



EDUCATIONAL OBJECTIVE: Readers will recognize the physiologic rationale for renal denervation and the findings from studies in humans

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Renal denervation to treat resistant hypertension: Guarded optimism

ABSTRACT

Renal sympathetic denervation has shown promise in treating hypertension resistant to drug therapy. This procedure lowers blood pressure via targeted attenuation of renal sympathetic tone, and it has a favorable safety profile. But although there is reason for cautious optimism, we should keep in mind that the mechanisms of hypertension are complex and multifactorial, and further study of this novel therapy and its long-term effects is needed.

KEY POINTS

Renal sympathetic nerves help regulate volume and blood pressure as they innervate the renal tubules, blood vessels, and juxtaglomerular apparatus. They carry both afferent and efferent signals between the central nervous system and the kidneys.

Surgical sympathectomy was done in the 1950s for malignant hypertension. It had lasting antihypertensive results but also caused severe procedure-related morbidity. A new percutaneous procedure for selective renal denervation offers the advantage of causing few major procedure-related adverse effects.

Selective renal denervation decreases norepinephrine spillover and muscle sympathetic nerve activity, evidence that the procedure reduces sympathetic tone.

The major clinical trials done so far have found that renal denervation lowers blood pressure significantly, and the reduction is sustained for at least 3 years.

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CAN A PERCUTANEOUS catheter-based procedure effectively treat resistant hypertension?

Radiofrequency ablation of the renal sympathetic nerves is undergoing randomized controlled trials in patients who have resistant hypertension and other disorders that involve the sympathetic nervous system. Remarkably, the limited results available so far look good.

See related editorial, page 498

This article discusses the physiologic rationale for renal denervation, the evidence from studies in humans of the benefits, risks, and complications of the procedure, upcoming trials, and areas for future research.

DESPITE MANY TREATMENT OPTIONS, RESISTANT HYPERTENSION IS COMMON

Hypertension is a leading reason for visits to physicians in the United States and is associated with increased rates of cardiovascular disease and death.^{1,2} A variety of antihypertensive agents are available, and the percentage of people with hypertension whose blood pressure is under control has increased over the past 2 decades. Nevertheless, population-based studies show that the control rate remains suboptimal.³ Effective pharmacologic treatment may be limited by inadequate doses or inappropriate combinations of antihypertensive drugs, concurrent use of agents that raise the blood pressure, noncompliance with dietary restrictions, and side effects that result in poor compliance with drug therapy.

Resistant hypertension is defined as failure to achieve goal blood pressure in patients who are adhering to full tolerated doses of an ap-

Resistant hypertension: full doses, an appropriate three-drug regimen that includes a diuretic

appropriate three-drug regimen that includes a diuretic.^{1,4,5} If we use these criteria, many patients labelled as having resistant hypertension probably do not truly have it; instead, they are nonadherent to therapy or are on an inadequate or inappropriate regimen. Although the true prevalence of resistant hypertension is not clear, estimates from large clinical trials suggest that about 20% to 30% of hypertensive patients may meet the criteria for it.⁴ For the subset of patients who have truly resistant hypertension, nonpharmacologic treatments such as renal sympathetic denervation are an intriguing avenue.

■ SURGICAL SYMPATHETIC DENERVATION: TRIED AND ABANDONED IN THE 1950s

More than a half century ago, a surgical procedure, thoracolumbar sympathectomy (in which sympathetic nerve trunks and splanchnic nerves were removed), was sometimes performed to control blood pressure in patients with malignant hypertension. This was effective but caused debilitating side effects such as postural hypotension, erectile dysfunction, and syncope.

Smithwick and Thompson⁶ reported that, in 1,266 hypertensive patients who underwent this procedure and 467 medically treated controls, the 5-year mortality rates were 19% and 54%, respectively. Forty-five percent of those who survived the surgery had significantly lower blood pressure afterward, and the antihypertensive effect lasted 10 years or more.

The procedure fell out of favor due to the morbidity associated with this nonselective approach and to the increased availability of drug therapy.

■ THE SYMPATHETIC NERVOUS SYSTEM IS A DRIVER OF HYPERTENSION

A variety of evidence suggests that hyperactivation of the sympathetic nervous system plays a major role in initiating and maintaining hypertension. For example, drugs that inhibit the sympathetic drive at various levels have a blood-pressure-lowering effect. Further, direct intraneural recordings show a high level of sympathetic nerve activity in

the muscles of hypertensive patients, who also have high levels of cardiac and renal norepinephrine “spillover”—ie, the amount of this neurotransmitter that escapes neuronal uptake and local metabolism and spills over into the circulation.⁷

The kidneys are supplied with postganglionic sympathetic nerve fibers that end in the efferent and afferent renal arterioles, the juxtaglomerular apparatus, and the renal tubular system. Studies in animals and humans have shown that an increase in efferent signals (ie, from the brain to the kidney) leads to renal vasoconstriction and decreased renal blood flow, increased renin release, and sodium retention.^{8,9} Afferent signals (from the kidney to the central nervous system), which are increased in states of renal ischemia, renal parenchymal injury, and hypoxia, disinhibit the vasomotor center (the nuclei tractus solitarii) in the central nervous system, leading to increased efferent signals to the kidneys, heart, and peripheral blood vessels (FIGURE 1).¹⁰

Enhanced sympathetic activity in patients with hypertension may play a role in subsequent target-organ damage such as left ventricular hypertrophy, congestive heart failure, and progressive renal damage.¹¹

Studies of renal denervation in animals, using surgical and chemical techniques, have further helped to establish the role of renal sympathetic nerves in hypertension.^{12,13}

■ CATHETER-BASED RENAL DENERVATION

Renal sympathetic nerves run through the adventitia of the renal arteries in a mesh-like pattern.

In the renal denervation procedure, a specially designed catheter is inserted into a femoral artery and advanced into one of the renal arteries. There, radiofrequency energy is applied to the endoluminal surface according to a proprietary algorithm, thereby delivering thermal injury selectively to the renal sympathetic nerves without affecting the abdominal, pelvic, or lower-extremity nerves. The energy delivered is lower than that used for cardiac electrophysiologic procedures.

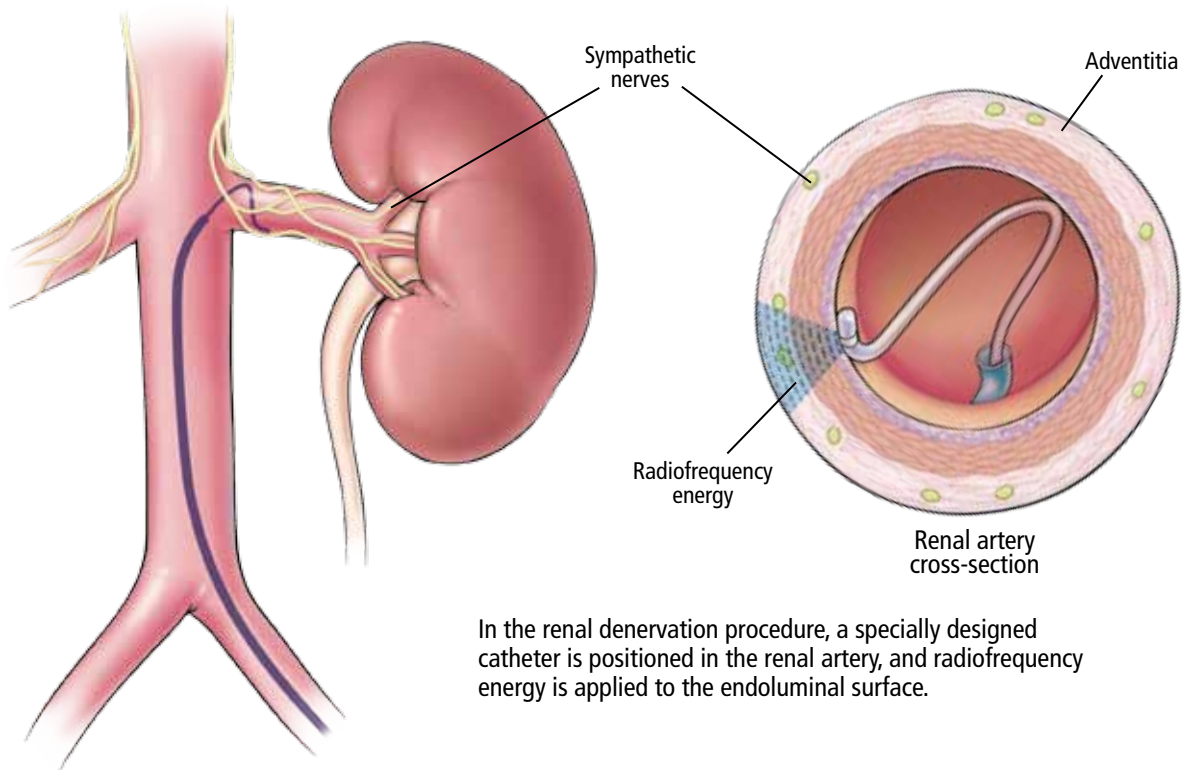
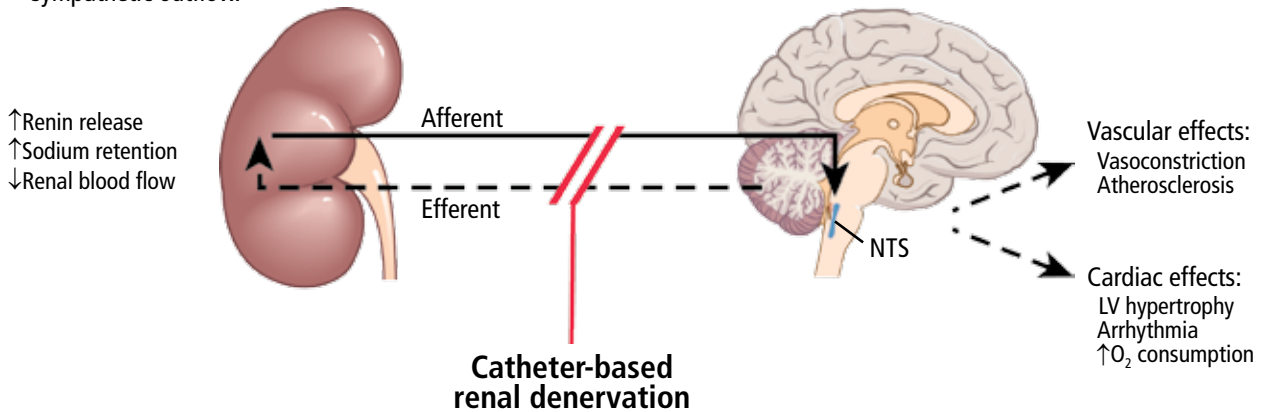
The nerves are not imaged or mapped before treatment. The procedure is performed on both sides, with four to six sites ablated in a

Ablating renal sympathetic nerves to treat resistant hypertension

In a new twist on an old idea, radiofrequency ablation of the renal sympathetic nerves via a percutaneous catheter is undergoing clinical trials to treat resistant hypertension.

Kidneys, in response to ischemia, send afferent sympathetic signals to the brain that disinhibit the nuclei tractus solitarii (NTS), increasing sympathetic outflow.

The NTS in the brainstem control efferent sympathetic signals from the brain to various organs of the body. Sympathetic signals raise blood pressure by increasing the heart rate, constricting arteries, and, in the kidney, increasing renin release and sodium and fluid retention.



In the renal denervation procedure, a specially designed catheter is positioned in the renal artery, and radiofrequency energy is applied to the endoluminal surface.

FIGURE 1

TABLE 1

The Symplicity HTN-1 and HTN-2 trials: Patients and methods

	SYMPPLICITY HTN-1 ¹⁴	SYMPPLICITY HTN-2 ¹⁵	
Study design	Proof-of-principle; nonrandomized	Randomized, controlled; unblinded to treatment	
Study sites	Five centers in Australia and Europe	24 centers in Australia, Europe, New Zealand	
Number of patients	45 ^a	106 (52 renal denervation, 54 controls)	
		Renal denervation group	Control group
Mean age (years)	58 ± 9	58 ± 12	58 ± 12
Race	96% white	98% white	96% white
Female	44%	35%	50%
Type 2 diabetes	31%	40%	28%
Baseline blood pressure (mm Hg)	177/101 (20/15)	178/97 (18/16)	178/98 (16/17)
No. of antihypertensive drugs	4.7 (1.5)	5.2 (1.5)	5.3 (1.8)
Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m ²)	81 (23)	77 (19)	86 (20)
Inclusion criteria	Office systolic blood pressure (SBP) ≥ 160 mm Hg on at least three antihypertensive drugs including one diuretic, or confirmed intolerance to medications	Office SBP ≥ 160 mm Hg (≥ 150 mm Hg in patients with diabetes) on at least three antihypertensive drugs	
Main exclusion criteria	Known cause of secondary hypertension Type 1 diabetes Pregnancy eGFR < 45 mL/min/1.73 m ² Hemodynamically significant valvular heart disease Existing permanent pacemaker or implantable cardioverter-defibrillator Use of clonidine, moxonidine, rilmenidine, or warfarin ^b Renovascular abnormalities	Type 1 diabetes Pregnancy eGFR < 45 mL/min/1.73 m ² Substantial stenotic valvular heart disease Existing permanent pacemaker or implantable cardioverter-defibrillator Renovascular abnormality Contraindication to magnetic resonance imaging Myocardial infarction, unstable angina, or cerebrovascular accident in previous 6 months	
Primary end points	Office blood pressure and procedural safety data before and at 1, 3, 6, 9, and 12 months after procedure ^c	Between-group change in seated office SBP from baseline to 6 months after procedure ^d	

^a This cohort was later expanded, and results were published on 153 patients at 19 centers in Australia, Europe, and the United States.¹⁶

^b Use of central sympatholytics was not an exclusion criterion for the expanded cohort.

^c Follow-up in the expanded cohort was reported at 1, 3, 6, 12, 18, and 24 months.¹⁶

^d Secondary end points were acute procedural safety; chronic procedural safety (including reduction of eGFR > 25% or new stenosis > 60% confirmed by angiography at 6 months); composite cardiovascular end point (myocardial infarction, sudden cardiac death, new-onset heart failure, death from progressive heart failure, cerebrovascular accident, aortic or limb revascularization procedure, lower limb amputation, death from aortic or peripheral arterial disease, dialysis, death because of renal failure, hospital admission for hypertensive emergency unrelated to nonadherence or nonpersistence with medications, and hospital admission for atrial fibrillation); 10 mm Hg or more systolic response at 6 months; achievement of target SBP; change in 24-hour ambulatory blood pressure; and change in home-based blood pressure measurements.

longitudinal and rotational manner in 2-minute treatments at each site, to cover the full circumference (FIGURE 1).

In the United States, the device (Symplicity Renal Denervation System; Medtronic, Inc, Mountain View, CA) is available only for investigational use.

Below, we briefly review the studies of renal denervation to date.

SYMPPLICITY HTN-1 Symplicity HTN-1 was a proof-of-principle study in 45 patients with resistant hypertension (TABLE 1).^{14,15}

Effect on blood pressure. Six months after renal denervation, blood pressure was significantly lower than at baseline ($-22/-11$ mm Hg, 95% confidence interval [CI] 10/5 mm Hg) in 26 patients available for follow-up. At 12 months, the difference from baseline was $-27/-10$ mm Hg (95% CI 16/11 mm Hg) in 9 patients available for follow-up (TABLE 2).¹⁴

Evidence of the durability of blood pressure reduction came from an expanded cohort of 153 patients followed for 2 years after denervation.¹⁶

Further follow-up data showed a sustained and significant blood pressure reduction through 3 years after denervation (unpublished results presented at the 2012 annual meeting of the American College of Cardiology). Notably, patients who were initially considered to be nonresponders (defined as failure of their blood pressure to go down by at least 10 mm Hg) were all reported to have a clinical response at 36 months.

Adverse events. In the initial and expanded cohorts combined, one patient suffered a renal artery dissection due to manipulation of the guiding catheter before the radiofrequency energy was delivered, and three patients developed a femoral pseudoaneurysm. No other long-term arterial complications were observed.

Comments. Limitations of this study included a small number of patients, no control group, and a primary outcome of a reduction in office blood pressure rather than in ambulatory blood pressure.

Additionally, although the authors concluded that there was no significant deterioration in renal function during the study period, we should note that in an additional follow-up period in this cohort, 10 patients with avail-

able 2-year data had a decrease in estimated glomerular filtration rate (eGFR) of -16.0 mL/min/1.73 m². In 5 patients who did not have spironolactone (Aldactone) or another diuretic added after the first year of follow-up, a lesser but significant decrease (-7.8 mL/min/1.73 m²) was noted. The investigators surmised that denervation may enhance diuretic sensitivity, leading to prerenal azotemia in some patients.¹⁷

■ SYMPPLICITY HTN-2

The Symplicity HTN-2 trial was a larger, randomized, efficacy study that built on the earlier results, providing additional evidence of therapeutic benefit.¹⁵

An international cohort of 106 patients with resistant hypertension, defined as systolic blood pressure of 160 mm Hg or higher (or ≥ 150 mm Hg in patients with type 2 diabetes) despite the use of three or more antihypertensive medications, were randomly assigned to undergo renal denervation with the Symplicity device ($n = 52$) or to continue their previous treatment with antihypertensive medications alone ($n = 54$). The primary effectiveness end point was the change in seated office blood pressure from baseline to 6 months (TABLE 1).

Effect on blood pressure. In the denervation group, at 6 months, office blood pressure had changed by a mean of $-32/-12$ mm Hg (standard deviation [SD] 23/11 mm Hg) compared with a mean change of 1/0 mm Hg (SD 21/10 mm Hg) in the control group. Forty-one (84%) of the 49 patients who underwent denervation had a decrease in systolic blood pressure of 10 mm Hg or more at 6 months compared with baseline values, while five (10%) had no decline in systolic blood pressure. Nineteen patients had a reduction in systolic pressure to less than 140 mm Hg in the denervation group.

A subset of patients (20 in the denervation group and 25 in the control group) underwent 24-hour ambulatory blood pressure monitoring at 6 months. This showed a similar though less pronounced fall in blood pressure in the denervation group and no change in the controls. A subanalysis that censored all data for patients whose medication was increased during the follow-up period showed a blood pres-

Sympathetic signals lead to renal vasoconstriction, decreased renal blood flow, increased renin release, and sodium retention

TABLE 2

The Symplicity HTN-1 and HTN-2 trials: Results

SYMPPLICITY HTN-1 ¹⁴				SYMPPLICITY HTN-2 ¹⁵			
Primary efficacy outcomes ^a				Renal denervation group		Control group	
	Period	Number of patients	Change in office systolic blood pressure (SBP), mm Hg (mean, 95% CI)	Period	Change in office SBP, mm Hg (mean, SD), n = 49 ^b	Period	Change in office SBP, mm Hg (mean, SD), n = 51 ^b
	1 mo	41 of 45	−14/−10 (4/3)	1 mo	−20/−7	1 mo	0/0
	3 mo	39 of 45	−21/−10 (7/4)	3 mo	−24/−8	3 mo	−4/−2
	6 mo	26 of 45	−22/−11 (10/5)	6 mo	−32/−12 (23/11)	6 mo	1/0 (21/10)
	9 mo	20 of 45	−24/−11 (9/5)				
	12 mo	9 of 45	−27/−17 (16/11)				
Short-term safety outcomes	Renal artery dissection related to catheter placement before energy delivery (n = 1) Femoral artery pseudoaneurysm at access site (n = 3) (In initial and expanded cohorts)			Intraprocedural bradycardia requiring atropine (7/52 patients) Postprocedural drop in blood pressure (n = 1) Femoral artery pseudoaneurysm at access site (n = 1)			
Long-term safety outcomes	No renal vascular complications noted with postprocedure imaging studies on follow-up			No renal vascular complications noted with post-procedure imaging studies on follow-up			
				Renal denervation group		Control group	
				Transient ischemic attack (n=1) Angina requiring a coronary stent (n=1) Hypotension (n=1) Hypertensive crisis (n=1) Admission for nausea or vomiting possibly related to hypertension (n=1)		Transient ischemic attack (n=2) Angina requiring a coronary stent (n=1)	
Nonresponders		6 (13%) of 45 patients had an SBP reduction < 10 mm Hg		5 (10%) of 49 patients in the renal denervation group and 24 (47%) of 51 controls had no decline in SBP 4 (8%) of 49 patients in the renal denervation group and 6 (12%) of 51 controls needed drug increases before their 6-month follow-up			

^a Primary efficacy outcomes in the expanded cohort in Symplicity HTN-1 showed the following results up to 24 months: 1 month −20/−10 (n = 138), 3 months −24/−11 (n = 135), 6 months −25/−11 (n = 86), 12 months −23/−11 (n = 64), 18 months −26/−14 (n = 36), and 24 months −32/−14 (n = 18)¹⁶

^b 3 patients lost to follow-up

CI = confidence interval; SD = standard deviation

sure reduction of $-31/-12$ mm Hg (SD 22/11 mm Hg) in the renal denervation group.

Adverse events. Procedure-related adverse events included a single femoral artery pseudoaneurysm, one case of postprocedural hypotension requiring a reduction in antihypertensive medications, and 7 (13%) of 52 patients who experienced intraprocedural bradycardia requiring atropine.

Effect on renal function. No significant difference was noted between groups in the mean change in renal function at 6 months, whether assessed by eGFR, serum creatinine level, or cystatin C level. At 6 months, no patient had a decrease of more than 50% in eGFR, although two patients who underwent renal denervation and three controls had more than a 25% decrease in eGFR.

At 6 months, the urine albumin-to-creatinine ratio had changed by a median of -3 mg/g (range $-1,089$ to 76) in 38 patients in the treatment group and by 1 mg/g (range -538 to 227) in 37 controls.

Most patients (88%) undergoing renal denervation underwent renal arterial imaging at 6 months, on which a single patient showed possible progression of an underlying atherosclerotic lesion that was unrelated to the procedure and that did not require intervention.

Denervation and the normal stress response. Whether renal denervation negatively affects the body's physiologic response to stress that is normally mediated by sympathetic nerve activity was addressed in an extended investigation of Symplicity HTN-2 using cardiopulmonary exercise tests at baseline and 3 months after renal denervation.¹⁸ In the denervation group, blood pressure during exercise was significantly lower at 3 months than at baseline, but the heart rate increase at different levels of exercise was not affected. Additionally, the resting heart rate was lower and heart rate recovery after exercise improved after the procedure, particularly in patients without diabetes.

Comments. The Symplicity HTN-2 trial benefited from a randomized trial design and strict inclusion criteria of treatment resistance, but it still had notable limitations. A pretrial evaluation for causes of secondary hypertension or white-coat hypertension was not explicitly

described. The control group did not undergo a sham procedure, and data analyzers were not masked to treatment assignment. Although not analyzed as a primary end point, the use of home-based and 24-hour ambulatory blood pressure assessment—measures important for determining white-coat hypertension—revealed substantial differences in blood pressure changes relative to office measurements. Because nearly all the patients (97%) were white, the generalizability of treatment results to black patients with resistant hypertension may be limited. Isolated diastolic hypertension (defined as diastolic pressure ≥ 90 mm Hg with systolic pressure < 140 mm Hg), which is more common in younger patients, was not studied.

■ DOES RENAL DENERVATION REDUCE SYMPATHETIC TONE?

A subgroup of 10 patients in the Symplicity HTN-1 trial whose mean 6-month office blood pressure was reduced by $22/12$ mm Hg underwent assessment of renal norepinephrine spillover. A substantial (47%) reduction in renal norepinephrine spillover was noted 1 month after the procedure.¹⁴

The investigators additionally described a marked reduction in renal norepinephrine spillover from both kidneys in one patient, with a reduction of 48% from the left kidney and 75% from the right kidney 1 month after the procedure. Whole-body norepinephrine spillover in this patient was reduced by 42%. This effect was accompanied by a 50% decrease in plasma renin activity and by an increase in renal plasma flow. Aldosterone levels were not reported.¹⁹

Thus, the decrease in renal norepinephrine spillover suggests a reduction of renal efferent activity, and the decrease in total body norepinephrine spillover suggests a reduction in central sympathetic drive via the renal afferent pathway.

Microneurography in this same patient showed a gradual reduction in muscle sympathetic nerve activity to normal levels, from 56 bursts per minute at baseline to 41 at 30 days and 19 at 12 months).¹⁹ Decreased renin secretion, via circulating angiotensin II, may affect central sympathetic outflow as well.

Comments. While these findings address

Mechanisms leading to hypertension are complex and multifactorial

some of the underlying mechanisms, the small number of patients in whom these studies were done limits the generalizability of the results. The impact of the procedure on renal hemodynamics will need to be studied, including possible direct effects of the procedure, and whether there are differences in different study populations or differences based on blood pressure levels.

■ WHICH PATIENTS RESPOND BEST TO THIS PROCEDURE?

Although the Symplicity HTN-2 investigators report some predictors of increased reduction in blood pressure on multivariate analysis, including increased blood pressure at baseline and reduced heart rate at baseline, these are not specific enough to enable patient selection.

Interestingly, results from the expanded cohort of the Symplicity HTN-1 study found that patients on central sympatholytic agents such as clonidine had a greater reduction in blood pressure, although the reason for this is unclear.¹⁶ Identifying specific predictors of treatment success at baseline will be essential in future studies.

The earlier Symplicity trials and the ongoing Symplicity HTN-3 trial are in patients who have high blood pressure not responding to three or more antihypertensive drugs. The mean baseline systolic blood pressure in the Symplicity HTN-1 and HTN-2 trials was 178 mm Hg, and patients were taking an average of five antihypertensive drugs (TABLE 1). It is not known whether denervation will produce similar blood-pressure-lowering results across the spectrum of hypertension severity.

■ WHAT ARE THE LONG-TERM RESULTS OF DENERVATION?

Enthusiasm for the results from the Symplicity trials is tempered by concerns about the durability of the effects of the procedure, the need for better understanding of the impact of renal denervation on a wide array of pathophysiologic cascades leading to hypertension, and the effect on renal hemodynamics.

Antihypertensive efficacy has been reported to persist up to 2 years after the procedure,¹⁶ with

recent unpublished data suggesting efficacy up to 3 years, but longer follow-up is needed to address whether these effects are finite.

Although reinnervation of afferent renal nerves has not been described, transplant models have shown anatomic regrowth of efferent nerves; the impact of this efferent reinnervation on blood pressure remains unclear. Experience from renal transplantation also shows that implanted kidneys that are “denervated” can still maintain fluid and electrolyte regulation.

Follow-up renal imaging in the Symplicity trials did not indicate renal artery stenosis at the sites of denervation in patients who underwent the procedure. Animal studies using the Symplicity catheter system showed renal nerve injury as evidenced by nerve fibrosis and thickened epineurium and perineurium, but no significant smooth muscle hyperplasia, arterial stenosis, or thrombosis by angiography or histology at 6 months.²⁰

■ WHAT ARE THE RISKS?

Adverse effects that were noted in the short term are detailed under discussion of the trials and in TABLE 2.

Long-term adverse events in the Symplicity HTN-2 trial that required hospitalization were reported in five patients in the denervation group and three patients in the control group (TABLE 2). These included transient ischemic attacks, hypertensive crises, hypotensive episodes, angina, and nausea.

Renal function was maintained for the duration of both trials, and details regarding eGFR change have been described above under the discussion of the trials.

Diffuse visceral pain at the time of the procedure is reported as an expected occurrence, managed with intravenous analgesic medications.

■ DOES SYMPATHETIC DENERVATION HAVE A ROLE IN OTHER CONDITIONS?

Interestingly, other sympathetically driven diseases, such as diabetes mellitus and polycystic ovary syndrome, may prove to be targets for this therapy in the future.²¹

Mahfoud et al²² conducted a pilot study in 37 patients with resistant hypertension undergoing renal denervation and 13 control

The investigators surmised that denervation may enhance diuretic sensitivity, leading to prerenal azotemia in some patients

patients. Fasting glucose levels declined from 118 ± 3.4 mg/dL to 108 ± 3.8 mg/dL after 3 months in the intervention group ($P = .039$), compared with no change in the control group. Insulin and C-peptide levels were also lower in the intervention group. The reported improvement in glucose metabolism and insulin sensitivity suggests that the beneficial effects of this procedure may extend beyond blood pressure reduction.

Brandt et al²³ reported regression of left ventricular hypertrophy and significantly improved cardiac functional parameters, including increase in ejection fraction and improved diastolic dysfunction, in a study of 46 patients who underwent renal denervation. This findings suggests a potential beneficial effect on cardiac remodeling.

Witkowski et al²⁴ reported lowering of blood pressure in 10 patients with refractory hypertension and obstructive sleep apnea who underwent renal denervation, which was accompanied by improvement of sleep apnea severity.

Ukena et al²⁵ reported reduction in ventricular tachyarrhythmias in two patients with congestive heart failure who had therapy-resistant electrical storm.

A recent pilot study in 15 patients with stage 3 and 4 chronic kidney disease (mean eGFR $31 \text{ mL/min/1.73 m}^2$) showed significantly improved office blood pressure control up to 1 year, restoration of nocturnal dipping on 24-hour monitoring, as well as a nonsignificant trend towards increased hemoglobin levels and decreased proteinuria. No additional deterioration of renal function was reported in these patients (2 patients had renal function assessed up to 1 year).²⁶

Thus, the benefits of this procedure may extend to other diseases that have a common underlying thread of elevated sympathetic activity, by targeting the “sympathorenal” axis.²⁷

■ GUARDED OPTIMISM AND FUTURE DIRECTIONS

Given the well-known cardiovascular risks and health care costs associated with uncontrolled hypertension and the continued challenge that physicians face in managing it,

novel therapies such as renal denervation may provide an adjunct to existing pharmacologic approaches.

While there is certainly cause for guarded optimism, especially with the striking blood pressure-lowering results seen in trials so far, it should be kept in mind that the mechanisms leading to the hypertensive response are complex and multifactorial, and further understanding of this therapy with long-term follow-up is needed. A comparison study with spironolactone, which is increasingly being used to treat resistant hypertension (in the absence of a diagnosis of primary aldosteronism)^{28,29} would help to further establish the role of this procedure.

Studies of carotid baroreceptor stimulation via an implantable device have shown sustained reduction in blood pressure in patients with resistant hypertension. A study comparing this technique with renal denervation for efficacy and safety end points could be considered in the future.^{30,31}

The planned Symplicity HTN-3 study in the United States will be the largest trial to date, with a targeted randomization of more than 500 patients using strict enrollment criteria, including the use of maximally tolerated doses of diuretics and more focus on the use of ambulatory blood pressure monitoring and on the blinding of participants. This study will help further analysis of this technology in a more diverse population.^{32,33}

Future studies should be designed to clarify pathophysiologic mechanisms, patient selection criteria, effects on target organ damage, and efficacy in patients with chronic kidney disease, obesity, congestive heart failure, and in less severe forms of hypertension.

■ A CALL FOR PARTICIPANTS IN A CLINICAL TRIAL

The Departments of Cardiology and Nephrology and Hypertension at Cleveland Clinic are currently enrolling patients in the Symplicity HTN-3 trial. For more information, please contact George Thomas, MD (thomasg3@ccf.org), or Mehdi Shishehbor, DO, MPH (shisheh@ccf.org), or visit www.simplifybptrial.com. ■

Forty-one (84%) of the 49 patients who underwent denervation had a decrease in systolic blood pressure of 10 mm Hg or more at 6 months

REFERENCES

- Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
- Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. National Center for Health Statistics. *Vital Health Stat* 13(169) 2011. http://www.cdc.gov/nchs/data/series/sr_13/sr13_169.pdf. Accessed April 24, 2012.
- Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA* 2010; 303:2043–2050.
- Persell SD. Prevalence of resistant hypertension in the United States, 2003–2008. *Hypertension* 2011; 57:1076–1080.
- Calhoun DA, Jones D, Textor S, et al; American Heart Association Professional Education Committee. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Circulation* 2008; 117:e510–e526.
- Smithwick RH, Thompson JE. Splanchnicectomy for essential hypertension; results in 1,266 cases. *J Am Med Assoc* 1953; 152:1501–1504.
- Schlaich MP, Sobotka PA, Krum H, Whitbourn R, Walton A, Esler MD. Renal denervation as a therapeutic approach for hypertension: novel implications for an old concept. *Hypertension* 2009; 54:1195–1201.
- Zanchetti AS. Neural regulation of renin release: experimental evidence and clinical implications in arterial hypertension. *Circulation* 1977; 56:691–698.
- Kon V. Neural control of renal circulation. *Miner Electrolyte Metab* 1989; 15:33–43.
- Campese VM. Neurogenic factors and hypertension in renal disease. *Kidney Int Suppl* 2000; 75:S2–S6.
- Mancia G, Grassi G, Giannattasio C, Seravalle G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension* 1999; 34:724–728.
- Campese VM, Ye S, Zhong H, Yanamadala V, Ye Z, Chiu J. Reactive oxygen species stimulate central and peripheral sympathetic nervous system activity. *Am J Physiol Heart Circ Physiol* 2004; 287:H695–H703.
- Katholi RE. Renal nerves in the pathogenesis of hypertension in experimental animals and humans. *Am J Physiol* 1983; 245:F1–F14.
- Krum H, Schlaich M, Whitbourn R, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. *Lancet* 2009; 373:1275–1281.
- Symplcity HTN-2 Investigators; Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplcity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010; 376:1903–1909.
- Symplcity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011; 57:911–917.
- Petidis K, Anyfanti P, Doumas M. Renal sympathetic denervation: renal function concerns. *Hypertension* 2011; 58:e19; author reply e20.
- Ukena C, Mahfoud F, Kindermann I, et al. Cardiorespiratory response to exercise after renal sympathetic denervation in patients with resistant hypertension. *J Am Coll Cardiol* 2011; 58:1176–1182.
- Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD. Renal sympathetic-nerve ablation for uncontrolled hypertension (letter). *N Engl J Med* 2009; 361:932–934.
- Rippy MK, Zarins D, Barman NC, Wu A, Duncan KL, Zarins CK. Catheter-based renal sympathetic denervation: chronic preclinical evidence for renal artery safety. *Clin Res Cardiol* 2011; 100:1095–1101.
- Schlaich MP, Straznicky N, Grima M, et al. Renal denervation: a potential new treatment modality for polycystic ovary syndrome? *J Hypertens* 2011; 29:991–996.
- Mahfoud F, Schlaich M, Kindermann I, et al. Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. *Circulation* 2011; 123:1940–1946.
- Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. *J Am Coll Cardiol* 2012; 59:901–909.
- Witkowski A, Prejbisz A, Florkzak E, et al. Effects of renal sympathetic denervation on blood pressure, sleep apnea course, and glycemic control in patients with resistant hypertension and sleep apnea. *Hypertension* 2011; 58:559–565.
- Ukena C, Bauer A, Mahfoud F, et al. Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. *Clin Res Cardiol* 2012; 101:63–67.
- Herring D, Mahfoud F, Walton AS, et al. Renal denervation in moderate to severe CKD. *J Am Soc Nephrol* 2012; May 17. [Epub ahead of print]
- Sobotka PA, Mahfoud F, Schlaich MP, Hoppe UC, Böhm M, Krum H. Sympatho-renal axis in chronic disease. *Clin Res Cardiol* 2011; 100:1049–1057.
- Chapman N, Dobson J, Wilson S, et al; Anglo-Scandinavian Cardiac Outcomes Trial Investigators. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension* 2007; 49:839–845.
- Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens* 2003; 16:925–930.
- Papademetriou V, Doumas M, Faselis C, et al. Carotid baroreceptor stimulation for the treatment of resistant hypertension. *Int J Hypertens* 2011; 2011:964394.
- Ng MM, Sica DA, Frishman WH. Rheos: an implantable carotid sinus stimulation device for the nonpharmacologic treatment of resistant hypertension. *Cardiol Rev* 2011; 19:52–57.
- US National Institutes of Health. Renal denervation in patients with uncontrolled hypertension (SYMPLICITY HTN-3). <http://www.clinicaltrials.gov/ct2/show/NCT01418261>. Accessed June 7, 2012.
- Kandzari DE, Bhatt DL, Sobotka PA, et al. Catheter-based renal denervation for resistant hypertension: rationale and design of the Symplcity HTN-3 trial. *Clin Cardiol* 2012 May 9. [Epub ahead of print]

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