Renal Denervation: Current Status and Future Applications

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Despite the variety of antihypertensive agents that are available, resistant hypertension remains a significant clinical problem and a substantial economic burden. Over the past several years, renal sympathetic denervation has been introduced as a potential therapeutic option for this clinical problem. It is a catheter-based procedure that is showing promising results and appears to be associated with minimal or low risk. Thus far, two completed clinical trials have demonstrated excellent safety and encouraging outcomes. A review of these trials is the focus of this article, in addition to the analysis of ongoing studies, and the possible future applications of this technique.

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KEY WORDS

Resistant hypertension • Renal sympathetic denervation • Sympathetic overactivity • Cardiovascular disease

Approximately 1 billion people, or 30% of adults worldwide, have essential hypertension.[1-6] Despite medical therapy, 9% of hypertensive patients are unable to control their blood pressure adequately.[7] This is known as *resistant hypertension*, and defined as an inability to control blood pressure despite being on at least three antihypertensive medications, one of which is a diuretic.[8] In the search for effective nonpharmacologic alternatives to address this issue, two techniques have been developed. One is baroreflex activation therapy, and the second is renal sympathetic denervation (RSD).

Baroreflex activation therapy is an invasive technique that consists of the subcutaneous implantation of a pulse generator at the level of the neck, which stimulates the ipsilateral carotid sinus. The carotid sinuses, as well as the aortic arch, have mechanoreceptors that discharge upon stretching, and through the glossopharyngeal and vagus nerves stimulate the parasympathetic system and inhibit sympathetic tone.[9] The number of impulses can be regulated to achieve the desired levels of arterial blood pressure.[10] In a randomized study, baroreceptor stimulation achieved a nonsignificant decrease in blood pressure in 54% of patients at 12 months.[10] This method is still being evaluated for both safety and efficacy.[11] The main focus of this article is the current status of RSD, as well as its future potential.

History and Pathophysiology of Hypertension

Although the pathophysiology of hypertension is complex and involves multiple mechanisms, as well as dietary and genetic factors, the role of the sympathetic nervous system is a major component in the development and maintenance of high blood pressure. Approximately half of patients with essential hypertension have an increased sympathetic tone compared with healthy individuals.[12-16] This enhanced sympathetic activity is not only a culprit in the pathogenesis of hypertension, but also in the target-organ damage that comes with it.[17] Prior to the current state of medication-oriented practice, surgical sympathectomy was an effective alternative for severely hypertensive patients. The results were excellent regarding blood pressure control, resulting in up to a 76% success rate.[18-20] However, the results came with disabling side effects, such as orthostatic hypotension, impotence, and syncope, and eventually the method was abandoned.

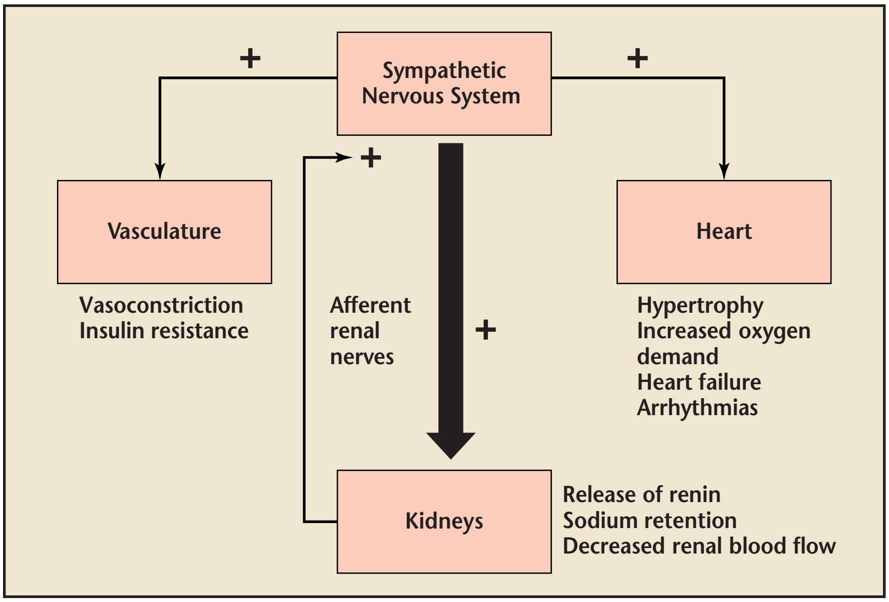

Figure 1. Renal interactions with the sympathetic nervous system.

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The initial antihypertensive drugs, such as the central sympathetic inhibitors methyldopa, clonidine, and guanethidine, are effective in controlling blood pressure; however, they are also associated with significant side effects.[21,22] Over the past several decades, drugs that block the renin-angiotensin-aldosterone system, along with diuretics and calcium channel blockers, have largely replaced the aforementioned medications. However, the initial treatments for hypertension gave us a perspective on the importance of the sympathetic nervous system in the development and maintenance of hypertension. In fact, it is known that the renal tubules, the juxtaglomerular apparatus, and the renal vasculature have extensive innervations by sympathetic fibers,[23] which are ultimately responsible for renin secretion from the kidneys through β1-receptor stimulation.[24] Also, the adrenergic system directly stimulates the renal tubules to reabsorb sodium,[25] and regulates renal plasma flow and glomerular filtration rate through vasoconstriction, all of which tend to increase systemic blood pressure (Figure 1).[26,27]

With this evidence of sympathetic activation,[28,29] the technique of catheter-based RSD was developed with the purpose of interfering with the autonomic afferent and efferent nerves that reach the kidneys. This is a minimally invasive procedure, performed under conscious sedation, in which both renal arteries are accessed with a catheter via the femoral artery. The flexible catheter has a tip with an electrode able to deliver low-power radiofrequency energy when it is applied to the endothelial surface of the vessel. The amount of energy delivered with each ablation is approximately 8 W. This low-energy radiofrequency disrupts the sympathetic nerve fibers located in the adventitia of the renal arteries. Usually a total of six ablations per artery are performed, each separated 1 to 2 cm from the other, both longitudinally and rotationally, and are applied from the distal to the proximal aspect of the vessel. The procedure takes less than 1 hour and recovery does not differ from that of cardiac catheterization.

Renal Denervation Trials

The initial trial that evaluated the effects of RSD was the Renal

Denervation in Patients With Uncontrolled Hypertension (Symplicity-HTN-1) study, which evaluated 45 patients with resistant hypertension.[30] The endpoints were office blood pressure and safety data at 0, 3, 6, 9, and 12 months. A reduction of systolic/diastolic blood pressure from baseline of 27/10 mm Hg (95% confidence interval [CI], 16/11 mm Hg) in nine patients was noted at follow-up. From an expanded cohort that included 153 patients, the results from 24 months of follow-up showed a reduction on average of systolic/diastolic pressure of 32/14 mm Hg.[31] The complications included three femoral artery pseudoaneurysms and one artery dissection, all managed medically with no long-term complications. The limitations of the study included the small number of patients, the use of office blood pressure as an endpoint as opposed to ambulatory 24-hour blood pressure monitoring, and no control group. It is important to note that the extended follow-up group demonstrated a drop in the estimated glomerular filtration rate of −16 mL/min/1.73 m^2 in the available 10 patients at 2 years. This drop in the glomerular filtration rate was attributed to prerenal azotemia due to enhanced response to diuretics after denervation.[32]

As a result of this trial, the Symplicity HTN-2 trial was performed.[33] This study randomized 106 patients with resistant hypertension to renal denervation plus standard therapy versus standard therapy alone, with the primary endpoint being office blood pressure at 6 months from baseline. It demonstrated a mean decrease of systolic/diastolic pressure of 32/12 ± 23/11 mm Hg, whereas the control group had no change in blood pressure. There was a subgroup of 20 patients that underwent 24-hour ambulatory blood pressure monitoring and demonstrated a mean decrease of 11/7 ± 15/11 mm Hg, compared with no change in blood pressure in the 25 patients in the control group. The renal function did not deteriorate in this study, and no major complications were reported. At 12-month follow-up, the denervation group (n = 47) showed a mean fall in systolic blood pressure of 28.1 mm Hg (95% CI, −35.4 to −20.7; $P < .001$).[34] There was also a crossover group at 6 months after the initial denervation for those patients in the control group who elected to receive renal denervation. A total of 35 patients did so, and reached significant decreases in mean systolic blood pressure at 6 months postprocedure from 190 ± 19.6 to 166.3 ± 24.7 mm Hg. The study reported no changes in renal function at 6 or 12 months after renal denervation.

Recently, a meta-analysis of 2 randomized trials and 10 observational studies with a total of 561 patients was reported.[35] In the controlled studies, at 6 months, a mean reduction of systolic and diastolic blood pressure was noted of 29 mm Hg (95% CI, 37.2-20.6) and 11 mm Hg (95% CI, 16.4-5.7), respectively, compared with medical therapy alone (both, $P < .0001$). In the observational studies, the mean reduction of systolic and diastolic blood pressure at 6 months was noted to be 25 mm Hg (95% CI, 30-20.1) and 10 mm Hg (95% CI, 12.5-7.5), respectively, compared with pretreatment values (both, $P < .0001$).

To further investigate this form of therapy, the Symplicity HTN-3 study was performed. This was a prospective, randomized, single-blind trial to evaluate the safety and effectiveness of RSD. It enrolled 535 patients with resistant hypertension. A sham procedure was performed in the patients randomized to the control group. The primary endpoint of the study was the change in office systolic blood pressure at 6 months; the 6-month change in the average 24-hour systolic blood pressure assessed by ambulatory blood pressure monitoring was a secondary endpoint. Although there were no safety concerns raised during the trial, it failed to show that treatment with this investigational procedure resulted in a sustained reduction in systolic blood pressure.[36]

Medtronics (Minneapolis, MN) has taken the lead in the development of this method within the United States although many other companies have also created renal denervation devices. The EnligHTN™ renal denervation system, from St. Jude Medical (St. Paul, MN), has been approved and is commercially available in Europe. It delivers radiofrequency ablation through a unique basket design; each placement of the ablation catheter allows a consistent and predictable pattern of four ablations in 90-second intervals. Compared with single electrode ablations, the multielectrode EnligHTN system has the potential to improve consistency and procedural reliability, save time, and result in workflow and cost efficiencies. Additionally, the minimal catheter repositioning may result in a reduction of contrast and radiation exposure. However, because of slow enrollment, St. Jude Medical announced the stoppage of the EnligHTN-IV study, a large phase III study in patients with resistant hypertension.[37]

Additional Findings After Renal Denervation

Many other favorable effects have been reported after denervation that may be better explained by the decrease in sympathetic tone rather than by a reduction in systemic blood pressure. These include a reduction in total body and renal norepinephrine spillover (28% and 47%, respectively), and decrease in sympathetic nerve traffic by 66%, accompanied by an increase in renal blood flow and a decrease in plasma renin activity. These mechanisms seem to be involved, at least in part, in the decrease in the severity of obstructive sleep apnea.[38] It has been postulated that the benefit of renal denervation in this case might come from an alteration in afferent signaling, causing a resetting of central sympathetic outflow at a lower homeostatic set-point. Improvement of insulin and glucose profiles has also been shown after renal denervation, with an association between reduction of total body spillover, sympathetic nerve activity, and improved insulin sensitivity.[39,40] Another added benefit is a reduction in left ventricular mass index,[33,41] as well as an increase in exercise tolerance.[42] Also noted is a lower blood pressure response during exercise without impact on the heart rate response, as well as a lower heart rate at rest and a faster heart rate recovery. In addition, there is evidence suggesting a reduction in atrial fibrillation,[43] as well as ventricular arrhythmias.[44,45] Other diseases that may potentially benefit from this new intervention include chronic heart failure[46,47] and chronic kidney disease.[48-50] However, the data of these secondary effects are very limited. Currently, there are ongoing clinical trials exploring these secondary effects, in addition to evaluating patients with less severe hypertension (Table 1).

Patient Selection for Renal Denervation Therapy

The European Society of Cardiology recently issued a consensus statement[51] considering RSD as a therapeutic option in patients with drug-resistant hypertension who

TABLE 1

Ongoing Trials in Renal Sympathetic Denervation

Study	N	Population	Comparator	Estimated Completion Date
Influence of Catheter-based Renal Denervation in Diseases With Increased Sympathetic Activity; NCT01888315	1000	HTN, T2D, CKD, CHF	Medical therapy only	January 2021
Impact of Sympathetic Renal Denervation: a Study in Patients After Renal Transplantation; NCT01899456	40	Renal transplantation with HTN	Medical therapy only	July 2014
Renal Denervation in Patients With Resistant Hypertension and Obstructive Sleep Apnea; NCT01366625	60	OSA with HTN	Medical therapy only	December 2014
Prairie Renal Denervation Study; NCT01832233	50	CKD with HTN	Medical therapy only	January 2018
Symplicity-4; NCT10972139	580	Moderate HTN	Medical therapy only	December 2015
HTN2DM; NCT01887067	15	T2D with HTN	Medical therapy only	June 2017
RESPECT-HF; NCT02041130	144	Heart failure with preserved systolic function	Medical therapy only	December 2016
Renal Denervation in CHF With Severe Systolic Dysfunction; NCT01870310	50	CHF with severe systolic dysfunction	Medical therapy only	June 2016
Metabolic Syndrome Study	60	Treatment of metabolic syndrome-associated HTN	Medical therapy only	January 2015

CHF, congestive heart failure; CKD, chronic kidney disease; HTN, hypertension; HTN2DM, Renal denervation therapy for resistant hypertension in type 2 diabetes mellitus; OSA, obstructive sleep apnea; RESPECT-HF, Renal denervation in heart failure patients with preserved ejection fraction; T2D, type 2 diabetes.

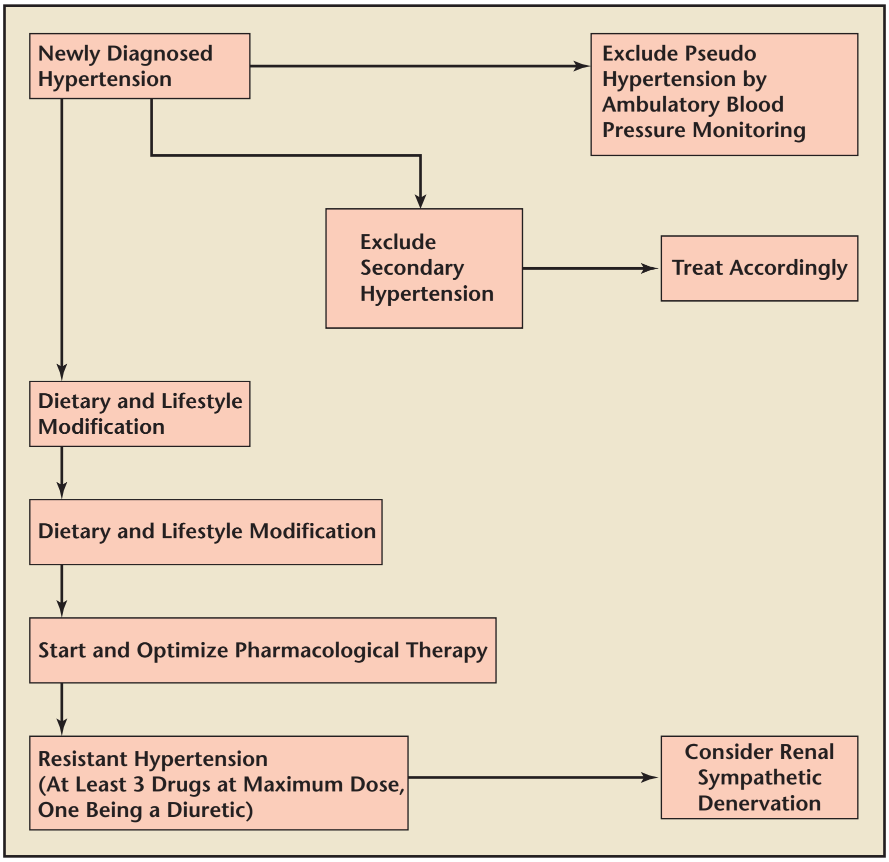

Figure 2. Appropriate patient selection for renal denervation therapy.

cannot achieve control with a combination of lifestyle and pharmacologic therapy (Figure 2). As a first step, pseudohypertension and secondary causes need to be excluded. Once the medications have been optimized and the patient still requires at least three different agents (one being a diuretic at maximal dose), performance of RSD may be considered (Table 2). The main exclusion criteria for RSD therapy include renal artery anatomy not suitable for treatment (main renal arteries < 4 mm in diameter or < 20 mm in length; hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery; history of prior renal artery intervention, including balloon angioplasty or stenting; multiple main renal arteries in either kidney), type 1 diabetes, myocardial infarction, unstable angina pectoris, cerebrovascular accident within the past 6 months, or hemodynamically significant valvular disease. It is important to note that this therapy is not yet available in the United States; it is presently experimental.

Conclusions

A reevaluation of RSD as a treatment of hypertension needs to be performed because of the negative results published regarding the Symplicity HTN-3 trial. Before the results released, consideration was being given to using RSD for milder cases of hypertension as a form of permanent therapy.[50] Along this line, Symplicity-HTN-4 was designed as a randomized controlled trial in RSD that will investigate the role of renal denervation system for the treatment of uncontrolled hypertension in patients with systolic blood pressure between 140 and 160 mm Hg, despite treatment with three or

TABLE 2

Patient Criteria That Need to Be Met Prior to Renal Sympathetic Denervation Therapy

Office-based systolic blood pressure ≥ 160 mm Hg (≥ 150 mm Hg in T2D)
≥ 3 antihypertensive drugs in adequate dosage and combination (including a diuretic)
Lifestyle modification
Exclusion of secondary hypertension
Exclusion of pseudoresistance using ambulatory blood pressure monitoring (average blood pressure of 130 mm Hg or mean daytime blood pressure of 135 mm Hg)
Preserved renal function (GFR ≥ 45 mL/min/1.73m^2)
Eligible renal arteries: no polar or accessory arteries, no significant renal artery stenosis, no prior revascularization

GFR, glomerular filtration rate; T2D, type 2 diabetes.

more antihypertensive medications of different classes.[52] This approach is supported by a pilot study of 54 patients with moderate-resistant hypertension (office blood pressure ≥ 140/90 mm Hg and ≤ 160/100 mm Hg, confirmed by 24-hour ambulatory blood pressure of ≥ 130/80 mm Hg), which demonstrated that RSD reduced office blood pressure at 6 months by a mean of 13/7 mm Hg, 14/7 mm Hg by 24-hour ambulatory blood pressure recording.[53] However, given the negative results of the Symplicity HTN-3 trial, enrollment in the Symplicity-HTN-4 trial has been temporarily suspended.

In summary, RSD appears to be appealing as a treatment for resistant hypertension; in addition, it could potentially be applied in a host of other conditions with sympathetic overactivity. Future large, randomized controlled clinical trials are warranted and essential in identifying which patients might benefit the most from this procedure, and what the long-term benefits and risks associated with this method might be. Considering the prevalence of hypertension as a major cause of cardiovascular disease worldwide, the global health and economic benefits of this procedure could be enormous. ■

The authors report no real or apparent conflicts of interest.

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MAIN POINTS

- *Resistant hypertension* is an inability to control blood pressure despite administration of at least three antihypertensive medications, one of which is a diuretic; it affects 9% of the approximately 1 billion people with hypertension worldwide.
- Baroreflex activation therapy and renal sympathetic denervation (RSD) have been examined as effective nonpharmacologic alternatives to address this serious medical condition. Baroreflex activation is still being evaluated for both safety and efficacy, and RSD is currently experimental in the United States.
- Catheter-based RSD was developed with the purpose of interfering with the autonomic afferent and efferent nerves that reach the kidneys.
- In addition to a reduction in systemic blood pressure, other favorable effects have been reported after denervation, including reduction in total body and renal norepinephrine spillover, decrease in sympathetic nerve traffic, increase in renal blood flow, and decrease in plasma renin activity.
- Considering the prevalence of hypertension as a major cause of cardiovascular disease worldwide, the global health and economic impact of this procedure could be enormous.

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