DOI: 10.55415/deep-2023-0020.v1

Advances in Renal Denervation in the Treatment of Hypertension

Bin Xiong[1], Shaojie Chen[2, 3], Weijie Chen[3*], Zhiyu Ling[3*], Yuehui Yin[3]

1. Department of Critical Care Medicine, The Second Affiliated Hospital, Chongqing Medical University, Chongqing, China;
2. Cardioangiologisches Centrum Bethanien (CCB), Kardiologie, Medizinische Klinik III, Agaplesion Markus Krankenhaus, Akademisches Lehrkrankenhaus der Goethe-Universität Frankfurt am Main, Frankfurt am Main, Germany.
3. Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China.

Correspondence to:

Zhiyu Ling, Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China. Email: lingzhiyu@cqmu.edu.cn; Tel.: +86-23-62887635.

AND

Weijie Chen, Department of Cardiology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, China. Email: cqmucwj@hospital.cqmu.edu.cn.

DOI: 10.55415/deep-2023-0020.v1

Advances in Renal Denervation in the Treatment of Hypertension

[Abstract] Hypertension can lead to a significant increase in the risk of cardiovascular events, with a high rate of disability and mortality. It is one of the common causes of cardiovascular and cerebrovascular accidents, which seriously affect patients' quality of life and lifespan. Currently, treatment strategies for hypertension are mainly based 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) provides a new concept for the treatment of hypertension. In recent years, studies on RDN have been carried out worldwide. This article reviews the latest preclinical research and clinical evidence.

[Keywords] Hypertension, Renal Denervation, Renal Nerve Electrical Stimulation, Review

1. Introduction

According to the guidelines for the management of arterial hypertension, lowering blood pressure (BP) with the use of antihypertensive medications reduces the risk of major cardiovascular events, heart failure (HF), stroke and coronary heart disease (CHD) [1-3]. Although there are various types of antihypertensive drugs with many different agents available as treatment options, the attainment rate of optimal BP reduction appears to be unsatisfactory [2, 4, 5]. Resistant hypertension (RH) is usually defined as BP that remains above guideline-specified targets despite the use of three or more antihypertensive agents at optimal or maximally tolerated doses, with one of those agents preferably being a diuretic [1-3, 6]. The management of RH involves both nonpharmacological strategies and pharmacological aspects. With the development of research on hypertension therapy, interventional or device therapy has become a novel option for patients. Nonpharmacological strategies to reduce BP include renal denervation (RDN), central arteriovenous fistula creation, baroreceptor

DOI: 10.55415/deep-2023-0020.v1

activation or modulation therapy, and lumbar sympathectomy [6]. RDN is a new interventional technique that modulates the sympathetic nerve fibers surrounding the renal artery, thereby reducing sympathetic nerve excitability and lowering BP. Including Symplicity HTN-1 [7] and Symplicity HTN-2 [8], a series of early clinical studies indicated that RDN significantly and safely reduced BP levels in patients with RH, while the Symplicity HTN-3 study [9] demonstrated the safety of RDN but showed negative results in terms of antihypertensive efficacy. After the Symplicity HTN-3 study, a series of recent clinical trials indicated that RDN can still produce a significant antihypertensive effect in patients with hypertension. Meanwhile, many basic studies have also found that by targeting the peripheral nerves of the renal artery, RDN has a good theoretical basis for reducing BP in hypertensive patients. In this review, we focus on the basic rationale, current technology, and recent clinical trials on RDN.

2. Basic rationale of RDN

The kidney is involved in the regulation of BP through the following mechanism: efferent sympathetic nerve activation leads to renal arteriolar constriction, decreased renal blood flow, and increased renin secretion, followed by renin-angiotensin-aldosterone system (RAAS) 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, leading to increased sympathetic efferents to the heart and other peripheral organs, ultimately resulting in increased systemic vascular resistance and elevated BP (Figure 1) [4, 10-12].

Based on this mechanism, the principle of RDN is to destroy the renal sympathetic afferent and efferent nerves to attenuate renal and systemic sympathetic nerve activity, thereby lowering BP (Figure 1). At present, radiofrequency (RF) ablation, ultrasound ablation (intravascular and extracorporeal denervation), balloon freezing, and renal adventitial injection of neurotoxin drugs can be used for

DOI: 10.55415/deep-2023-0020.v1

sympathetic denervation. These methods have been evaluated in patients with hypertension, with the first two methods receiving the most attention, as evidenced by sham-controlled studies. The main findings are as follows.

3. Radiofrequency-Based RDN

3.1 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], showed that RDN significantly reduced systolic and diastolic BP levels in patients with RH without 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 this 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 end point was the change in office systolic BP at 6 months, with a superiority margin of 5 mmHg; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic BP. The primary safety end point was a composite of major adverse events [9]. Although the trial confirmed the safety of RDN, it failed to demonstrate the superiority of the RDN group over the sham group in terms of BP-lowering efficacy. There is great controversy about the results of the Symplicity HTN-3 study. Subsequently, Kandzari *et al*. performed post hoc analyses and found that several potential factors, such as lack of standardized procedural treatment recommendations leading to incomplete RDN, limited experience of the interventionists, changes in antihypertensive medications throughout the study, lifestyle changes, and variation in adherence to medication, may have contributed to the negative results of the Symplicity HTN-3 study [13]. In addition, the antihypertensive effect of patients with more ablation sites is still more significant than that of the sham group [13]. Insufficient denervation is one of the important factors affecting the antihypertensive effect of RDN. Therefore,

DOI: 10.55415/deep-2023-0020.v1

how to improve and ensure the effectiveness of denervation has been the key point 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 end point 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 [14]. Only approximately 50% of the patients in both groups were adherent to their prescribed medication [14, 15]. A post hoc analysis of the DENERHTN trial identified that nonadherence to treatment was a major determinant of the difference between office systolic and daytime ambulatory BP [16]. 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, suggesting that the following two questions need to be addressed. One is the requirement to select RDN-eligible patients. Second, the effect of a single-electrode wire-type beam-frequency guide tube to block the renal artery nerve is not sufficient. This has prompted subsequent new RDN studies with updated patient selection criteria and the use of a second-generation multielectrode catheter that permits multiple, simultaneous, and more complete circumferential ablations, as well as access to distal arterial branches following bifurcation of the main renal artery.

3.2 Clinical Trials of the Second-Generation Catheter System

The second-generation RF energy-based catheter was a four-electrode spiral RF catheter that could simultaneously ablate the renal artery in four quadrants (superior, inferior, anterior, and posterior quadrants). The ablation range was expanded from the main renal artery to any branch renal artery with a diameter of 3 mm to 8 mm, and the average ablation points per side were approximately 20 points to 25 points. Based on

DOI: 10.55415/deep-2023-0020.v1

these properties of the catheter, the researchers conducted studies of RDN in patients without (SPYRAL HTN-OFF MED) and with (SPYRAL HTN-ON MED) antihypertensive medications [17]. The two studies had essentially the same eligibility criteria. Both pilot trials demonstrated significantly greater 24-hour ambulatory BP changes from baseline in the RDN group compared to sham controls at interim analysis [18, 19].

Following a positive pilot trial [18], the SPYRAL HTN-OFF MED (SPYRAL Pivotal) trial, as an international, prospective, single-blinded, sham-controlled trial, was conducted [20]. 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 basically consistent, the primary analysis combined evidence from the SPYRAL pilot study (n = 80) and the pivotal 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. Compared to the sham group, 24-hour systolic BP was –3.9 mmHg (Bayesian 95% CI: from –6.2 mmHg to –1.6 mmHg), and office systolic BP was –6.5 mmHg (95% CI: –9.6 mmHg to –3.5 mmHg) in the treatment group (Table 1). No major device-related or procedural-related safety events occurred up to 3 months [20].

Because long-term efficacy and safety data from RCTs of RDN are lacking, the SPYRAL HTN-ON MED trial was conducted [21]. The trial compared changes in ambulatory and office BP measurements between the RDN group and sham control group up to 36 months. The results showed that 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) [21]. In addition, the time in therapeutic range (TTR) was used to evaluate the effect of BP reduction in this trial. The results showed that RDN could significantly improve 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, with an "always on" effect. Therefore, compared with a sham procedure, RF ablation-based RDN resulted in clinically meaningful BP-lowering effects within 36 months, independent of antihypertensive medications, and without safety concerns. RDN can achieve long-term effective and stable BP reduction in patients with poorly controlled hypertension. This provides a more comprehensive evidence-based approach to the application of RDN in patients with RH [21]. In addition, the American Heart Association (AHA) Scientific Sessions 2022 announced the 6-month follow-up results of SPYRAL HTN-ON MED Expansion (NCT04311086) [22]. However, the primary endpoint was not met in the RDN group compared with the sham control group (the change in 24-hour systolic BP was -6.5 mmHg with RDN and -4.5 mmHg with sham treatment; adjusted treatment difference, -1.9 mmHg, P = 0.12) [22]. However, the secondary end point 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) [22]. The primary safety endpoint was met with a low incidence of procedural-related and clinical adverse events. We are still optimistic about the results of this clinical study, which is still expected to provide hope for the future use of RDN as an interventional treatment for hypertensive patients with poor BP control.

Long-term outcomes (follow-up 36 months) of the Symplicity HTN-3 trial showed that the change in office systolic BP was -26.4 ± 25.9 mmHg with RDN and -5.7 ± 24.4 mmHg with sham (adjusted treatment difference -22.1 mmHg, 95% CI: from -27.2 mmHg to -17.0 mmHg; P ≤ 0.0001, Table 1) at 36 months [23]. 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 mm Hg, 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, with consistent and

DOI: 10.55415/deep-2023-0020.v1

significant results with imputation. Rates of adverse events were similar across treatment groups, with no evidence of late-emerging complications from RDN.

The Global SYMPLICITY Registry (GSR) [24-27] is a prospective, open-label, international, multicenter observational study for assessment of the safety and effectiveness of RDN among real-world patients treated with the Symplicity RDN system (single-electrode Symplicity Flex™ catheter or the multielectrode Symplicity Spyral™ catheter). The results showed that 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 hypertensive patients treated with the RDN technique [27]. Further analysis of the correlation between TTR and the incidence of major cardiovascular events, such as cardiac death, myocardial infarction, and stroke, found 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 reduced the incidence of major cardiovascular events between 6 and 36 months after the RDN procedure by 15% ($P < 0.001$) [27].

From the results of these studies, the clinical benefit of RF ablation for RDN can be evaluated in four dimensions. First, RDN can significantly lower BP and reduce 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 that pose a high risk of cardiovascular events. Third, RF-based RDN can improve the rate of BP control. Finally, RF-based RDN can improve the TTR and reduce the risk of major cardiovascular events.

3.3 Renal Nerve Electrical Stimulation-Guided RDN

It is well known that the principle of the number of catheter ablations and even of clinical treatment is "less is more". Medtronic's Spyral catheter tries to compensate for the deficiency of the system that cannot determine the renal sympathetic nerve site by taking a new approach to win by quantity. The average procedure time was 99.6 min, and the total number of ablations was 46.9 per patient, creating a new concept of "more is better" [20]. The Medtronic Spyral Global study also confirms the safety of

DOI: 10.55415/deep-2023-0020.v1

RDN in lowering BP, which has advantages over drugs in terms of nonadherence and "always on" antihypertensive efficacy [24-27].

At present, a reduction in BP was not observed among approximately 25% to 30% of patients undergoing RDN [28, 29], which is proposed to be due to the distribution of different types of nerves around the renal artery. However, the current clinical practice of RDN in the treatment of hypertension cannot accurately map the renal sympathetic nerves that may lead to BP elevation. Based on this important clinical need, a renal nerve mapping/selective ablation strategy is being developed.

In 2013, Chinushi *et al*. [30] introduced electrical stimulation of the renal artery for the first time to explore the functional localization of renal autonomic nerves in dogs. They found that renal nerve electrical stimulation (RNS) increases BP via an increase in central sympathetic nervous activity. This study established RNS as a feasible and promising method to locate renal nerves to guide RDN. Several subsequent animal experiments [31-34] also confirmed that electrical stimulation of the renal artery nerve caused an increase in BP, but this trend was attenuated after mapping and ablation with a catheter, which means that renal nerves were successfully ablated. In addition, the animal experimental study conducted by Lu *et al*. [31] and Yu *et al*. [35] showed that the sites of BP elevation by electrical stimulation of the renal artery were mainly distributed in the proximal and middle segments of the renal artery and less distributed in the distal segment of the renal artery. Similar to previous animal studies, the clinical study by Chen *et al*. [36] showed that proximal RDN has a similar efficacy and safety profile compared with full-length RDN and proposed the proximal artery as the key portion for RDN. In addition, Konstantinos *et al*. [37] used the ConfidenHT system to perform simple renal artery electrical stimulation on 20 hypertensive patients in 2018. The results showed that when the current was 2 mA, the BP response at the renal artery ostium was more obvious, but the difference 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). This suggests that RNS can be performed safely and

DOI: 10.55415/deep-2023-0020.v1

effectively along the renal artery and results in a large variation in temporary BP changes per patient and per anatomic location; moreover, RNS might help optimize the treatment effect and select potential responders to renal sympathetic denervation [37].

Similar to previous experimental studies, several preliminary clinical trials [38-41] have confirmed that renal nerve mapping/selective ablation-based RDN can significantly reduce 24-hour ambulatory BP in patients with RH. Gal *et al*. [38] 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 (4 to 6 ablation sites per artery), 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 was increased 43.1±14.7 mmHg before RDN compared with 9.3±10.5 mmHg after RDN ($P = 0.002$). The mean BP on ambulant BP monitoring (ABPM) was reduced from 153.3±12.9/89.0±3.5 mmHg to 135.0±9.4/73.6±13.5 mmHg, and antihypertensive drug use was reduced to a mean of 3.5 (range: 1 to 6) at the 6-month follow-up after the RDN procedure [38]. Consistent with previous studies, de Jong *et al*. [39] found that RNS resulted in 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 ABPM was 153±11 mmHg before RDN and decreased to 137±10 mmHg at the 3- to 6-month follow-up ($P = 0.003$) [39]. In addition, Xu *et al*. [41] found similar results, and they confirmed that the BP-elevation response during RF ablation could 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 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 [29, 42]. Currently, several clinical trials (SMART study [43] NCT02761811 and SMART OFF-MED study NCT03885843) in which RNS is being used to guide RDN to treat hypertension are ongoing. The results of these studies are expected.

DOI: 10.55415/deep-2023-0020.v1

At present, the mechanism of RNS-guided RDN is not clear, but the theoretical basis of this technology can be explained in detail from three aspects: anatomy, physiology and histology. In 2014, Sakakura *et al*. [44] 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 was higher than that in the distal segment of the renal artery [44]. Subsequently, another anatomical study [45] 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 found that electrical stimulation of these different types of sites increased the BP when stimulating the hot spot, decreased the BP when stimulating the cold spot, and did not cause significant changes in BP when stimulating the neutral spot. The results of histological studies also proved that the nerve distribution around the renal artery was related to the strong response site (SRS, which is the site of the maximum increase in systolic BP during electrical stimulation of the renal nerve > 10 mmHg) and the weak response site (WRS, which is 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 in the area adjacent to the strong response point were significantly greater than those around the weak stimulation point [32, 42, 46, 47].

4. Ultrasound-Based RDN

4.1 Intravascular Ultrasound

The application of intravascular ultrasound energy in the denervated renal artery nerve catheter system is based on the physical characteristic that 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 study of RADIANCE-HTN using this device

DOI: 10.55415/deep-2023-0020.v1

(Paradise, ReCor Medical) consists of two studies, the SOLO study [48-50] without antihypertensive agents and the TRIO study [51] 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) [48]. 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) [49]. 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 [50]. This study suggests that RDN is still safe and effective in mid- and long-term follow-ups. The RADIANCE-HTN TRIO study, designed to evaluate the safety and efficacy of the Paradise system in patients with RH, demonstrated that ultrasound RDN treatment resulted in a significant reduction in BP at 2 months compared with sham surgery in patients with RH who were resistant to standard triple antihypertensive therapy (Table 1) [51]. The RADIOSOUND-HTN study [52] 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), of which group one was significantly better than group two, but there was no significant difference for either group one *vs.* group three or group two *vs.* group three, and there was no significant difference in safety among the three groups [52]. However, the REQUIRE trial [53],

DOI: 10.55415/deep-2023-0020.v1

which is the first trial of intravascular ultrasound ablation of renal arterial nerves in Asian patients with RH, has achieved negative results (Table 1). The reasons behind this will be worthy of further exploration, and more trials may be needed to evaluate the efficacy and safety of this treatment.

Recently, 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 [54-56]. 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 and had been treated with 0-2 antihypertensive drugs, with 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 four-week drug washout period (withdrawal of antihypertensive drugs), patients with baseline BP meeting the criteria (daytime ambulatory BP ≥ 135/85 mmHg and < 170/105 mmHg) were obtained, and eligibility for surgery was confirmed by renal angiography. The success rate of ultrasound RDN surgery was more than 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). 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 reductions of at least 5 mmHg, and 48% had BP reductions of at least 10 mmHg. Nearly two-thirds of patients had a positive response to ultrasound RDN, indicating that the technique is effective for the vast majority of patients. A reduction of 10 mmHg in systolic BP can

DOI: 10.55415/deep-2023-0020.v1

reduce the risk of cardiovascular and cerebrovascular events by more than 20% on average, which suggests that ultrasound RDN can theoretically improve the outcome of at least half of patients. There were 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.

RADIANCE Ⅱ was well designed, and the results reconfirmed that ultrasound RDN can significantly reduce BP in patients with mild-to-moderate hypertension who did not take hypertension drugs, providing a large-scale evidence-based basis for ultrasound RDN and more strongly proving the safety and effectiveness of ultrasound RDN technology. However, there are still some limitations. First, the study only selected patients with mild-to-moderate hypertension without comorbidities or a cardiovascular and cerebrovascular history, which was limited and could not well suggest that it is more suitable for the audience of ultrasound RDN. Second, similar to other blinded RDN trials, the RADIANCE Ⅱ study still does not have reliable markers of ablation success and predictors of responsiveness. Finally, the RADIANCE II study is only two months old, 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.

4.2 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 were conducted to optimize targeting and therapeutic dose levels and explore lesion patterns prior to initiation of human trials. Swine or canines were used because their renal systems are similar to those of humans. Several experimental studies [57-61] 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 carried out. From August 2013 to May 2014, Rong *et al*. [62] used high-intensity focused ultrasound (HIFU)-based RDN to treat 10 patients with RH. The results showed that their BP decreased −29.2

DOI: 10.55415/deep-2023-0020.v1

± 6.8/−11.2 ± 9.7 mmHg at 6 months of follow-up. No serious complications were observed during the study. This indicates that HIFU-based RDN is safe and effective, but larger samples of randomized, controlled, double-blind clinical trials are needed for validation. In addition, the WAVE series of clinical trials was used to verify 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 subjects also used targeted catheters, and in the latter 22 subjects, only the renal artery was tracked using surface Doppler ultrasound to locate the ultrasound focus. The WAVE I, II and III series of prospective single-arm cohort clinical trials showed that RDN with this device was safe and effective in the treatment of RH [61, 63]. Subsequently, the WAVE IV phase II clinical trial was carried out using a randomized, double-blind, sham-operated control method, and patients with RH were enrolled 1:1. The trial had to be terminated early because no significant difference in BP between the two groups was found in the first 81 patients at 12 and 24 weeks of follow-up (Table 1) [64]. In the future, there is an urgent need 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.

5. Conclusion

This review describes possible mechanisms of RDN in the treatment of hypertension, treatment techniques, and important clinical trials that have been published. RDN is still 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 a favorable effect on BP reduction in some patients. However, the pathophysiological mechanism of hypertension in different patients can be different, the renal artery anatomy in different patients can be inconsistent, the principles of different types of RDN

DOI: 10.55415/deep-2023-0020.v1

technology may not be the same, and the experience and technical level of different surgeons are inconsistent. These four "inconsistencies" will inevitably affect the effectiveness and safety of RDN treatment, as well as the application value and clinical status in antihypertensive therapy.

In general, it is reasonable to perform RDN treatment in mature medical centers for patients whose BP is not satisfactorily controlled after lifestyle intervention and adequate treatment with multiple antihypertensive drugs, for patients with significant hypersympathetic manifestations, or for patients who cannot tolerate antihypertensive drugs. It is believed that with the development of related technology and the continuous improvement of treatment equipment, RDN will play a more important role in the field of hypertension treatment in the future.

At present, it is far from sufficient to only use the clinic and ambulatory BP decreases to evaluate the success of ablation. New biological indicators (biological markers reflecting the successful ablation site, markers reflecting sympathetic nerve activation, etc.) as markers of successful ablation still need to be further studied. These studies will provide a basis for the treatment of RDN in hypertension and other fields. Therefore, the following points can be considered for further research on RDN. First, more targeted research can be carried out on some controversial issues. For example, the selected population did not include the elderly population because the arterial stiffness of elderly individuals is high and the success rate of ablation is relatively low; thus, a comparison between the elderly and the nonelderly populations can be performed. In addition, the consideration of different ethnic groups can also be investigated. Some studies have found that RDN works better for Asians and less well for black Africans. Second, we can continue to explore the indicators of successful renal artery nerve ablation. At present, the sign of successful RF ablation is only reflected in the reduction of BP, and whether some indicators reflecting the degree of sympathetic nerve stimulation can be added is worth studying. Third, the updating of the equipment can be evaluated. Currently, there are many kinds of ablation catheters with different effects. It is worth studying what kind of results will be brought by the

DOI: 10.55415/deep-2023-0020.v1

improvement of equipment. Finally, the comparison of ablation methods, whether to choose RNS or other methods, the adaptive population of each method, and the advantages of each method also need to be further studied.

In summary, the efficacy and safety of RDN for hypertension have been verified in a series of randomized controlled trials. However, there are still some issues that need to be considered and refined, such as how to find suitable patients, how to determine the surgical end point, how to predict the BP response, and whether RDN can be used as an independent first-line treatment scheme for hypertensive patients. All of these aspects should be further explored and studied.

Acknowledgments

We would like to thank everyone who contributed to this research.

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.

Funding

This research is funded by Program for Youth Innovation in Future Medicine, Chongqing Medical University (Grant number W0078 for Z-Y L, Grant number W0112 for W-J C), Kuanren Talents Program of the Second Affiliated Hospital of Chongqing Medical University, Chongqing, China (received by Z-Y L with the grant number of 2020-7, received by W-J C with the grant number of kryc-yq-2103), and General Project of the National Natural Science Foundation of China (32071110, Y-H Y). However, the funding agencies had no influence on the study design, study performance, data collection, data analysis, data interpretation, or manuscript preparation.

DOI: 10.55415/deep-2023-0020.v1

References

1. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C *et al*. **2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**. *Circulation* 2018, **138**(17):e426-e483.
2. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M *et al*. **2018 ESC/ESH Guidelines for the management of arterial hypertension**. *Eur Heart J* 2018, **39**(33):3021-3104.
3. Rabi DM, McBrien KA, Sapir-Pichhadze R, Nakhla M, Ahmed SB, Dumanski SM *et al*. **Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children**. *Can J Cardiol* 2020, **36**(5):596-624.
4. Lauder L, Azizi M, Kirtane AJ, Böhm M, Mahfoud F. **Device-based therapies for arterial hypertension**. *Nat Rev Cardiol* 2020, **17**(10):614-628.
5. Degirmenci H, Duman H, Demirelli S, Bakirci EM, Hamur H, Inci S *et al*. **Assessment of effect of irbesartan and nebivolol on the left atrium volume and deformation in the patients with mild-moderate hypertension**. *Eur Rev Med Pharmacol Sci* 2014, **18**(6):781-789.
6. Bourque G, Hiremath S. **Rethinking Resistant Hypertension**. *J Clin Med* 2022, **11**(5).
7. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K *et al*. **Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study**. *Lancet* 2009, **373**(9671):1275-1281.
8. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. **Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial**. *Lancet* 2010, **376**(9756):1903-1909.
9. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT *et al*. **A controlled trial of renal denervation for resistant hypertension**. *N Engl J Med* 2014,

DOI: 10.55415/deep-2023-0020.v1

370(15):1393-1401.

10. Li L, Hu Z, Xiong Y, Yao Y. **Device-Based Sympathetic Nerve Regulation for Cardiovascular Diseases**. *Front Cardiovasc Med* 2021, **8**:803984.
11. Mahfoud F, Schlaich MP, Lobo MD. **Device Therapy of Hypertension**. *Circ Res* 2021, **128**(7):1080-1099.
12. Lauder L, Bohm M, Mahfoud F. **The current status of renal denervation for the treatment of arterial hypertension**. *Prog Cardiovasc Dis* 2021, **65**:76-83.
13. Kandzari DE, Bhatt DL, Brar S, Devireddy CM, Esler M, Fahy M *et al*. **Predictors of blood pressure response in the SYMPLICITY HTN-3 trial**. *Eur Heart J* 2015, **36**(4):219-227.
14. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P *et al*. **Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial**. *Lancet* 2015, **385**(9981):1957-1965.
15. Azizi M, Pereira H, Hamdidouche I, Gosse P, Monge M, Bobrie G *et al*. **Adherence to Antihypertensive Treatment and the Blood Pressure-Lowering Effects of Renal Denervation in the Renal Denervation for Hypertension (DENERHTN) Trial**. *Circulation* 2016, **134**(12):847-857.
16. Hamdidouche I, Gosse P, Cremer A, Lorthioir A, Delsart P, Courand PY *et al*. **Clinic Versus Ambulatory Blood Pressure in Resistant Hypertension: Impact of Antihypertensive Medication Nonadherence: A Post Hoc Analysis the DENERHTN Study**. *Hypertension* 2019, **74**(5):1096-1103.
17. Kandzari DE, Kario K, Mahfoud F, Cohen SA, Pilcher G, Pocock S *et al*. **The SPYRAL HTN Global Clinical Trial Program: Rationale and design for studies of renal denervation in the absence (SPYRAL HTN OFF-MED) and presence (SPYRAL HTN ON-MED) of antihypertensive medications**. *Am Heart J* 2016, **171**(1):82-91.
18. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA *et al*. **Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial**. *Lancet* 2017, **390**(10108):2160-2170.

DOI: 10.55415/deep-2023-0020.v1

19. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S *et al*. **Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial**. *Lancet* 2018, **391**(10137):2346-2355.

20. Böhm M, Kario K, Kandzari DE, Mahfoud F, Weber MA, Schmieder RE *et al*. **Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial**. *Lancet* 2020, **395**(10234):1444-1451.

21. Mahfoud F, Kandzari DE, Kario K, Townsend RR, Weber MA, Schmieder RE *et al*. **Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial**. *The Lancet* 2022, **399**(10333):1401-1410.

22. Kandzari DE. **Effect of Radiofrequency Renal Denervation on Blood Pressure in the Presence of Antihypertensive Drugs: 6-Month Primary Results from the SPYRAL HTN-ON Med Expansion Randomized Trial** [https://clinicaltrialresults.org/dr-david-kandzari-and-dr-c-michael-gibson-discuss-spyral-htn-on-effect-of-radiofrequency-renal-denervation-on-blood-pressure-in-the-presence-of-antihypertensive-drugs-6-month-primary-re/]

23. Bhatt DL, Vaduganathan M, Kandzari DE, Leon MB, Rocha-Singh K, Townsend RR *et al*. **Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial**. *Lancet* 2022.

24. Mahfoud F, Böhm M, Schmieder R, Narkiewicz K, Ewen S, Ruilope L *et al*. **Effects of renal denervation on kidney function and long-term outcomes: 3-year follow-up from the Global SYMPLICITY Registry**. *Eur Heart J* 2019, **40**(42):3474-3482.

25. Ott C, Mahfoud F, Mancia G, Narkiewicz K, Ruilope LM, Fahy M *et al*. **Renal denervation in patients with versus without chronic kidney disease: results from the Global SYMPLICITY Registry with follow-up data of 3 years**. *Nephrol Dial Transplant* 2022, **37**(2):304-310.

DOI: 10.55415/deep-2023-0020.v1

26. Schmieder RE, Mahfoud F, Mancia G, Narkiewicz K, Ruilope L, Hutton D *et al*. **Clinical Event Reductions in High-Risk Patients After Renal Denervation Projected from the Global SYMPLICITY Registry**. *Eur Heart J Qual Care Clin Outcomes* 2022.

27. Mahfoud F, Mancia G, Schmieder RE, Ruilope L, Narkiewicz K, Schlaich M *et al*. **Cardiovascular Risk Reduction After Renal Denervation According to Time in Therapeutic Systolic Blood Pressure Range**. *J Am Coll Cardiol* 2022, **80**(20):1871-1880.

28. Zhou H, Li Y, Xu Y, Liu H, Lai Y, Tan K *et al*. **Mapping Renal Innervations by Renal Nerve Stimulation and Characterizations of Blood Pressure Response Patterns**. *J Cardiovasc Transl Res* 2022, **15**(1):29-37.

29. Zhou H, Xu Y, Chen W, Wang L, Du H, Liu H *et al*. **Present Evidence of Determinants to Predict the Efficacy of Renal Denervation**. *Int J Hypertens* 2022, **2022**:5694127.

30. Chinushi M, Izumi D, Iijima K, Suzuki K, Furushima H, Saitoh O *et al*. **Blood pressure and autonomic responses to electrical stimulation of the renal arterial nerves before and after ablation of the renal artery**. *Hypertension* 2013, **61**(2):450-456.

31. Lu J, Wang Z, Zhou T, Chen S, Chen W, Du H *et al*. **Selective proximal renal denervation guided by autonomic responses evoked via high-frequency stimulation in a preclinical canine model**. *Circ Cardiovasc Interv* 2015, **8**(6).

32. Liu H, Chen W, Lai Y, Du H, Wang Z, Xu Y *et al*. **Selective Renal Denervation Guided by Renal Nerve Stimulation in Canine**. *Hypertension* 2019, **74**(3):536-545.

33. Chen W, Du H, Lu J, Ling Z, Long Y, Xu Y *et al*. **Renal Artery Vasodilation May Be An Indicator of Successful Sympathetic Nerve Damage During Renal Denervation Procedure**. *Sci Rep* 2016, **6**:37218.

34. Lai Y, Zhou H, Chen W, Liu H, Liu G, Xu Y *et al*. **The intrarenal blood pressure modulation system is differentially altered after renal denervation guided by different intensities of blood pressure responses**. *Hypertens Res* 2022.

35. Yu L, Huang B, Wang Z, Wang S, Wang M, Li X *et al*. **Impacts of Renal Sympathetic Activation on Atrial Fibrillation: The Potential Role of the Autonomic Cross Talk Between Kidney and Heart**. *J Am Heart Assoc* 2017, **6**(3).

DOI: 10.55415/deep-2023-0020.v1

36. Chen W, Ling Z, Du H, Song W, Xu Y, Liu Z *et al*. **The effect of two different renal denervation strategies on blood pressure in resistant hypertension: Comparison of full-length versus proximal renal artery ablation**. *Catheter Cardiovasc Interv* 2016, **88**(5):786-795.

37. Tsioufis KP, Feyz L, Dimitriadis K, Konstantinidis D, Tousoulis D, Voskuil M *et al*. **Safety and performance of diagnostic electrical mapping of renal nerves in hypertensive patients**. *EuroIntervention* 2018, **14**(12):e1334-e1342.

38. Gal P, de Jong MR, Smit JJ, Adiyaman A, Staessen JA, Elvan A. **Blood pressure response to renal nerve stimulation in patients undergoing renal denervation: a feasibility study**. *J Hum Hypertens* 2015, **29**(5):292-295.

39. de Jong MR, Adiyaman A, Gal P, Smit JJ, Delnoy PP, Heeg JE *et al*. **Renal Nerve Stimulation-Induced Blood Pressure Changes Predict Ambulatory Blood Pressure Response After Renal Denervation**. *Hypertension* 2016, **68**(3):707-714.

40. de Jong MR, Hoogerwaard AF, Gal P, Adiyaman A, Smit JJ, Delnoy PP *et al*. **Persistent Increase in Blood Pressure After Renal Nerve Stimulation in Accessory Renal Arteries After Sympathetic Renal Denervation**. *Hypertension* 2016, **67**(6):1211-1217.

41. Xu Y, Xiao P, Fan J, Chen W, Du H, Ling Z *et al*. **Blood pressure elevation response to radiofrequency energy delivery: one novel predictive marker to long-term success of renal denervation**. *J Hypertens* 2018, **36**(12):2460-2470.

42. Tan K, Lai Y, Chen W, Liu H, Xu Y, Li Y *et al*. **Selective renal denervation guided by renal nerve stimulation: mapping renal nerves for unmet clinical needs**. *J Hum Hypertens* 2019, **33**(10):716-724.

43. Wang J, Sun N, Ge J, Jiang H, Yin Y, Chen M *et al*. **Rationale and Design of Sympathetic Mapping/Ablation of Renal Nerves Trial (SMART) for the Treatment of Hypertension: a Prospective, Multicenter, Single-Blind, Randomized and Sham Procedure-Controlled Study**. *J Cardiovasc Transl Res* 2022.

44. Sakakura K, Ladich E, Cheng Q, Otsuka F, Yahagi K, Fowler DR *et al*. **Anatomic assessment of sympathetic peri-arterial renal nerves in man**. *J Am Coll Cardiol* 2014, **64**(7):635-643.

DOI: 10.55415/deep-2023-0020.v1

45. van Amsterdam WA, Blankestijn PJ, Goldschmeding R, Bleys RL. **The morphological substrate for Renal Denervation: Nerve distribution patterns and parasympathetic nerves. A post-mortem histological study**. *Ann Anat* 2016, **204**:71-79.

46. Fudim M, Sobotka AA, Yin YH, Wang JW, Levin H, Esler M *et al*. **Selective vs. Global Renal Denervation: a Case for Less Is More**. *Curr Hypertens Rep* 2018, **20**(5):37.

47. Kiuchi MG, Esler MD, Fink GD, Osborn JW, Banek CT, Böhm M *et al*. **Renal Denervation Update From the International Sympathetic Nervous System Summit: JACC State-of-the-Art Review**. *J Am Coll Cardiol* 2019, **73**(23):3006-3017.

48. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J *et al*. **Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial**. *Lancet* 2018, **391**(10137):2335-2345.

49. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Lobo MD *et al*. **Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control Following Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial**. *Circulation* 2019.

50. Azizi M, Daemen J, Lobo MD, Mahfoud F, Sharp ASP, Schmieder RE *et al*. **12-Month Results From the Unblinded Phase of the RADIANCE-HTN SOLO Trial of Ultrasound Renal Denervation**. *JACC Cardiovasc Interv* 2020, **13**(24):2922-2933.

51. Azizi M, Sanghvi K, Saxena M, Gosse P, Reilly JP, Levy T *et al*. **Ultrasound renal denervation for hypertension resistant to a triple medication pill (RADIANCE-HTN TRIO): a randomised, multicentre, single-blind, sham-controlled trial**. *Lancet* 2021, **397**(10293):2476-2486.

52. Fengler K, Rommel KP, Blazek S, Besler C, Hartung P, von Roeder M *et al*. **A Three-Arm Randomized Trial of Different Renal Denervation Devices and Techniques in Patients With Resistant Hypertension (RADIOSOUND-HTN)**. *Circulation* 2019, **139**(5):590-600.

53. Kario K, Yokoi Y, Okamura K, Fujihara M, Ogoyama Y, Yamamoto E *et al*. **Catheter-based ultrasound renal denervation in patients with resistant hypertension: the randomized, controlled REQUIRE trial**. *Hypertens Res* 2022, **45**(2):221-231.

DOI: 10.55415/deep-2023-0020.v1

54. Kirtane A. **Ultrasound renal denervation lowers BP at 2 months vs. sham: RADIANCE II** [https://www.healio.com/news/cardiac-vascular-intervention/20220918/ultrasound-renal-denervation-lowers-bp-at-2-months-vs-sham-radiance-ii]

55. Kirtane A. **Endovascular Ultrasound Renal Denervation to Treat Uncontrolled Hypertension: Primary Results of the Randomized, Sham-Controlled RADIANCE II Pivotal Trial** [https://www.tctmd.com/slide/endovascular-ultrasound-renal-denervation-treat-uncontrolled-hypertension-primary-results]

56. Kirtane A. **The RADIANCE II study: two months outcomes of a randomized trial of renal denervation versus a sham procedure for uncontrolled moderate hypertension** [https://www.pcronline.com/News/Whats-new-on-PCRonline/2022/TCT-2022/RADIANCE-II-study-two-months-outcomes-randomized-trial-renal-denervation-vs-sham-procedure-for-uncontrolled-moderate-hypertension]

57. Wang Q, Guo R, Rong S, Yang G, Zhu Q, Jiang Y *et al*. **Noninvasive renal sympathetic denervation by extracorporeal high-intensity focused ultrasound in a pre-clinical canine model**. *J Am Coll Cardiol* 2013, **61**(21):2185-2192.

58. Koopmann M, Shea J, Kholmovski E, de Bever J, Minalga E, Holbrook M *et al*. **Renal sympathetic denervation using MR-guided high-intensity focused ultrasound in a porcine model**. *J Ther Ultrasound* 2016, **4**:3.

59. Shea J, de Bever J, Kholmovski E, Beal H, Hadley JR, Minalga E *et al*. **Effect of applied energy in renal sympathetic denervation with magnetic resonance guided focused ultrasound in a porcine model**. *J Ther Ultrasound* 2017, **5**:16.

60. Liao Q, Yang F, Xiong B, Zheng X, Wang Y, Qian J *et al*. **Optimal Strategy for HIFU-Based Renal Sympathetic Denervation in Canines**. *Front Cardiovasc Med* 2021, **8**:739560.

61. Schmieder RE, Ott C, Bramlage P. **Non-invasive Renal Denervation: Update on External Ultrasound Approaches**. *Curr Hypertens Rep* 2016, **18**(6):48.

62. Rong S, Zhu H, Liu D, Qian J, Zhou K, Zhu Q *et al*. **Noninvasive renal denervation for resistant hypertension using high-intensity focused ultrasound**. *Hypertension* 2015,

DOI: 10.55415/deep-2023-0020.v1

66(4):e22-25.

63. Neuzil P, Ormiston J, Brinton TJ, Starek Z, Esler M, Dawood O *et al*. **Externally Delivered Focused Ultrasound for Renal Denervation**. *JACC Cardiovasc Interv* 2016, **9**(12):1292-1299.

64. Schmieder RE, Ott C, Toennes SW, Bramlage P, Gertner M, Dawood O *et al*. **Phase II randomized sham-controlled study of renal denervation for individuals with uncontrolled hypertension - WAVE IV**. *J Hypertens* 2018, **36**(3):680-689.

65. Rao A, Krishnan N. **Update on Renal Sympathetic Denervation for the Treatment of Hypertension**. *Curr Cardiol Rep* 2022, **24**(10):1261-1271.

66. Weber M, Mahfoud F, Schmieder R, Kandzari D, Tsioufis K, Townsend R *et al*. **Renal Denervation for Treating Hypertension: Current Scientific and Clinical Evidence**. *JACC Cardiovascular interventions* 2019, **12**(12):1095-1105.

DOI: 10.55415/deep-2023-0020.v1

Table 1 Clinical trials of renal denervation in the treatment of hypertension.

Trial (publication year)	Device (manufacturer)	Catheter Features	RDN (*n*)	Control (*n*)	Primar
SYMPLICITY HTN-1 (2009) [7]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	45	-	**Change in office systolic BP** repeated-measures ANOVA P = systolic BP −22 mmHg (95% CI: − **Change at 12 months:** office sy 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** control 1±21 mmHg, P < 0.0001
SYMPLICITY HTN-3 (2014, 2022) [9, 23]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	364	171	**Change in office systolic BP at** versus sham −11.7±25.9 mmHg, P = **36 months:** RDN -15.6±20.8 mm adjusted treatment difference -16.5 mmHg), P ≤ 0.0001. **Change in of** −26.4±25.9 mmHg versus sham − difference −22.1 mmHg (95% CI: 0.0001
DENERHTN (2015) [14]	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	53	53	**Change in daytime systolic BP at** CI: −19.7 mmHg to −11.9 mmH antihypertensive therapy −9.9 mm mmHg), a baseline-adjusted differ mmHg to −0.5 mmHg), P = 0.0329
Global SYMPLICITY Registry (2019,	Symplicity Flex (Medtronic)	Monoelectrode, radiofrequency	2237 (2019), 3077	-	**Change in systolic BP at 6 mo** mmHg, P < 0.0001; 24-h systolic **36 months:** changes were −16.7 ± 2

DOI: 10.55415/deep-2023-0020.v1

2022) [24, 27]			(2022)		office systolic BP and 24-h systolic
SPYRAL HTN-OFF MED (2017) [18]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	38	42	**Change in 24-h systolic BP at 3** −9.1 mmHg to −2.0 mmHg) vers mmHg to 2.9 mmHg), adjusted d mmHg to −0.2 mmHg), P = 0.041 **months:** RDN −10.0 mmHg (95% versus sham −2.3 mmHg (95% CI: difference -7.7 mmHg (95% CI: 0.0155
SPYRAL Pivotal (2020) [20]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	166	165	**Change in 24-h systolic BP at 3** −6.4 mmHg to −2.9 mmHg) vers mmHg to 0.9 mmHg), adjusted dif CI: –6.2 mmHg to –1.6 mmHg), P= **at 3 months:** RDN −9.2 mmHg (9 versus sham −2.5 mmHg (95% CI: difference – 6.5 mmHg (95% C 0.0001
SPYRAL HTN-ON MED (2018, 2022) [19, 21]	Spyral (Medtronic)	Multielectrode, helical, radiofrequency	38	42	**Change in 24-h systolic BP at 6** −12.7 mmHg to −5.3 mmHg) vers mmHg to 2.0 mmHg), P = 0.0051 **months:** RDN −18.7±12.4 mmH adjusted treatment difference −10. −3.3 mmHg), P = 0.0039
RADIOSOUND-H	Spyral	Multielectrode,	39/39	-	**Change in daytime systolic BP**

DOI: 10.55415/deep-2023-0020.v1

TN (2019) [52]	(Medtronic)	helical, radiofrequency			RDN of the main renal radiofrequency-based RDN of th
RADIANCE-HTN SOLO (2018, 2019, 2020) [48-50]	Paradise (ReCor Medical)	Endovascular ultrasound	74	72	−8.3±11.7 mmHg versus ultraso (ANOVA P = 0.038); overall chang **Change in daytime ambulatory** −8.5±9.3 mmHg versus sham − difference −6.3 mmHg (95% CI: 0.0001. **Change in daytime ambul** −18.1±12.2 mmHg versus sham − difference −4.3 mmHg (95% CI: − **Change in 24-h systolic BP at** versus sham −14.9±12.8 mmHg, mmHg (95% CI: −7.7 mmHg to **office systolic BP at 6 months:** R −15.9±17.2 mmHg, adjusted treatm −8.1 mmHg to 0.7 mmHg), P = 0. **systolic BP at 12 months:** RD −15.8±13.1 mmHg, adjusted treatm −5.9 mmHg to -1.3 mmHg), P = 0.2 **months:** RDN −15.1±12.4 mmH adjusted treatment difference −2.4 mmHg), P = 0.156. **Change in of** −18.1±14.9 mmHg versus sham − difference −6.3 mmHg (95% CI: −1
	Paradise (ReCor Medical)	Endovascular ultrasound	42	-	

DOI: 10.55415/deep-2023-0020.v1

RADIANCE-HTN TRIO (2021) [51]	Paradise (ReCor Medical)	Endovascular ultrasound	69	67	**Change in daytime ambulatory s** mmHg (95% CI: −16.4 mmHg to (95% CI: −10.3 mmHg to 1.8 mmH mmHg (95% CI: −8.5 mmHg to −0 **systolic BP at 2 months:** RDN −8 0.0 mmHg) versus sham -2.9 mm mmHg), adjusted treatment differen to −0.3 mmHg), P = 0.016. **Chang** RDN −9.0 mmHg (95% CI: −19.5 -4.0 mmHg (95% CI: −12.0 mmH difference −7.0 mmHg (95% CI: −1
RADIANCE II (2022 TCT conference) [54-56]	Paradise (ReCor Medical)	Endovascular ultrasound	150	74	**Change in daytime ambulatory s** mmHg versus sham −1.8 mmHg mmHg, 95% CI: −9.3 mmHg to −3.
REQUIRE (2022) [53]	Paradise (ReCor Medical)	Endovascular ultrasound	72	71	**Change in 24-h systolic BP at 3** −10.4 mmHg to −2.8 mmHg) vers mmHg to −2.7 mmHg), adjusted tr CI: −5.5 mmHg to 5.3 mmHg), P =
WAVE IV (2018) [64]	Surround Sound System (Kona Medical)	High-intensity focused ultrasound	42	39	**Change in 24-h systolic BP at 24** sham −5.90±15 mmHg, P = 0.770 weeks by −12.8±26 and −23±20 mr

P values are for the difference between the treatment and control groups, except as indicated otherwise. 2 RDN, renal denervation; TCT, American Transcatheter Cardiovascular Therapeutics conference. [a] P valu baseline and follow-up.

DOI: 10.55415/deep-2023-0020.v1

Figure legends

Fig 1. A diagram of the efferent and afferent pathways interrupted by renal denervation. Modified from *Curr Cardiol Rep. 2022 Oct;24(10):1261-1271* [65] and *JACC Cardiovasc Interv. 2019 Jun 24;12(12):1095-1105* [66]. BP, blood pressure; HR, heart rate; LVH, left ventricular hypertrophy; RAAS, renin-angiotensin-aldosterone system; RDN, renal denervation.