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Research Article

The Current Status of Renal Denervation in Hypertension Management

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Abstract

Introduction: Hypertension is still one of the major causes of cardiovascular disease and death worldwide. Despite lifestyle modifications and medical treatment, blood pressure control rates remain suboptimal. The sympathetic nervous system plays a significant role in the pathophysiology of hypertension. Inhibition of the sympathetic nervous system leads to a reduction in blood pressure. In light of this, a catheter-based renal denervation procedure has been developed to selectively ablate the renal sympathetic nerves in order to lower blood pressure.

Discussion: Renal denervation targets the afferent and efferent sympathetic nerves along the renal arteries. Interruption of the renal nerve fibers in the perivascular space reduces sympathetic-mediated renal vascular resistance, renin release, and sodium reabsorption. Consequently, the mechanisms driving systemic hypertension are gradually disrupted, and blood pressure falls over time. The current main methods of renal denervation are radiofrequency energy, ultrasound, and perivascular neurotoxin injection. Recent randomized sham-controlled trials have shown that renal denervation effectively and safely reduces blood pressure by approximately 5 to 10 mmHg in various hypertensive patients. It is important to have a multidisciplinary team of hypertension specialists and interventional experts to select appropriate patients for renal denervation. Shared decision-making is essential to consider hypertension-mediated organ damage, cardiovascular risk, and patient preferences.

Conclusion: Catheter-based renal denervation is a relatively new treatment modality that provides meaningful and sustained reductions in blood pressure with an acceptable safety profile. Currently, it is recommended for patients with uncontrolled or resistant hypertension despite optimal lifestyle changes and medical treatment.

More Information

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Introduction

Hypertension (HT) is the most common Cardiovascular (CV) disease around the world. A reduction in high Blood Pressure (BP) is associated with decreased CV morbidity and mortality [1,2]. However, BP control rates remain low despite recommendations for lifestyle changes and antihypertensive medications. Patient nonadherence, medication intolerance, physician inertia, complex polypharmacy, and true resistant HT are the main reasons for failure to achieve optimal BP control [3,4]. Therefore, new treatment modalities are needed to improve BP management.

The sympathetic nervous system plays a significant role in the pathophysiology of HT. Therefore, catheter-based Renal Denervation (RDN) procedures have been created to selectively ablate the renal sympathetic nerves [4-6]. Recent landmark trials such as the SPYRAL HTN-OFF MED [7], the SPYRAL HTN-ON MED [8], the RADIANCE-HTN SOLO [9], the RADIANCE II [10] and the RADIANCE-HTN TRIO [11] indicate that RDN has modest but meaningful effects in the management of HT. According to current HT guidelines, RDN is a safe, effective, and evidence-based option without any reported short or long-term adverse effects when combined with medication therapy for patients with resistant or uncontrolled HT [1,2].

This review aims to provide a comprehensive and up-to-date overview of RDN as a therapeutic option in the management of hypertension, focusing on its underlying mechanisms, current clinical evidence, patient selection criteria, safety profile, and relevant guideline recommendations.

Discussion

Although imbalances in the renin-angiotensin-aldosterone system are the main cause of HT, sympathetic nervous system activation also plays a significant role [12]. Increased sympathetic activity reduces arterial distensibility, which

raises pulse pressure and systolic BP. In addition, sympathetic stimulation of arterioles causes neural vasoconstriction [13]. Activation of renal sympathetic nerves further increases BP by enhancing sodium reabsorption and renin release [13]. Over time, arteriolar hypertrophy develops, which maintains high total peripheral resistance [13]. RDN is a catheter-based percutaneous procedure that targets the afferent and efferent sympathetic nerves along the renal arteries. Interruption of the renal nerve fibers in the perivascular space reduces sympathetic-mediated renal vascular resistance, renin release, and sodium reabsorption. Consequently, the mechanisms driving systemic HT are gradually disrupted, and BP falls over time [4-6].

The current main methods of RDN are radiofrequency energy, ultrasound, and perivascular neurotoxin injection. The Symplicity Spyral radiofrequency RDN system (Medtronic, Inc., Dublin, Ireland) uses a helical catheter with four electrodes to deliver medium-frequency alternating current and generate heat. This heat does not harm the renal artery wall but causes neurolysis in perivascular sympathetic nerves up to 7 mm away. The system targets the sympathetic nerves of the main, accessory, and distal renal branches and provides real-time impedance and temperature monitoring to ensure safety and efficacy [5,6,14]. The Paradise system (ReCor Medical Inc., Palo Alto, CA, USA) is an ultrasound-based RDN device that uses a balloon-mounted catheter with ultrasound transducers to deliver circumferential energy. The balloon is perfused with cooled sterile water to protect the arterial wall. This technique targets the main and accessory renal arteries measuring 3–8 mm in diameter [5,6,14]. The Peregrine system (Ablative Solutions, Inc., Wakefield, MA, USA) is an alcohol-based RDN device with retractable microneedles that penetrate the arterial wall to inject dehydrated ethanol into the perivascular space. Ethanol directly induces chemical ablation by causing neurolysis. This method is primarily applied to the main and accessory renal arteries. The Peregrine system does not require an external energy generator [5,6,14].

The first sham-controlled randomized trial, SYMPLICITY HTN-3, was designed to evaluate the efficacy of RDN in patients with resistant HT [15]. However, the results were unexpected, likely due to inadequate ablation and suboptimal patient selection. Later, second-generation trials using improved radiofrequency and ultrasound RDN devices have demonstrated modest but significant reductions in systolic BP of 5–10 mmHg [6,14-16]. The SPYRAL HTN-OFF MED studies showed that radiofrequency RDN decreased 24-hour systolic BP by 3.9 to 5.0 mmHg in patients not taking antihypertensive medications [7,17]. Similarly, the RADIANCE trials demonstrated that ultrasound RDN reduced daytime systolic BP by 6.3 mmHg in patients not taking antihypertensive medications [9,10]. On the other hand, the SPYRAL HTN-ON MED study found that radiofrequency RDN lowered 24-hour systolic BP by 7.0 mmHg more than sham treatment at six months in patients with uncontrolled HT who were taking one to three antihypertensive drugs [8]. The RADIANCE HTN-TRIO study found that ultrasound RDN reduced daytime systolic BP by 4.5 mmHg more than sham treatment at two months in patients with resistant HT who were taking stable triple therapy [11]. Follow-up data from the Global SYMPLICITY Registry [18], SYMPLICITY HTN-3 trial [19], SPYRAL HTN-ON MED pilot trial [20] and RADIANCE-HTN SOLO trial [21] showed that these BP reductions can last for up to three years. Additionally, a single-center open-label study showed that these effects might persist for as long as ten years [22].

Resistant HT is defined as uncontrolled office BP (≥140/≥90 mmHg), confirmed by out-of-office BP measurements, despite appropriate lifestyle modifications and the intake of a triple-drug combination including a diuretic at maximally tolerated doses [23]. Patients with resistant HT who fail to achieve target BP despite optimal medical therapy, patients with uncontrolled hypertension accompanied by high cardiovascular risk or end-organ damage, patients with medication non-adherence, patients on multiple medications due to comorbid conditions, patients unwilling to undergo long-term pharmacotherapy, and patients with true intolerance to antihypertensive agents are considered appropriate candidates for RDN [23,24]. RDN is not recommended for patients with renal fibromuscular dysplasia, renal artery stenosis greater than 50%, recent renal artery stenting within the past three months, an eGFR below 40–45 mL/min/1.73 m^2, a single functioning kidney, or a history of renal transplantation [14]. RDN has no significant procedural risks beyond those associated with femoral access, such as hematoma, pseudoaneurysm, or arteriovenous fistula formation. The rate of de novo renal artery stenosis is approximately 0.2% per year, which occurs mainly within the first six months. This is similar to rates observed in general hypertensive populations. Three-year follow-up data from the Global SYMPLICITY Registry demonstrated no late safety concerns, including no significant deterioration in kidney function or increase in renal artery stenosis beyond expected rates [3,14,18,23].

The 2024 ESC Hypertension Guidelines [2] state that catheter-based RDN may be considered to reduce BP in patients with resistant HT whose BP remains uncontrolled despite treatment with a combination of three antihypertensive drugs, including a thiazide or thiazide-like diuretic (Class IIb, Level B). In addition, RDN may be considered for patients with increased cardiovascular risk and uncontrolled HT on fewer than three antihypertensive drugs (Class IIb, Level A). These recommendations apply when the patient chooses to undergo RDN after a shared risk–benefit discussion and multidisciplinary assessment at a medium-to-high-volume center [2]. RDN is not recommended as a first-line treatment to lower BP due to the absence of sufficient evidence (Class III, Level C). Furthermore, RDN is not recommended for patients with moderate to severe renal impairment (eGFR < 40 mL/min/1.73 m^2) or for those with secondary HT until more evidence becomes available (Class III, Level C) [2].

Conclusion

Catheter-based RDN is a relatively new treatment that selectively ablates the renal sympathetic nerves to decrease BP. It provides meaningful and sustained reductions in BP with an acceptable safety profile. Currently, it is recommended for patients with uncontrolled or resistant HT despite optimal lifestyle changes and medical treatment. It is also beneficial for patients who are unable to tolerate long-term medication or who are unwilling to take it. The successful integration of RDN into clinical practice requires careful patient selection and a multidisciplinary approach. Experienced interventionalists in invasive renal procedures are needed to ensure optimal outcomes and manage potential complications.

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