



Renal Denervation for the Treatment of Hypertension Unnerving or Underappreciated?

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Hypertension is a major, modifiable risk factor for cardiovascular disease, CKD, and mortality (1). As guidelines recommend more stringent BP goals, achieving these benchmarks often requires multiple medications, which can yield high dosing complexity, pill burden, expense, and drug intolerance. There is a dearth of options available to treat hypertension without exacerbating polypharmacy or in the setting of multidrug intolerance. Although invasive renal denervation technologies have been available in Europe and other parts of the world for several years, they are not yet approved by the US Food and Drug Administration. Inconsistent results across early trials and low perceived benefit relative to potential risks have contributed to skepticism about renal denervation among US providers. Nonetheless, with an aging population and in the absence of novel antihypertensive therapies, there may be value in reconsidering these nonpharmacological methods for the right patients.

What is the premise behind renal denervation? Increased renal sympathetic activity results in (1) increased renin secretion mediated by direct adrenergic innervation of the juxtaglomerular apparatus, (2) increased renal tubular sodium reabsorption and sodium retention mediated by direct contact between nerve endings and basolateral membranes of renal tubular epithelial cell throughout the nephron, and (3) renal vasoconstriction, resulting in decreased GFR and renal blood flow (2). In the 1930s to 1950s, surgical sympathectomies were performed in patients with uncontrolled BP, which were ultimately abandoned due to high rates of disabling side effects coupled with discovery of oral antihypertensive drugs. More recently, endovascular renal denervation offered a safer approach to reducing localized renal sympathetic activity by using catheter-based ablation techniques in the main renal arteries in both kidneys. In preclinical translational studies, afferent sensory and sympathetic efferent renal denervation were correlated with decreased renal norepinephrine spillover and increased renal plasma flow (2); afferent denervation was also correlated with decreased central sympathetic nervous system activity. Renal Denervation in Patients With Uncontrolled Hypertension 2 (SYMPPLICITY-HTN 2), an early unblinded renal denervation trial, reported a 32/12 mmHg lower in-office systolic and diastolic BP respectively at 6 months in patients with resistant

hypertension who underwent single electrode radiofrequency catheter-based renal denervation, compared with routine antihypertensive medication management. Overall, <5% of patients who underwent renal denervation experienced procedural adverse events, portraying it at that time as a promising and relatively safe procedure.

However, the SYMPPLICITY-HTN 3 trial, which enrolled more than 500 participants with resistant hypertension, demonstrated no difference in BP reduction with renal denervation compared with more appropriate sham-control procedures. SYMPPLICITY-HTN 3 was criticized by denervation enthusiasts for several study design limitations, including variable number of ablations, enrollment of a heterogeneous patient population (*e.g.*, patients with isolated systolic hypertension, who previously showed relatively poor response to denervation) with frequent drug changes and variable adherence to medications, and reliance on a large number of centers with little practical experience in renal denervation (3,4). More recent trials addressed these issues by introducing standardized study design features, namely, only including participants with combined systolic and diastolic hypertension; using standardized protocols for antihypertensive medication with washout and standardized titration; monitoring for antihypertensive medication adherence; targeting neuroanatomy with more advanced catheter designs; and requiring that procedures be performed by a single, experienced interventionalist at each center (5–8).

To date, three randomized, multicenter, single-blinded, sham-controlled trials have reported results using these improved approaches: SPYRAL HTN OFF-MED, SPYRAL HTN ON-MED, and A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE-HTN SOLO). All three trials reported consistent reductions in ambulatory and office BP in the short (2–3 months) and medium term (6 months) postprocedure with radiofrequency (SPYRAL trials) or highly focused ultrasound-based (RADIANCE-HTN SOLO) denervation (5–7). In the SPYRAL HTN OFF-MED pivotal trial, 311 participants were enrolled with office systolic BP 150–180 mmHg off all antihypertensive medications. The trial used circumferential radiofrequency ablation, which is small enough to reach the distal renal artery (where nerves are closest to the lumen) and accessory vessels. The mean change in daytime

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ambulatory systolic BP was -3.9 mm Hg (95% confidence interval [95% CI], -6.2 to -1.6) and the mean change in office systolic BP was -6.5 mm Hg (95% CI, -9.6 to -3.5) at 3 months in participants who underwent denervation compared with sham control (5). In the SPYRAL HTN ON-MED radiofrequency ablation proof-of-concept trial, 467 participants were enrolled with office systolic BP 150–180 mmHg, office diastolic BP ≥ 90 mmHg, and 24-hour ambulatory systolic BP 140–170 mmHg on 1–3 antihypertensive medications. The adjusted mean change in daytime ambulatory systolic BP was -7.4 mmHg (95% CI, -12.5 to -2.3) at 6 months in participants who underwent radiofrequency ablation compared with sham control; however, medication adherence was only about 60% and varied over the study (6).

In the RADIANCE-HTN SOLO proof-of-concept trial, 146 participants were enrolled with daytime ambulatory BP $\geq 135/85$ mmHg and $< 170/105$ mmHg after 1 month of discontinuing up to two antihypertensive medications. The trial used circumferential ultrasound ablation with penetration to the renal artery adventitia. The adjusted mean change in daytime ambulatory SBP was -6.3 mm Hg (95% CI, -9.4 to -3.1) at 2 months in participants who underwent denervation compared with sham control. From 2 to 6 months after randomization, participants underwent antihypertensive medication intensification if needed. However, the treatment difference persisted between the two arms in favor of renal denervation at 6 months (-4.3 mm Hg; 95% CI, -7.9 to 0.6), with fewer antihypertensive medications needed in the denervation arm (0.9 ± 0.9 versus 1.3 ± 0.9) (7). At 12 months postrandomization, the difference in systolic BP between denervation and sham dissipated (-2.3 mm Hg; 95% CI, -5.9 to 1.3 mmHg), but the number of antihypertensive medications was lower in the denervation arm (1.0 versus 1.4, $P=0.02$) along with a lower defined daily dose (1.4 versus 2.2, $P=0.01$). The RADIANCE-HTN TRIO study is an ultrasound-based ablation proof-of-concept trial in 136 participants with severe resistant hypertension. The trial completed enrollment and reportedly demonstrated efficacy, with anticipated publication of results in 2021.

Randomized controlled trial evidence supports that renal denervation is a safe and efficacious invasive procedure to modestly reduce BP among patients with moderate and severe resistant hypertension and elevated cardiovascular risk. Although the single-center Randomized Comparison of Ultrasound Versus Radiofrequency Denervation in Patients With Therapy Resistant Hypertension (RADIO-SOUND) trial observed lower BP with ultrasound-based ablation compared with two methods of radiofrequency ablation at 3 months (9), these findings require corroboration with multicenter, long-term data. Notably, there was substantial variability in the response of individual participants across trials, with 60%–70% of participants demonstrating a clinically significant BP response to denervation (≥ 5 mmHg change in ambulatory daytime systolic BP). Identifying the characteristics of these select participants and whether BP reduction is sustained long term is crucial to better understanding the clinical applications of renal denervation. There are no readily available biomarkers to determine efficacy at the time of the procedure. Furthermore, trials have taught us that denervation is operator dependent; its effectiveness may vary across providers, particularly those with less experience performing the procedure. Only a

longer duration of postprocedural follow-up will ascertain clinically meaningful success; it remains unclear if the effects will last years or dissipate with regrowth of renal efferent nerves. Finally, the effect on cardiovascular outcomes has not yet been determined.

An ambulatory systolic BP reduction of 5 mm Hg generally corresponds to the benefit from one effective antihypertensive drug (10). One can easily argue against the expense and risks of an invasive procedure when the same effect may be gained by a simple oral antihypertensive medication. Medication nonadherence and variable adherence among participants of denervation trials were real issues. Although one may interpret this as rationale to enforce stricter adherence to drugs, real-world experience has shown us this is difficult for many patients. If adherence cannot be followed in the strictly monitored setting of a clinical trial, it seems less justifiable to rely on it as the only option to achieve BP control in real-life clinical care. To that end, for select persons with moderate to severe resistant hypertension who are not willing to take additional medications to achieve adequate BP control or who experience multidrug intolerance, denervation may be a valuable therapy.

In summary, practical management of BP is complicated by underlying pathophysiology, medication prescription inertia, variable medication adherence, and potential intolerance to multiple medications. Renal denervation is a safe and efficacious procedure in lowering BP in the short term to a similar degree as that afforded by a single antihypertensive medication. Not everyone who underwent denervation in trials was guaranteed significant BP reduction. Denervation does not seem to affect kidney function; however, patients with moderate to severe CKD and ESKD were excluded from large international trials, and smaller studies suggest limited utility in this population. While waiting to learn more about the long-term risks and benefits of these approaches, it is important to identify subpopulations that are most likely to benefit from the procedure, such as those at high risk of cardiovascular disease. Referral for denervation should be a shared decision between the patient and provider, informed by individualized risk/benefit profiles. Although many providers understandably struggle to see its utility, renal denervation may serve as welcome reprieve for patients who would rather undergo an invasive procedure than add yet another medication.

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