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Renal Denervation: Is It Ready for Prime Time?

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Abstract

Purpose of Review Interventional cardiology and in particular the field of renal denervation is subject to constant change. This review provides an up to date overview of renal denervation trials and an outlook on what to expect in the future.

Recent Findings After the sham-controlled SYMPLICITY HTN-3 trial dampened the euphoria following early renal denervation trials, the recently published results of the sham-controlled SPYRAL HTN and RADIANCE HTN trials provided proof-of-principle for the blood pressure-lowering efficacy of renal denervation. However, these studies underline the major issue of patients' non-adherence to antihypertensive medication as well as the need for reliable patient- and procedure-related predictors of response.

Summary The second generation of sham-controlled renal denervation trials provided proof of principle for the blood pressure-lowering efficacy of RDN. However, larger trials have to assess long-term safety and efficacy.

Keywords Renal denervation · Device-based therapy · Hypertension · Interventional cardiology

Introduction

Hypertension is one of the most prevalent public health concerns and is associated with congestive heart failure, chronic kidney disease, and stroke [1]. In Europe, up to 55% of the population suffers from arterial hypertension [2–4], and the prevalence is steadily increasing. Despite the availability of safe and effective antihypertensive drugs [1, 5], blood pressure (BP) control to target values remains insufficient in about one-third of all patients treated. Owing to the revised BP targets in the recently published American [6] and European [7] guidelines for arterial hypertension, the number of patients with uncontrolled hypertension has increased [8]. Among other reasons, non-adherence to antihypertensive medication contributes to the large number of patients with uncontrolled hypertension [9]. Therefore, device-based therapies for arterial hypertension should not only be considered as an addition to the existing pharmacological treatment but also in patients unable or unwilling to take antihypertensive medications [10, 11]. Increased sympathetic nerve activity plays a crucial role in the development of arterial hypertension [12]. Activation of efferent renal nerves can cause volume and sodium retention, reduction of renal blood flow, and activation of the renin-angiotensin-aldosterone system (RAAS) [13]. Furthermore, afferent sympathetic nerve fibers were shown to increase whole body sympathetic tone [13]. Catheter-based RDN was introduced as a minimally invasive therapy to reduce afferent and efferent renal nerve signaling and thereby reducing systemic sympathetic nerve activity.

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From SYMPLICITY to SPYRAL and RADIANCE

The open-label SYMPLICITY HTN-1 and HTN-2 trials demonstrated a significant decline of office BP (OBP) following RDN using a monoelectrode radiofrequency RDN (RF-RDN) catheter in patients with resistant hypertension [14, 15]. Several observational studies [16, 17] as well as national and international registries [17–19] were able to confirm these encouraging results. In contrast, the controversially discussed randomized, sham-controlled SYMPLICITY HTN-3 trial failed to show superiority of RDN over sham in patients with resistant hypertension, because of a pronounced drop in systolic OBP in the RDN and sham group [20]. Several confounders such as inadequate patient selection, insufficient procedures, changes in antihypertensive medication, and limited experience of the interventionalists were thought to contribute to the neutral results [21]. However, the study indicated the continued safety of the procedure [22].

In the DENER-HTN trial, 106 patients with resistant hypertension were prescribed to a standardized stepped-care antihypertensive drug regimen [23]. After 4 weeks, patients were randomized to RDN plus optimal medical therapy or optimal medical therapy alone [23]. At 6 months, the decrease in daytime systolic ABP was more pronounced in the RDN group (baseline-adjusted difference between RDN and control group − 5.9 mmHg, 95%CI − 11.3 to − 0.5) [23]. Of note, there was a considerable variability in interindividual BP change and high rates of non-adherence to antihypertensive drugs [24, 25]. The SPYRAL HTN and RADIANCE HTN trials were designed to address methodological shortcomings of the SYMPLICITY HTN trials (Table 1) [26].

The randomized, sham-controlled SPYRAL HTN-OFF MED trial only included therapy-naïve patients or patients after 4-week discontinuation of antihypertensive medications in order to provide proof-of-principle for the BP-lowering efficacy of RDN utilizing a helical multielectrode RF-RDN catheter [28••]. The prospectively planned interim analysis after 80 patients had completed the 3-month follow-up showed a greater reduction of systolic 24-h ambulatory BP (ABP) in the RDN group compared with the sham group (Fig. 1) [28••]. Although the study was not powered for efficacy endpoints, it provided proof-of-principle for the BP-lowering efficacy of RF-RDN [28••]. Similarly, endovascular ultrasound-based RDN (US-RDN) reduced daytime ABP at 2 months in the absence of medications compared with a sham procedure (Fig. 1) [29••]. After the initial 2 months of follow-up, a standardized stepped care therapy was initiated if the average BP at home exceeded 135 mmHg or 85 mmHg in systolic or diastolic BP, respectively [30]. Although most patients required additional antihypertensive therapy, fewer drugs were administered in the RDN group (0.9 ± 0.9 vs. 1.3 ± 0.9, $p = 0.010$) [30]. However, the between-group difference in ABP-reduction at 6 months remained significant in favor of RDN (difference adjusted for baseline BP and number of medications − 4.3 mmHg, 95%CI − 7.9 to − 0.6, $p = 0.024$) [30].

The SPYRAL HTN-ON MED study assessed the efficacy of RDN in addition to stable antihypertensive drug therapy [26]. At the primary endpoint of 6 months, the reduction in systolic ABP was more pronounced in the RDN compared with the sham group (Fig. 1) [31]. Further, the study showed that systolic ABP continued to decrease between 3- and 6-month follow-up. Of note, almost half of the patients in RDN trials were not completely adherent to their antihypertensive therapy despite the awareness of toxicological assessment [31, 32]. Therefore, RDN trials have reawakened the issue of patients' non-adherence to medication, in arterial hypertension but also in other chronic conditions.

Importantly, the second generation of sham-controlled studies provided proof for the BP-lowering efficacy and added to the growing body of evidence that indicates the safety of RDN.

Change in Methodology and Technology

From SYMPLICITY to SPYRAL and RADIANCE HTN, the procedure itself and the technology of RDN catheter systems have been revised significantly [28••, 31]. Several preclinical and clinical studies were conducted in the aftermath of the controversially discussed SYMPLICITY HTN-3 trial and have significantly improved our understanding of renal arterial anatomy and sympathetic innervation [33, 34].

In the SYMPLICITY HTN-3 trial, only main renal arteries were treated [22]. However, the knowledge of renal sympathetic nerve distribution has significantly evolved recently. Sympathetic nerve fibers originate from ganglia surrounding the abdominal aorta and then approach the vessels lumen conically during the course of the renal artery [35]. The overall number of nerves surrounding the renal artery is highest in the proximal segment whereas the density of sympathetic nerve fibers close to the arteries' lumen is larger in distal compared with proximal segments [35]. Therefore, the number of nerves affected by RDN increases from proximal to distal when assuming a constant depth of penetration (Fig. 2) [36, 37]. In preclinical studies, increasing the numbers of ablations in the main renal artery did not further decrease the kidney norepinephrine concentration or axon density, whereas treatment of renal arteries and their branches reduced variability in response and caused a greater reduction of norepinephrine and axon density [38]. Furthermore, fewer ablations were required when treating branches compared with the main renal artery to achieve a significant reduction in kidney norepinephrine concentrations [39]. These findings are in line with a clinical study in which the combined ablation of the main renal artery and its branches improved BP-lowering efficacy of RDN [40].

Table 1 Key features of the SYMPLICITY HTN-3 [20], SPYRAL HTN [26], and RADIANCE HTN [27] trials

	SYMPLICITY HTN-3	SPYRAL HTN	RADIANCE HTN
Sites	USA	USA, Europe, Japan, Australia	USA, Europe
Technology	Single-electrode radiofrequency catheter	Multi-electrode radiofrequency catheter	Ultrasound renal denervation catheter
Ablation pattern	Main artery	Main and accessory arteries (including branches)	Main and accessory arteries (including branches)
Blood pressure inclusion criteria	Systolic OBP ≥ 160 mmHg and systolic 24 h-ABP ≥ 135 mmHg	OBP 150–179/≥ 90 mmHg and systolic 24 h-ABP 140–169 mmHg	Solo cohort: daytime ABP 135–169/85–104 mmHg after 4-week wash-out Trio cohort: OBP ≥ 140/90 mmHg and daytime ABP ≥ 135/85 mmHg
ISH	Yes	No	No
Regimen	Range of medication regimens allowed for enrolment	Standardized medication regimen	Standardized medication regimen
Absence of medications	Only patients with resistant hypertension	OFF-MED trial including therapy-naïve patients or patients after wash-out	Solo cohort including therapy-naïve paitents or patients considered to be safely washed-out
Drug adherence testing	No	Yes	No
Interventionalists' experience	Varied level of experience	Experienced proceduralists	Experienced proceduralists
Primary efficacy endpoint	OBP	24 h-ABP	Daytime ABP

ABP ambulatory blood pressure, *ISH* isolated systolic hypertension, *OBP* office blood pressure

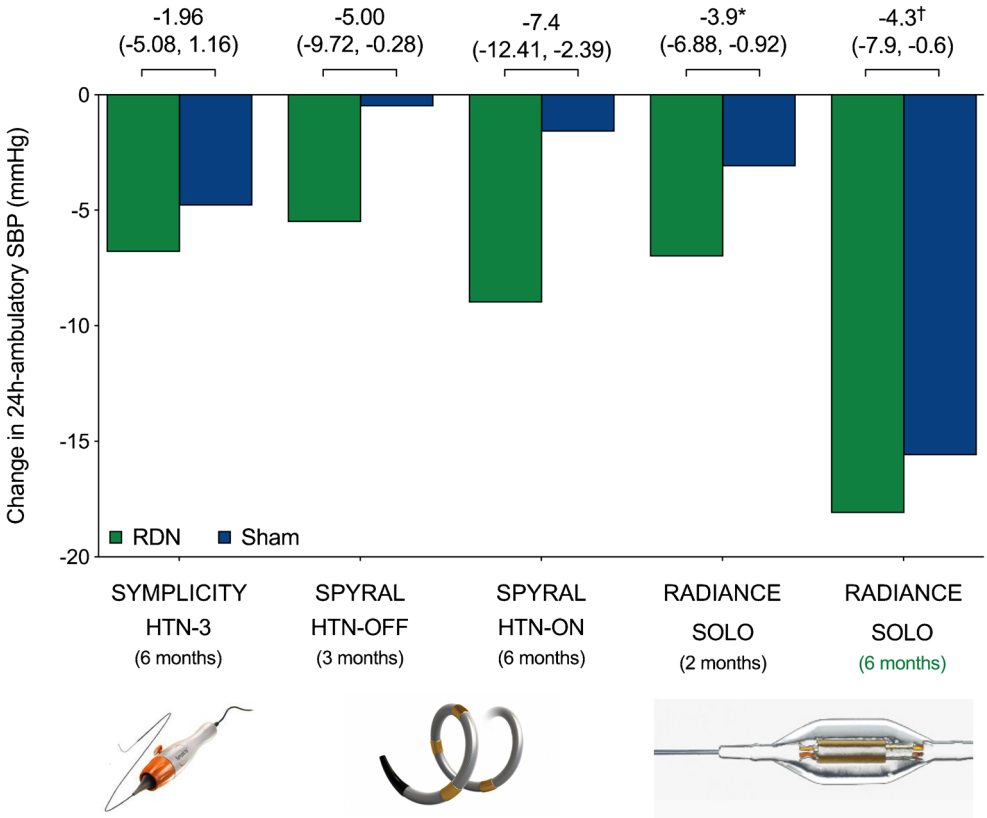

Fig. 1 Change in 24-h ambulatory systolic blood pressure (SBP) in sham-controlled RDN trials. *Mean between-group difference adjusted for baseline SBP. †Mean between-group difference adjusted for baseline SBP and number of antihypertensive drugs. Values are mean (95% confidence intervals)

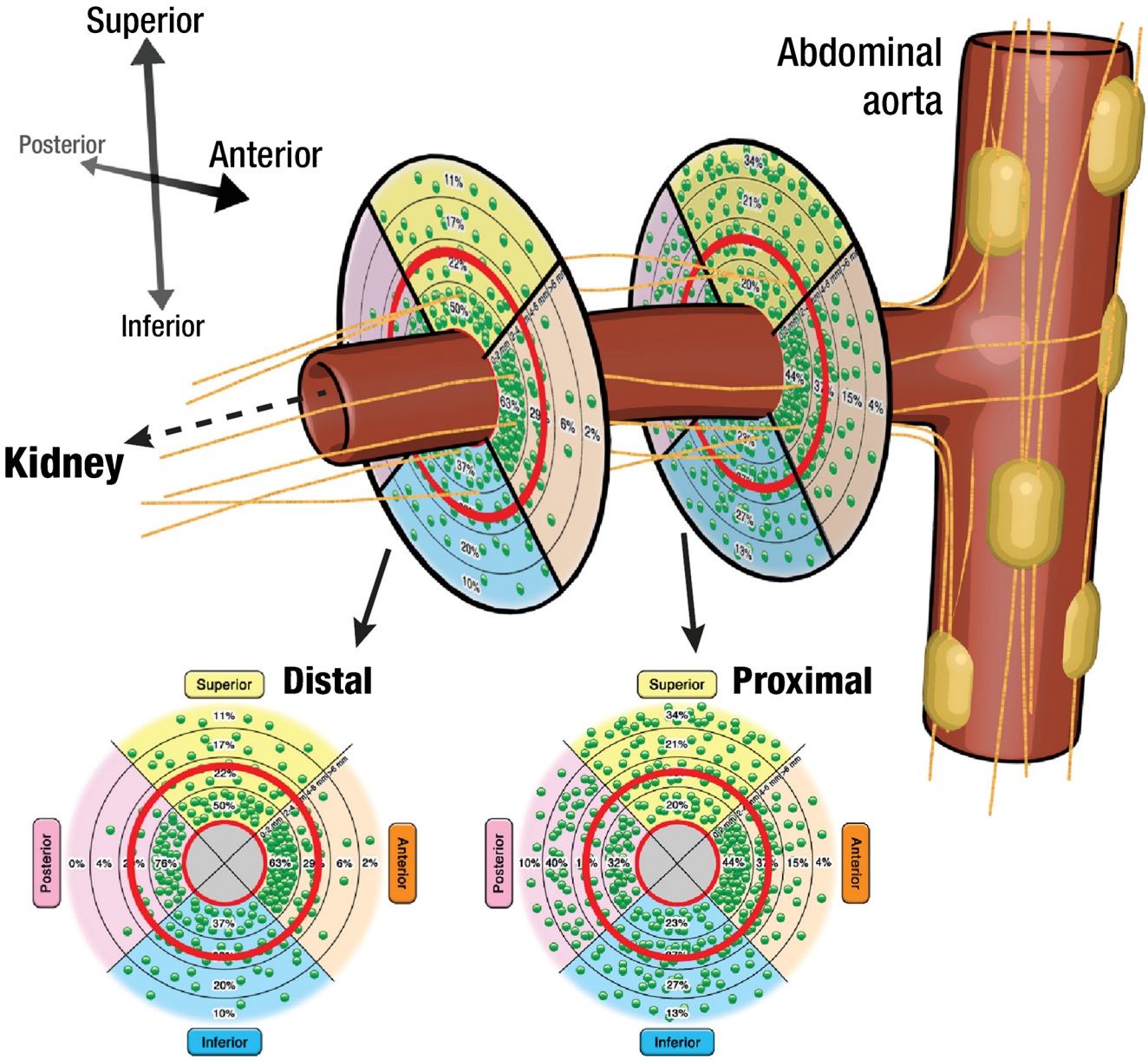

Fig. 2 Schematic illustration of the renal artery with its surrounding nerves. The sympathetic fibers originate from the abdominal ganglia and run conically to the distal part of the vessel. The *lower circles* show the distribution of nerves stratified according to total number (each *green dot* represents 10 nerves), relative number as percent per segment, and distance from the lumen in relative (modified from Mahfoud et al. 2015 Eur Heart J 36:199–202, by permission of Oxford University Press) [36]

Since there are significant differences in the circumferential distribution of renal sympathetic nerves [35], a circumferential four-quadrant ablation may increase the likelihood of successful nerve disruption [41].

Refined RDN catheters allow a more efficient procedure in a shorter time. The Symplicity Spyral RF-RDN catheter (Medtronic Vascular, Santa Rosa, CA, USA), for example, consists of four electrodes in a pre-shaped spiral configuration [26]. After retracting the guidewire proximally, the catheter tip expands radially and thereby increases the likelihood of sufficient wall contact [26]. The Paradise US-RDN catheter system (ReCor Medical, Palo Alto, CA, USA) uses therapeutic ultrasound energy which causes frictional heating of the adventitia while a fluid-filled balloon cools the endothelium and media of the renal artery [42]. In contrast to RF- and US-RDN catheters which interrupt nerve signaling by thermal ablation, the Peregrine catheter (Ablative solutions, San Jose, CA, USA) causes neurolysis by infusing alcohol via three micro-needles which are inserted through the media of the vessel [43]. All of these RDN catheter systems are currently under investigation in randomized, sham-controlled trials (Table 2).

Table 2 Currently enrolling sham-controlled trials for renal denervation in patients with hypertension

Technology	Study name	Regime
Radiofrequency	SPYRAL HTN-OFF MED (SPYRAL PIVOTAL)	- Double-blind, randomized (1:1), sham-controlled - Drug-naïve patients or patients considered to be safely washed-out - $n = 433$
	SPYRAL HTN-ON MED	- Double-blind, randomized (2:1), sham-controlled - Stable on 1,2 or 3 meds for 6 weeks - $n = 340$
	EnligHTNed IDE	- Double-blind, randomized (2:1), sham-controlled - Single-pill combination three drugs - $n =$ to be determined
Ultrasound	RADIANCE HTN	- Double-blind, randomized (1:1), sham controlled - Solo cohort: Drug-naïve patients or patients considered to be safely washed-out - Trio cohort: stable regimen with ARB/CCB/Thiazide - $n = 292$
	REQUIRE	- Double-blind, randomized (1:1), sham controlled - Patients with resistant hypertension on standard of care medication in Japan, and South Korea. - $n = 140$
Alcohol	TARGET BP OFF-MED	- Double-blind, randomized (1:1), sham-controlled - Drug-naïve patients or patients considered to be safely washed-out - $n = 90$

ARB angiotensin-receptor blocker, *CCB* calcium channel blocker

Source: ClinicalTrials.gov.

Perspectives

The variability of individual BP response to RDN remains considerable. Therefore, selecting patients with high likelihood of response is of high priority. Both RF- and US-RDN have proven their BP-lowering efficacy in meticulously conducted sham-controlled trials [28••, 29••, 31] though US-RDN treatment of the main artery was followed by a more pronounced BP reduction compared with RF-RDN of the main artery in patients with at least one main renal artery with a diameter ≥ 5.5 mm [44]. Differences in penetration depth of the different RDN systems (6–7 mm for US-RDN vs. 3–4 mm for RF-RDN) may explain these findings [42, 45]. Of note, there was no difference in the BP reduction following US-RDN compared with the combined treatment of the main renal arteries and branches, which is indeed considered the standard treatment technique using an RF-RDN catheter [44]. However, these findings should be confirmed in a properly sized, multicenter trial with longer follow-up. The results of this head-to-head comparison cannot be translated to hypertensive in general which were shown to have smaller renal arteries in average [33]. Furthermore, it is a future task to identify the most appropriate device for every single patient.

As treatment success cannot be monitored intraprocedurally, catheter-based RDN remains a black box procedure. Several biomarkers such as neuropeptide Y and brain-derived neurotrophic factor have been investigated, but none provided reliable prognostic information for future BP response [46–48]. A recent analysis of the SPYRAL HTN-OFF MED trial has shown that patients with a baseline 24-h heart rate above the median had a greater BP reduction following RDN [49]. If confirmed in a larger trial, high average 24-h heart rate may be used to identify patients with a high likelihood of response [49]. Currently, renal nerve stimulation, which acutely raises BP, is investigated as an invasive mapping tool to locate renal nerves [50]. However, large randomized controlled studies are needed to confirm its benefit.

Beyond arterial hypertension, catheter-based RDN is currently being investigated in other conditions associated with overactivity of the sympathetic nervous system [51, 52], in particular, atrial fibrillation [53, 54]. A small pilot study indicated that RDN might improve the burden of atrial fibrillation in hypertensive patients with symptomatic paroxysmal or persistent atrial fibrillation [55]. In a randomized controlled trial, 27 patients with refractory paroxysmal or persistent atrial fibrillation and drug-resistant hypertension underwent pulmonary vein isolation alone ($N = 14$) or in combination with

RDN ($N = 13$) [56]. At 12-months, 69% of the patients treated with pulmonary vein isolation and RDN were free of atrial fibrillation while, in contrast, only 29% of the patients in the control group were free of atrial fibrillation [56]. Results of the larger Symplicity AF trial (NCT02064764), a prospective, multicenter, feasibility trial, investigating pulmonary vein isolation in combination with RDN compared with pulmonary vein isolation only are eagerly awaited.

Until today, data on the durability of BP-lowering efficacy and long-term safety are lacking. In a preclinical study, tissue levels of norepinephrine did not recover despite morphological evidence for re-innervation within 12 weeks after RDN [57]. These findings are duplicated by the SPYRAL HTN-ON MED and the RADIANCE-HTN SOLO trials which have demonstrated a continued decrease of BP until 6 months [29••, 31]. In the single-arm Global SYMPLICITY Registry (GSR), 1742 patients were eligible for the 3-year follow-up, which currently represents the largest available cohort of patients undergoing RDN for arterial hypertension [58]. The BP reductions at 6 months were sustained out to 3 years while no long-term safety concerns were observed [58].

Conclusion

In spite of the massive setback following the SYMPLICITY HTN-3 trial, recent sham-controlled trials providing proof of principle for the BP-lowering efficacy have put RDN back on track. Before RDN is ready for prime time, several issues have to be resolved: it is crucial to (1) assess long-term safety and efficacy, (2) evaluate the effects of RDN on cardiovascular end-organ damage, (3) identify patients with the highest likelihood of response, and (4) to come up with a method to predict future response and directly read-out treatment success.

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Compliance with Ethical Standards

Conflict of Interest Felix Mahfoud received speaker honoraria and scientific support from Medtronic and Recor, and is supported by Deutsche Hochdruckliga, Deutsche Gesellschaft für Kardiologie, and Deutsche Forschungsgemeinschaft (SFB TRR 219).

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- • Of importance
- •• Of major importance

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