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Coronary Artery Disease (D Feldman and V Voudris, Section Editors)

Renal Artery Denervation for Hypertension

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Abstract

Purpose of review Hypertension (HTN) has a growing impact, already affecting over 1 billion people. An estimated 2–16% of those with HTN have resistant HTN. The sympathetic nervous system (SNS) is a recognized contributor to the pathophysiology of resistant HTN. Current hypertensive pharmacotherapy has not fully targeted the SNS; therefore, the SNS has become a prominent research therapeutic target. This review summarizes the evidence and rationale behind renal denervation (RDN) therapy and the technology available.

Recent findings Prior to the SYMPLICITY HTN-3 clinical trial, trials found RDN to be an effective procedure to control resistant hypertension. The failure of SYMPLICITY HTN-3 to meet its primary efficacy endpoint sparked further studies to address potential shortcomings. The subsequent SPYRAL program trials demonstrated efficacy of RDN therapy in a controlled manner; however, they were not adequately powered. Ongoing research is examining new, innovative RDN technology as well as defining appropriate patients to target for treatment.

Summary The data currently available for RDN in HTN and other states of SNS activation suffer from potential biases and limitations, highlighting the need for continued exploration. Contemporary studies are more promising and hypothesis-generating. Future trials and continued device innovation will be crucial for understanding the clinical applications of RDN therapy.

Introduction

Epidemiology of hypertension

Hypertension (HTN) impacts over 1 billion adults worldwide, including more than 30% of the population over 20 years of age [1–3]. Globally, the number of individuals with HTN has increased by close to 500 million since 2000, with a majority of this increase in low and middle income countries [1]. It is projected that by 2030, ~ 41.4% of US adults will have HTN, defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg [4] and higher if threshold of SBP ≥ 130 mmHg is used.

High blood pressure (BP) is a major cause of mortality, accounting for an estimated 7.6 million deaths annually worldwide. It is also a significant risk factor for cardiovascular and cerebrovascular disease and contributes to ~ 50% of coronary heart disease and stroke [5]. With this knowledge has come the introduction of new guidelines that incorporates lower blood pressure goals, with hope that this will translate into a reduction in cardiovascular and cerebrovascular disease events. In comparison to prior HTN guidelines, the 2017 American College of Cardiology/American Heart Association guideline for prevention, detection, evaluation, and management of high blood pressure in adults recommends treating SBP/DBP to < 130/80 mmHg for all adults [6]. Data from the US National Health and Nutrition Examination Surveys (NHANES) from 2011 to 2014 shows the prevalence of HTN to be 45.6% according to the new guideline definitions, increasing the number of US adults with HTN from 72.2 million to 81.9 million [7].

What is resistant hypertension

Resistant HTN is an increasingly common clinical problem encountered by both primary care physicians and specialists. The American Heart Association defines resistant HTN as blood pressure above goal despite concurrent use of at least three antihypertensive medication classes, with one ideally being a diuretic and all agents prescribed at doses that provide optimal benefit [8]. Estimates on the prevalence of resistant HTN vary between 2 and 16% of the hypertensive population [4, 9, 10]. According to NHANES, this has increased over time from 5.5% in 1988 to 1994, 8.5% in 1999 to 2004, and more recently, 11.8% in 2005 to 2008 [4].

The strongest predictor of lack of BP control is older age, specifically those greater than 75 years have a fourfold increased risk of difficult to control pressure [11, 12]. Other risk factors for treatment resistance include higher baseline SBP, chronic kidney disease (serum creatinine greater than 1.5), obesity, and left ventricular (LV) hypertrophy [11, 13]. Furthermore, patients with resistant HTN are at higher risk for future adverse events, particularly cardiovascular events [9]. The lack of efficacy of pharmacologic therapy in managing this condition emphasizes the importance of finding new effective treatment options.

The underlying cause of resistant HTN is poorly understood but is almost always multifactorial. In addition to lifestyle factors, such as obesity, dietary salt, and alcohol intake, medications such as nonsteroidal anti-inflammatory medications can also contribute to treatment resistance. Despite appropriate lifestyle and pharmacologic therapy, there is a subset of patients with persistent and poorly controlled HTN, thereby renewing interest in the role of the sympathetic nervous system (SNS) in this condition.

The rationale for renal denervation

The central SNS effects on BP were understood as early as the 1900s and further elucidated with testing in both human and animal models [14, 15]. This "neuroadrenergic hypothesis" of HTN involves the renin-angiotensin system (RAS), as the SNS and the RAS are closely linked. The renal SNS plays a crucial role in regulation of sodium excretion, renin secretion, and renal hemodynamics [16]. The kidneys are innervated by two sets of sympathetic nerves: the efferent sympathetic nerves from the CNS and the afferent sympathetic sensory

nerves from the kidneys to hypothalamus. The efferent fibers to the kidney arise from the second sympathetic ganglion and form a network within the renal artery adventitia [17]. Increased renal sympathetic nerve activity contributes to rise in BP through three main mechanisms: (1) tubular reabsorption of urinary sodium and therefore water, (2) reduction of renal blood flow, and (3) release of renin, thereby activating the RAS cascade. Most of the actions of the RAS are executed by Angiotensin II. Angiotensin II acts as a powerful vasoconstrictor in multiple organs, is involved in regulation of renal sodium and water excretion directly and indirectly via aldosterone secretion, and participates in vascular, tubular, and growth-promoting activities in the kidney [18, 19]. The RAS system has therefore been a prominent therapeutic and research target in HTN over the past few decades.

Traditional hypertensive pharmacotherapy has been inadequate in targeting the central SNS [19]. Regional splanchnicectomy was trialed in the mid 1900s but associated with significant morbidity and mortality [20]. This, however, provided the basis for further research and investigation of innovative approaches including percutaneous renal sympathetic denervation.

The renal denervation (RDN) procedure itself is minimally invasive and involves endovascular access via the femoral artery. A catheter-mounted device is advanced into the renal artery and uses radiofrequency, ultrasound, or medications to non-selectively ablate both inbound and outbound neural fibers causing global renal denervation (Fig. 1). Fluoroscopy with radio-opaque contrast is used to position the RDN catheter. Intravenous heparin is administered during the procedure. The procedure generally takes < 1 h with catheter

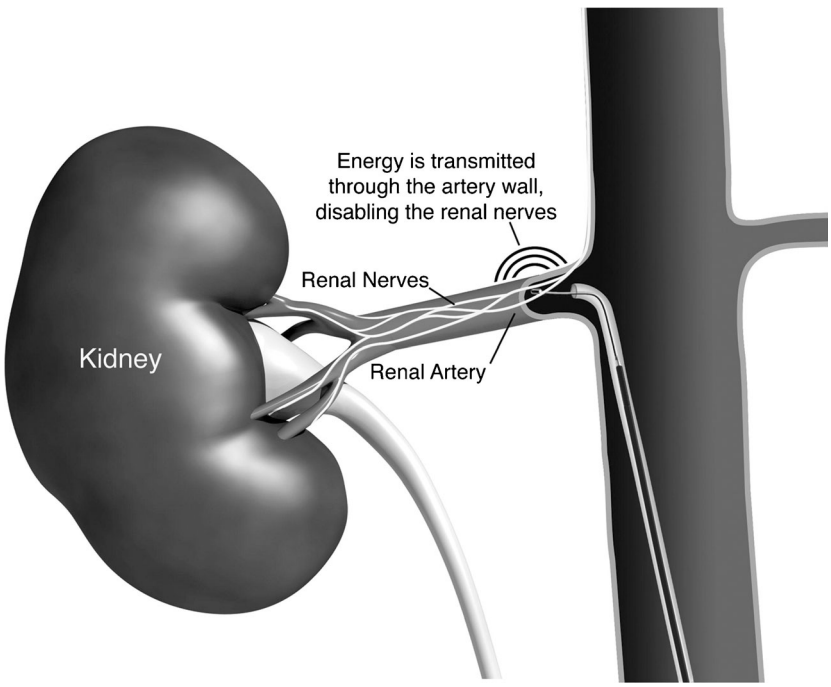

Fig. 1. Schematic representation of catheter-based renal denervation technique. In this procedure, a specialized catheter is positioned in the renal artery and utilized to deliver ablative energy to the luminal surface. Reprinted with permission from Rocha-Singh K. Catheter-based renal denervation for blood pressure reduction. *Cath Lab Digest* 2009 June;17(6):8–11. Copyright HMP.

and femoral sheath removal at the end of the case, similar to a cardiac catheterization.

Initial renal denervation clinical trials

SYMPLICITY HTN-1 was the first proof-of-concept trial to evaluate RDN in a cohort of 45 patients [21•]. At 12 months, office-based blood pressure (OBP) measurement was reduced by 27/17 mmHg. Both the initial results of this trial and subsequent results at 36-month post-intervention showed a significant reduction in OBP compared with standard medical therapy, thereby triggering further interest in RDN therapy [22, 23]. A similar beneficial effect of RDN therapy was seen in the first randomized controlled trial, SIMPLICITY HTN-2. In a cohort of 106 patients, OBP measurements in the RDN group were reduced by 32/12 mmHg, with a between-group difference at 6 months of 33/11 mmHg [24•]. Critics raised multiple concerns about SYMPLICITY HTN-1 and SYMPLICITY HTN-2 trials including the following: (1) the trial was not blinded, (2) the absence of a sham-controlled design, (3) the secondary causes of HTN were not excluded, (4) the medication adherence was not measured in the control group, (5) the absence of differentiation between OBP and ambulatory blood pressures (ABP), and (6) the need for further characterization of renovascular safety of RDN therapy. Later trials incorporated ABP, given that ABP is 30–40% lower than OBP [25]. Additionally, there were incomplete data regarding optimal vascular sites of ablation and lack of data on procedural durability. These concerns were the catalyst for the design and execution of subsequent studies.

SYMPLICITY HTN-3, a randomized, sham-controlled study with 535 patients, addressed many of the shortcomings of initial RDN trials [24•, 26•, 27]. In addition to having a sham arm, the use of ABP monitoring minimized measurement error, white-coat effect, and had greater reproducibility of patients' BP [27]. Surprisingly, SYMPLICITY HTN-3 failed to demonstrate a BP-lowering effect of RDN compared to the sham control group at both 6 and 12-month post-randomization. A between-group difference of 2.4 mmHg and 2.0 mmHg was seen in OBP and 24 h ABP measurements, respectively [26•, 28]. Randomization in this study was also stratified by race (African American versus non-African American) and by study center. There was a significant reduction in office SBP in the non-African American subgroup receiving RDN therapy compared with sham (6.6 mmHg between group difference, $P = 0.01$). The largest reduction in office SBP (7.1 mmHg) was seen in the non-African American patients not on vasodilators. Baseline medication prescriptions between the two subgroups were examined, and African American patients were more likely to be prescribed vasodilators [29•]. Potential shortcomings in the execution of this study discussed in post hoc analysis were (1) trial medications were not standardized or prescribed according to guidelines and (2) lack of standardization with regard to operator experience, number of ablation per artery, and ablation location. Additionally, it is noteworthy that 40% of trial participants required changes in medication regimen for various reasons and it is unknown the effect of this on the primary efficacy outcome.

Post hoc analysis of the SYMPLICITY HTN-3 trial identified factors that should be considered regarding patient cohort selection in future investigation. One multivariate analysis identified baseline SBP ≥ 180 mmHg, non-use of vasodilators, and non-use of aldosterone antagonist use as positive predictive factors of reduction in office SBP at 6 months after RDN therapy. Additionally, the number of ablations (> 9) and ablation in all four quadrants of the renal artery was positively predictive for reduction in office SBP. Racial differences in effectiveness of RDN therapy were also noted as discussed above [29•]. Another study by Kario et al. found obstructive sleep apnea patients to be more responsive to RDN compared to the sham group [30].

The DENERHTN trial, published in 2015, addressed concerns regarding earlier trials' lack of antihypertensive standardization [31]. The incremental benefit of adding RDN to standardized stepped-care antihypertensive treatment (SSAHT) for patients with resistant HTN was assessed. Patients were placed on a standardized antihypertensive regimen for 4 weeks to confirm resistant HTN. After this, patients were randomized to RDN in addition to SSAHT versus SSAHT alone. Additionally, drug adherence was assessed at every clinic visit using the Morisky Medication Adherence Scale questionnaire. The results of this trial were different from the SYMPLICITY HTN-3 and somewhat perplexing. RDN plus SSAHT was effective at reducing ABP, showing a 6 mmHg greater reduction in 24 h ABP compared to medication alone. However, there was no significant difference in OBP between the groups. There was a high degree of medication noncompliance in this trial, close to 50%; however, there was no difference in treatment adherence between the groups [32••]. Table 1 summarizes the initial RDN clinical trials.

SYMPLICITY HTN-3 and DENERHTN trials ignited interest in the technical aspects of RDN therapy, as well as further analyses to better characterize patient populations that may be more responsive to RDN. Numerous companies then began to focus on optimizing novel RDN system and catheter designs and advanced ablation technologies with the renal nerve anatomy in mind. For these reasons, SYMPLICITY HTN-4, which was planned to follow SYMPLICITY HTN-3 to investigate patients with solely moderate uncontrolled HTN (SBP 140–160 mmHg)], was halted early after the negative results of SYMPLICITY-HTN 3 were released.

Device innovation

Current RDN therapy utilizes energy, either radiofrequency or ultrasound, to disrupt renal nerves within the renal artery wall, thereby reducing sympathetic efferent and sensory afferent signaling to and from the kidneys.

Early SYMPLICITY trials (1–3) used a single-node renal denervation catheter (Symplicity Flex) in the main renal arteries before branch bifurcation. This catheter delivered multiple ablations; however, it was operator-dependent as the catheter had to be repositioned for each ablation. Additionally, RDN in only the main renal artery may have a negative effect on success of ablation, as nerve density is thought to be greater in the distal portion of the artery [36, 37]. In animal models, targeted treatment of the renal artery branches or distal segment

Table 1. Summary of renal denervation trials

Trial name and year	SYMPLICITY HTN-1 [21•], 2009	SYMPLICITY HTN-2 [24•], 2010	SYMPLICITY HTN-3 [26•, 28], 2014	DENERHTN [31], 2015	SPYRAL HTN-OFF MED [33••], 2017	SPYRAL HTN-ON MED [34••], 2018	RADIANCE-HTN SOLO [35••], 2018
Design	Open-label, cohort, proof-of-concept trial	Open-label, international, prospective, RCT	Prospective, single-blind, sham-controlled, RCT	Prospective, multicenter, open-label, RCT	International, single-blind, sham-controlled, proof-of-concept, RCT	International, single-blind, sham-controlled, proof-of-concept, RCT	International, multicenter, single-blind, sham-controlled, RCT
Major inclusion/ exclusion criteria	1. SBP ≥ 160 mmHg despite treatment with ≥ 3 antihypertensive meds, including 1 diuretic or confirmed intolerance to meds 2. eGFR ≥ 45 mL/min per 1.73m^2 3. Age 18 years 4. Exclusions: renovascular abnormalities, valvular disease, DM1, ICD or pacemaker, treatment with clonidine, moxonidine, rilmenidine, or warfarin	1. SBP ≥ 160 mmHg (≥ 150 mmHg for patients with DM2), despite taking ≥ 3 antihypertensive meds 2. Age 18–85 years 3. Exclusions: stenotic valvular heart disease, pregnancy, ACS/CVA in previous 6 months, renal artery stenosis, previous renal artery intervention, eGFR < 45 mL/min per 1.73m^2, DM1, renal artery < 4 mm in diameter, or renal segment < 20 mm	1. Office SBP ≥ 160 mmHg on ≥ 3 antihypertensive meds, including diuretic 2. Age 18–80 years. 3. Exclusions: ambulatory SBP < 135 mmHg, eGFR < 45 mL/min per 1.73m^2, secondary cause of HTN, > 1 hospitalization for HTN emergency in the previous year, renal artery stenosis > 50%, renal artery aneurysm, prior renal artery intervention, renal artery < 4 mm in diameter, or renal segment < 20 mm	1. Age 18–75 years 2. Office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, despite ≥ 3 antihypertensives, including 1 diuretic 3. Suitable renal artery anatomy on CTA, MRA or angiogram in past year 4. Exclusions: secondary HTN, eGFR < 40 mL/min per 1.73m^2	1. Drug-naïve or discontinued treatment 2. Age 20–80 years 3. Office SBP 150–180 mmHg AND mean systolic ABP 140–170 mmHg at second screening 4. Office DBP ≥ 90 mmHg	1. Age 20–80 years 2. Office SBP 150–180 mmHg AND systolic ABP 140–170 mmHg at second screening 3. Office DBP ≥ 90 mmHg 4. 1–3 antihypertensive meds	1. Age 18–75 years 2. ABPM 140/90–180/110 mmHg on 0–2 antihypertensive meds OR < 140/90 on 1–2 antihypertensive meds 3. eGFR ≥ 40 mL/min per 1.73m^2 4. Exclusions: ACS or CVA events
Number of participants	45	RDN = 52, control = 54	RDN = 364, sham = 171	RDN = 53, control = 53	RDN = 38, sham = 42	RDN = 38, sham = 42	RDN = 74, sham = 72
Mean age (years)	58	RDN = 58, control = 58	RDN = 57.9, sham = 56.2	RDN = 55.2, control = 55.2	RDN = 56, sham = 53	RDN = 53.9, sham = 53.0	RDN = 54.4, sham = 53.8
Primary endpoint	Office-based SBP reduction of ≥ 10 mmHg at 1, 3, 6, 9, 12 months; ≥ 20 mmHg (rigorous measure of response)	Between-group in average office SBP from baseline to 6 months	Between-group in average office SBP from baseline to 6 months	Mean in daytime ambulatory SBP from baseline to 6 months	Between-group in ABP from baseline to 3 months	Between-group in ABP from baseline to 6 months	Mean in daytime ABP from baseline to 2 months
Efficacy results	Significant reduction in SBP and DBP (P = 0.026 for SBP, P = 0.027 for DBP)	Significant reduction of BP at 6 months in the RDN compared to control group (33/11 mm Hg, P < 0.01 for SBP and DBP)	No significant reduction in BP at 6 months between RDN and sham arm (absolute difference 2.39 mmHg, 95% CI – 6.89 to 2.12, P = 0.26)	Significant reduction in baseline to 6 months SBP in RDN group compared to control (RDN group – 15.8 mmHg vs control – 9.9 mmHg, P = 0.033)	Significant reduction at 3 months for the RDN group compared to sham for 24-h ambulatory SBP and office SBP. (SBP difference 5 mmHg, DBP difference 4.4 mmHg). Same difference was documented for 24-h DBP and office DBP (SBP 7.7 mmHg, DBP 4.9 mmHg)	Significant reduction of ABP at 6 months in RDN group. 24-h ambulatory SBP 9.0 mmHg vs 1.6 mmHg (P = 0.005), 24 h DBP 6.0 vs 1.9 mmHg (P-0.03). Office BPs with same results.	Significant reduction in daytime ABP at 2 months in RDN group (– 8.5 mmHg vs – 2.2 mmHg, P = 0.0001).

ABPM ambulatory blood pressure monitoring, *ACS* acute coronary syndrome, *CI* confidence interval, *CVA* cerebrovascular disease, *DBP* diastolic blood pressure, *DM* diabetes mellitus, *HTN* hypertension, *RCT* randomized controlled trial, *RDN* renal denervation, *SBP* systolic blood pressure

of the main renal artery resulted in a greater reduction in axon density compared to conventional treatment of the main renal artery [38]. This perhaps has profound clinical implications for reductions in sympathetic activity.

Improved understanding of renal anatomy has led to the innovation of new technology. The next-generation Symplicity catheter, the Symplicity Spyral catheter, is a multielectrode, helical catheter that is able to deliver circumferential ablations to both the renal artery and branch vessels. This catheter also has a self-expandable design that enables it to be placed in smaller caliber renal artery branches (3-8 mm in diameter). Additionally, it uses a cooling balloon to reduce risk of heat-induced tissue damage.

Multiple subsequent multielectrode devices have also emerged (Table 2). The EnligHTN catheter was designed with an expandable electrode basket, with the basket coming in two sizes. Each basket activation results in four ablations. The Vessix Vascular V2 system and OneShot are both balloon catheters. The Vessix Vascular V2 balloon system minimizes energy loss in the blood stream by occluding the renal artery. This catheter is available in multiple sizes, and the electrodes are placed in direct contact with the renal artery allowing precise treatment. The OneShot catheter is one of the only irrigated systems. Irrigation with saline is delivered throughout the procedure along the electrode to minimize endothelial tissue damage, facilitating prolonged contact times. Overall, multielectrode catheters significantly shorten overall procedure time and deliver RF in a more predictable way.

More recently, ultrasound RDN technologies have been tested. The Paradise system is a balloon catheter that has cooling fluid within it to allow simultaneous RDN and cooling. There is no direct contact between the ablation probe and endothelium, minimizing endothelial damage. The balloon is positioned in the center of the artery, allowing energy to be delivered uniformly. It takes 7 s for this system to disrupt renal nerves at a depth of 1 to 6 mm. Table 2 details the abovementioned devices.

Innovation of RDN technology is still ongoing. Ultrasound RDN devices are the furthest along in testing and show promise for a non-invasive method without any known major safety issues. The Kona Medical system delivers focused energy from an external probe with real-time monitoring using external imaging [44]. Other techniques less validated are cryoablation, ionizing radiation, and pharmacologic ablation. Cryoablation, cooling of tissues to ≤ 40 °C resulting in intracellular crystal formation and death, has shown efficacy in pilot studies for patients who are non-responders to radiofrequency RDN [45]. Ionizing radiation for neural ablation using the CyberHeart radiosurgery system has successfully demonstrated ablation of renal sympathetic nerves in a preclinical porcine animal model. Norepinephrine levels were evaluated and shown to be significantly lower post procedure, providing further evidence of neural destruction [46]. Lastly, pharmacologic ablation technology has the potential to precisely achieve near complete nerve ablation without injury to surrounding structures. One such system is the Peregrine System. This device has three microneedles that inject alcohol directly into the adventitial and periadventitial space. First-in-human experience with this approach of chemical neurolysis has shown promising results [47]. Other neurolytic agents, such as vincristine, are under investigation which will

likely lead to the testing and innovation of more chemical-based RDN technology [48].

Contemporary clinical trials

The SPYRAL research program incorporated many of the lessons learned from previous trials, including a greater focus on patient selection to create a more homogenous population and on average, more ablations involving distal artery and branches compared with SYMPLICITY trials. These studies included 80 patients.

SPYRAL HTN-OFF MED is a sham control RCT that evaluated RDN therapy in the absence of any antihypertensive medication [33••]. Prior to randomization, patients in this study underwent a medication washout period of 3–4 weeks. RDN therapy was applied using the Symplicity Spyral multi-electrode catheter (Medtronic Inc.) and the Symplicity G3 (Medtronic Inc.) generator. To minimize technical variability, the trial restricted the procedure to one physician per trial center. The SPYRAL HTN-OFF MED trial demonstrated a significant and substantial reduction in both office BP and 24-h ABP at 3-month post-randomization (7.7/4.9 mmHg office BP and 5.0/4.4 mmHg 24-h ABP) [33••]. This study also eliminated many confounding factors in evaluation of RDN therapy and provided biologic proof of efficacy of RDN therapy in reducing BP. Soon after these results, SPYRAL HTN-ON MED showed ongoing efficacy of RDN therapy in the setting of antihypertensive medication use. In contrast to SPYRAL HTN-OFF MED, the patients included in SPYRAL HTN-ON MED had poorly controlled BPs in the setting of up to three standard antihypertensive medications [34••]. At 6 months, 24-h ABP and OBP significantly declined in those who received RDN therapy (7.4/4.1 mmHg 24-h ABP and 7.7/3.5 mmHg OBP). The characteristics and primary efficacy results of these clinical trials are detailed in Table 1.

Although SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED both demonstrated efficacy of RDN therapy in a controlled manner, they were not powered for efficacy endpoints due to their small sample sizes. The use of Spyral catheters in these studies standardized RDN; however, there remains no practical method to verify renal nerve destruction. Lastly, the SPYRAL HTN-ON MED patient population included those with mild to moderate HTN and excluded those with office SBP > 180 mmHg. This differs from patients included in the clinical trials prior to SPYRAL, who had severe resistant HTN, SBP ≥ 160 mmHg.

The RADIANCE-HTN trial was designed to minimize the confounding effect of antihypertensive medications, medication adherence, and placebo effect. This study evaluates patients in two cohorts, SOLO in the USA and TRIO in Europe. In RADIANCE-HTN SOLO, patients with mild to moderate systolic and diastolic HTN were randomized to either RDN or sham procedure after a 4-week medication washout period. All patients remained off antihypertensives until 2 months after randomization unless BP was too high at follow-up, office BP ≥ 180/110 mmHg or home BP ≥ 170/105 mmHg. Early results from the RADIANCE-HTN SOLO trial have shown overall reductions in BP in the RDN group at 2 months, similar to those seen in SPYRAL HTN-OFF MED. The primary outcome, daytime ambulatory SBP, declined by 8.5 mmHg in the RDN

Table 2. RDN devices

Device type	Symplicity Flex	Symplicity Spyral	OneShot	EnligHTN	Vessix Vascular	Paradise System
Manufacturer	Medtronic	Medtronic	Covidien	St. Jude	Boston Scientific	ReCor Medical
Size (French)	6F	4/6F	7F	8F	8F	6F
Energy (RF/US)	RF	RF	RF	RF	RF	US
Electrode/ polarity	1, unipolar	4, unipolar	1, unipolar	4, unipolar	8, bipolar	1 transducer
Design	Single-tip catheter, delivers series of ablations in a helical pattern	Monorail with spiral distal tip, electrodes fire simultaneously	Over-the-wire balloon with surrounding spiral electrode	Basket catheter containing electrodes, electrodes fire simultaneously	Over-the- wire balloon with helical pattern of electrodes, electrodes fire simultaneously	Distal, pressurized fluid-filled balloon that delivers US energy circumferentially
Procedure	4–8 ablations, 2 min each	4 ablations, 1 min	1 ablation, 2 min	2 basket activations, 6 min/activation	8 ablations, 30 s	2 sonifications, 7 s each
Irrigated	No	No	Yes	No	No	Yes
Study	SYMPLICITY HTN-1 [21•] SYMPLICITY HTN-2 [24•] SYMPLICITY HTN-3 [26•]	SPYRAL HTN-OFF MED [33••] SPYRAL HTN-ON MED [34••]	RHAS [39] RAPID [40]	EnligHTN [41]	REDUCE-HTN [42]	RADIANCE-HTN [35••] REQUIRE [43]

US ultrasound, *RF* radiofrequency

group versus 2.2 mmHg in the sham group ($P = 0.0001$) [35••]. Only initial 2-month results have been released, but patients will be followed for 3 years. Analysis of the RADIANCE-HTN SOLO trial has highlighted the importance of completeness of ablation. The effect of RDN was approximately halved, damped BP reduction by 5.5 mmHg, when renal accessory arteries < 2 mm were not treated. This finding will likely lead to further refinement of the procedure and devices to achieve ablation of smaller arteries [49].

More recently, a three-arm randomized trial, RADIOSOUND-HTN, compared RDN devices and techniques and indicates further promising results for ultrasound ablation. In this study, patients were randomized to 1 of 3 groups: (1) RDN of main renal arteries only using Symplicity Spyral catheter, (2) RDN of main renal arteries and accessories using Symplicity Spyral catheter, or (3) RDN of main renal arteries using Paradise catheter. Those use received ultrasound RDN of the main renal artery had a greater reduction in BP compared to those who received RF ablation (– 13.2 vs 6.5 mmHg at 3 months, $P = 0.042$). There was no difference in BP reduction in the patients who received RF ablation of the main renal artery and accessories compared to either group [50••]. Although a starting point, multicenter studies with longer follow-up are needed for further head-to-head comparisons.

Renal denervation safety

The reporting of complications or adverse effects associated with RDN therapy is non-standardized, and most published studies include a short duration of follow-up, between 6 months and 1 year. The composite complication rate is estimated to be low at < 1.5% [51].

An Agency for Healthcare Research and Quality (AHRQ) commissioned report examined safety of RDN. Approximately, half of randomized controlled trials and comparative cohort studies reported complications and safety events [52]. Renal artery injury, such as dissection or stenosis, comprises 0.5% of complications (range 0–2.3%). In SYMPLICITY HTN-3, there was only one reported case of re-stenosis [53]. Renal dysfunction following the procedure, defined as > 50% change in renal function, accounts for 0.3% of complications (range 0–4.5%). A recent systematic review and meta-analysis demonstrated no adverse effects of catheter-based RDN on renal function at a mean follow-up of 9.1 months [54]. The true incidence of chronic complications, such as renal artery stenosis and renal dysfunction, is difficult to determine given there are no controlled studies performed for direct comparison.

Vascular access site complications involving the femoral artery, including pseudoaneurysm or hematoma, is estimated to comprise 0.7% of complications. However, the AHRQ report discussed above had a large range in reported adverse vascular access site events between studies, ranging from 0.3 to 44.4% of patients in the study [52]. It is postulated that vascular access site injury correlates to operator experience and similar to complication rates for femoral cardiac catheterization and intervention.

Systemic effects of RDN, such as embolization resulting in end organ damage, are rare. Studies cite a 0.3% risk of embolization as an adverse event [52]. RDN therapy is associated with a sevenfold increased risk of bradycardia, although commonly transient and intraprocedural [55]. Hypotensive and

hypertensive episodes have also been described in literature; however, meta-analysis and pooled data have shown that there is no increased risk compared to standard treatment [55]. Other less cited adverse events include renal artery vasospasm, syncope, and flank pain.

Cardiovascular morbidity in those with resistant hypertension

The benefits of successful treatment of resistant HTN are substantial. The first organized data to demonstrate a benefit of BP reduction was from an outcomes study funded by the Veterans Administration published in 1967. A 96% reduction in cardiovascular events was seen with the use of triple antihypertensive therapy compared to placebo in patients with severe HTN, defined by DBP 115–129 mmHg [56]. Confirmation of this has been seen in subsequent investigation. Post hoc analysis of the Australian National Blood Pressure study showed a 25% reduction in overall mortality with BP treatment [57]. More recently, a prospective 4-year observational study corroborated these findings showing that severe resistant HTN is an independent predictor for cardiovascular outcome (odds ratio 2.3), even after controlling for established risk factors [58].

Other benefits of treatment of HTN include improvement in LV hypertrophy, diastolic dysfunction, obstructive sleep apnea (OSA) severity, and renal function. The degree of improvement of these clinical factors with treatment of HTN varies. Among Systolic Blood Pressure Intervention Trial participants with baseline LV hypertrophy, those assigned to intensive treatment (target SBP < 120 mmHg) were 66% more likely to show improvement in LV hypertrophy [59]. Similarly, normalization of diastolic function is associated with good BP control [60]. With regard to OSA, treatment of HTN confers a reduction in the apnea–hypopnea index. A systematic review and meta-analysis demonstrated a mean decrease in apnea–hypopnea index of 5.69 with treatment of HTN. The effect increased to – 14.52 with the use of diuretics. Unlike LV hypertrophy and diastolic dysfunction, the mean BP change did not impact the degree of improvement in the index [61]. In addition, reduction in BP is renoprotective, especially in patients with chronic kidney disease. One of the most important mechanisms is the antiproteinuric effect of a lower BP. The Irbesartan Diabetic Nephropathy Trial demonstrated that SBP > 149 mmHg is associated with a 2.2-fold elevated risk of doubling serum creatinine or end-stage renal disease compared to SBP < 134 mmHg [62].

Future directions

With the current devices and therapy, RDN is a relatively safe procedure. More recent data show that RDN is also efficacious. Currently, the European Society of Hypertension and European Society of Cardiology 2013 guidelines confer RDN a class IIB recommendation for treatment of patients with arterial HTN [63]. It is possible, and likely, that RDN is more beneficial for specific subgroups of patients and further data are warranted to identify the cohort of patients that will benefit the most from therapy. Studies have shown that there is heterogeneity in BP response, with predictors of a profound respond to RDN being younger vascular age, higher baseline BP, and combined diuretic therapy [64].

Clinical studies and post hoc analyses postulate that RDN many have a greater effect in non-African Americans [53]. The degree of denervation required needs further investigation as this may need to be adjusted per patient based on race and/or other factors.

Development of RDN technology and technique is ongoing. Invasive RDN catheter design has already advanced regarding precision of denervation and modifications to minimize endothelial damage. Durability of BP lowering effect of RDN has been demonstrated up to 3 years; however, long-term outcomes are unclear. Additionally, there are no head-to-head comparisons of RDN technologies; therefore, it is difficult to determine which, if any, are superior.

Several trials are already planned or in progress. In RADIANCE-HTN TRIO, an ongoing study in Europe, patients with mild–moderate HTN are prescribed a fixed dose, triple HTN combination pill for 4 weeks prior to randomization to sham procedure or RDN therapy [43]. REQUIRE is a similarly designed study to evaluate those with resistant HTN on standard of care medication regimen in Japan and Korea [43]. The primary endpoint of this study is reduction in 24-h ambulatory SBP at 3 months. The promising results of the SYPRAL HTN-OFF MED initiated a subsequent trial called SPYRAL HTN Pivotal. The SYPRAL HTN Pivotal trial is a large (433 patients), multicenter (50 sites), international (USA, Europe, Australia, Japan), 1:1 randomized, sham-controlled study that will further investigate the BP-lowering effect and safety of RDN in the absence of medication. Recruitement to the SPYRAL HTN-ON MED study is still in progress with an estimated enrollement of 340 participants [34••]. Lastly, the RADIANCE-II trial is underway. RADIANCE-II is a randomized, sham-controlled, blinded study that will study the safety and efficacy of the Paradise system's ability to lower BP in patients with moderate HTN.

Outside of the realm of resistant HTN, RDN technology may be applicable to other states of chronic SNS activation such as heart failure, atrial fibrillation, OSA, and insulin sensitivity. There are several pilot studies or small RCTs demonstrating potential benefit in these conditions. In patients with heart failure with reduced ejection fraction, the REACH study showed improvement in symptoms and exercise capacity with RDN therapy [65]. Subsequent investigations demonstrated there is also an improvement in cardiac function with RDN [66, 67]. RDN has also been shown to improve diastolic function and LV structure as evidenced by one study showing a decrease in mean interventricular septal thickness, LV mass index, and LV filling pressures 6 months after RDN compared to controls [68]. Arrhythmias can often be potentiated by SNS activation. An RCT randomized patients with atrial fibrillation to pulmonary vein isolation alone versus pulmonary vein isolation accompanied by RDN and demonstrated a lower rate of recurrent atrial fibrillation in the RDN group [69]. OSA is a common co-morbid condition seen with HTN. The Wisconsin Sleep Cohort Study showed a clear relationship between severity of the apnea–hypopnea index and risk of development of HTN within 4 years [70]. OSA causes hypoxic stimulation of the SNS. RDN therapy in those with OSA and resistant HTN has been shown to improve the apnea–hypopnea index and lowers blood pressure in the absence of weight changes [71]. Lasty, HTN is closely associated with glucose metabolism and insulin resistance. A pilot study enrolled 50 patients with therapy-resistant HTN. Patients treated with RDN

were found to have significant reduction in fasting glucose, insulin, and C-peptide levels after 3 months compared to controls [72].

Overall, the data currently available for RDN in HTN and other states of SNS activation suffer from potential biases and highlight the need for continued exploration. Multiple confirmatory RCTs in progress will hopefully address these questions, and the results will be crucial for understanding the clinical application of RDN therapy.

Compliance with Ethical Standards

Conflict of Interest
Lauren S. Ranard and Rajesh V. Swaminathan declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

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- • Of importance
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