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REVIEW

Advances in Renal Denervation in the Treatment of Hypertension

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Abstract

Hypertension significantly increases the risk of cardiovascular events and it is associated with high rates of disability and mortality. Hypertension is a common cause of cardiovascular and cerebrovascular accidents, which severely affect patients' quality of life and lifespan. Current treatment strategies for hypertension are based primarily on medication and lifestyle interventions. The renal sympathetic nervous system plays an important role in the pathogenesis of hypertension, and catheter-based renal denervation (RDN) has provided a new concept for the treatment of hypertension. In recent years, studies on RDN have been performed worldwide. This article reviews the latest preclinical research and clinical evidence for RDN.

Keywords: Hypertension; Renal Denervation; Renal Nerve Electrical Stimulation; Review

Introduction

According to the guidelines for the management of arterial hypertension, lowering blood pressure (BP) with antihypertensive medications decreases the risk of major cardiovascular events, heart failure, stroke and coronary heart disease [1–3]. Although various types of antihypertensive drugs and agents are available as treatment options, they do not result in a satisfactory rate of attainment of optimal BP decrease [2, 4, 5]. Resistant hypertension (RH) is usually defined by BP remaining above guideline-specified targets despite the use of three or more antihypertensive agents at optimal or maximally tolerated doses, preferably with one of those agents being a diuretic [1–3, 6]. The management of RH involves both nonpharmacological and pharmacological strategies. With the development of research on hypertension therapy, interventional or device therapy has become a novel option for patients. Nonpharmacological strategies to decrease BP include renal denervation (RDN), central arteriovenous fistula creation, baroreceptor activation or modulation therapy, and lumbar sympathectomy [6]. RDN is a new interventional technique that modulates the sympathetic nerve fibers surrounding the

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renal artery, thereby decreasing sympathetic nerve excitability and consequently BP. Several early clinical studies, including Symplicity HTN-1 [7] and Symplicity HTN-2 [8], indicated that RDN significantly and safely decreases BP levels in patients with RH, whereas the Symplicity HTN-3 study [9] has demonstrated the safety of RDN but has shown negative results in terms of antihypertensive efficacy. After the Symplicity HTN-3 study, several recent clinical trials have indicated that RDN has substantial antihypertensive effects in patients with hypertension. Meanwhile, many basic science studies have demonstrated that, RDN targets the peripheral nerves of the renal artery, thus providing a good theoretical basis for decreasing BP in patients with hypertension. In this review, we focus on the basic rationale, current technology, and recent clinical trials on RDN.

Basic Rationale for RDN

The kidneys are involved in the regulation of BP through the following mechanism: efferent sympathetic nerve activation leads to renal arteriolar constriction; decreased renal blood flow; increased renin secretion; renin-angiotensin-aldosterone system activation; water and sodium retention; and finally increased blood volume and systemic BP (Figure 1). In addition, stimuli such as renal ischemia, hypoxia, and oxidative stress activate renal afferent sympathetic nerves through baroreceptors and chemoreceptors, which in turn stimulate the hypothalamus, thereby increasing sympathetic efferents to the heart and other peripheral organs, and ultimately increasing systemic vascular resistance and BP (Figure 1) [4, 12–14].

On the basis of this mechanism, the principle of RDN is to destroy the renal sympathetic afferent and efferent nerves, and attenuate renal and systemic sympathetic nerve activity, thereby decreasing BP (Figure 1). Currently, radiofrequency (RF) ablation, ultrasound ablation (intravascular and extracorporeal denervation), balloon freezing, and renal adventitial injection of neurotoxin drugs can be used for sympathetic denervation. These methods have been evaluated in patients with hypertension, and the first two methods have received the most attention in sham-controlled studies. The main findings are as follows.

Radiofrequency-Based RDN

Clinical Trials of the First-Generation Catheter System

The first-generation RF energy-based catheter system for RDN is a single-electrode linear RF catheter, represented by Symplicity Flex™. Two previously published studies using this system, the Symplicity HTN-1 study (45 patients) [7] and the Symplicity HTN-2 study (106 patients) [8], have reported that RDN significantly decreases systolic and diastolic

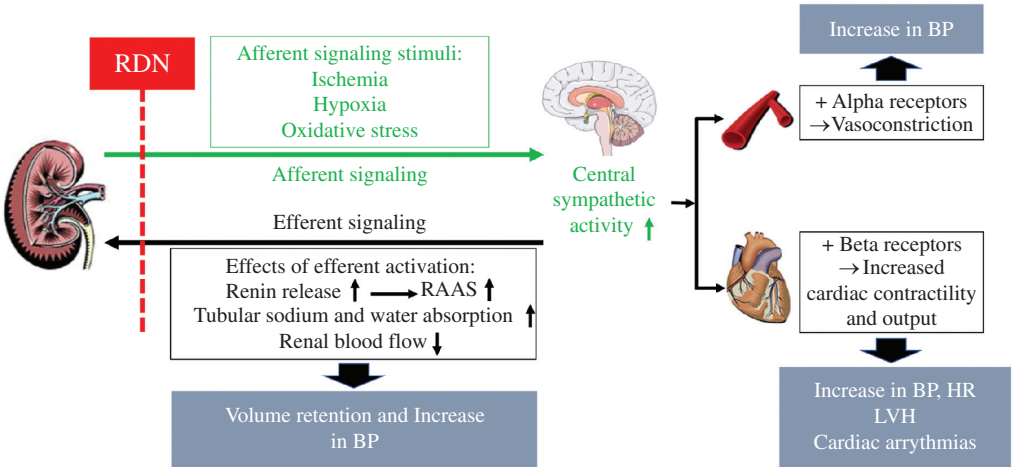

Figure 1 Diagram of the Efferent and Afferent Pathways Interrupted by Renal Denervation.
Modified from *Curr Cardiol Rep 2022 Oct;24(10):1261–71* [10] and *JACC Cardiovasc Interv 2019 Jun 24;12(12):1095–105* [11]. BP, blood pressure; HR, heart rate; LVH, left ventricular hypertrophy; RAAS, renin-angiotensin-aldosterone system; RDN, renal denervation.

BP in patients with RH, without causing significant adverse events or complications during 3 years of follow-up. The first larger, prospective, multicenter, randomized, single-blind, sham-controlled Symplicity HTN-3 study [9] was subsequently conducted. In that trial, 535 patients with drug-resistant hypertension were randomly assigned in a 2:1 ratio to undergo RDN (n=364) or a sham procedure (n=171) [9]. The primary efficacy endpoint was the change in office systolic BP at 6 months, with a superiority margin of 5 mmHg; a secondary efficacy endpoint was the change in mean 24-hour ambulatory systolic BP. The primary safety endpoint was a composite of major adverse events [9]. Although the trial confirmed the safety of RDN, it did not demonstrate the superiority of RDN over the sham treatment in terms of BP-lowering efficacy. The results of the Symplicity HTN-3 study are therefore highly controversial. Subsequently, Kandzari et al. performed post hoc analyses and found that several potential factors, such as a lack of standardized procedural treatment recommendations leading to incomplete RDN, limited experience of interventionists, changes in antihypertensive medications throughout the study, lifestyle changes, and variation in adherence to medication, might have contributed to the negative results of the Symplicity HTN-3 study [15]. In addition, the antihypertensive effects in patients with more ablation sites remained more significant than those in the sham group [15]. Insufficient denervation is an important factor affecting the antihypertensive effects of RDN. Therefore, how to improve and ensure the effectiveness of denervation has been a focus of subsequent research.

The controlled DENERHTN study included 106 patients with RH who were randomly assigned to RDN plus standardized stepped-care antihypertensive treatment or the same antihypertensive treatment alone. The primary endpoint of change in daytime ambulatory systolic BP at 6 months was met with a baseline adjusted difference of −5.9 mmHg (95% CI: −11.3 mmHg to −0.5 mmHg, P=0.0329, Table 1) between the RDN and the control groups [17]. Only approximately 50% of patients in both groups adhered to the prescribed medication [17, 34]. A post hoc analysis of the DENERHTN trial has identified that nonadherence to treatment is a major determinant of the difference between office systolic and daytime ambulatory BP [35]. However, regardless of their adherence to medication, patients treated with RDN experienced a greater decrease in BP than those receiving standardized stepped-care antihypertensive treatment alone.

These published studies have also shown that the results of clinical trials using such devices are highly uncertain. Therefore, the requirement to select RDN-eligible patients, and the insufficient effects of a single-electrode wire-type beam-frequency guide tube to block the renal artery nerve remained to be addressed. Consequently, subsequent RDN studies have been conducted with updated patient selection criteria and the use of a second-generation multielectrode catheter that permits multiple, simultaneous, and more comprehensive circumferential ablation, as well as access to distal arterial branches following the bifurcation of the main renal artery.

Clinical Trials of the Second-Generation Catheter System

The second-generation RF energy-based catheter was a four-electrode spiral RF catheter capable of simultaneous ablation of the renal artery in four quadrants (superior, inferior, anterior, and posterior). The ablation range was expanded from the main renal artery to any branch renal artery with a diameter of 3–8 mm, and the average numbers of ablation points per side were approximately 20–25 points. On the basis of these catheter properties, researchers have conducted studies of RDN in patients without (SPYRAL HTN-OFF MED) and with (SPYRAL HTN-ON MED) antihypertensive medications [36]. The two studies had similar eligibility criteria. Both pilot trials have demonstrated significantly greater 24-hour ambulatory BP changes with respect to baseline in the RDN group than the sham control group in interim analysis [20, 22].

After a positive pilot trial [20], the SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial, an international, prospective, single-blinded, sham-controlled trial, was conducted [21]. The coprimary efficacy endpoints were baseline-adjusted changes in 24-hour systolic BP and office systolic BP from baseline to 3 months after RDN. Because the design of the two studies was essentially consistent, the primary analysis combined evidence from the SPYRAL pilot

Table 1 Clinical Trials of Renal Denervation in the Treatment of Hypertension.

Trial (publication year)	Device (manufacturer)	Catheter features	RDN (*n*)	Control (*n*)	Primary outcome
SYMPLICITY HTN-1 (2009) [7]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	45	-	**Change in office systolic BP at 1, 3, 6, 9, and 12 months:** repeated-measures ANOVA P=0.026. **Change at 6 months:** office systolic BP −22 mmHg (95% CI: −32 mmHg to −12 mmHg), P<0.001. **Change at 12 months:** office systolic BP −27 mmHg (95% CI: −43 mmHg to −11 mmHg), P<0.001.
SYMPLICITY HTN-2 (2010) [8]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	52	54	**Change in office systolic BP at 6 months:** RDN −32±23 mmHg versus control 1±21 mmHg, P<0.0001.
SYMPLICITY HTN-3 (2014, 2022) [9, 16]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	364	171	**Change in office systolic BP at 6 months:** RDN −14.1±23.9 mmHg versus sham −11.7±25.9 mmHg, P=0.26. **Change in 24-h systolic BP at 36 months:** RDN −15.6±20.8 mmHg versus sham −0.3±15.1 mmHg, adjusted treatment difference −16.5 mmHg (95% CI: −20.5 mmHg to −12.5 mmHg), P≤0.0001. **Change in office systolic BP at 36 months:** RDN −26.4±25.9 mmHg versus sham −5.7±24.4 mmHg, adjusted treatment difference −22.1 mmHg (95% CI: −27.2 mmHg to −17.0 mmHg), P≤0.0001.
DENERHTN (2015) [17]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	53	53	**Change in daytime systolic BP at 6 months:** RDN −15.8 mmHg (95% CI: −19.7 mmHg to −11.9 mmHg) versus standardized stepped-care antihypertensive therapy −9.9 mmHg (95% CI: −13.6 mmHg to −6.2 mmHg), baseline-adjusted difference −5.9 mmHg (95% CI: −11.3 mmHg to −0.5 mmHg), P=0.0329.
Global SYMPLICITY Registry (2019, 2022) [18, 19]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	2237 (2019), 3077 (2022)	-	**Change in systolic BP at 6 months:** office systolic BP −12.8±26.2 mmHg, P<0.0001; 24-h systolic BP −7.2±17.8 mmHg, P<0.0001. **Changes at 36 months:** −16.7±28.4 mmHg and −9.0±20.2 mmHg for office systolic BP and 24-h systolic BP, respectively.
SPYRAL HTN-OFF MED (2017) [20]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	38	42	**Change in 24-h systolic BP at 3 months:** RDN −5.5 mmHg (95% CI: −9.1 mmHg to −2.0 mmHg) versus sham −0.5 mmHg (95% CI: −3.9 mmHg to 2.9 mmHg), adjusted difference −5.0 mmHg (95% CI: −9.9 mmHg to −0.2 mmHg), P=0.0414. **Change in office systolic BP at 3 months:** RDN −10.0 mmHg (95% CI: −15.1 mmHg to −4.9 mmHg) versus sham −2.3 mmHg (95% CI: −6.1 mmHg to 1.6 mmHg), adjusted difference −7.7 mmHg (95% CI: −14.0 mmHg to −1.5 mmHg), P=0.0155.

Table 1 (continued)

Trial (publication year)	Device (manufacturer)	Catheter features	RDN (*n*)	Control (*n*)	Primary outcome
SPYRAL Pivotal (2020) [21]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	166	165	**Change in 24-h systolic BP at 3 months:** RDN −4.7 mmHg (95% CI: −6.4 mmHg to −2.9 mmHg) versus sham −0.6 mmHg (95% CI: −2.1 mmHg to 0.9 mmHg), adjusted difference −3.9 mmHg (Bayesian 95% CI: −6.2 mmHg to −1.6 mmHg), P=0.0005. **Change in office systolic BP at 3 months:** RDN −9.2 mmHg (95% CI: −11.6 mmHg to −6.9 mmHg) versus sham −2.5 mmHg (95% CI: −4.6 mmHg to −0.4 mmHg), adjusted difference −6.5 mmHg (95% CI: −9.6 mmHg to −3.5 mmHg), P<0.0001.
SPYRAL HTN-ON MED (2018, 2022) [22, 23]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	38	42	**Change in 24-h systolic BP at 6 months:** RDN −9.0 mmHg (95% CI: −12.7 mmHg to −5.3 mmHg) versus sham −1.6 mmHg (95% CI: −5.2 mmHg to 2.0 mmHg), P=0.0051. **Change in 24-h systolic BP at 36 months:** RDN −18.7±12.4 mmHg versus sham −8.6±14.6 mmHg, adjusted treatment difference −10.0 mmHg (95% CI: −16.6 mmHg to −3.3 mmHg), P=0.0039.
RADIOSOUND-HTN (2019) [24]	Spyral (Medtronic) Paradise (ReCor Medical)	Multielectrode, helical, radiofrequency Endovascular ultrasound	39/39 42	- -	**Change in daytime systolic BP at 3 months:** radiofrequency-based RDN of the main renal artery −6.5±10.3 mmHg versus radiofrequency-based RDN of the main renal artery and branches −8.3±11.7 mmHg versus ultrasound-based RDN −13.2±13.7 mmHg (ANOVA P=0.038); overall change −9.5±12.3 mmHg (P<0.001)[a].
RADIANCE-HTN SOLO (2018, 2019, 2020) [25–27]	Paradise (ReCor Medical)	Endovascular ultrasound	74	72	**Change in daytime ambulatory systolic BP at 2 months:** RDN −8.5±9.3 mmHg versus sham −2.2±10.0 mmHg, adjusted treatment difference −6.3 mmHg (95% CI: −9.4 mmHg to–3.1 mmHg), P=0.0001. **Change in daytime ambulatory systolic BP at 6 months:** RDN −18.1±12.2 mmHg versus sham −15.6±13.2 mmHg, adjusted treatment difference −4.3 mmHg (95% CI: −7.9 mmHg to −0.6 mmHg), P=0.024. **Change in 24-h systolic BP at 6 months:** RDN −16.5±11.8 mmHg versus sham −14.9±12.8 mmHg, adjusted treatment difference −4.3 mmHg (95% CI: −7.7 mmHg to −1.0 mmHg), P=0.012. **Change in office systolic BP at 6 months:** RDN −18.2±14.2 mmHg versus sham −15.9±17.2 mmHg, adjusted treatment difference −3.7 mmHg (95% CI: −8.1 mmHg to 0.7 mmHg), P=0.102.

Table 1 (continued)

Trial (publication year)	Device (manufacturer)	Catheter features	RDN (*n*)	Control (*n*)	Primary outcome
					Change in daytime ambulatory systolic BP at 12 months: RDN −16.5±12.9 mmHg versus sham −15.8±13.1 mmHg, adjusted treatment difference −2.3 mmHg (95% CI: −5.9 mmHg to −1.3 mmHg), P=0.201. **Change in 24-h systolic BP at 12 months:** RDN −15.1±12.4 mmHg versus sham −15.3±12.4 mmHg, adjusted treatment difference −2.4 mmHg (95% CI: −5.8 mmHg to −0.9 mmHg), P=0.156. **Change in office systolic BP at 12 months:** RDN −18.1±14.9 mmHg versus sham −13.6±17.2 mmHg, adjusted treatment difference −6.3 mmHg (95% CI: −11.1 mmHg to −1.5 mmHg), P=0.010.
RADIANCE-HTN TRIO (2021) [28]	Paradise (ReCor Medical)	Endovascular ultrasound	69	67	**Change in daytime ambulatory systolic BP at 2 months:** RDN −8.0 mmHg (95% CI: −16.4 mmHg to 0.0 mmHg) versus sham −3.0 mmHg (95% CI: −10.3 mmHg to 1.8 mmHg), adjusted treatment difference −4.5 mmHg (95% CI: −8.5 mmHg to −0.3 mmHg), P=0.022. **Change in 24-h systolic BP at 2 months:** RDN −8.5 mmHg (95% CI: −15.1 mmHg to 0.0 mmHg) versus sham −2.9 mmHg (95% CI: −12.6 mmHg to 2.5 mmHg), adjusted treatment difference −4.2 mmHg (95% CI: −8.3 mmHg to −0.3 mmHg), P=0.016. **Change in office systolic BP at 2 months:** RDN −9.0 mmHg (95% CI: −19.5 mmHg to −1.5 mmHg) versus sham −4.0 mmHg (95% CI: −12.0 mmHg to 9.0 mmHg), adjusted treatment difference −7.0 mmHg (95% CI: −13.0 mmHg to 0.0 mmHg), P=0.037.
RADIANCE II (2022 TCT conference) [29–31]	Paradise (ReCor Medical)	Endovascular ultrasound	150	74	**Change in daytime ambulatory systolic BP at 2 months:** RDN −7.9 mmHg versus sham −1.8 mmHg (adjusted treatment difference −6.3 mmHg, 95% CI: −9.3 mmHg to −3.2 mmHg), P<0.0001.
REQUIRE (2022) [32]	Paradise (ReCor Medical)	Endovascular ultrasound	72	71	**Change in 24-h systolic BP at 3 months:** RDN −6.6 mmHg (95% CI: −10.4 mmHg to −2.8 mmHg) versus sham −6.5 mmHg (95% CI: −10.3 mmHg to −2.7 mmHg), adjusted treatment difference −0.1 mmHg (95% CI: −5.5 mmHg to 5.3 mmHg), P=0.971.
WAVE IV (2018) [33]	Surround Sound System (Kona Medical)	High-intensity focused ultrasound	42	39	**Change in 24-h systolic BP at 24 weeks:** RDN −7.11±13 mmHg versus sham −5.90±15 mmHg, P=0.770. **Change in office systolic BP** at 24 weeks by −12.8±26 and −23±20 mmHg, P=0.133.

P values indicate the difference between the treatment and control groups, unless indicated otherwise. 24-h, 24-hour; BP, blood pressure; RDN, renal denervation; TCT, American Transcatheter Cardiovascular Therapeutics conference. [a]P values indicate the difference between baseline and follow-up.

study (n=80) and the critical trial (n=251) by using a Bayesian approach. The primary and secondary efficacy endpoints were met, with a posterior probability of superiority greater than 0.999 for both. In the treatment group, compared with the sham group, the 24-hour systolic BP was –3.9 mmHg (Bayesian 95% CI: from –6.2 mmHg to –1.6 mmHg), and the office systolic BP was –6.5 mmHg (95% CI: –9.6 mmHg to –3.5 mmHg) (Table 1). No major device-associated or procedural-associated safety events occurred during a follow-up of 3 months [21].

To address the lack of long-term efficacy and safety data from RCTs of RDN, the SPYRAL HTN-ON MED trial was conducted [23]. The trial compared changes in ambulatory and office BP measurements between the RDN group and sham control group until 36 months. With similar medical therapy, the 24-hour systolic BP decreased over time in both groups from baseline to 36 months. The change in 24-hour systolic BP was −18.7±12.4 mmHg with RDN and −8.6±14.6 mmHg with the sham procedure (adjusted treatment difference −10.0 mmHg; 95% CI: from −16.6 mmHg to −3.3 mmHg; P=0.0039, Table 1) [23]. In addition, the time in therapeutic range (TTR) was used to evaluate the BP lowering effects in this trial. RDN significantly improved the TTR of patients, according to either office BP or 24-hour BP (28.0% *vs.* 13.0%, P=0.015; 21.0% *vs.* 10.6%, P=0.030), and the benefit was independent of drug treatment and showed an "always on" effect. Therefore, compared with the sham procedure, RF ablation-based RDN resulted in clinically meaningful BP-lowering effects within 36 months, independently of antihypertensive medications, and without safety concerns. RDN can achieve long-term effective and stable BP decreases in patients with poorly controlled hypertension. This study has provided a more comprehensive evidence-based approach to RDN for patients with RH [23]. In addition, the American Heart Association Scientific Sessions 2022 announced the 6-month follow-up results of SPYRAL HTN-ON MED Expansion (NCT04311086) [37]. However, the primary endpoint was not met in the RDN group compared with the sham control group (change in 24-hour systolic BP of −6.5 mmHg with RDN and −4.5 mmHg with sham treatment; adjusted treatment difference −1.9 mmHg, P=0.12) [37]. However, the secondary endpoint was met. At 6 months, the change in office systolic BP was −9.9 mmHg with RDN and −5.1 mmHg with the sham procedure (adjusted treatment difference −4.9 mmHg, P=0.001) [37]. The primary safety endpoint was met, and a low incidence of procedural-related and clinical adverse events was observed. We remain optimistic about the results of this clinical study, which may provide hope for the future use of RDN as an interventional treatment for patients with hypertension with poor BP control.

The long-term outcomes (follow-up 36 months) of the Symplicity HTN-3 trial have shown a change in office systolic BP of −26.4±25.9 mmHg with RDN and −5.7±24.4 mmHg with the sham treatment (adjusted treatment difference −22.1 mmHg, 95% CI: from −27.2 mmHg to −17.0 mmHg; P≤0.0001, Table 1) at 36 months [16]. At 36 months, the change in 24-hour systolic BP was −15.6±20.8 mmHg with RDN and −0.3±15.1 mmHg with the sham procedure (adjusted treatment difference −16.5 mmHg, 95% CI: −20.5 mmHg to −12.5 mmHg; P ≤ 0.0001, Table 1). Without imputation, the TTR in the RDN group was significantly higher than that in the sham group (18% *vs.* 9%, P≤0.0001), despite a similar medication burden, and consistent and significant results with imputation were observed. The rates of adverse events were similar across treatment groups, and no evidence of late-emerging complications from RDN was found.

The Global SYMPLICITY Registry [18, 19, 38, 39] is a prospective, open-label, international, multicenter observational study for assessment of the safety and effectiveness of RDN in real-world patients treated with the Symplicity RDN system (single-electrode Symplicity Flex™ catheter or the multielectrode Symplicity Spyral™ catheter). The TTR (office systolic BP ≤ 140 mmHg and/or mean systolic BP ≤ 130 mmHg) was as high as 34.9% at 3 years after denervation in more than 3000 patients with hypertension treated with the RDN technique [19]. Further analysis of the correlation between TTR and the incidence of major cardiovascular events, such as cardiac death, myocardial infarction, and stroke, has indicated that the higher the TTR, the lower the incidence of major cardiovascular events. Specifically, a 10% increase in TTR between 0 and 6 months after RDN decreased the incidence of major cardiovascular events between

6 and 36 months after the RDN procedure by 15% ($P<0.001$) [19].

According to the results of these studies, the clinical benefit of RF ablation for RDN can be evaluated in four dimensions. First, RDN significantly decreases BP and the risk of cardiovascular events. Second, in terms of the 24-hour antihypertensive effect, RDN shows a 24-hour continuous online antihypertensive effect after RDN, including night and early-morning periods, which pose a high risk of cardiovascular events. Third, RF-based RDN can improve the rate of BP control. Finally, RF-based RDN improves the TTR and decreases the risk of major cardiovascular events.

Renal Nerve Electrical Stimulation-Guided RDN

The guiding principle for the number of catheter ablations and clinical treatment is that "less is more." Medtronic's Spyral catheter is aimed at improving the efficacy of renal denervation by a novel designed catheter to advance more distal of renal artery to conduct more ablation lesions. The average procedure time is 99.6 min, and the total number of ablations is 46.9 per patient, thus resulting in a new concept of "more is better" [21]. The Medtronic Spyral Global study has also confirmed the safety of RDN in lowering BP, and indicated its advantages over drugs in terms of nonadherence and "always on" antihypertensive efficacy [18, 19, 38, 39].

A decrease in BP is not observed among approximately 25% to 30% of patients undergoing RDN [40, 41], possibly because of the distribution of different types of nerves around the renal artery. However, current clinical practice using RDN for the treatment of hypertension cannot accurately map the renal sympathetic nerves that may lead to BP elevation. On the basis of this important clinical need, a renal nerve mapping/selective ablation strategy is being developed.

In 2013, Chinushi et al. [42] first introduced electrical stimulation of the renal artery to explore the functional localization of renal autonomic nerves in dogs. They have found that renal nerve electrical stimulation (RNS) increases BP via increasing central sympathetic nervous activity. This study has established RNS as a feasible and promising method to locate renal nerves to guide RDN. Several subsequent animal experiments [43–46] have also confirmed that electrical stimulation of the renal artery nerve increases BP, but this trend is attenuated after mapping and ablation with a catheter, thus indicating successful renal nerve ablation. In addition, animal experimental studies conducted by Lu et al. [43] and Yu et al. [47] have indicated that the sites of BP elevation by electrical stimulation of the renal artery tend to be distributed primarily in the proximal and middle segments of the renal artery rather than in the distal segment of the renal artery. Similarly to previous animal studies, the clinical study by Chen et al. [48] has indicated that proximal RDN has a similar efficacy and safety profile to that of full-length RDN; the authors have proposed that the proximal artery is the key target portion for RDN. In addition, Konstantinos et al. [49] used the ConfidenHT system to perform simple renal artery electrical stimulation in 20 patients with hypertension in 2018. When the current was 2 mA, the BP response at the renal artery ostium was clearer, but the difference between ostium and non-ostium locations was not statistically significant. However, at 4 mA, the BP response was significantly higher at the ostium of the renal artery than at other sites (including mid, distal, or branch sites). These findings suggest that RNS can be performed safely and effectively along the renal artery, but it results in a large variation in temporary BP changes according to the individual patient and anatomic location; moreover, RNS might help optimize the treatment effects and select potential responders to renal sympathetic denervation [49].

Similarly to previous experimental studies, several preliminary clinical trials [50–53] have confirmed that renal nerve mapping/selective ablation-based RDN significantly decreases 24-hour ambulatory BP in patients with RH. Gal et al. [50] performed the first feasibility study of RDN guided by RNS in patients with RH. First, RNS was performed at four sites in the renal arteries, and then a standard RDN procedure was performed (four to six ablation sites per artery), which was followed by repeated RNS at the same site with a maximum BP increase. The systolic BP response to RNS at the site of maximum response increased 43.1 ± 14.7 mmHg before RDN compared with 9.3 ± 10.5 mmHg after RDN ($P=0.002$). The mean BP in ambulatory BP monitoring decreased from $153.3 \pm 12.9/89.0 \pm 3.5$ mmHg

to 135.0±9.4/73.6±13.5 mmHg, and antihypertensive drug use decreased to a mean of 3.5 (range: 1 to 6) at the 6-month follow-up after the RDN procedure [50]. In agreement with findings from previous studies, de Jong et al. [51] have observed a systolic BP increase of 50±27 mmHg before RDN and a systolic BP increase of 13±16 mmHg after RDN (P<0.001). The average systolic BP, according to ambulatory BP monitoring, was 153±11 mmHg before RDN and decreased to 137±10 mmHg at the 3-to 6-month follow-up (P=0.003) [51]. In addition, Xu et al. [53] have found similar results and have confirmed that the BP-elevation response during RF ablation may be an effective intraprocedural predictive marker for the long-term procedural success of RDN. These studies initially demonstrated the safety and feasibility of RNS-guided RDN, and suggest that the blunted response of RNS-induced BP elevation after RDN can be used as an acute endpoint to evaluate the efficacy of RDN and predict long-term BP response [41, 54]. Several ongoing clinical trials (the SMART study [55] NCT02761811 and SMART OFF-MED study NCT03885843) are using RNS to guide RDN in hypertension treatment, and the results of these studies are pending.

The mechanism of RNS-guided RDN is unclear, but the theoretical basis of this technology can be explained in detail from three aspects: anatomy, physiology, and histology. In 2014, Sakakura et al. [56] performed anatomic assessment of sympathetic peri-arterial renal nerves in humans. The proportion of renal afferent nerves distributed in the proximal segment of the renal artery has been found to be higher than that in the distal segment of the renal artery [56]. Subsequently, another anatomical study [57] has confirmed that approximately 73.5% of the nerves around the renal artery are sympathetic nerves, which are called "hot spots" in mapping; 17.9% are parasympathetic nerves (also known as "sympathetic inhibitory nerves"), which are called "cold spots"; and another 8.7% are "neutral spots." Further physiological studies have indicated that electrical stimulation of these different site types increases the BP when stimulating hot spots, decreases the BP when stimulating cold spots, and does not cause significant changes in the BP when stimulating neutral spots. The results of histological studies have also indicated that the nerve distribution around the renal artery is associated with the strong response site (the site of the maximum increase in systolic BP during electrical stimulation of the renal nerve > 10 mmHg) and the weak response site (the site of the maximum increase in systolic BP during electrical stimulation of the renal nerve). The number of nerves and the total area of nerve truncation adjacent to the strong response point are significantly greater than those around the weak stimulation point [44, 54, 58, 59].

Ultrasound-Based RDN

Intravascular Ultrasound

The application of intravascular ultrasound energy in the denervated renal artery nerve catheter system is based on the physical characteristic in which its penetration distance (from 4 mm to 8 mm) is longer than that of the RF (less than 4 mm), and circular emission can theoretically damage an increasing number of renal nerves farther from the renal artery intima in four quadrants. The multicenter, randomized, double-blind, sham-operated controlled RADIANCE-HTN study of this device (Paradise, ReCor Medical) consists of two studies: the SOLO study [25–27] without antihypertensive agents and the TRIO study [28] with lock-in antihypertensive agents. A total of 146 patients with mild-to-moderate hypertension (74 in the RDN group and 72 in the control group) were enrolled in the RADIANCE SOLO study. At 2 months, the average daytime ambulatory systolic BP decreased by 8.5±9.3 mmHg in the RDN group and 2.2±10.0 mmHg in the sham group; the baseline adjusted difference between groups was –6.3 mmHg (95% CI: –9.4 mmHg to –3.1 mmHg, P<0.001, Table 1) [25]. After 2 months, the dosage of antihypertensive drugs was titrated according to the BP in both groups. The difference between baseline and drug-adjusted values at 6 months was –4.3 mmHg (95% CI: –7.9 mmHg to –0.6 mmHg, P=0.002, Table 1) [26]. At 12 months, the RDN versus sham adjusted difference was 2.3 mmHg (95% CI: –5.9 mmHg to 1.3 mmHg; P=0.201, Table 1) for daytime ambulatory systolic BP and –6.3 mmHg (95% CI: –11.1 mmHg to –1.5 mmHg; P=0.010, Table 1) for office systolic BP [27]. This study suggests that RDN remains safe and effective

in mid- and long-term follow-up. The RADIANCE-HTN TRIO study, designed to evaluate the safety and efficacy of the Paradise system in patients with RH, has demonstrated that ultrasound RDN treatment results in a significantly lower BP at 2 months than sham surgery in patients with RH resistant to standard triple antihypertensive therapy (Table 1) [28]. The RADIOSOUND-HTN study [24] has compared the antihypertensive effects of intravascular ultrasound or radiofrequency RDN. A total of 120 patients with RH were randomly divided 1:1:1 into three groups: group one underwent intravascular ultrasound-based RDN of the main renal artery; group two underwent radiofrequency-based RDN of the main renal arteries; and group three underwent radiofrequency-based RDN of the main renal arteries, side branches, and accessories. The total daytime ambulatory systolic BP decreased by 9.5±12.3 mmHg at 3 months (Table 1), and the effects in group one were significantly better than those in group two, but no significant differences were observed between group one and group three, or between group two and group three; moreover, no significant differences in safety were observed among the three groups [24]. However, the REQUIRE trial [32], the first trial of intravascular ultrasound ablation of renal arterial nerves in Asian patients with RH, has reported negative results (Table 1). The reasons for these findings are worthy of further exploration, and more trials may be required to evaluate the efficacy and safety of this treatment.

The 2022 American Transcatheter Cardiovascular Therapeutics (TCT 2022) conference officially announced the results of the larger RADIANCE study, namely the multicenter randomized controlled study RADIANCE II [29–31]. The study enrolled 224 patients (mean age, 55 years) with mild-to-moderate hypertension from March 2019 to May 2022. All patients had uncontrolled hypertension; had been treated with zero to two antihypertensive drugs; and had a daytime systolic BP of 135–170 mmHg and a daytime diastolic BP of 85–105 mmHg, no previous cardiovascular or cerebrovascular events, no type 1 or uncontrolled type 2 diabetes mellitus, no severe renal insufficiency, and good renal anatomy. Patients were then assigned to the ultrasound RDN group (n=150) and the sham-operated control group (n=74) in a 2:1 ratio. After a 4-week drug washout period (withdrawal of antihypertensive drugs), patients with a baseline BP meeting the criteria (daytime ambulatory BP ≥ 135/85 mmHg and < 170/105 mmHg) were selected, and eligibility for surgery was confirmed by renal angiography. The success rate of ultrasound RDN surgery exceeded 98%. At 2 months, the daytime ambulatory systolic BP declined 7.9 mmHg in the RDN group and 1.8 mmHg in the sham group (between-group difference in means, –6.3 mmHg; 95% CI: –9.3 mmHg to –3.2 mmHg; P<0.0001, Table 1). As stratified by baseline BP (< 145 mmHg, 145–153 mmHg, > 153 mmHg), the daytime ambulatory BP decreased by 6.1 mmHg, 8.2 mmHg, and 9.6 mmHg after 2 months, respectively. Patients with higher baseline BP had a more significant decrease in BP. The effect of the RDN group was always better than that of the sham control group. Overall, 64% of patients who received ultrasound RDN had BP decreases of at least 5 mmHg, and 48% had BP decreases of at least 10 mmHg. Nearly two-thirds of patients had a positive response to ultrasound RDN, thus indicating that the technique is effective for most patients. A decrease of 10 mmHg in systolic BP decreases the risk of cardiovascular and cerebrovascular events by more than 20% on average, thereby suggesting that ultrasound RDN can theoretically improve the outcome of at least half of patients. No major adverse events in either group at 30 days, and no evidence of new-onset renal artery stenosis in either group at 6 months were observed.

RADIANCE II was well designed, and the results reconfirmed that ultrasound RDN significantly decreases BP in patients with mild-to-moderate hypertension who did not take hypertension drugs, thus providing a large-scale evidence base for ultrasound RDN, and supporting the safety and effectiveness of ultrasound RDN technology. However, some limitations remain. First, the study selected only patients with mild-to-moderate hypertension without comorbidities or a cardiovascular and cerebrovascular history. Second, similarly to other blinded RDN trials, the RADIANCE II study lacks reliable markers of ablation success and predictors of responsiveness. Finally, the RADIANCE II study is only observed at 2 months, and further long-term follow-up is needed to ensure the continuity and safety of

ultrasound RDN technology. For example, long-term efficacy and safety evaluations should be continued for 60 months.

Extracorporeal Focused Ultrasound

Extracorporeal focused ultrasound ablation of the renal nervous system was developed to avoid the invasive shortcomings of the above two types of intracavity RDN, and a comprehensive series of preclinical studies has been conducted to optimize targeting and therapeutic dose levels and explore lesion patterns before the initiation of human trials. Swine or canines were used, because their renal systems are similar to those of humans. Several experimental studies [60–64] have shown that extracorporeal focused ultrasound ablation of the renal artery and nerve is safe and effective.

In addition, a series of clinical studies have been performed. From August 2013 to May 2014, Rong et al. [65] used high-intensity focused ultrasound-based RDN to treat ten patients with RH, whose BP decreased $-29.2\pm6.8/-11.2\pm9.7$ mmHg after 6 months of follow-up. No serious complications were observed during the study. These findings indicate that high-intensity focused ultrasound-based RDN is safe and effective. However, larger sample randomized, controlled, double-blind clinical trials are needed for validation. In addition, the WAVE series of clinical trials has verified the efficacy and safety of the Surround Sound system (Kona Medical Co. Ltd.). In the WAVE I (24 patients) and WAVE II (18 patients) trials, targeted catheters were used to ensure ultrasound focus on the renal artery while ablation was performed. In the WAVE III trial, the first five of 27 participants also used targeted catheters, and in the latter 22 participants, only the renal artery was tracked with surface Doppler ultrasound to locate the ultrasound focus. The WAVE I, II, and III series of prospective single-arm cohort clinical trials have indicated that RDN with this device is safe and effective in the treatment of RH [64, 66]. Subsequently, the WAVE IV phase II clinical trial was performed with a randomized, double-blind, sham-operated control design, and patients with RH were enrolled 1:1. The trial was terminated early because no significant difference in BP between groups was found in the first 81 patients at 12 and 24 weeks of follow-up (Table 1) [33]. In the future, an urgent need remains for more and larger multicenter, randomized, controlled, double-blind clinical studies of RDN based on extracorporeal focused ultrasound to formally evaluate its safety and efficacy.

Conclusion

This review described possible mechanisms of RDN in the treatment of hypertension, treatment techniques, and important clinical trials that have been published. RDN remains in the research and exploration stage, and has not been routinely used in clinical practice. From the perspective of pathophysiology, the sympathetic nervous system plays an important role in the occurrence and maintenance of hypertension. As shown in clinical trials, RDN may have favorable effects on decreasing BP in some patients. However, the pathophysiological mechanism of hypertension may vary among patients: renal artery anatomy can be inconsistent among patients, the principles of different types of RDN technology may not be the same, and the surgeons' experience and technical proficiency vary. These four aspects will inevitably affect the effectiveness and safety of RDN treatment, as well as the application value and clinical status in antihypertensive therapy.

In general, performing RDN treatment in mature medical centers seems reasonable for patients whose BP is not satisfactorily controlled after lifestyle intervention and adequate treatment with multiple antihypertensive drugs, for patients with substantial hypersympathetic manifestations, or for patients who cannot tolerate antihypertensive drugs. With the development of related technology and continuing improvement in treatment equipment, RDN is expected to play a more important role in the field of hypertension treatment in the future.

At present, using only clinical and ambulatory BP decreases to evaluate the success of ablation is far from sufficient. New biological indicators (reflecting the successful ablation site, sympathetic nerve activation, etc.) as markers of successful ablation must be further studied, to provide a basis for the use of RDN for hypertension and in other fields. Therefore, the following points may be considered in further research on RDN. First, more targeted

research could be performed on some controversial issues. For example, the selected population did not include older individuals, because of their relatively high arterial stiffness and low success rate of ablation; thus, a comparison between older and younger populations should be performed. In addition, different ethnic groups should investigated, given that some studies have found that RDN works relatively better for people of Asian descent and less well for people of African descent. Second, the indicators of successful renal artery nerve ablation could be further explored. At present, the sign of successful RF ablation is reflected only in the decrease in BP, and whether some indicators reflecting the degree of sympathetic nerve stimulation might be added is worthy of studying. Third, updating of equipment could be evaluated. Currently, many types of ablation catheters with different effects are available. The results gained by improvements in equipment should be investigated. Finally, the comparison of ablation methods, whether to choose RNS or other methods, the appropriate candidates of each method, and the advantages of each method must be further studied.

In summary, the efficacy and safety of RDN for hypertension have been verified in a series of randomized controlled trials. However, several issues remain to be considered and refined, such as how to identify suitable patients, how to determine surgical endpoints, how to predict the BP response, and whether RDN can be used as an independent first-line treatment scheme for patients with hypertension. All these aspects should be further explored and studied.

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Conflicts of Interest

No competing financial interests exist regarding this work.

Author Contributions

B X contributed to the writing of the manuscript; S-J C, W-J C, and Z-Y L revised the manuscript; and Z-Y L and Y-H Y contributed to the design of the project.

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