STATE-OF-THE-ART PAPER

International Expert Consensus Statement

Percutaneous Transluminal Renal Denervation for the Treatment of Resistant Hypertension

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Catheter-based radiofrequency ablation technology to disrupt both efferent and afferent renal nerves has recently been introduced to clinical medicine after the demonstration of significant systolic and diastolic blood pressure reductions. Clinical trial data available thus far have been obtained primarily in patients with resistant hypertension, defined as standardized systolic clinic blood pressure ≥160 mm Hg (or ≥150 mm Hg in patients with type 2 diabetes) despite appropriate pharmacologic treatment with at least 3 antihypertensive drugs, including a diuretic agent. Accordingly, these criteria and blood pressure thresholds should be borne in mind when selecting patients for renal nerve ablation. Secondary forms of hypertension and pseudoresistance, such as nonadherence to medication, intolerance of medication, and white coat hypertension, should have been ruled out, and 24-h ambulatory blood pressure monitoring is mandatory in this context. Because there are theoretical concerns with regard to renal safety, selected patients should have preserved renal function, with an estimated glomerular filtration rate ≥45 ml/min/1.73 m². Optimal periprocedural management of volume status and medication regimens at specialized and experienced centers equipped with adequate infrastructure to cope with potential procedural complications will minimize potential patient risks. Long-term safety and efficacy data are limited to 3 years of follow-up in small patient cohorts, so efforts to monitor treated patients are crucial to define the long-term performance of the procedure. Although renal nerve ablation could have beneficial effects in other conditions characterized by elevated renal sympathetic nerve activity, its potential use for such indications should currently be limited to formal research studies of its safety and efficacy. (J Am Coll Cardiol 2013;62:2031–45) © 2013 by the American College of Cardiology Foundation

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Resistant hypertension is a common and growing yet neglected clinical problem. General practitioners and specialist physicians are frequently faced with the challenging task of managing these patients. A novel interventional treatment approach based on transluminal radiofrequency (RF) ablation of renal nerves has recently been introduced into clinical medicine in Australia, Europe, and other countries and has sparked substantial interest from affected patients, treating and referring practitioners and physicians, interventionalists, and health care providers. In view of the limited clinical trial data available, it appeared timely and important to summarize the views of an international panel to provide some guidance with regard to the indications, methods, and safety of transluminal renal nerve ablation. The recommendations in this statement are based on the interpretation of clinical trial data available to date and are intended to facilitate a better understanding of the safety, effectiveness, and limitations of this technology, with a particular focus on appropriate patient selection.

There is a lack of data on the exact prevalence of resistant hypertension, which is commonly defined as blood pressure (BP) higher than target levels despite the use of 3 antihypertensive agents in adequate doses from different classes, including a diuretic agent (1). Evidence from the National Health and Nutrition Examination Survey and from large randomized clinical trials indicates that 20% to 30% of patients with hypertension require 3 or more antihypertensive agents to achieve BP targets. Recent data from the National Health and Nutrition Examination Survey indicate that 12.8% of the antihypertensive drug–treated population fulfilled the criteria of resistant hypertension (2). Data from a large Spanish registry suggested that resistant hypertension is present in 12% of the treated hypertensive population, but among them, more than one-third have normal ambulatory BP (3). Data from 205,750 patients with incident hypertension revealed that 1.9% developed resistant hypertension within a median of 1.5 years from initial treatment (0.7 cases per 100 person–years of follow-up) (4). Failure to reach target BP levels despite therapeutic intervention leaves patients at high risk for major cardiovascular events (4,5).

**Sympathetic nervous system and BP control.** The sympathetic nervous system plays an important role in circulatory and metabolic control and is a major contributor to the development of hypertension (6,7), mediated via sodium and water retention, increased renin release, and alterations of renal blood flow. Accordingly, direct targeting of the sympathetic nervous system is a logical therapeutic approach for the treatment of hypertension.

**Specific role of renal nerves for hypertension and cardiovascular outcomes.** The kidneys have a dense aff erent sensory and efferent sympathetic innervation. Renal sensory afferent nerve activity directly influences sympathetic outflow to the kidneys and other highly innervated organs involved in cardiovascular control (8,9) (Fig. 1). Afferent and efferent sympathetic nerves can interact to modulate sympathetic activity (10). Abrogation of renal sensory afferent nerves reduces both BP and organ-specific damage caused by chronic sympathetic overactivity in various experimental...
models (11,12). Although afferent activity cannot be quantified in humans, there is strong evidence that it modulates the level of central sympathetic outflow. Assessment of regional overflow of norepinephrine (NE) from the kidneys to plasma has demonstrated that renal NE spillover rates can be markedly elevated in patients with essential hypertension (13) and are associated with hypertensive end-organ damage such as left ventricular hypertrophy (14).

Catheter-Based Renal Nerve Ablation

**Method.** Against this background, a novel catheter-based approach to selectively denervate the human kidneys was recently introduced (15). In this approach, renal nerve ablation is achieved percutaneously via the lumen of the renal artery using RF energy. Other treatment modalities, such as ultrasound, cryoablation, and perivascular delivery of neurotoxins, are currently being investigated and briefly reviewed in the Online Appendix. Although most intraluminal approaches share many of the principal features, the approach for RF ablation used in the clinical trials currently available is described here.

Access to the renal artery is typically gained using a 6-F to 9-F sheath introduced into the femoral artery. A renal artery angiogram is obtained to assess anatomic suitability and to exclude significant renal artery stenosis or other relevant renal artery pathology. Each renal artery should have a diameter of ≥4 mm and a length of ≥20 mm to allow adequate application of RF energy and a sufficient number of RF ablation treatments (≥4). Smaller dimensions may interfere with the application of RF energy because of lower blood flow and reduced cooling effects and may predispose to vascular spasm. Local application of vasodilators such as nitroglycerin may be useful to prevent or revert spasm of renal arteries.

To identify abnormal vascular anatomies that may interfere with the ablation procedure, renal vascular imaging should be carried out before renal denervation (RDN). An aortogram obtained before selective renal angiography at the time of intervention is helpful to identify the presence of multiple renal arteries.

The treatment catheter is introduced through a 6-F to 9-F guiding catheter into the renal artery and placed distally before the first branch of the renal artery under fluoroscopic guidance to ensure close and stable contact with the vessel wall. Discrete low-energy RF ablations are then applied from distally to proximally within each renal artery (Fig. 2). RF ablation in areas with atherosclerotic plaques should be avoided. The duration of the procedure is typically 30 to 60 min. Minor vascular irregularities likely representing intimal edema can often be observed directly after the procedure at the treatment sites. These are typically not flow limiting and commonly resolve by the end of the procedure.

**Periprocedural and post-procedural management.** **PAIN MANAGEMENT.** The ablation procedure is typically accompanied by diffuse, visceral, nonradiating abdominal pain, which does not persist beyond the RF energy application and should be managed using intravenous analgesic and anxiolytic or sedative medications. Vital signs, including BP, heart rate, and oxygen saturation, should be monitored during the procedure.
SYSTEMIC ANTICOAGULATION AND ANTIPLATELET THERAPY. Before the procedure, appropriate systemic anticoagulation should be attained and verified by activated clotting time, with a target of 200 to 250 s. Recent data from a porcine model (16) and from human studies using optical coherence tomography (17) demonstrate the possible occurrence of endothelial-intimal edema and thrombus formation. Periprocedural antiplatelet therapy may therefore be advisable in patients undergoing RDN. Although this has not been investigated in clinical trials, the use of 250 mg of acetylsalicylic acid during the procedure and 75 to 100 mg/day for up to 4 weeks after RDN has been suggested (18).

ASSESSMENT OF EFFICACY. It is important to note that BP rarely changes directly after the procedure. It often takes several weeks to months for BP reductions to occur. Patients should be informed accordingly to avoid unrealistic expectations. Currently, there is no reliable clinical parameter available that would allow the prediction of the BP response in an individual patient or to assess the degree of RDN achieved. The exact mechanisms by which RDN results in a BP reduction are not yet fully established but seem to include a reduction in sympathetic activation, total peripheral resistance, renin release, and alterations of water and sodium handling.

There is currently no readily available variable to monitor the efficacy of the procedure itself. Conceptually, assessment of muscle sympathetic nerve activity (MSNA) would be a good candidate variable for this purpose, but the method is not suitable for everyday clinical practice. Nevertheless, in a report on a single patient, a progressive reduction in MSNA was obtained over time and paralleled by a reduction in BP (19). Data from a larger cohort of 25 patients with resistant hypertension confirm a significant reduction in MSNA after RDN (20).

Theoretically, a lack of effect on BP could be explained by 1 or more of these 3 factors: 1) a procedure failure, that is, that the procedure did not result in sufficient ablation of nerves to provoke a BP-lowering response; 2) a pathophysiology failure, that is, that overactivity of renal nerves was not a significant contributor to the elevated BP in a given patient; and 3) despite the procedure being technically successful, the cardiovascular system is unable to respond with a lowering of BP, for instance because of arteries that are too stiff or calcified to dilate. Thus far, it is impossible to clearly distinguish among these possibilities.

Clinical studies. Clinical data are currently available from 2 trials assessing the safety and efficacy of RDN (15,21). Both of these studies were carried out in patients who were resistant to conventional pharmacologic treatment as defined by the failure to achieve systolic BP <160 mm Hg (or <150 mm Hg in patients with diabetes) despite adequate doses of at least 3 antihypertensive drugs from different classes, typically including a diuretic agent (1).

THE SYMPLECT HTN-1 TRIAL. The initial trial (Symplicity HTN-1 [Renal Sympathetic Denervation in Patients With Treatment-Resistance Hypertension]) was designed as an observational first-in-human evaluation of the safety and BP-lowering efficacy of selective RDN (15). A total of 45 consecutive patients (mean age 58 ± 9 years) with a mean BP of 177/101 ± 20/15 mm Hg were included. Patients were on a mean of 4.7 ± 1.5 antihypertensive drugs. The procedure was associated with significant reduction in both systolic and diastolic office BPs at 1, 3, 6, 9, and 12 months, with mean decreases in office BP of −14/−10 ± 4/3, −21/−10 ± 7/4, −22/−11 ± 10/5, −24/−11 ± 9/5, and −27/−17 ± 16/11 mm Hg, respectively. To assess physiological responses to RDN, radiotracer dilution methodologies were applied to assess the overflow of NE from the kidneys into the circulation before and after the procedure. Analyses from 10 patients revealed a substantial reduction in mean NE spillover of 47% (95% confidence interval: 28% to 65%) at 1 month after bilateral denervation.

THE SYMPLECT HTN-2 TRIAL. After this first-in-human proof-of-concept and safety study, a randomized controlled clinical trial (Symplicity HTN-2) was initiated that included a total of 106 patients from 24 centers in Australia and Europe (21). Patients were randomized in a 1:1 ratio to renal ablation treatment (n = 52) or a control group (n = 54). Both groups had similar baseline characteristics and antihypertensive regimen with the exception of estimated glomerular filtration rate (eGFR), which was lower in the active treatment group (77 vs. 86 ml/min, p = 0.013).
The difference in the primary endpoint of seated office BP between the RDN group and the control group was 33/11 mm Hg (p < 0.001 for both systolic and diastolic BP), resulting in a mean BP of 147/84 mm Hg in the RDN group at 6 months (from 178/96 mm Hg at baseline, p < 0.001), while no change in BP was observed in the control group (178/97 mm Hg at baseline and 179/96 mm Hg at 6 months, p = 0.77) (Fig. 3). Home BP recordings confirmed the observed office BP changes, with reductions by 20 ± 17 mm Hg systolic and 12 ± 11 mm Hg diastolic in the RDN group. In contrast, systolic (2 ± 13 mm Hg) and diastolic (0 ± 7 mm Hg) home BP did not change significantly in the control group. The absolute difference between the groups was 22/12 mm Hg (p < 0.001).

Ambulatory BP measurements were available from only 20 patients in the treatment group and 25 patients in the control group. Ambulatory systolic BP was reduced by −11 ± 15 mm Hg (p = 0.006) and ambulatory diastolic BP by −7 ± 11 mm Hg (p = 0.014) at 6 months post-procedurally in the RDN group, whereas no changes were observed in the control group (systolic BP: −3 ± 19 mm Hg; diastolic BP: −1 ± 12 mm Hg). RDN resulted in control of BP, defined as systolic BP <140 mm Hg, in 39% of patients, whereas only 3% of patients in the control group achieved BP control. Twenty percent of the patients who underwent RDN had reductions in drug treatment before the 6-month follow-up visit, whereas antihypertensive drug treatment was reduced in only 6% patients in the control group (p = 0.04). Eight percent of patients in the RDN group and 12% of patients in the control group had increases in drug treatment before the 6-month follow-up visit (p = 0.74).

Recently published data on longer-term follow-up, including 6-month crossover results, indicate that 12 months after the procedure, the mean decrease in office systolic BP in the initial RDN group was similar to the 6-month decrease. The mean systolic BP of the crossover group 6 months after the procedure was also significantly lowered (from 190.0 ± 19.6 to 166.3 ± 24.7 mm Hg, a change of −23.7 ± 27.5 mm Hg; p < 0.001) (22).

**THE SYMPLECTIC HTN-3 TRIAL.** Following the unblinded evidence from Symplicity HTN-1 and Symplicity HTN-2, to eliminate the possibility that patient awareness of the procedure or subconscious observer bias might be contributing, a larger multicenter, prospective, single-blind, randomized controlled study of the safety and effectiveness of RDN in subjects with uncontrolled hypertension is currently ongoing in the United States, the Symplicity HTN-3 trial. The inclusion criteria are very similar to those of Symplicity HTN-2, with even more stringent medication requirements, as described in detail elsewhere (23). A total of 530 patients with resistant hypertension will be randomized in a 2:1 ratio to undergo either RDN or a sham procedure. Additionally, all subjects will undergo ambulatory blood pressure monitoring (ABPM). Results

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**Figure 3** Changes in Office DBP and SBP in the RDN Group and the Control Group in the Symplicity HTN-2 Trial

*p < 0.0001, p = 0.002, p = 0.005. Reprinted with permission from Esler et al. (21). ANOVA = analysis of variance; DBP = diastolic blood pressure; RDN = renal denervation; SBP = systolic blood pressure; Symplicity HTN = Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension.
are expected to be available in early 2014 and will provide valuable information with reduced scope for behavioral bias.

REAL-WORLD EXPERIENCE. An increasing number of reports on smaller case series are available. A recent report published in abstract form summarizes the experience from 8 European centers (24). Office and ambulatory BP measurements were extracted from the medical files of 73 patients with resistant hypertension before and 6 months after RDN. Office systolic and diastolic BP decreased by 18.7 ± 2.7/7.5 ± 1.7 mm Hg (p < 0.001), while ambulatory systolic and diastolic BP decreased by 6.7 ± 2.1/4.2 ± 1.3 mm Hg (p = 0.002). The proportion of patients with reductions in systolic office BP of >10 mm Hg was 64%.

The relevance of drug adherence has been highlighted by a small observational study (25). To be eligible for RDN, patients required an ambulatory daytime systolic BP >135 mm Hg after witnessed intake of their antihypertensive drugs. When these criteria were applied, only 6 of 18 patients were still eligible for RDN. This study documents the insidious nature of pharmaceutical nonadherence and reinforces the need for chronic hypertension therapies that respect patient choice not to adhere to long-term polypharmacy.

Another recent report summarizes data from 346 uncontrolled hypertensive patients from 10 centers in Europe and Australia (26). Patients were separated according to daytime ABPM into 303 with true-resistant hypertension (office systolic BP 172.2 ± 22 mm Hg, 24-h systolic BP 154 ± 16.2 mm Hg) and 43 with pseudoresistant hypertension (office systolic BP 161.2 ± 20.3 mm Hg, 24-h systolic BP 121.1 ± 19.6 mm Hg). At 3-month, 6-month, and 12-month follow-up, office SBP was reduced by 21.5, 23.7, and 27.3 mm Hg and office diastolic BP by 8.9, 9.5, and 11.7 mm Hg (n = 245, 236, and 90, p < 0.001 for all), respectively. In patients with true treatment resistance, significant reductions in 24-h systolic BP (−10.1, −10.2, and −11.7 mm Hg, p < 0.001) and diastolic BP (−4.8, −4.9, and −7.4 mm Hg, p < 0.001) were evident at 3, 6, and 12 months, respectively. Although office BP was reduced to a similar extent in patients with pseudoresistant hypertension, no effect on BP as assessed by ABPM was observed in this cohort (Fig. 4).

More recently, the effects of RDN on BP in patients with moderately resistant hypertension (i.e., office BP ≥140/90 mm Hg despite the use of at least 3 antihypertensive drugs, including a diuretic agent, in adequate doses) were described (27). In this study, a total of 54 patients with office BP ≥140/90 and <160/100 mm Hg and confirmed diagnoses of resistant hypertension by 24-h ABPM (BP ≥130/80 mm Hg) underwent RDN. At 6 months after the procedure, office BP was reduced by −13.7 mm Hg (systolic: 151 ± 6 vs. 138 ± 21 mm Hg, p < 0.001; diastolic: 83 ± 10 vs. 75 ± 11 mm Hg, p < 0.001). Ambulatory BP measurements were available from 36 patients and revealed a reduction in mean 24-h BP of 14/7 mm Hg. In 51% of patients, office BP was controlled to <140/90 mm Hg after RDN.

Figure 4 Changes in Office DBP and SBP and ABP in Patients With True Treatment-Resistant Hypertension and Those With Pseudoresistant Hypertension

Reprinted with permission from Mahfoud et al. (26). ABP = ambulatory blood pressure; DBP = diastolic blood pressure; SBP = systolic blood pressure.
Another smaller study in a similar cohort of 20 patients with office systolic BPs of 140 to 160 mm Hg despite ≥3 antihypertensive medications who underwent RDN revealed BP reductions of a similar magnitude of 13.1 ± 13.6 mm Hg systolic and 5.0 ± 8.3 mm Hg diastolic office BP at 6 months (28). Compared with baseline, the mean ambulatory systolic and diastolic 24-h BPs were reduced by 11.3 ± 8.6 and 4.1 ± 7.3 mm Hg at 6 months, respectively. Although these preliminary data are encouraging, other studies suggest that patients with milder resistant hypertension do not show consistent decreases in BP at 3 or 6 months after RDN (29).

In this context, it is noteworthy that the reduction in mean BP on ABPM after RDN was generally less pronounced than the reduction in office BP. This is not surprising and a well-known phenomenon observed in many other BP-lowering trials. However, the magnitude of the difference between office and ambulatory BP changes appears to be somewhat more pronounced than that observed in BP-lowering trials using pharmacological approaches, as recently discussed in detail (30) (Online Fig. 1).

**LONGER-TERM EFFICACY.** The long-term durability of the procedure remains an important question. A recent analysis of patients treated with catheter-based RDN in a non-randomized and uncontrolled fashion (total n = 153) demonstrated reductions in mean office BP of 23/11, 26/14, and 32/14 mm Hg at 12-month, 18-month, and 24-month follow-up (31), respectively (Fig. 5). Very recently, data on an expanded group of patients from that cohort including 59 patients who had been followed through to 2 years and 24 patients through to 3 years after RDN have been presented and demonstrated that the mean BP change after RDN was −33/15 mm Hg at 2 years and −33/19 mm Hg at 3 years, with increasing rates of BP response defined as a reduction of systolic BP of >10 mm Hg over time. These data indicate that RDN results in significant and durable reductions of systolic BP in patients with treatment-resistant hypertension and suggest that even patients with minimal initial reductions in BP may have significant reductions later on, a finding that needs to be taken into account should a repeated RDN procedure ever be considered. Further and longer studies are required to ascertain the durability of RDN.

**SAFETY.** In Symplicity HTN-1, vascular safety analysis consisting of renal angiography at 14 to 30 days after the procedure and magnetic resonance angiography at 6 months after the procedure revealed no instances of renal artery aneurysm or stenosis or other long-term adverse events. Using the first-generation RF catheter, 1 renal artery dissection occurred in 1 patient before energy delivery, which required stenting and resolved without further adverse consequences. Renal function was not compromised. The impact on eGFR was neutral with −1.4 ml/min (95% confidence interval: −4.6 to 1.7 ml/min) at 3 months and −2.8 ml/min (95% confidence interval: −6.4 to 0.8 ml/min) at 12 months. In the extended Symplicity HTN-1 cohort (n = 153), a total of 3 groin pseudoaneurysms occurred. One patient required stenting of a renal artery ostial stenosis that was present at baseline but had grown by 6 months. Of note, no RF energy had been delivered in this location.

In Symplicity HTN-2, periprocedural events requiring treatment were rare and consisted of 1 femoral artery pseudoaneurysm, 1 post-procedural decrease in BP resulting in a reduction in antihypertensive drugs, 1 urinary tract infection, 1 extended hospital admission for assessment of paraesthesia, and 1 case of back pain that was treated with analgesics and resolved after 1 month. Seven of 52 patients (13%) who underwent RDN had transient intraprocedural bradycardia requiring atropine. Renal function, as assessed by serum creatinine, eGFR, and cystatin C levels, were unchanged from baseline in both groups at 6 months. Six-month renal vascular imaging identified 1 patient with possible progression of an underlying atherosclerotic lesion, which required no therapy.

Two recently published case reports describe the development and progression of a renal artery stenosis (32,33) and a potential link with the RDN procedure. Long-term follow-up of treated patients with repeat imaging of the renal arteries will be required to adequately address this issue.

In addition to BP lowering, RDN has been shown to reduce heart rate (34) (Fig. 6) and to reduce BP during exercise without compromising chronotropic competence (35).

**Additional Potential Beneficial Effects of Renal Denervation**

A series of studies have reported on the effects of RDN on aspects other than BP reduction. The majority of these studies were observational and uncontrolled and comprised...
small study cohorts with only short-term follow-up. They therefore need to be interpreted with appropriate caution. Clearly, larger, adequately designed studies are necessary, and many are currently being undertaken to confirm or reject these initial findings. Nevertheless, pathophysiologic considerations suggest that some of these initial findings may have potential clinical relevance.

**Glucose metabolism.** Hypertension is frequently associated with metabolic alterations. Sympathetic activation has been identified as an important contributor to this detrimental clinical scenario (36). Sympathoinhibition would therefore be expected to improve glycemic control (37). In a subcohort of the Symplicity HTN-2 trial, patients from both the RDN (n = 37) and control groups (n = 13) underwent detailed assessment of glucose metabolism. Levels of fasting glucose, insulin, C-peptide, glycosylated hemoglobin, and calculated insulin sensitivity (homeostasis model assessment of insulin resistance) improved significantly after 3 months. Mean 2-h glucose levels during oral glucose tolerance tests were also reduced significantly by 27 mg/dl (p = 0.012), while there were no significant changes in BP or in any of the metabolic markers in the control group (38) (Fig. 7).

**Left ventricular hypertrophy.** Additional factors that may translate into better outcomes after RDN include improvements in cardiac baroreflex sensitivity and a reduction in left ventricular mass (19). These initial findings from a single case report have now been confirmed in a larger cohort of 46 patients with resistant hypertension for which they underwent RDN (39). RDN was not only associated with substantial reductions in systolic and diastolic BP (−22.5/−7.2 mm Hg at 1 month and −27.8/−8.8 mm Hg at 6 months, p < 0.001 at each time point) but also significantly reduced mean interventricular septal thickness and LV mass index at 1 and 6 months, respectively (Fig. 8). Diastolic function was also improved, as assessed by mitral valve lateral E/E ratio, which decreased after RDN from 9.9 ± 4.0 to 7.9 ± 2.2 at 1 month and 7.4 ± 2.7 at 6 months (p < 0.001), indicating reduction of left ventricular filling pressures. No such changes were observed in a matched group of 18 control patients. These data may indicate that the effects of RDN go beyond that of merely reducing BP and may contribute to regression of hypertensive end-organ damage.

**Atrial fibrillation.** Both animal and human studies suggest that the autonomic nervous system plays an important role in the initiation and maintenance of atrial fibrillation (AF). A recent study by Pokushalov et al. (40) reported that RDN reduced AF recurrence when combined with pulmonary vein isolation (PVI). In this study, 27 patients with hypertension with histories of symptomatic paroxysmal or persistent AF were enrolled, 14 of whom underwent PVI only and 13 of whom were treated with PVI and RDN. At 12-month follow-up, patients in the PVI plus RDN group experienced significant reductions in atrial fibrillation (AF) (from 181 ± 7 to 156 ± 5 mm Hg, p < 0.001) and diastolic (from 97 ± 6 to 87 ± 4 mm Hg, p < 0.001) BP and had a substantially lower rate of recurrence of AF. Nine of the 13 patients (69%) treated with PVI plus RDN were free of AF, whereas this was the case in only 4 of the 14 patients (29%) in the PVI-only group (p = 0.033). Although optimized BP control might play a considerable role in decreasing the development of recurrence of AF, this study raises the possibility that reducing sympathetic drive with RDN may reduce the rate of AF recurrence in patients with resistant hypertension. However, in a recent letter to the editor, several concerns were raised pertaining to the design of the study, insufficient description of methods, and inconsistencies with data reporting and statistics (41). Further studies are needed to assess the therapeutic potential of RDN in the setting of AF.

**Heart failure.** Heart failure is commonly characterized by substantial neurohormonal activation directed particularly to the heart and kidneys, providing a theoretical basis for the potential usefulness of targeting renal nerves with RDN in this context. A small pilot study including 7 patients with chronic mild to moderate systolic heart failure (mean ejection fraction 43 ± 15%) did not raise any procedural or safety concerns (42), particularly no major decrease in BP despite low baseline levels and no change in renal function, and demonstrated a mild improvement in 6-min walking distance, while ejection fraction and other cardiac structural and functional changes were not changed significantly after 6 months. Larger clinical trials are ongoing to delineate the potential role of RDN in heart failure.

**Chronic and end-stage kidney disease.** Sympathetic activation is a hallmark of chronic kidney disease but generally neglected as a therapeutic target (43). Given the relevance of both renal efferent and afferent nerves in this
condition (11,12), these patients may derive specific benefit from an intervention targeting the renal nerves (44). A recent proof-of-concept study in 15 patients with resistant hypertension (mean BP 174 ± 22/91 ± 16 mm Hg despite the use of 5.6 ± 1.3 antihypertensive drugs) and moderate to severe chronic kidney disease (mean eGFR 31.2 ± 8.9 ml/min/1.73 m²) in whom office and ambulatory BP and serum biochemistry were obtained before and at 1-month, 3-month, 6-month, and 12-month follow-up after RDN revealed a favorable safety profile with no compromise of treated arteries evident on angiographic evaluation and preserved renal function up to 12-months follow-up (45). Office systolic and diastolic BP decreased by -32 ± 18/ -15 ± 12 mm Hg at 6-month follow-up (p < 0.001). Nighttime ambulatory BP was significantly reduced (p < 0.05), resulting in restoration of a more physiologic dipping pattern (45). Although renal hemodynamic status has not been assessed in this chronic kidney disease cohort, recent data from a larger cohort of 100 patients with resistant hypertension and eGFRs >45 ml/min/1.73 m² demonstrated that RDN reduced the renal resistive index at 3-month and 6-month follow-up (46). Although mean cystatin C, eGFR, and urinary albumin excretion remained unchanged after RDN, the number of patients with microalbuminuria or macroalbuminuria decreased (46). Whether these potentially beneficial changes in renal hemodynamic status may translate into improved renal outcomes in patients with resistant hypertension and various stages of chronic kidney disease needs to be determined.

Sympathetic tone is substantially enhanced in patients with end-stage renal disease and may play a role in the high rate of cardiovascular events in these patients (47). Nephrectomy of the native nonfunctioning kidney in patients with or without kidney transplantation resulted in a reduction of MSNA (48). A preliminary proof-of-concept study of RDN was performed in 12 patients with end-stage renal disease and uncontrolled hypertension (49). Standardized BP measurements were obtained in all patients on dialysis-free days at baseline and follow-up. The mean of office BP was 170.8/ 89.2 mm Hg despite the use of a mean of 3.8 ± 1.4 antihypertensive drugs. Three of 12 patients could not undergo RDN because of atrophic renal arteries. Compared with baseline, office systolic BP was reduced (from 166 ± 16.0 to 148 ± 11, 150 ± 14, and 138 ± 17 mm Hg, respectively), whereas there was no change in the 3 nontreated patients. Measures of renal NE spillover and MSNA were available in 2 patients before and after RDN, and these markers were substantially reduced by RDN. These initial results indicate that there is high sympathetic drive in end-stage renal disease, and it can be reduced by RDN, resulting in a significant BP reduction. Whether this translates into improved outcomes in these high-risk patients requires confirmation in appropriately designed, larger population studies.

**Patient Selection**

On the basis of the available data from clinical studies, only those patients who have severe treatment-resistant
hypertension, defined as office systolic BP $\geq 160$ mm Hg ($\geq 150$ mm Hg in patients with type 2 diabetes) despite treatment with $\geq 3$ antihypertensive drugs of different types, including one diuretic agent, at adequate doses should undergo renal nerve ablation (Fig. 9). Elevated BP should be confirmed by 24-h ABPM, because up to one-third of patients with treatment-resistant hypertension have normal BP outside the office (50). Every effort should have been made to identify and reverse contributing lifestyle factors and discontinue or minimize the use of substances that can increase BP. Secondary causes of hypertension should have been re-evaluated and excluded, as previously summarized (51) (Table 1). Careful attention should have been paid to exclude nonadherence to drug therapy as an important and often neglected cause of treatment resistance (52). The importance of systematic screening to assess eligibility for RDN was highlighted in a recent study demonstrating that 2 of 3 patients with suspected resistant hypertension were found to be ineligible if the aforementioned criteria were applied, primarily because of previously undiagnosed secondary hypertension, white coat hypertension, or BP lower than currently recommended thresholds (53).

In the Symplicity HTN-1 and Symplicity HTN-2 studies, patients were excluded if renal function was reduced to an eGFR $< 45$ ml/min/1.73 m$^2$. Contrast media are administered during the procedure. Patients with markedly reduced glomerular filtration rates may be particularly vulnerable to acquiring acute renal failure. The cholesterol embolus syndrome is a potential risk if there is renal atherosclerosis (54). Even in dialysis patients, loss of residual renal function and diuresis may have a negative impact on quality of life and prognosis. Currently, RDN in patients with advanced chronic kidney disease (glomerular filtration rate $< 45$ ml/min/1.73 m$^2$) is therefore recommended only in clinical trials.

**Background therapy.** Whether only patients who have tried aldosterone antagonists should be eligible for renal nerve ablation is controversial. Systolic BP reductions up to 25 mm Hg have been reported after administering spironolactone as a fourth antihypertensive agent (55,56), but not all patients respond to such an extent. A randomized controlled trial suggested that the incremental effect on office systolic BP was only 6.5 mm Hg (57). Long-term treatment with spironolactone is hampered by side effects such as gynecomastia, while eplerenone currently has the drawback of relatively high cost. Furthermore, there is a risk for hyperkalemia with aldosterone antagonists, which requires monitoring. Although the incidence of hyperkalemia may numerically be low, patients with treatment-resistant hypertension in general receive already 1 or 2 agents blocking the renin-angiotensin system and may already have reduced renal function (eGFR $< 60$ ml/min/1.73 m$^2$), both factors that increase the incidence of hyperkalemia. Spironolactone increases potassium levels, especially in white subjects (58,59),

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**Figure 8** Changes in LVH After Bilateral RD in 46 Patients With Resistant Hypertension Compared With 18 Control Patients Who Did Not Undergo Renal Denervation

Comparison of LVMI (A), IVSTD (B) and reduction of LVMI (C) between the RDN and control group, and individual changes in LVMI in patients who did undergo RD (D) at various time points. Reprinted with permission from Brandt et al. (39). LVH = left ventricular hypertrophy; LVMI = left ventricular mass index; IVSTD = end-diastolic interventricular septum thickness; RD = renal denervation.
and its widespread initiation after publication of the Randomized Aldactone Evaluation Study was accompanied by an increase in hospitalizations for hyperkalemia (60), although this has been put in perspective by others (59). Moreover, if unexpected circumstances occur that compromise renal function, such as the administration of nonsteroidal anti-inflammatory drugs or volume loss with diarrhea, the rate of hyperkalemia may increase further. Thus, an individualized approach balancing the pros and cons of lifelong administration of aldosterone antagonists is preferential.

There is no sufficient clinical research experience of renal nerve ablation in the setting of hemodynamically or anatomically significant renal artery abnormalities (e.g., stenosis or fibromuscular dysplasia), previous renal artery interventions including previous renal stent procedures, unstable clinical conditions (e.g., acute cardiovascular events), or in children or patients with preeclampsia. These should, therefore, currently be considered contraindications in routine clinical practice.

**General requirements for sites involved in RDN procedures.** In patients with difficult-to-control BP, secondary forms of hypertension should be suspected and excluded. RDN is not the first-line therapy for such patients. A detailed screening program should be completed to exclude curable forms of secondary hypertension. Specialized centers are typically best equipped to perform thorough diagnostic investigations and provide the expertise and infrastructure for appropriate patient management and selection, procedure implementation, management of potential complications, and the essential follow-up.

Although the clinical experience with RDN is mounting, with more than 6,000 treated patients worldwide, it cannot yet be rated as a standard procedure in resistant hypertension. It should be offered only to selected patients in whom the present danger from hypertensive complications such as death, myocardial infarction, and stroke exceed the potential for long-term harm from the procedure, for which the 36 months of follow-up of patients in clinical trials may not yet be sufficient to be definitively excluded.

**Patient follow-up.** Regular follow-up visits after RDN are necessary to assess short-term and long-term safety and efficacy and to adjust patients’ BP medications if required. Given the known limitations of conventional clinic BP readings, additional measures such as systematic home BP monitoring (61) and ABPM should be implemented as part of the follow-up of treated patients. The first scheduled follow-up should occur within the first 4 weeks after the procedure and then at 3, 6, and 12 months, with subsequent yearly visits. In addition to BP measurements, assessment of renal function (serum creatinine, eGFR, electrolytes) is mandatory. Repeat renal artery imaging at 6 months or later after RDN is recommended to exclude any post-procedural structural alterations, particularly if BP has not dropped or has even increased. Depending on pre-existing comorbidities, repeat electrocardiography, echocardiography, assessment of glucose metabolism (fasting glucose, insulin, glycosylated hemoglobin, oral glucose tolerance test), measurement of urinary albumin and creatinine ratios and protein excretion, assessment of markers of arterial stiffness, and other tests can provide additional information on the therapeutic effects of RDN but are not mandatory.

**Figure 9 Patient Assessment to Determine Eligibility for RDN**

The flowchart describes the recommended pathway to assess eligibility for renal denervation (RDN). Patients who present with presumed treatment resistance should undergo a series of diagnostic tests to confirm true treatment resistance. Furthermore, reversing of contributing factors and optimization of pharmacotherapy should be attempted before RDN is considered. Throughout this process, communication between hypertension specialists, interventional cardiologists, and other health care providers involved in the patient’s care is essential. ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CTA = computed tomographic angiography; eGFR = estimated glomerular filtration rate; MRA = magnetic resonance angiography; OSA = obstructive sleep apnea; SBP = systolic blood pressure; US = ultrasound.
### Table 1  Clinical Features and Diagnostics of Secondary Causes of Hypertension

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Clinical Features</th>
<th>Screening Test</th>
<th>Additional/Confirmatory Test</th>
</tr>
</thead>
</table>
| Renal vascular disease           | • ARAS  
  • Rapid deterioration of renal function (especially after administration of RAS-modulating agents)  
  • Onset of hypertension after age 50 yrs  
  • Flash pulmonary edema  
  • Length difference ≥ 1.5 cm between the kidneys  
  • FMD  
  • Early-onset hypertension (particularly in young women) | • Renal duplex ultrasonography           | • MRI  
  • CT  
  • DSA |
| Renal parenchymal disease        | • Clinical history (including)  
  • Recurring UTI  
  • Analgesic abuse  
  • Familial diseases  
  • Anemia  
  • Fluid overload | • eGFR  
  • Urine dipstick (e.g., erythrocytes, leukocytes, proteinuria)  
  • Urine albumin/creatinine ratio | • Renal ultrasonography  
  • Kidney biopsy (in reasonable cases) |
| Primary hyperaldosteronism       | • Muscle weakness  
  • Hypokalemia (occasional)  
  • Incidentaloma | • Aldosterone-renin ratio (at best under standardized conditions) | • Oral sodium loading  
  • Saline infusion  
  • Fludrocortisone suppression test  
  • Captopril challenge  
  • CT  
  • Adrenal vein sampling |
| OSA                              | • Daytime hypersomnia  
  • Frequent nocturnal arousals  
  • Morning asthenia with or without headache  
  • Severe snoring | • Specific questionnaires  
  • Polygraphy (ambulant) | • Polysomnography (sleep center) |
| Drug-induced hypertension        | • Detailed medical history (including OTC medicines) |                                   |                              |
| Pheochromocytoma                 | • Hypertension (paroxysmal or sustained)  
  • Headache  
  • Sweating  
  • Palpitations  
  • Fasting hyperglycemia  
  • Incidentaloma  
  • Genetic predisposition | • Urinary fractionated metanephrines  
  • Plasma-free metanephrines | • CT  
  • MRI  
  • $^{123}$I-labeled MIBG scintigraphy  
  • Genetic screening |
| Cushing’s syndrome               | • Classical physical findings  
  • Central obesity  
  • Moon face  
  • Buffalo hump  
  • Red striae  
  • Hirsutism  
  • Glucose intolerance/diabetes  
  • Menstrual irregularities | • 24-h urinary cortisol excretion  
  • Dexamethasone suppression test  
  • Exclusion of exogenous glucocorticoid intake | • MRI  
  • CT  
  • CRH testing |
| Coarctation of the aorta         | • Headache  
  • Hypertension in the upper extremities with lower extremity pressure  
  • Discrepancies between bilateral brachial blood pressure  
  • Congenital heart disease | • Chest radiography  
  • Echocardiography | • MRI |

Reprinted with permission from Ott et al. (51).  
ARAS = atherosclerotic renal artery stenosis; CRH = corticotropin-releasing hormone; CT = computed tomography; DSA = digital subtraction angiography; eGFR = estimated glomerular filtration rate; FMD = fibromuscular dysplasia; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; OSA = obstructive sleep apnea; OTC = over-the-counter; RAS = renin-angiotensin system.
Study Limitations

The studies carried out so far have been restricted to patients with severe and treatment-resistant hypertension with systolic BP >160 mm Hg. These results cannot be simply extrapolated to less severe forms or secondary forms of hypertension.

Although uncontrolled, follow-up data are available beyond 3 years by now, this may not yet be sufficient to ascertain the long-term durability of the effect. Indeed, renal and heart transplantation models indicate that renal nerves have the potential to regrow anatomically after injury, raising the possibility of finite time limits in the physiologic effects of the procedure. However, on the basis of previous data, it appears unlikely that the human kidney achieves functional reinnervation (62), and the physiologic importance of anatomic regrowth of efferent nerve fibers in sustaining BP remains unproven. If functional reinnervation occurred, perhaps mirrored by BP elevations, the issue of repeat renal nerve ablation would have to be explored.

Theoretical concerns relate to the altered responsiveness to certain stimuli in the absence of sufficient renal sympathetic innervation. The renal nerves are only 1 component of the complex mechanisms that make up baroreceptor function. For instance, the direct effects of the baroreceptor arch on peripheral vascular resistance are unaffected. The experience from kidney transplantation in humans, in the process of which sympathetic nerves of the kidneys are severed, is perhaps the most persuasive evidence to demonstrate that the denervated kidney is capable of maintaining electrolyte and volume homeostasis, suggesting that selective ablation of renal nerves is unlikely to result in adverse consequences.

Follow-up imaging of renal arteries 6 months after RDN did not reveal evidence of major vascular damage. Published data reporting on 2-year follow-up in a cohort of 153 patients treated with RDN did not report major vascular abnormalities. However, imaging studies of the renal vasculature were not part of the routine investigation at 1-year and 2-year follow-up.

Currently, there are no clinical trial data available to indicate the effects of RDN on cardiovascular outcomes.

Several technical aspects also require attention. These include the management of patients with dual renal arteries and accessory arteries that may not be accessible for renal nerve ablation, as well as the role of RDN in patients with renal artery stenosis, a condition that is characterized not only by activation of the renin-angiotensin system but also by heightened sympathetic drive (63).

As indicated earlier, only a limited number of ambulatory BP measurements were extractable from study-controlled patients. In the Symplicity HTN-2 trial, only 20 patients in the RDN group and 25 patients in the control group had evaluable measurements (>70% successful readings) (21). The difference in reduction of systolic BP after 6 months was less pronounced, with only 8 mm Hg between the RDN and control groups. Whether this is a manifestation of inadvertently biased measurement of BP by physicians aware of treatment allocation or a reflection of a larger effect on the alerting response is currently unknown. Ambulatory BP data from the Symplicity HTN-3 trial will provide important insights.

Finally, there is only limited information to what extent the RDN procedure is able to interfere with afferent sensory nerve traffic and efferent sympathetic renal innervation. Elaborate microneurographic measurements (MSNA) are currently the only way to quantify sympathetic nerve activity. Further studies need to be conducted to address this issue.

Conclusions

Evidence from the available clinical trials indicate that catheter-based RF ablation of renal nerves improve BP control in patients with resistant hypertension, with a safety profile to 3 years that seems acceptable for the degree and reliability of BP improvement. The effects of RDN appear to be mediated via interference with both efferent sympathetic and afferent sensory nerves and may extend beyond BP control.

RDN should currently be considered only in patients whose BP cannot be controlled by a combination of lifestyle modification and pharmacologic therapy that is tailored according to current guidelines. It is not known whether RDN may be useful in less severe forms of hypertension or in other conditions characterized by heightened renal sympathetic nerve activity, such as heart failure, metabolic syndrome, heart arrhythmias such as AF, chronic and end-stage renal disease, and others. It is therefore not recommended to perform RDN in these patient cohorts outside of appropriately designed clinical trials.

Information on the long-term safety and efficacy of the RDN procedure is being collected in national and international registries.

Many uncertainties remain. One is the longer term, when the risk for cardiovascular events grows, as does the opportunity to benefit from event prevention; and meanwhile, the potential for currently unrecognized complications might grow along with the natural accumulation of unrelated adverse events. A second is the suitability for patients outside the idealized group of patients who tend to volunteer for randomized controlled trials. A third is how to balance the desirability of BP control, individual patients’ desire to feel confident that their BP is controlled, their reluctance to take very large numbers of tablets, their reluctance to undergo irreversible and invasive procedures, and the cost of the procedure versus the cost and consequences of letting BP continue uncontrolled. While addressing these issues, an accurate assessment of daily life BP control is an essential requirement, and systematic use of home BP monitoring and/or ABPM is thus mandatory. Clinicians must consider
all of these in the context of individual patients to give advice in a suitable perspective.

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For supplementary material and a figure and a table, please see the online version of this article.