, one of which is a diuretic. Desired BP is less than 140/90 mmHg [16, 17].

In the current literature, confounding grouping effects exacerbate the degree of difficulty in establishing an RH diagnosis and discerning its true prevalence. Often, uncontrolled hypertensive patients are mistakenly grouped with true RH patients. Uncontrolled hypertension (UHTN) is not

the same as RH [18]. UHTN includes patients with pseudo-resistant hypertension [16-18]. BP measurement should be confirmed with 24-hour ambulatory BP monitoring [18, 19]. It is important to note that prescribing a fourth antihypertensive drug with continued failure to achieve desired BP is still to be considered RH [16, 19].

Epidemiological studies have provided evidence that the pathogenesis of RH is likely multifactorial and elucidated a variety of risk factors that increase the likelihood of RH development [20]. Further, increased susceptibility in RH development has been observed with increasing age, obesity, black race, and renal dysfunction. The higher susceptibility of these population subsets may be attributed to an increased risk of drug resistance. Notably, studies have confirmed the heightened prevalence of RH and comorbidities such as cardiovascular disease, and diabetes mellitus [21].

Pseudo-resistant HTN is a term that describes HTN that is not adequately controlled and appears resistant to treatment. However, the HTN these individuals are experiencing can be attributed to other factors. These factors include, but are not limited to: inaccurate BP measurements, inconsistencies in adherence to medications, incorrect management of antihypertensive therapies, poor obedience to lifestyle and dietary changes that facilitate lower BP, and white coat hypertension [16, 19, 22, 23].

Apparent RH occurs in patients that have uncontrolled BP (>140/90 mmHg) despite being prescribed three or more

antihypertensive medications [22, 23]. This differs from true RH because although patients may be prescribed the correct cocktail and dosage of drugs, however, their compliance to the said regimen is unknown and thus they have been classified as pseudo-resistant hypertension [22-24].

### 3.1. Etiology and Risk Factors of Resistant Hypertension

The potential causes attributable to the development of RH are likely multifaceted and thus intrinsically presents difficulties in establishing a diagnosis [4, 21]. An extensive evaluation is necessary to accurately diagnose patients with true RH to decrease the prevalence of confounding grouping effects. Suboptimal antihypertensive therapy is a significant risk factor that must be assessed before true RH diagnosis [4, 21].

Evaluation of patient adherence, the effectiveness of drug administration, adequacy of the current combination of antihypertensive drugs, and the degree of volume expansion are necessary [19, 25, 26]. Patient lifestyle and diet patterns should also be considered prior to diagnosis. True RH may be mistakenly diagnosed in patients who are obese, take high-salt diets, sedentary lifestyle, and have excessive alcohol intake [21, 27]. Further, physicians may overzealously assign a diagnosis of true RH without considering factors such as inappropriate blood pressure measurement, pseudo-resistant hypertension, and white coat hypertension. Upon excluding the possible factors listed above, the potential

**Table 1. Causes of resistant hypertension. Table adapted from Doroszko et al. [30].**

Hypervolemia	<ul style="list-style-type: none"> <li>• Impaired kidney function:             <ul style="list-style-type: none"> <li>○ Defective pressure natriuresis                 <ul style="list-style-type: none"> <li>a) Chronic kidney disease</li> <li>b) Renal artery stenosis (increased renin, angiotensin, aldosterone levels with sodium retention)</li> </ul> </li> </ul> </li> <li>• Heart failure (aggravate sodium retention), drugs cause sodium retention (mineralocorticoid receptor agonist, estrogens, non-steroidal anti-inflammatory drugs),</li> <li>• Fluid retention caused by vasodilators dilates arterioles and stimulates RAAS (minoxidil, hydralazine, alpha blockers),</li> <li>• Ineffective use of diuretics</li> </ul>
The Activity of Neuronal Sympathetic System	<ul style="list-style-type: none"> <li>• Inappropriate renal sympathetic nerve activity</li> <li>• Chronic stress</li> <li>• Chronic pain</li> <li>• Hypertension provoked by fear, hyperventilation, paroxysm of panic fear (vasoconstriction)</li> </ul>
Drugs	<ul style="list-style-type: none"> <li>• Non-steroidal anti-inflammatory drugs NSAIDs (inhibition of renal prostaglandin production, decrease renal blood flow, retain sodium),</li> <li>• Glucocorticosteroids,</li> <li>• Licorice (suppress the metabolism of cortisol by beta-hydroxysteroid dehydrogenase and stimulate mineralocorticoid receptor),</li> <li>• Erythropoietin stimulating agents (increase vascular production of vasoconstrictors, e.g. thromboxane),</li> <li>• Cyclosporine/tacrolimus (enhance sympathetic nervous system activity, renal vasoconstriction, sodium and water retention),</li> <li>• Antidepressants (monoaminoxidase inhibitors), sympathomimetic (nasal decongestants),</li> <li>• Oral contraceptives with estrogen,</li> <li>• Anti-VEGF (VEGF stimulate nitric oxide production and vasodilatation),</li> <li>• Cocaine, amphetamine</li> </ul>

causes of true RH can be more accurately determined. A summary of the possible causes of true RH is shown in Table 1 [28-30].

At present, there is a limited number of studies evaluating the genetic components contributing to the development of RH. One study found that genetic variants of the beta and gamma subunits present in the epithelial sodium channel (ENaC) were significantly more prevalent in patients with RH [21]. Despite these findings, ENaC variants did not display significantly different activity. Additional studies have cited a myriad of ENaC, mineralocorticoid receptor, and CYP enzyme variants that are common in patients with RH. However, in order to determine the clinical significance of such a vast number of variants more comprehensive research, such as genome-wide association study, is required [21, 31, 32].

Secondary causes of RH have been noted as common and an important contributor to drug resistance, despite their unknown prevalence [21, 33]. Isolation and treating potentially underlying causes of RH are an important approach when attempting to overcome treatment resistance [34]. The most common secondary causes of RH are outlined in Table 2. Additionally, albeit less common secondary causes of RH include pheochromocytoma, Cushing's disease, hyperparathyroidism, hypo/hyperthyroidism, aortic coarctation, acromegaly, congenital adrenal hyperplasia, and intracranial tumor [21, 25, 30, 33].

#### 4. RENAL ARTERY ARCHITECTURE AND INNERVATION

##### 4.1. Renal Artery Anatomy

Typically, each kidney is assumed to be supplied by a single renal artery. Despite this, variant numbers of renal arteries supplying the kidney are common. This information is viewed as salient knowledge when considering renal transplantation and RDN [40]. Especially when determining if patients are candidates for RDN, multiple renal arteries have suggested that individuals with multiple or accessory renal arteries have an increased risk of HTN [40, 41]. Fig. 1 demonstrates variations in the blood supply to the kidney.

Further studies have shown that patients possessing multiple renal arteries and having a high renin activity are more

prone to developing HTN [42]. This is also of importance when discussing the efficacy and inclusion criteria of RDN clinical studies. Investigation of RDN efficacy provides evidence that the reduction of BP is less in patients with multiple renal arteries due to inadequate denervation of multiple renal arteries [43, 44]. This has been seen in individuals possessing accessory renal arteries and undergoing RDN treatment and experiencing smaller degrees of BP reduction compared to persons without accessory vessels [3] which supports arguments that accessory branch RDN is salient to achieve maximum reductions in BP [45, 46]. Another important facet of renal arteries and RDN is the variations displayed in the micro-anatomy of the perivascular tissues [47]. Nonhomogeneous distribution and dimensions of muscle, fibrous sheaths, veins, and lymph nodes distort the delivery of RF used in RDN, lowering the ablation efficacy of renal perivascular sympathetic nerve bundles [47].

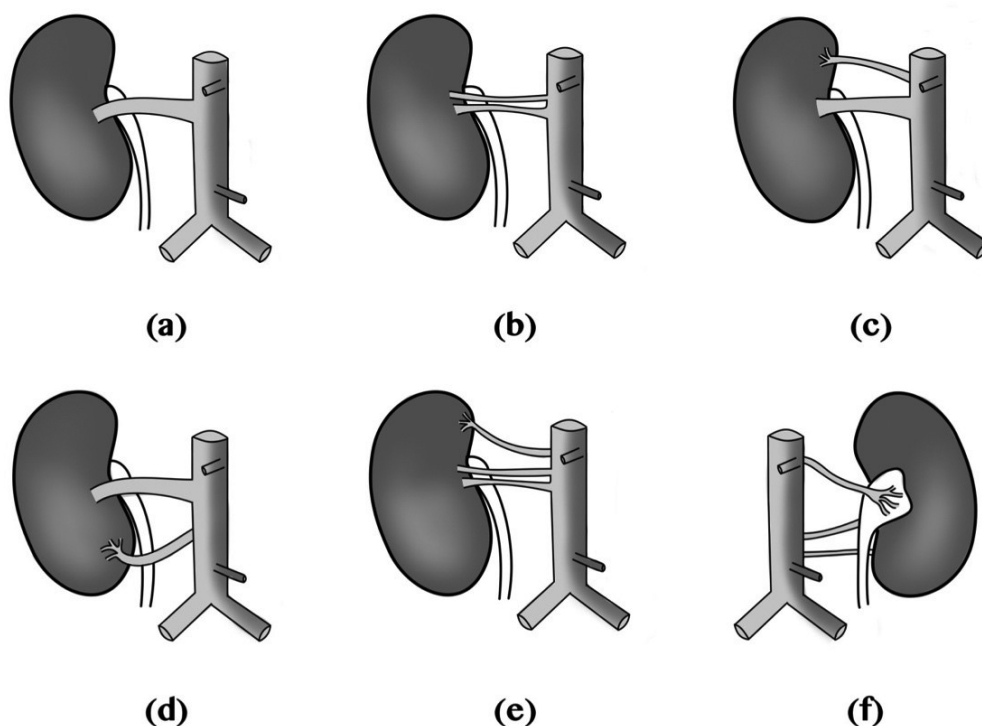
##### 4.2. Sympathetic Innervation and Physiology of the Renal Arteries

RH has been linked to changes in sympathetic outflow and increased renal sympathetic nerve activity (RSNA). Chronic activation of the sympathetic nervous system and RSNA leads to increased levels of catecholamine spillover that affect the renal system and systemic vasculature [48, 49]. Specifically, renal sympathetic efferent and afferent nerves are located adjacent to the adventitious layer of the renal artery and are critical in the increased production of catecholamines that contribute to HTN [50, 51].

Origins of renal sympathetic innervation are observed in the CNS and project from a variety of brain nuclei. Predominantly the raphe nucleus, rostral ventrolateral medulla, an A5 group and the paraventricular nucleus project to the intermediolateral column of the spinal cord [14, 52]. Preganglionic fibers from this column project and exit the spinal cord at the thoracic and lumbar sympathetic trunks. After exiting from the thoracic and lumbar trunks, fibers travel along the sympathetic chain, paravertebral ganglia or the aorticorenal, splanchnic, celiac, and superior mesenteric ganglia. Upon reaching these ganglia, synapses between the pre- and post-ganglionic are created and then projected to the kidney [52]. The sympathetic nerves enter the kidney *via* the renal hilum after traveling near the renal artery [52]. Studies

**Table 2. Most common secondary causes of resistant hypertension and associated pathophysiological explanation.**

Secondary Cause	Effect on Resistant Hypertension
Obstructive Sleep Apnea	If left untreated, intermittent hypoxemia and/or increased upper airway resistance increases sympathetic nervous system activity. Increased reactive oxygen species decrease nitric oxide bioavailability [21, 25, 33, 35].
Chronic Kidney Disease (CKD)	The bidirectional relationship between CKD and HTN represents prevalent comorbidity. Decreased renal function causing sodium and fluid retention, decrease in nitric oxide production, increased sympathetic and renin-angiotensin-aldosterone systems increase drug resistance [21, 25, 33].
Primary Aldosteronism (PA)	PA, with or without hypokalemia, is the most common cause of secondary RH [21]. PA suspected drug resistance is attributed to the inability of salt and water excretion [33, 34, 36-38].
Renal Artery Stenosis (RAS)	Atherosclerotic RAS, as well as fibromuscular dysplasia in younger patients. Decreased renal perfusion pressure leads to an increase in renin, angiotensin, and aldosterone levels with sodium retention [30, 39].



**Fig. (1).** Anatomy of renal arterial supply. Types and incidence rate reported in a study of 534 individuals<sup>40</sup>. **a:** Single Renal Artery (81.64%) **b:** Double Renal Arteries (17.43%) **c:** Single Renal Artery and One Upper Artery (6.93%) **d:** Single Renal Artery and One Lower Artery (3.00%) **e:** Double Renal Arteries and One Lower Artery (0.56%) **f:** Double Renal Arteries and One Upper Artery (0.37%). Illustrations adapted from Khamanarong *et al.*

have demonstrated that as these projections travel into the hilum, there is an increase in renal sympathetic activity, causing contraction of vascular smooth muscles cells of the renal artery [50, 52].

Upon stimulation of efferent sympathetic nerves, individuals demonstrate increased norepinephrine release, increased renin secretion from the juxtaglomerular apparatus, decreased renal blood flow, increased fluid retention and increased renal tubular sodium retention [11, 53]. Elevated levels of renal norepinephrine increase the likelihood of spillover effects, which can contribute significantly to individuals developing primary HTN [54]. The spillover affects local and systemic vasculature *via* alpha- and beta-adrenergic signaling [54, 55]. It is important to note that the renal response to sympathetic activity is necessary for typical cardiovascular homeostasis, but also has implications for developing HTN when a prolonged increase in the renal sympathetic nerve activity causes deficits in renal excretory functions and thus increases arterial pressure [56-58].

Renal afferent fibers project signals to the hypothalamus to stimulate increased sympathetic activity and have been shown to cause hypertension and increased systemic vascular resistance [56]. Changes in renal afferent fiber activity are mediated by mechanoreceptors and chemoreceptors located within the renal pelvic wall adjacent to the renal artery [59, 60]. These fibers facilitate changes through substance P and calcitonin gene-related peptide [50]. Mechanoreceptors respond to the stretch, and chemoreceptors detect renal ischemia [55]. Projections to the hypothalamus and posterior

pituitary increase the release of antidiuretic hormone and oxytocin [55]. The increased sympathetic renal activity also leads to an increase in the release of norepinephrine and renin levels, thus increasing the amount of renal vasoconstriction, with its primary effects arising in the afferent arteriole. This vasoconstriction leads to decreased renal blood flow, lower glomerular filtration rate, and increased tubular reabsorption [53].

## 5. MECHANISM OF RENAL DENERVATION

Despite pharmacological and nonpharmacological efforts to ameliorate the effects of true RH, current therapies often fall short of their goals. In recent years, RDN has been proposed and tested as an alternative to typical treatment regimens [27]. This procedure uses catheter-based radiofrequency or ultrasound energy to ablate the sympathetic nerves in the renal arteries and has been implicated in several animal studies [61-63] and clinical trials to lower BP.

Deleterious effects of the heightened RSNA on pharmacological management, leading to RH, have been explicitly shown and, further, implore for a novel RDN protocol to be established [64]. Increased RSNA leading to RH seems to be indefatigable and unmistakable when measuring renal norepinephrine spillover, which is heightened in individuals experiencing RH. Norepinephrine spillover can be determined *via* isotope dilution measurements of the outward flux of norepinephrine [65-67].

The rationale underpinning catheter-based RDN includes decreases in efferent sympathetic signaling to kidneys and

**Table 3. Current renal denervation catheters and the ablative process.**

Catheter	Mechanism of Ablation
PARADISE™ Renal Denervation System	A transducer at the top of the catheter uses ultrasound energy to ablate sympathetic nerves. High-frequency sound waves are emitted circumferentially. Around the transducer, a water balloon is used, is inflated and allows cooling of the arterial wall and the shape allows uniform distribution of energy. Each ultrasound energy delivery consists of emission of 25 or 30 watts for 7 seconds. Starting in the distal portion of the renal artery, ultrasound energy is delivered to three locations as the catheter is pulled back towards the ostium [70].
OneShot™ Renal Denervation System	Use of an irrigated radiofrequency (RF) balloon with a radio frequency generator located in the center. The balloon has irrigation holes that allow the flow of saline along the electrode to ameliorate damage to non-target tissue. To achieve a spiral pattern of RF energy delivery, a mono-polar silver electrode is mounted on the balloon in a helical configuration. The balloon length is 20 mm and has available diameters of 5, 6, and 7 mm [71].
Vessix™ Renal Denervation System	A balloon catheter with an over-the-wire design allows for the transmission of radiofrequency energy <i>via</i> multiple bipolar electrodes. Electrodes are arranged in a helical pattern. The balloon diameter sizes range from 4 mm up to 7 mm and may have between 4 and 8 bipolar electrodes that vary according to the size. Treatments last 30 seconds and the temperature is maintained at 68°C [72].
EnligHTN™ Renal Denervation System	An expandable catheter with 4 platinum-iridium ablation electrodes that deliver RF to the arterial wall and sense temperature at the site of ablation. The desired temperature is 75°C with each electrode having a maximum magnitude of 6 W. The distal portion of the basket with electrodes is deflectable to allow proper positioning. The diameter of the basket ranges from 4 mm to 8 mm [73, 74].
Symplicity™ Renal Denervation System	A catheter with a monopolar platinum-radium electrode located at the distal tip is connected to a standard dispersive electrode. The design was proposed to allow cooling of the arterial wall by blood flow past the catheter. An 8 W RF is delivered between 4 to 6 times starting in the distal portion of the renal artery and moving proximally with each subsequent delivery [75].

afferent renal signaling to the CNS, reduction in norepinephrine spillover, restoration of natriuresis, increase in renal blood flow, and lower plasma renin activity [48, 68]. As a result of decreased sympathetic tone and NE spillover, reductions in BP may be attributed to a decrease in vascular constriction. Specifically, a decrease in stimulation of the beta-adrenergic receptors of the JGA reduces renin secretion and decreases stimulation of RAAS, thus attenuating increases in volume that are subsequent to typical stimulation [44]. The second includes decreased stimulation to the alpha-adrenergic receptors, a major factor in vascular constriction.

Several different catheters have been developed and used in clinical trials that are discussed below. Results from the recent study, SPYRAL HTN-OFF MED, provide encouragement to the utility of multi-electrode RDN systems [69]. This proof-of-concept trial presented that a novel multi-electrode catheter-based RDN system was utilized in a trial to evaluate the effect of denervation on BP in non-medicated patients with mild to moderate HTN. The study provided evidence that patients assigned to the RDN group exhibited significant reductions in office and 24-hour ambulatory blood pressure [69].

The major goal is to ablate the afferent and efferent sympathetic nerves that may be contributed to pharmacologically resistant RH. The table below discusses and differentiates catheters that have been used in clinical trials including catheters from PARADISE™ Renal Denervation System, OneShot™ Renal Denervation System, Vessix™ Renal Denervation System, EnligHTN™ Renal Denervation System, and Symplicity™ Renal Denervation System (Table 3). Using the femoral artery for access, a catheter is guided to the renal artery.

## 6. TRIALS OF SYMPATHETIC DENERVATION

An eclectic range of clinical trials have been performed using RDN in hopes of ameliorating RH. Below we have discussed all the currently published trials, providing the name of the trial, the study design, the types of catheter used, results and their limitations. The most prevalent system used is the Symplicity™ Renal Denervation System, despite the serious limitations discussed below. Notably, emphasis on the type of study design and the significance of findings should be noted, with a Randomized sham-controlled trial being optimal and single-arm studies being performed early on (Table 4).

## 7. STRENGTHS AND LIMITATIONS OF RDN THERAPY

Currently, the efficacy of RDN in reducing BP is unclear resulting from the inconsistencies of clinical trials. Variable clinical utility of RDN in present clinical trials may be attributed to the numerous limitations of each trial that is cited in the table above. Major contributing factors such as inadequate denervation achievable from current catheter systems, inexperienced operators, drug nonadherence, and perhaps most importantly, no established assessment available to ascertain the extent of denervation achieved by the procedure. These factors may account for the lackluster effects of RDN found in hard outcomes cited in the current literature. One meta-analysis of RDN studies has provided low-quality evidence that the procedure is not significantly associated with a lower risk of myocardial infarction, ischemic stroke, and unstable angina [27].

While each of the clinical trials had its own patient inclusion and exclusion criteria, more precise patient selection

**Table 4. The current catalog of clinical trials in renal denervation, emphasizing the types of research design used, the segregation of groups, the catheter used, primary and secondary endpoints, and the major limitations of each study.**

Trial	Study Design	Groups	Catheter Type	Results	Limitations
Desch <i>et al.</i> [76]	Randomized Sham-Controlled Trial Resistant Hypertension	Denervation (n=35)	Symlicity™ Renal Denervation System	No significant reduction in 24-hour systolic BP at 6 months between groups in intention to treat cohort ( $p=0.15$ ). Significant reduction in 24-hour systolic BP at 6 months between groups in the per-protocol cohort ( $p=0.046$ ).	Smaller sample size increases the probability of type II error, reflected in the discrepancies seen in the intention to treat and per-protocol cohorts, variable ablation times, subjective measure of medication adherence, and use of The Symlicity™ Flex catheter as compared to newer devices with multiple electrodes.
		Sham procedure (n=36)	Simulated procedure		
SYMPPLICITY HTN-3 [77]	Randomized Sham-Controlled Trial Resistant Hypertension	Denervation (n=316)	Symlicity™ Renal Denervation System	No significant between-group difference in the change in office BP at 6 months ( $p=0.26$ ) or in ambulatory BP ( $p=0.98$ ).	Medication adherence was not confirmed, inexperienced catheter operators, placebo effect, Hawthorne effect, and incorrect patient subset.
		Sham procedure (n=158)	Simulated procedure		
DENERHTN [78]	Multicenter Prospective Open-Label Randomized Controlled Trial Resistant Hypertension	Denervation plus SSAHT (n=48)	Symlicity™ Renal Denervation System	Significant reduction in ambulatory systolic BP of denervation group plus SSAHT compared to SSAHT alone at 6 months ( $p=0.0329$ ).	A weak research study using an open-label with blind assessment of ambulatory BP and lack of sham procedure.
		SSAHT (n=52)	SSAHT protocol alone		
PRAGUE-15 [79]	Multicenter Prospective Open-Label Randomized Controlled Trial Resistant Hypertension	Denervation plus optimal antihypertensive treatment (n=52)	Symlicity™ Renal Denervation System	No significant between-group difference in the change in systolic office BP at 6 months or in twenty-four-hour ambulatory blood pressure.	A relatively small number of participants and lack of sham procedure.
		Control (n=54)	Intensified pharmacological treatment		
SYMPPLICITY HTN Japan [80]	Prospective Randomized Controlled Trial Resistant Hypertension	Denervation group (n=22)	Symlicity™ Renal Denervation System	No significant between-group difference in systolic BP ( $p=0.169$ )	A small number of participants, lack of experienced catheter operators, Hawthorne effects, and lack of blinded sham control.
		Control (n=19)	Established antihypertensive therapy		
Global SYMPPLICITY Registry [81]	Multicenter Prospective Open-Label Controlled Trial Resistant Hypertension	Denervation treatment (n=998)	Symlicity™ Renal Denervation System	Significant reduction in office SBP ( $p<0.001$ ) and 24-hour SBP ( $p<0.001$ ) in patients with baseline SBP >140 mmHg	Lack of randomization, lack of defined enrollment criteria, non-standardize follow-up procedures, and most importantly, a lack of a control group.
REDUCE-HTN [72]	Multicenter Prospective Single-Arm Resistant Hypertension Study	Denervation treatment (n=142)	The Vessix Renal Denervation System	Significant reduction in office-based BP at 1 month sustained at 6-month follow-up ( $p<0.05$ )	Weak research design, using a single-arm, increasing the possibility for confounding effects of antihypertensive medications, patient-reported medication adherence, and lack of sham-control group.

(Table 4) contd....

Trial	Study Design	Groups	Catheter Type	Results	Limitations
RAPID [82]	Multicenter Prospective Single-Arm Resistant Hypertension Study	Denervation treatment (n=50)	OneShot™ Renal Denervation System	Significant reduction in SBP/DBP at 1, 3, 6, 12 months ( $p<0.0001/p=0.0009$ , $p=0.0002/p=0.0014$ , $p<0.0001/p=0.0002$ , and $p<0.0001/p=0.0014$ )	Lack of a control arm, small sample size, and poor adherence to baseline drug regimen.
Fadl Elmula et al. [83]	Prospective Randomized Controlled Trial Resistant Hypertension	Denervation treatment (n=9)	Symplicity™ Renal Denervation System	SBP and diastolic BP were significantly lower in the drug-adjusted group at 6 months ( $p=0.002$ , $p=0.004$ , respectively)	A small number of patients and lack of sham control group.
		Control (n=10)	Clinically adjusted drug treatment		
ENCOREd meta-analysis [84]	Meta-analysis of Randomized Clinical Resistant Hypertension Trials	Denervation treatment (n=588)	Symplicity™ Renal Denervation System and optimized antihypertensive treatment	No significant reduction in office SBP and 24-hour SBP ( $p=0.47$ , $p=0.11$ )	Limitations are based on studies that are reviewed in the meta-analysis, including but not limited to, lack of sham group and small number of participants.
		Control (n=397)	Optimized antihypertensive treatment		
ABPM meta-analysis [85]	Multicenter Prospective Single-Aim Resistant Hypertension Study	Denervation treatment (n=303 True RHTN)	Symplicity™ Renal Denervation System	Office and 24-hour SBP and DBP was significantly reduced at 3, 6, and 12-month follow-up ( $p<0.001$ for all)	Limitations are based on studies that are reviewed in the meta-analysis, including but not limited to, lack of sham group and a small number of participants.
Heidelberg registry [86]	Single Center Prospective Resistant Hypertension Study	Denervation treatment (n=63)	Radiofrequency-based Symplicity™ catheter	Significant reduction in office SBP at 6 months ( $p<0.005$ )	Presence of pseudo-RHTN was not ruled out in all participants, lack of sham control group, lack of 24-hour ABPM, and suboptimal therapy in certain patients (n=10)
EnligHTN-1 [73, 74]	Multicenter Prospective Non-Randomized Resistant Hypertension Study	Denervation treatment (n=46)	EnligHTN™ Ablation Catheter	Significantly reduced office SBP and DBP at 1, 3 and 6 months ( $p<0.0001$ )	Small sample sizes and lack of concurrent sham-control group.
Moderate CKD [87]	Prospective Non-Randomized Resistant Hypertension and CKD Study	Denervation treatment (n=15)	Symplicity™ Renal Denervation System	Significantly reduced office SBP and DBP ( $p<0.05$ ). and significantly reduced tight-time ambulatory BP ( $p<0.05$ ) without acute changes in GFR at 6-month follow up.	A small number of participants and lack of sham-control group.
SYMPPLICITY HTN-2 [88]	Multicenter Prospective Randomized Resistant Hypertension Study	Denervation treatment (n=49)	Symplicity™ Renal Denervation System	Significant reduction in SBP and DBP in denervation compared to control group at 6-month follow up ( $p<0.0001$ ) without changes in renal function.	Limitations included a small number of participants and lack of sham-control group.
		Control (n=51)	Optimized antihypertensive treatment		
SYMPPLICITY HTN-1 [89]	Open-Label Non-Randomized Resistant Hypertension Study	Denervation treatment (n=88)	Symplicity™ Renal Denervation System	Significant reduction in SBP and DBP at 36-month follow up ( $p=0.05$ ).	Limitations included small number of participants and lack of sham-control group.

**Abbreviations:** SSAHT, standardized stepped-care antihypertensive treatment; DBP, diastolic blood pressure; SBP, systolic blood pressure.



may be necessary to determine RDN's true efficacy, albeit difficult. An important consideration to add to future studies criteria is the assessment of SNS activity. Currently, the readily available tests are urine and plasma NE concentrations, which are imprecise [90]. Testing the activation of renal sympathetic outflow *via* NE spillover measurements elucidates a more specific and efficacious measurement for inclusion criteria [90]. It has also been suggested that younger patient cohorts may be more responsive to RDN treatments, as they have a shorter duration of experiencing hypertensive vascular remodeling and may be reversible [90, 91].

## 8. FUTURE DIRECTIONS AND PERSPECTIVES

The last 3 years have been a rocky road for RDN as a treatment modality for RH. The unexpected results from the Symplicity HTN-3 [77] trial raised a series of important questions relating more generally to the clinical concept of treatment-resistant hypertension and its management, and more specifically to the efficacy of RDN as a therapeutic approach to lower BP. Importantly, after a period of astonishment, perplexity, and reflection, these findings triggered a large number of experimental and additional studies in humans to better understand the anatomical, physiological, and technical subtleties surrounding this therapeutic concept. We have learned a great deal in the many aspects summarized above, and the latest evidence available from both experimental and human investigations paired with ongoing studies addressing some of the most pressing issues such as direct assessment of the efficacy of current RDN approaches to actually achieve sufficient denervation of the kidney, justify an optimistic outlook. At this stage, RDN remains a viable option for the treatment of resistant hypertension.

The initial inception of RDN was followed with a copious amount of support in the scientific community. Early clinical trials provided substantial evidence that the use of RDN can lower BP in patients with RH. However, many of these trials lacked a sham control, and the recent findings from RCT sham-controlled trials have presented varying evidence regarding the efficacy of RDN on BP reduction. The true efficacy of RDN cannot be ascertained until further research provides trials that address the problems illuminated in past literature.

Albeit primary and secondary endpoints have been suboptimal in certain trials, these trials were able to establish rudimentary principles that are not trivial components of RH. Importantly, it has been noted that efferent renal sympathetic can be ablated with luminal RF and ultrasonic energy, BP reductions were achieved, lasting beyond 3 years of follow-up, without damage to renal function, and RDN has rarely caused new renal artery stenosis [64, 89].

Deleterious effects of the heightened RSNA on pharmacological management, leading to RH, have been explicitly shown and, further, implore for a novel RDN protocol to be established [64]. Increased RSNA leading to RH seems to be indefatigable and unmistakable when measuring renal norepinephrine spillover which is heightened in persons experiencing RH. Norepinephrine spillover can be determined *via*

isotope dilution measurements of the outward flux of norepinephrine [65-67]. The heightened activity of RSNA has additional effects on the juxtaglomerular apparatus secretion of renin, sodium reabsorption, renal blood flow and decreases in natriuresis [44].

As previously stated, norepinephrine spillover is a crucial component in developing resistance to standard pharmacological agents used to treat HTN [48, 68]. Despite the myriad of literature owing to its importance and validity of the regional measurement of norepinephrine spillover, only a single clinical trial (SYMPPLICITY-1) confirmed denervation *via* local spillover measurements [3, 64, 89]. Information gathered from future studies needs to include norepinephrine spillover measurements in conjunction with distal renal artery ablation to develop a protocol which will allow practitioners to responsibly increase RF or ultrasonic energy delivery points [92, 93].

Novel RDN protocols must also account for the density of nerve bundles that reside distal to the renal artery, as previous studies that have been suboptimal have focused ablation on the proximal portion of the renal arteries [77, 94]. Moreover, the variable micro-anatomy of the surrounding tissues juxtaposed to the renal arteries. Idiosyncrasies in an individual's lymphatic tissue, fibrous muscle sheaths, veins, and skeletal muscle distort RF energy delivery to the sympathetic nerve bundles [47, 64]. The perivascular anatomy may either deflect RF energy and/or limit ablation depth by absorbing energy before reaching nerves [47, 64].

Additionally, increased scrutiny on research design must be implemented in future studies that will attempt to aid in determining the actual effectiveness of RDN in RH [95]. It is imperative for future trials to include sham procedures, 24-hour ambulatory blood pressure recordings as primary endpoints, increased efficacy, and precision of operators of ablation devices, in addition to knowledge of the variations in perivascular anatomy that facilitate inconsistent RF energy delivery [90, 96].

## CONCLUSION

HTN, characterized by a BP higher than 130/80 mmHg, affects more than 1 billion people worldwide [2]. Patients with HTN are at increased risk for stroke, cardiovascular disease, and chronic renal failure [2, 3]. Recent advancements in pharmacology and awareness have increased the ability of physicians and patients to manage HTN. Despite this, a subset of individuals with HTN is unable to reduce BP with optimal non-pharmacological and pharmacological treatments. Specifically, RH is defined as patients taking three different classes of antihypertensive medications, including a diuretic, and not achieving BP lower than 140/90 mmHg [8].

Current literature has provided an eclectic range of studies supporting the connection between increased outflow of the RSNA and its connection to RH [11, 53]. Increased activity leads to increased sympathetic discharge from efferent and afferents located within the renal artery. Overall, increased sympathetic tone causes increased NE spillover, disrupts natriuresis, decreases renal blood flow, increases

RAAS stimulation, and increases vasoconstriction [11, 53]. This information is underpinning the rationale for catheter-based RDN as a promising therapeutic option [64, 97]. Ablation of afferent and efferent nerves in the renal artery is suspected to reverse the effects of increased RSNA.

#### CONSENT FOR PUBLICATION

Not applicable.

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None.

#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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