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REVIEW

Renal Denervation for Resistant Hypertension: A Concise Update on Treatment Options and the Latest Clinical Evidence

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ABSTRACT

Evidence from recent sham-controlled trials supports the use of endovascular renal denervation (RDN) to lower blood pressure in general as well as in treatment-resistant hypertension. According to recent studies, the effects of RDN are long lasting. Newer technologies using multipolar radiofrequency catheters and an additional ablation of the renal side branches as well as ultrasound with improved circumferential tissue penetration have made these advances possible. This has initiated a change of the perspective on RDN in clinical guidelines and has thereby set a cornerstone for a broader clinical application of RDN in the future.

Keywords: Renal denervation; Hypertension; Blood pressure

Key Summary Points

Recent trials support a long-lasting efficacy of renal denervation in lowering blood pressure in patients with resistant hypertension as an adjunct to conventional drug- and lifestyle-based treatment.

The new devices for renal denervation available on the market generate more thorough ablation patterns and thereby ensure an efficient procedure.

Adaption of the clinical guidelines to the new scientific evidence has already started, and renal denervation might play an important role in the future management of arterial hypertension.

RESISTANT HYPERTENSION

Blood pressure (BP) control in patients with arterial hypertension is one of the most important tasks for health care systems worldwide. While control of BP can be achieved in many patients by lifestyle modification and medical treatment, in other cases these approaches fail, which results in resistant hypertension (RH) [1]. RH is usually defined as persisting hypertensive

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BP values, confirmed by ambulatory or home BP measurement despite (1) exclusion of secondary causes of hypertension, (2) optimal lifestyle measures, and (3) treatment with at least three different antihypertensive drug classes including at least one diuretic [1]. While the prevalence of RH varies through various epidemiological studies, a recent meta-analysis found a prevalence of 10–15% in patients with arterial hypertension [2]. Patients with RH are at an elevated cardiovascular risk and show markedly increased rates of stroke, myocardial infarction, and various other cardiovascular morbidities [3, 4].

Similar to the general treatment of hypertension, lowering BP results in a significant reduction of major cardiovascular events and sequelae [5, 6]. However, while there is evidence of a BP-lowering effect for a combination of up to four drug classes [7–10], in most patients with RH, treatment is characterized by multidrug combinations with low scientific evidence of their BP-lowering effects and low drug adherence is frequent [11]. Beyond drug treatment, lifestyle optimization can reduce BP, as supported by a recent study on an intensified lifestyle modification over several weeks [12], but there are concerns about the durability of such a complex intervention.

With the frequently low adherence in patients suffering from RH and the often-limited durability of lifestyle interventions, an additional long-lasting, adherence-independent treatment as adjunct to the existing therapies is necessary. As such, renal denervation (RDN) is gaining increasing clinical importance.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by the author.

RENAL DENERVATION

Sympathetic denervation of the renal arteries was first established in the 1920s and 1930s by using surgical splanchnicectomy [13, 14] and was once considered a standard treatment of arterial hypertension. It was also associated with reduced mortality when compared to untreated hypertension [15, 16]. The idea behind RDN is a reduction in renal and systemic sympathetic activity, which is associated with a reduction of renin–angiotensin–aldosterone activity, salt and water retention, and central sympathetic activation via the medulla oblongata [17–19]. With the advent of medical antihypertensive treatment options and in light of frequent side effects of the surgical treatment, the rather invasive surgical procedure was abandoned.

Following the same principles as the surgical approach, catheter-interventional RDN was invented at the beginning of the twenty-first century, when prevalence of hypertension and also RH were increasing worldwide as an adjunct to an often futile multidrug treatment in RH.

Catheter-interventional RDN uses an endovascular technique: via transfemoral puncture, a guiding catheter is inserted into the renal artery and a treatment catheter is placed in the artery's lumen. Radiofrequency or ultrasound energy or ethanol is then applied through the renal artery wall to ablate the sympathetic nerve fibers adjacent to the vessel's course (Fig. 1).

BLOOD PRESSURE REDUCTION AFTER RENAL DENERVATION

Recent evidence from four randomized, sham-controlled trials on RDN shows a consistent reduction of both ambulatory and office BP after the procedure for two different RDN technologies, a radiofrequency and an ultrasound-based approach [20–23]. Two of these trials enrolled patients with treatment-resistant hypertension (Table 1).

Office BP was reduced by roughly 10 mmHg throughout these trials, which is usually associated with approximately 20% fewer cardiovascular events in larger-scale analyses on medical antihypertensive treatment [5]. Other than medical management of hypertension, which frequently shows fluctuating BP-lowering effects, RDN is characterized by a so-called *always on* effect with a continuous BP reduction throughout 24 h of the day [20]. As especially nocturnal hypertension and increased morning

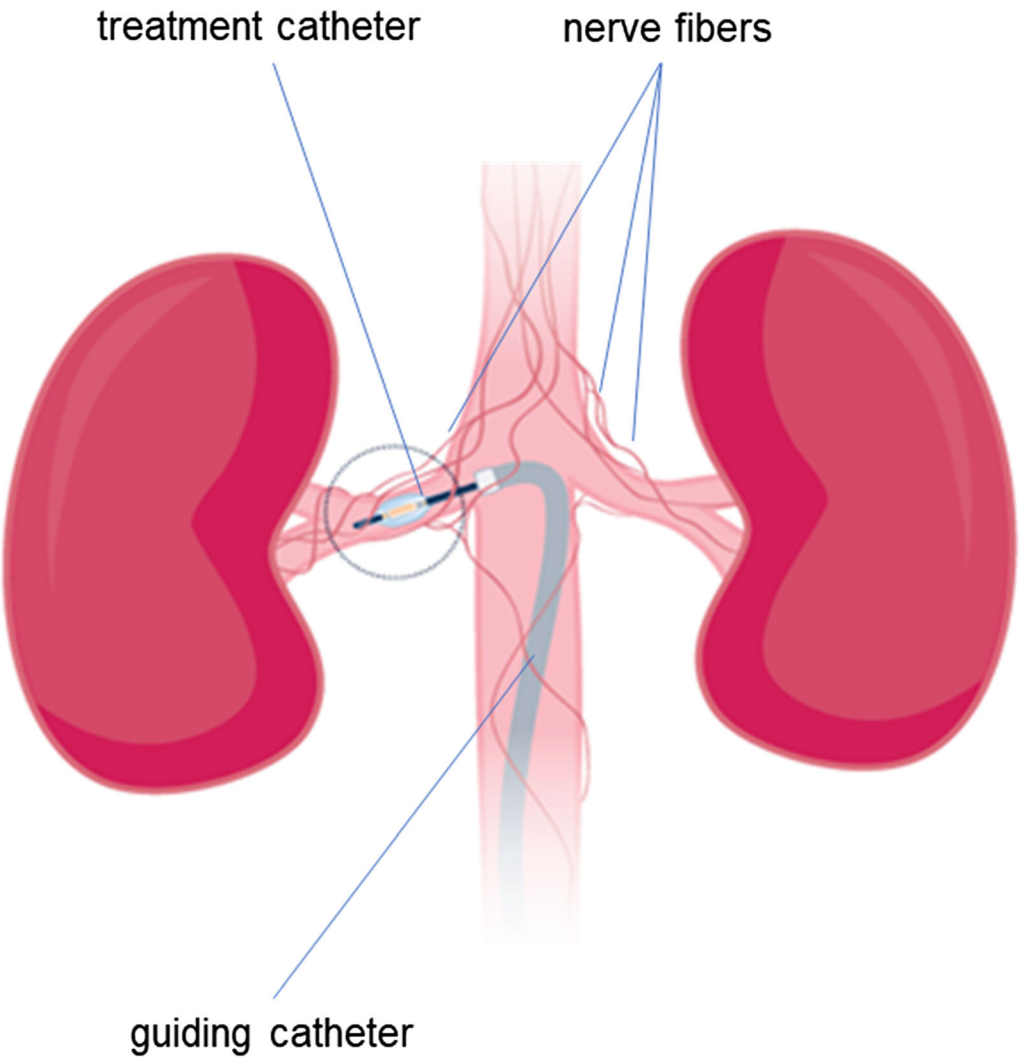

Fig. 1 Schematic illustration of catheter-interventional renal denervation

surge of BP are associated with cardiovascular events, RDN treatment could be even more preventive than medical management. Recent data from a single-arm study shows at least some association between BP and cardiovascular event reduction in a cohort of patients with severely treatment-resistant hypertension [27]: In patients with a significant BP response after the intervention, a combined clinical endpoint of cardiovascular death, ischemic stroke, intracranial bleeding, acute myocardial infarction, critical limb ischemia, and acute renal failure was less frequent than in patients without a significant BP change after a median follow-up of 4 years. It is very likely that the favorable association between BP lowering with antihypertensive drug treatment and a reduction of cardiovascular events can be observed after RDN therapy, too.

Along with the beneficial long-term effects of RDN, there is by now convincing evidence on the durability of BP reduction after RDN: The large-scaled Global Symplicity Registry found a consistently reduced BP up to 3 years after RDN in more than 1700 patients without any relevant safety-related events. Similarly, a recent analysis of the sham-controlled SPYRAL-HTN-ON-MED study which used state-of-the-art multipolar radiofrequency ablation with treatment of renal side branches found a significant

Table 1 Recent studies on renal denervation in hypertension and BP-lowering effects

Title	Number	Year	Condition	Comparator	Systolic blood pressure reduction
Spryal-HTN-Off-MED [24]	80	2017	Off-med cohort	RDN vs. Sham (1:1)	5.5 mmHg (ABPM) 10.0 mmHg (OBP)
SPYRAL-HTN-ON-MED [23]	80	2018	50% resistant hypertension	RDN vs. Sham (1:1)	9.0 mmHg (ABPM) 9.4 mmHg (OBP)
RADIANCE-SOLO [21]	146	2018	Off-med cohort	RDN vs. Sham (1:1)	7.0 mmHg (ABPM) 10.8 mmHg (OBP)
3-year follow-up from the Global SYMPLICITY Registry [25]	1742	2019	Hypertension with 4.5 drug classes on average	None (single-arm)	8.0 mmHg (ABPM) 16.5 mmHg (OBP)
Alcohol-mediated renal denervation using the Peregrine System [26]	45	2020	Resistant hypertension	None (single-arm)	11.0 mmHg (ABPM) 18.0 mmHg (OBP)
SPRYAL-Off-MED-PIVOTAL [22]	331	2020	Off-med cohort	RDN vs. Sham (1:1)	4.7 mmHg (ABPM) 9.2 mmHg (OBP)
RADIANCE-TRIO [20]	136	2021	Resistant hypertension	RDN vs. Sham (1:1)	8.5 mmHg (ABPM) 9.0 mmHg (OBP)

ABPM ambulatory blood pressure measurement, *OBP* office blood pressure

BP reduction for up to 3 years after RDN when compared to a sham procedure [28].

Notably, despite convincing effects of RDN on BP, most patients enrolled in the last trials remain with BP values outside the recommended treatment goals. Therefore, RDN should be thought of as an adjunct to the existing drug- and lifestyle-based therapy rather than as their replacement. Nevertheless, RDN altogether shows a long-lasting, clinically significant BP reduction.

TREATMENT MODALITIES

Traditionally, radiofrequency catheters were used for RDN procedures, and state-of-the-art radiofrequency devices using multipolar ablation patterns are still the cornerstone of RDN treatment (Fig. 2). There is a large database on safety and efficacy for radiofrequency RDN from real-world data supporting its use to treat hypertension [29–31].

While initial studies focused on ablation of the main renal arteries, animal studies suggested a more complete denervation when ablating the renal arteries' side branches [32]. This was supported by clinical data from a matched analysis and one randomized trial showing superior BP reduction with an additional side-branch ablation [33, 34]. This approach was also applied in recent randomized trials on radiofrequency RDN and was found superior over sham treatment [22, 23]. Therefore, side-branch ablation should be considered

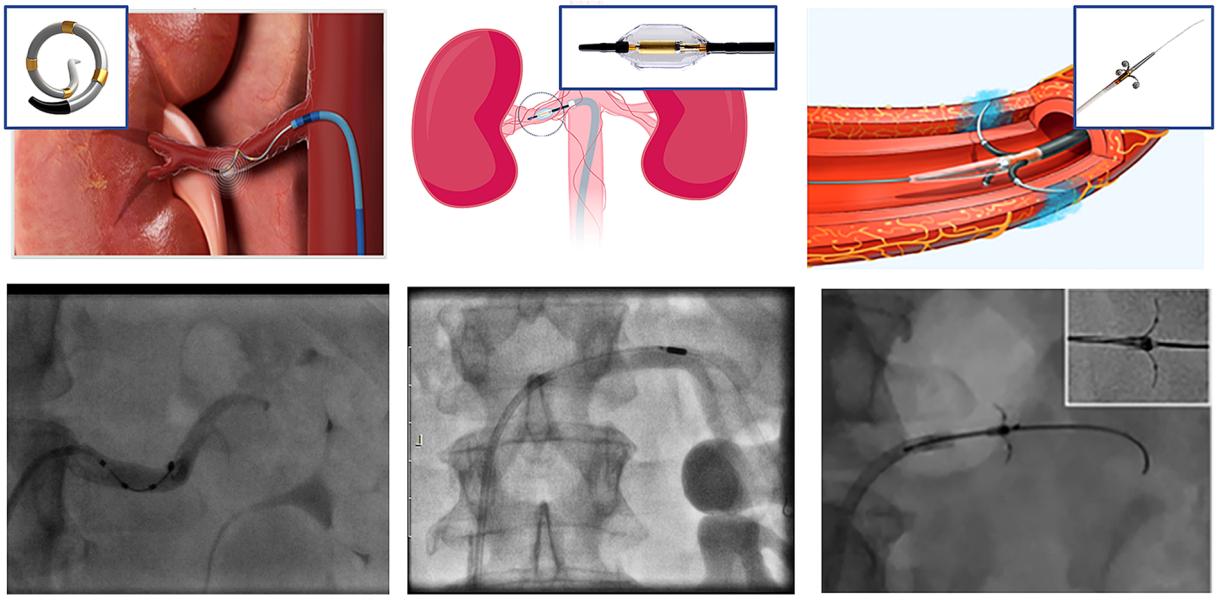

Fig. 2 Different treatment modalities for renal denervation: radiofrequency ablation (Spyral catheter, Medtronic, left), endovascular ultrasound ablation (Paradise catheter, ReCor Medical, mid), and chemical ablation (Peregrine catheter, Ablative Solutions, right)

as a standard approach when using radiofrequency ablation catheters if anatomically feasible.

The second RDN modality which has proven superiority over sham treatment is an endovascular ultrasound-based approach. This technology uses thermal energy to create circumferential ablation patterns. It uses a water-irrigated balloon to cool and preserve the arterial wall. This allows application of higher energy doses with better tissue penetration and thereby eliminates the necessity for an additional side-branch ablation. This system has proven its efficacy in drug-naïve patients as well as in those with treatment-resistant hypertension [20, 21].

A third, needle-based system uses alcohol for chemical ablation of the renal nerves [35]. The first single-arm study shows promising results for BP reduction with an acceptable safety profile [26]. Two multicenter trials are currently enrolling patients to further evaluate the efficacy and safety of this technology [36]. Until then, this device is reserved for study purposes only.

There is a paucity of data on the optimal technology and technique for RDN. Besides the aforementioned comparisons of main renal artery versus additional side-branch ablation, one single-center randomized trial compared radiofrequency ablation of the main renal artery with additional side-branch ablation and ultrasound ablation of the main renal artery as a three-arm randomized trial. Therein, ultrasound RDN was found superior to radiofrequency ablation of the main renal artery, while an additional side-branch ablation did not differ significantly from either of the other two approaches [37]. While this supports the use of newer RDN devices, further data from multicenter randomized trials are necessary to draw definitive conclusions on the optimal technology for RDN. Until such studies become available, using last-generation devices and including side-branch ablation when using radiofrequency catheters seems a reasonable approach.

FUTURE PERSPECTIVES

While cumulating evidence shows beneficial effects of RDN in RH, one frequently unresolved issue is reimbursement when planning

procedures for clinical use outside of studies. This is mostly caused by the neutral results of the now outdated SYMPLICITY-HTN-3 study [38] and the resulting class III recommendation in the current guidelines for the treatment of arterial hypertension of the European Society of Cardiology [1]. Nevertheless, a recent consensus document of the European Society of Hypertension recommends RDN as a third option in addition to lifestyle modification and drug treatment, especially if the patient's preference is a device-based approach [39]. With the now clear evidence of a clinically significant BP reduction after RDN, an additional update of the European guidelines for arterial hypertension seems necessary and is eagerly awaited to allow for a broader clinical use of RDN again.

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