# Catheter-Based Sympathetic Renal Denervation

A novel strategy for the treatment of resistant hypertension.

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Despite continued advances in its diagnosis, treatment, and public awareness, hypertension continues to affect cardiovascular health. Hypertension is a significant risk factor for stroke, coronary artery disease, heart failure, vascular disease, and chronic renal failure. It is estimated that there are 230 million hypertensive patients in the United States, Western Europe, and Japan and more than 1 billion worldwide. Hypertension is also estimated to contribute to nearly 7.1 million deaths annually.[1] There are substantial societal costs associated with these staggering statistics: The American Heart Association estimates the annual health care costs of hypertension to be in excess of $73 billion and rising.[2] Unfortunately, in the face of these substantial costs, it is estimated that approximately 65% of hypertensive patients are either untreated and/or uncontrolled.[3] Within this large cohort, an estimated 10% of patients have resistant hypertension, which is defined as blood pressure that remains above goal despite the use of three antihypertensive agents of different classes.[3] This definition focuses attention on a group of patients who are at high risk for having a reversible cause of hypertension and/or who may benefit from consideration of special diagnostic or therapeutic considerations.

Atherosclerotic renal artery stenosis is frequently considered in the differential diagnosis of patients with resistant hypertension;[4] although percutaneous renal artery stent revascularization may benefit some patients,[5] a recent randomized clinical trial[6] and a governmental meta-analysis[7] failed to demonstrate a medical benefit regarding improvement in renal function or blood pressure control. Thus, patients with multidrug-resistant hypertension remain at risk of the morbid and mortal consequences of uncontrolled hypertension. In this large cohort, there is a need for adjunctive therapies to supplement the current pharmacologic treatment regimens.

Neurohormonal signaling to and from the kidneys via the sympathetic nervous system and the renin-angiotensin system play a role in the long-term control of blood pressure. The current antihypertensive pharmaceuticals (eg, diuretics, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers, angiotensin-receptor blockers, calcium-channel blockers, alpha blockers, vasodilators) all act to reduce the consequences of elevated neurohormonal activation. Another potential therapeutic approach would be to mechanically or electrically disrupt the nerve pathways between the sympathetic nervous system and the kidney. Data from a recent proof-of-concept study[8] and preliminary United States pilot data provide growing clinical evidence that a novel, minimally invasive, percutaneous renal sympathetic denervation using radiofrequency energy can safely and substantially reduce blood pressure in patients with hypertension that is resistant to medical therapy.

## THE ROLE OF RENAL SYMPATHETIC NERVES IN THE PATHOGENESIS OF HYPERTENSION

The renal nerves play an essential role in the long-term regulation of blood pressure through reduction of renal blood flow, rightward shifting of the pressure-natriuresis curve, excess renin production (efferent

nerves), and through outbound renal sympathetic signaling (afferent nerves) with signals that are integrated in the central nervous system and cause upregulation of systemic sympathetic outflow. Both human and experimental animal models have established that renal sympathetic nerves contribute to the pathogenesis of hypertension. The human kidney is richly innervated with postganglionic sympathetic fibers to both renal arterioles, juxtaglomerular apparatus, proximal renal tubule, loop of Henle, and distal renal tubule. Depending on the specific physiologic setting, the effect may be mediated by preferential activation of either the efferent or afferent renal sympathetic nerves. Importantly, the inputs to control the efferent renal nerve activity are many and involve the aortic and carotid baroreflexes in the modulation of central sympathetic outflow and thus efferent renal nerve activity. Cardiac stretch receptors with vagal afferents also modulate efferent renal sympathetic activity. Finally, renorenal reflexes can alter the level of efferent nerve activity in the contralateral kidney.

The renal vasculature often receives greater sympathetic activation than other vascular beds, particularly in patients with hypertension. The disproportionate increase in renal sympathetic activity results in increased renal vascular resistance compared to the general circulation; this causes increased plasma renin activity and directly and indirectly facilitates sodium and water retention and can reduce renal blood flow. Increased efferent renal sympathetic activity can also facilitate the development of hypertension by shifting the relationship of the arterial pressure—renal sodium excretion interaction. Therefore, interruption of the renal nerves has been shown to delay the development of hypertension in animal models in which increased sympathetic nerve activity has been implicated.[9-11] In these models, denervation delays the development of hypertension and results in greater sodium excretion. There is also functional evidence that renal afferent nerves may affect central structures known to be involved in cardiovascular regulation; the disruption of these afferent renal nerves in renovascular and chronic renal failure models results in the attenuation of hypertension.

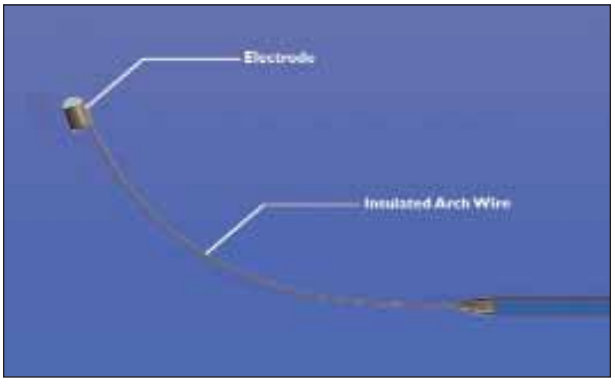


**Figure 1. Symplicity catheter (Ardian, Inc., Palo Alto, CA).**

> "Renal artery stenting inconsistently reduces blood pressure in patients with hemodynamically significant flow obstruction, suggesting a possible neurologic association with hypertension."

Although most studies of renal artery stenosis have focused on the activity of the renin-angiotensin system in its pathogenesis, the renal sympathetic nervous system plays an important role in the maintenance of renovascular hypertension. Importantly, increased sympathetic activity also contributes to hypertension in patients with chronic renal failure, and the normalization of central sympathetic outflow can be achieved by bilateral surgical renal denervation. Renal artery stenting inconsistently reduces blood pressure in patients with hemodynamically significant flow obstruction, suggesting a possible neurologic association to hypertension. As such, there are animal and human data suggesting the fundamental role of the renal sympathetic afferent and efferent nerves in the development and maintenance of hypertension and its subsequent role in cardiovascular, cerebrovascular, and chronic renal failure.

## CATHETER-BASED RENAL DENERVATION

Before the advent of modern pharmacological therapies to attenuate the contribution of the renal nerves to hypertension, surgical approaches such as splanchnicectomy and even radical sympathectomy were successful in lowering arterial pressure in patients with uncontrolled high blood pressure.[12] These invasive surgical approaches were associated with high perioperative morbidity and mortality rates and long-term complications including bowel, bladder, and erectile dysfunction, as well as postural hypotension.

A recent proof-of-concept trial has shown that the application of discrete low-dose radiofrequency energy to the renal artery endothelial surface results in the effective blocking of nerve conduction through sympathetic nerve fibers via a percutaneous, minimally invasive, catheter-based procedure.[8] These investigators delivered the treatment catheter (Symplicity catheter) (Figure 1) via a guide catheter, which was introduced through the common femoral artery to apply up to six

radiofrequency ablations of up to 8 watts and 2-minute duration to each renal artery. Treatments were delivered distally to proximally from the first main renal artery bifurcation to the ostium and were spaced longitudinally and rotationally under fluoroscopic guidance (Figure 2). The generator monitored catheter tip temperature and impedance to deliver the appropriate radiofrequency energy as defined by a preprogrammed algorithm.

In this seminal study, investigators enrolled 50 patients, excluding five patients from treatment due to either accessory renal artery anatomy or short main renal arterial segment, which precluded the opportunity to obtain at least four ablations. Ten patients underwent staged denervation procedures, in which single kidney procedures were followed by angiography 30 days later to demonstrate vascular integrity before denervating the second kidney, and a third angiogram was obtained 14 days later. The remaining patients underwent simultaneous bilateral renal artery denervation. In this cohort, the median procedure time was 38 minutes. Of the 45 treated patients, one developed a renal artery dissection before the delivery of radiofrequency energy; the dissection was successfully sealed by a renal artery stent without further complication. A femoral artery pseudoaneurysm developed in an additional patient, requiring analgesics and antibiotic therapy. Visceral pain occurred only during radiofrequency energy delivery and was successfully managed with common catheterization lab narcotics.

Renal artery safety, assessed via short-term (14–30 days) repeat angiography, and 6-month magnetic resonance angiography or computed tomographic angiography, now available in 34 patients, revealed no luminal irregularities at any treatment site. This was consistent with preclinical experiments.

This uncontrolled feasibility trial identified a sustained and significant blood pressure reduction of more than 25 mm Hg in patients who enrolled with elevated blood pressure despite three antihypertensive medications, including a diuretic. Eighty-five percent of the patients responded to therapy with more than a 10-mm Hg reduction of blood pressure. To confirm the effectiveness of this therapy to ablate efferent sympathetic nerves, renal noradrenaline spillover, the difference between renal uptake of noradrenaline and production of noradrenaline (a measure of sympathetic activation of the kidney), was measured bilaterally, employing the isotope dilution renal noradrenaline spillover method (Esler Method) before therapy and at 15- to 30-day follow-up. This assay confirmed a mean posttreatment reduction in noradrenaline levels of 47%, ($P < .023$; 95% confidence interval, 28%–65%) in 10 patients.

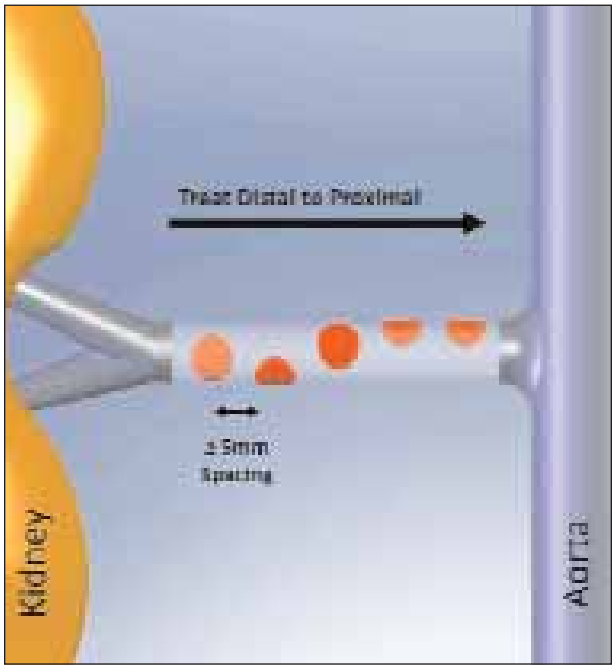


**Figure 2. Symplicity catheter treatments are delivered distally to proximally and are spaced longitudinally and circumferentially.**

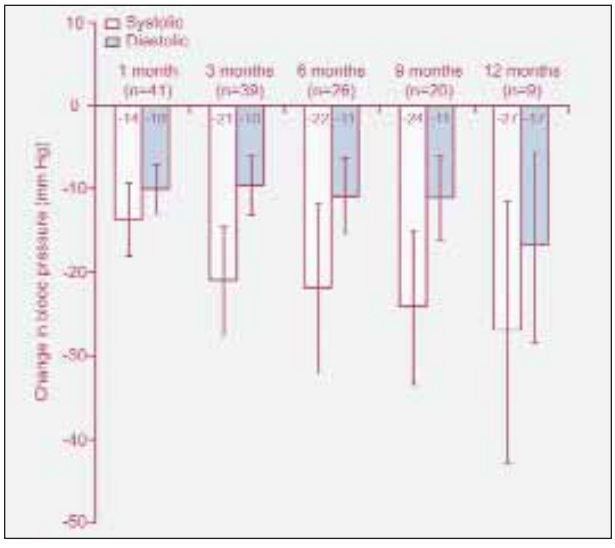


**Figure 3. Change in blood pressure (95% confidence interval) at 1, 3, 6, 9, and 12 months.**

A randomized controlled trial of more than 110 patients with multidrug-resistant hypertension is currently enrolling in Europe and Australia to more fully evaluate the effectiveness and durability of this novel catheter-based therapy. Limited feasibility trials in hypertension and end-stage renal disease are currently enrolling in the United States, and additional studies in

patients with chronic kidney disease and heart failure are anticipated. Additionally, a next-generation, lower-profile, 6-F–compatible Symplicity treatment catheter with a flexible, steerable tip has been developed and will be evaluated in future clinical trials.

## CASE STUDY

The patient was a 40-year-old woman with a long history of hypertension (resistant to multiple medications), hyperlipidemia, and obesity. Before treatment, her blood pressure was 171/109 mm Hg while taking eight antihypertensive medications from the following classes: beta blocker, angiotensin receptor blocker, thiazide diuretic, calcium channel blocker, vasodilator, and a centrally acting alpha-2 agonist. In a 33-minute procedure, we applied four 2-minute radiofrequency energy applications to each renal denervation. Pain was managed using midazolam and fentanyl.

Because of substantial reductions in blood pressure 2 weeks after renal denervation, all antihypertensive medications, except the beta blocker, were stopped. Despite discontinuing seven of the eight baseline medications, the patient had normalized blood pressure at 1 month (138/90 mm Hg). At 6 months, her blood pressure was 131/81 mm Hg.

## INTERPRETATION AND CONCLUSION

The importance of the kidney in long-term blood pressure control is well known. Therapeutic renal sympathetic denervation in patients with resistant hypertension resulted in a 14-mm Hg decrease in systolic blood pressure at 1 month, which progressively improved to a 27-mm Hg decrease in systolic blood pressure by 12 months (Figure 3). These data suggest that a major result of this procedure is disruption of afferent renal nerves as a stimulus of central sympathetic outflow, which results in a lower arterial pressure and allows for reverse vascular remodeling including the renal arterioles with decreasing renal vascular resistance over time.[13] Support for this interpretation of these data comes from experimental animal studies in which interruption of renal sensory afferent nerves not only lowers blood pressure but also attenuates end-organ damage caused by chronic sympathetic nervous system activity.[14-17]

The attenuation of hypertension of this magnitude by catheter-based renal sympathetic denervation in combination with pharmacologic therapy is likely to be valuable in decreasing the risks of stroke, left ventricular hypertrophy, heart failure, and chronic renal failure. If larger randomized studies of catheter-based renal sympathetic denervation confirm this quick, outpatient procedure to be safe, durable, and effective, this novel new strategy will likely be widely used in the treatment of hypertension.[18] ■

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